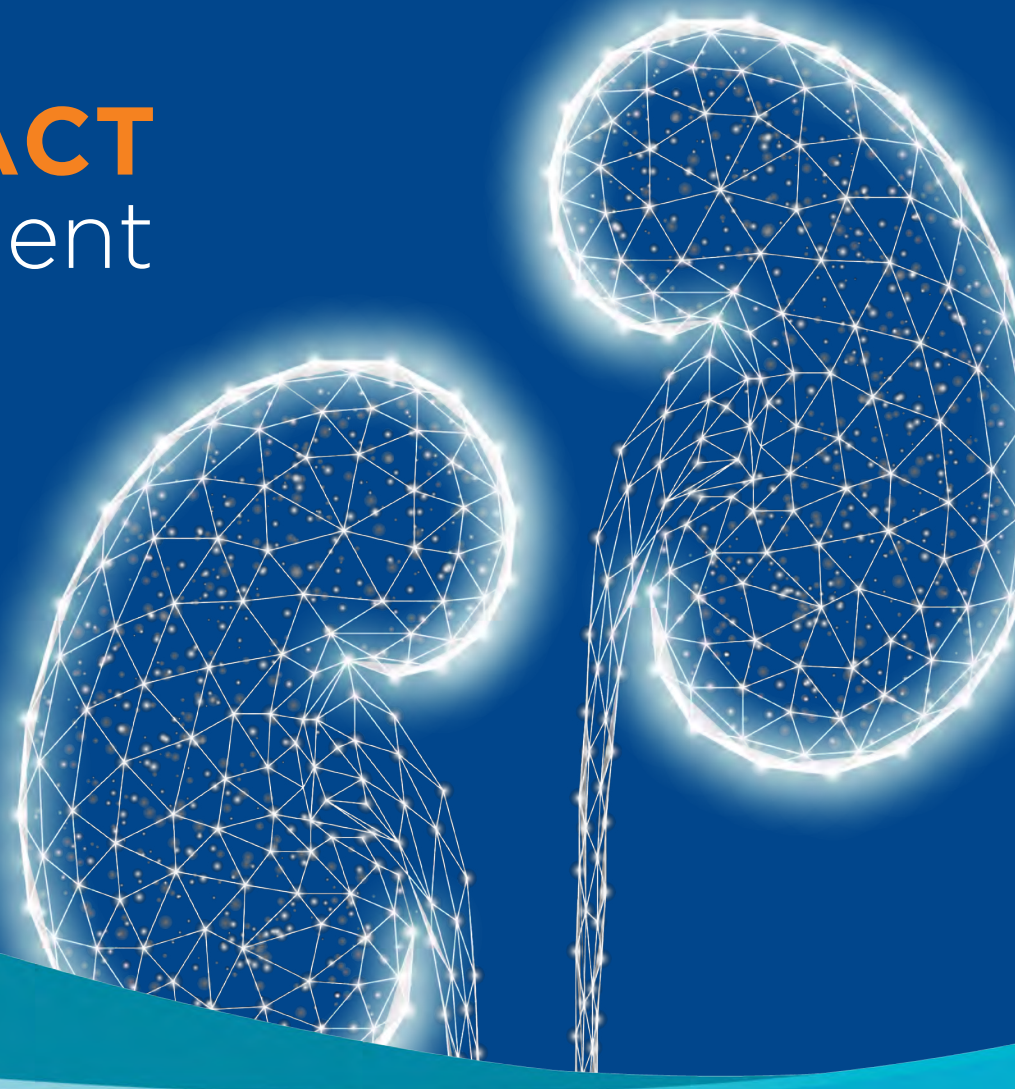
Kidney Week Edition

JASN

Journal of the American Society of Nephrology

ABSTRACT Supplement



KIDNEY WEEK 2021

Abstract Supplement

Abstract Publication
More than 3,000 abstracts are published in this supplement. Abstracts are arranged by the abstract type**, then by presentation date* for orals, and then by chronological publication number. Abstracts with a "PUB" number will not be presented at the ASN Annual Meeting.

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

The presenting author's name is underlined.

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

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

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

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TH-OR01

The Relationship Between Intravenous Fluid Administration and Renal Outcomes After Angiography

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Background: Contrast associated AKI (CA-AKI) may result in prolonged hospital stay and increased mortality. Fluids remain the mainstay for prevention. There is a lack of consensus on the optimal fluid rate and amount. Using the PRESERVE dataset, we studied the effect of peri-procedure fluid administration strategies on CA-AKI and 90-day need for dialysis, death, or a 50% increase in serum creatinine

Methods: We conducted a secondary analysis of 4993 of PRESERVE participants who received either IV saline or IV bicarbonate prophylaxis. Although fluid type was randomized, strategy of administration was at the discretion of the clinician. We divided the study group into quartiles by total fluid volume. Multivariable analysis was performed using logistic regression adjusting for age, history of heart failure, diabetes mellitus, left ventricular end-diastolic pressure, baseline glomerular filtration rate, procedure type, inpatient vs. outpatient status, and duration. We also tested for the interaction between fluid volume and duration of fluid administration categorized as <6 or ≥6 hours

Results: Compared to the highest quartile (Q4) of fluid volume, there was a significantly increased risk of the primary 90 day end point in quartile 1. There were no differences between quartiles 2 and 3 compared to quartile 4. There was no significant difference in the incidence of CA-AKI across the groups. The interaction between volume and duration of fluid administration was not significant

Conclusions: We found that fluid volumes <964 ml may be associated with an increased risk for the primary outcome although residual confounding cannot be excluded; and that administering higher volumes over a total duration of <6 hours seem to be equally protective. The utility of high volume, short duration fluid administration protocols will facilitate the safe performance of out-patient procedures.

	Quartiles of Total Fluid Volume			
	Q1 (N=1169)	Q2 (N=1165)	Q3 (N=1171)	Q4 (N=1166)
Volume ml, Mean (SD)	701 (157)	964 (42)	1140 (64)	1478 (216)
Duration hr, Mean (SD)	6.9 (2.4)	7.9 (2.5)	8.2 (2.5)	9.6 (3.4)
CA-AKI, OR (95% CI)	1.2 (0.7-2.2)	0.8 (0.4-1.5)	1.2 (0.7-2.0)	Ref
90 day outcome, OR (95% CI)	2.2 (1.1-4.7)	1.6 (0.7-3.5)	1.7 (0.8-3.6)	Ref

TH-OR02

AKI in Patients Treated with Immune Checkpoint Inhibitors

Shruti Gupta, David E. Leaf. ICPi-AKI Consortium *Brigham and Women's Hospital Department of Medicine, Boston, MA.*

Background: Data on immune checkpoint inhibitor-associated acute kidney injury (ICPi-AKI) are largely limited to single-center case series. We performed a multicenter study, the largest to date, to investigate risk factors, clinicopathologic features, outcomes, and survival in patients with ICPi-AKI.

Methods: We collected detailed data on 429 patients with ICPi-AKI and 429 controls who received ICPis contemporaneously but did not develop ICPi-AKI from 30 international sites. Multivariable logistic regression was used to identify predictors of ICPi-AKI and its recovery.

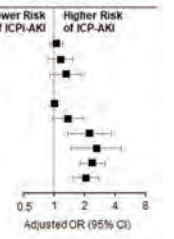
Results: ICPi-AKI occurred at a median of 16 weeks (IQR, 8-32) following ICPi initiation. Lower baseline eGFR, proton pump inhibitor (PPI) use, and prior or concomitant extrarenal immune-related adverse events (irAEs) were associated with a higher risk of ICPi-AKI (Figure A). Acute tubulointerstitial nephritis was the most common lesion on biopsy (125/151 biopsied patients [82.7%]). Hematuria, pyuria, and proteinuria were present in only 30-60% of patients with ICPi-AKI, and were more common in patients with greater severity of AKI. Renal recovery occurred in 276 patients (64.3%) at a median of 7 weeks (IQR, 3-10) following ICPi-AKI. Treatment with steroids was associated with higher odds of renal recovery (adjusted OR, 1.81; 95% CI, 1.01-3.27) (Figure B), particularly when initiated within 3 days of ICPi-AKI diagnosis (adjusted OR, 1.77; 95% CI, 1.01-3.13). Steroid use was also associated with a lower risk of death (adjusted HR, 0.52; 95% CI, 0.36-0.75). Of 121 patients rechallenged, only 20 (16.5%) developed recurrent ICPi-AKI.

Conclusions: Lower baseline eGFR, PPI use, and extrarenal irAEs are each independent risk factors for ICPi-AKI. Two thirds of patients have renal recovery following ICPi-AKI. Early treatment with steroids is associated with renal recovery and better overall survival.

A

Predictors of ICPi-AKI

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.17 (1.04-1.31)	1.05 (0.92-1.21)
Male sex	1.16 (0.88-1.52)	1.15 (0.86-1.53)
Combination ICPi therapy	1.42 (1.01-1.98)	1.30 (0.90-1.87)
Baseline eGFR (ml/min/1.73m²)		
≥90 (REF)	1	1
60-89	1.54 (1.13-2.10)	1.36 (0.95-1.94)
45-59	2.48 (1.59-3.87)	2.23 (1.35-3.68)
<45	1.92 (1.74-4.89)	2.62 (1.47-4.65)
PPI use*	2.55 (1.92-3.40)	2.40 (1.79-3.23)
Prior or concomitant extrarenal irAEs**	2.19 (1.65-2.91)	2.07 (1.53-2.78)



B

Predictors of Renal Recovery after ICPi-AKI

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years)	1.13 (0.95-1.34)	0.94 (0.75-1.18)
Male sex	1.81 (1.21-2.71)	1.45 (0.89-2.36)
White	1.71 (1.04-2.82)	1.19 (0.66-2.16)
Combination Therapy	1.76 (1.07-2.89)	1.13 (0.63-2.05)
Baseline eGFR (per 10 points)	0.76 (0.69-0.83)	0.79 (0.66-0.90)
Lung cancer	0.40 (0.26-0.62)	0.48 (0.28-0.80)
Concomitant ATIN-causing medication*	1.52 (1.02-2.28)	1.74 (1.07-2.81)
Concomitant extrarenal irAEs**	1.69 (1.06-2.71)	1.45 (0.85-2.52)
≥2+ Blood on urinalysis	0.38 (0.22-0.68)	0.46 (0.23-0.94)
≥2+ Leukocyte esterase on urinalysis	0.39 (0.23-0.66)	0.57 (0.31-1.04)
≥1 g/g UPCR	0.38 (0.19-0.75)	0.54 (0.23-1.23)
Stage 3 AKI	0.29 (0.19-0.43)	0.36 (0.22-0.59)
Treated with corticosteroids***	1.56 (0.95-2.57)	1.81 (1.01-3.27)

TH-OR03

The Incidence and Risk Factors of AKI Among People with HIV on Antiretroviral Treatment

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Background: The epidemiology of hospitalized acute kidney injury (AKI) among people with HIV (PWH) in the era of modern antiretroviral therapy for all PWH is not well-characterized.

Methods: We evaluated the incidence and risk factors for hospitalized AKI from 2005-2015 in a prospective study of PWH from the Johns Hopkins HIV Clinical Cohort. We defined hospitalized AKI as ≥0.3 mg/dL rise in serum creatinine (SCr) within any 48-hour period or 50% increase in SCr from baseline and assessed associations of risk factors with incident AKI using multivariate Cox regression models.

Results: Most participants (75%) were Black, 34% were female, mean age was 43 years and mean eGFR 106 mL/min/1.73 m^2. The incidence of AKI fluctuated annually, peaking at 40 per 1,000 person-years (PY) (95% CI: 22-69) in 2007, and reached a nadir of 20 per 1,000 PY (95% CI: 11-34) in 2010 (Figure). After multivariable adjustment, characteristics independently associated with AKI included Black race (HR=2.44; 95% CI: 1.42-4.20), hypertension (HR=1.61; 95% CI: 1.09-2.38), dipstick proteinuria >1+ (HR=1.78; 95% CI:1.06-2.97), history of AIDS (HR=1.82; 95% CI: 1.29-2.56), CD4 count <200 cells/mm^3 (HR=1.46; 95% CI: 1.02-2.07), and lower serum albumin (HR=2.87 per 0.1 mg/dL; 95% CI: 2.78-2.97).

Conclusions: In this contemporary cohort of PWH, the annual incidence of first AKI fluctuated during the study period. Attention to modifiable AKI risk factors and social determinants of health may further reduce AKI incidence among PWH.

Funding: NIDDK Support

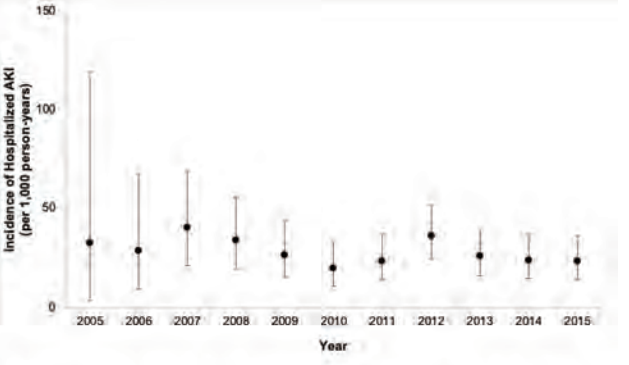

Figure 1: Crude incidence of first acute kidney injury (AKI) by calendar year among people living in HIV from 2005-2015 enrolled in the Johns Hopkins HIV Clinical Cohort (JHHCC).

TH-OR04

Nephrotoxin Exposure and AKI: A Magnitude Assessment Using NINJA Methodology in the Adult Population

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Background: The Nephrotoxic Injury Negated by Just-in Time Action (NINJA) program was designed to identify pediatric patients with high exposure to nephrotoxic medications (NTMx) and to reduce rates of acute kidney injury (AKI). In children, this program resulted in a 23.8% reduction in NTMx-AKI. However, equivalent rates of NTMx-AKI in adults are largely unknown. We report rates of NTMX-AKI in adults through application of the NINJA screening tool in an adult population.

Methods: Adult non-ICU patients admitted to the University of Iowa hospital between January 1, 2019 and December 31, 2019 were included in this retrospective analysis. We excluded emergency department encounters, pregnant patients admitted for delivery, and patients with end-stage kidney disease. High NTMx exposure was defined per NINJA protocol as receiving ≥ 3 NTMx on one day or intravenous aminoglycoside or vancomycin for ≥ 3 days (list of NTMx previously published). Patient charts were screened daily by an automated NINJA algorithm for high NTMx exposure and for AKI, defined as a creatinine increase of ≥0.3 mg/dL or to 1.5x baseline. Patients could have more than one NTMx exposure or AKI episode if separated by 48 hours from resolution of a prior event. NTMX-AKI was defined as an AKI event occurring during or within 48 hours of a high NTMx exposure.

Results: There were 4,596/33,835 (13.6%) patients with at least one day of high-NTMx exposure, and 17,254/144,997 (11.9%) of hospital days met high NTMx exposure criteria. AKI of any etiology was seen in 3,398 (10%) of patients, of which 1,467 (43.2%) also had at least one day of high-NTMx exposure. In 943 of these 1467 cases (64.3%), NTMx exposure preceded AKI development, by a median of 5 days. There were 6,038 total exposures and 1,131 NTMx-AKI events, for an AKI rate of 18.7% following high NTMx exposure. Serum creatinine was checked on 89% of days on or within 48 hours of high NTMx exposure.

Conclusions: Rates of NTMx exposure in adults are substantial, accounting for 12% of all hospitalized patient-days. Rates of AKI following high NTMx exposure were 18.7%, suggesting that high NTMx exposure is a contributing factor in a large number of AKI cases. These findings support implementation of interventions like the NINJA program in adults in order to reduce rates of NTMx-AKI.

TH-OR05

Proton Pump Inhibitor Exposure and Risk of AKI after Cardiac Surgery

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Background: Although postoperative acute kidney injury (AKI) is a serious and common complication of cardiac surgery, strategies for prevention are limited. A close link between proton pump inhibitor (PPI) usage and chronic kidney disease has been recently proposed. Therefore, the association between PPI exposure and AKI development after cardiac surgery was evaluated.

Methods: This retrospective study was conducted by analyzing two cohorts based on tertiary hospital-based electronic medical records and nationwide health insurance information. The Severance cardiac surgery cohort consisted of 6,555 patients aged ≥18 years who underwent cardiac surgery between May 2011 and September 2020. From the National Health Insurance Service-senior (NHIS-senior) cohort, 2,939 patients aged ≥60 years who underwent cardiac surgery between 2004 and 2015 were selected. Preoperative PPI exposure was defined as a PPI prescription record within 3 weeks before cardiac surgery. Primary outcome was AKI requiring dialysis (AKI-dialysis) and secondary outcomes were in-hospital mortality and hospital and intensive care unit (ICU) stay durations.

Results: In the Severance cardiac surgery cohort (mean age, 62.0 years; male, 60.1%) after propensity score matching, incident AKI-dialysis (5.5% vs. 3.2%, $P = 0.002$) and in-hospital mortality (4.7% vs. 3.2%, $P = 0.038$) were significantly higher among PPI-exposed than PPI non-exposed patients. In addition, median (IQR) hospital (17.0 [12.0-27.0] vs. 14.0 [11.0-19.0], $P < 0.001$) and ICU (3.0 [2.0-5.0] vs. [2.0-4.0], $P < 0.001$) stay durations were longer in patients exposed to PPI than in those who were not. Multivariable conditional logistic analyses revealed that PPI exposure was significantly associated with incident AKI-dialysis (OR, 2.20; 95% CI, 1.40-3.46) and in-hospital mortality (OR, 1.53; 95% CI, 1.03-2.27). The NHIS-senior cohort (mean age, 72.4 years; male, 58.7%) revealed comparable findings, showing that PPI exposure was significantly associated with incident AKI-dialysis (OR, 2.29; 95% CI, 1.60-3.29) and in-hospital mortality (OR, 2.25; 95% CI, 1.46-3.45).

Conclusions: Preoperative PPI exposure was associated with incident AKI in patients undergoing cardiac surgery, suggesting that PPI exposure could be a modifiable risk factor for AKI in these patients.

TH-OR06

Readmission and Mortality After AKI Hospitalization

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Background: Acute kidney injury (AKI) associates with high morbidity/mortality, but we lack robust data to quantify short to long-term real-world outcomes after an AKI hospitalization. We derived a synthetic retrospective cohort of hospitalized AKI subjects from Optum Clinformatics, a large claims database, to quantify mortality and all-cause/selected rehospitalizations 90 days and 1 year after an AKI event.

Methods: All AKI hospitalizations between 1/2007 and 9/2020 who had >2 years of continuous enrollment free of AKI hospitalization were identified (n=594,509) from the Optum database and propensity score matched to 594,509 control subjects who were hospitalized for a non-AKI cause.

Results: Mean age (SD) of the AKI cohort was 74.1 (13.1) years and 47.6% were women, 73.7% were white, 14.1% were Black, 9.7% were Hispanic, and 2.5% were Asian, which was similar to the matched non-AKI cohort. 55.9% of AKI and 26.5% of matched non-AKI group were hospitalized in the 2 years before the index admission. 50.3% of AKI group had CKD and 34.9% had heart failure, similar to the matched non-AKI group. One-year unadjusted cumulative incidence of all-cause rehospitalization was higher in AKI vs matched non-AKI patients in the presence and absence of pre-existing CKD ($p<0.01$). Adjusting for baseline characteristics, AKI was associated with a higher rate of hospital readmission from any cause [Hazard ratio (HR) 1.77; 95%CI 1.75-1.80; death as competing risk], heart failure (HR 3.16; 95%CI 3.00-3.32), pneumonia (HR 1.64; 95%CI 1.54-1.75), sepsis (HR 3.06; 95%CI 2.92-3.21), and ESRD (HR 7.88; 95%CI 1.88-33.07) in the 90 days after discharge compared to the non-AKI group. Both crude and adjusted mortality rates were higher in the AKI group compared to the non-AKI at 90 (HR 3.04; 95%CI 2.98- 3.09) and 365 days (HR 2.39; 95%CI 2.36-2.42) and persisted when the groups were stratified by CKD status (vs without, $p<0.01$).

Conclusions: AKI hospitalization substantially increases the risk for subsequent death, hospitalization, heart failure, pneumonia, and sepsis compared to non-AKI hospitalization. These findings show novel interventions that mitigate the high burden of morbidity and mortality after an AKI hospitalization event are needed.

Funding: Other NIH Support - Kidney, Urology, Hematology

TH-OR07

Cardiovascular Drug Use After AKI Among Hospitalized Patients with a History of Myocardial Infarction: A Population-Based Study

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Background: Patients who survive an episode of acute kidney injury (AKI) are at increased risk of cardiovascular morbidity and mortality but may receive fewer cardioprotective drugs than patients without AKI. Our main objective was to evaluate the use of cardiovascular drugs after AKI among hospitalized patients with myocardial infarction (MI).

Methods: We conducted a population-based study of patients aged ≥ 66 years old with a prior history of MI, hospitalized from January 1, 2008, to March 31, 2017. We ascertained AKI using KDIGO serum creatinine criteria. We used propensity score matching to assemble a cohort of patients with and without AKI. The primary outcome was time to receipt of prescriptions for ACEi/ARB, beta-blocker, and statin (all 3 drugs) within one year of hospital discharge. We utilized proportional subdistribution hazards regression, accounting for the competing risk of death, to determine the cumulative incidence of receipt of cardiovascular drugs after AKI compared to patients without AKI.

Results: We identified 28,871 patients with AKI, of whom 21,452 were matched 1:1 to similar patients without AKI. Acute kidney injury was associated with a 7% (95% CI 5-9%) lower likelihood of receiving all 3 cardiovascular drug classes within one year of hospital discharge. This result was largely driven by a 13% (95% CI 11-15%) lower likelihood of ACEi/ARB prescription across all categories of AKI severity. Lower use of beta-blockers and statins was observed in severe AKI. Conversely, AKI was associated with more frequent use of loop diuretics (sHR=1.20, 95% CI 1.17-1.23) and mineralocorticoid receptor antagonists (sHR=1.22, 95% CI 1.15-1.28). The use of most medications stabilized at 3 months post-AKI.

Conclusions: In patients with a history of myocardial infarction, survivors of AKI were less likely to receive prescriptions for all 3 cardiovascular drug classes with strong evidence (ACEi/ARB, beta-blocker, and statin) and more likely to receive loop diuretics and mineralocorticoid receptor antagonists within one year of hospital discharge. Most medication changes stabilized at 3 months, indicating a critical timeframe to provide follow-up care.

TH-OR08

IMPROVE AKI: A Cluster-Randomized Trial of Team-Based Coaching Interventions to Improve AKI

Jeremiah R. Brown,[1] Richard J. Solomon,[2] Meagan E. Stabler,[1] Sharon E. Davis,[3] Kevin C. Cox,[1] Dax Westerman,[3] Chad A. Dorn,[3] James O'Malley,[1] Michael E. Matheny.[3] *[1]Dartmouth College Geisel School of Medicine, Hanover, NH; [2]University of Vermont College of Medicine, Burlington, VT; [3]Vanderbilt University, Nashville, TN.*

Background: Over 2 million people in the U.S. undergo cardiac catheterization procedures each year with acute kidney injury (AKI) occurring in up to 14% of all patients. However, orders are often not standardized to ensure adequate oral and intravenous fluids, reduced NPO time, and limited contrast dye dose across or within hospitals to prevent AKI. Therefore, we hypothesized that providing team-based coaching in a Virtual Learning Collaborative (VLC) would reduce post-procedural AKI incidence compared to Technical Assistance (TA), both with and without Automated Surveillance Reporting (ASR).

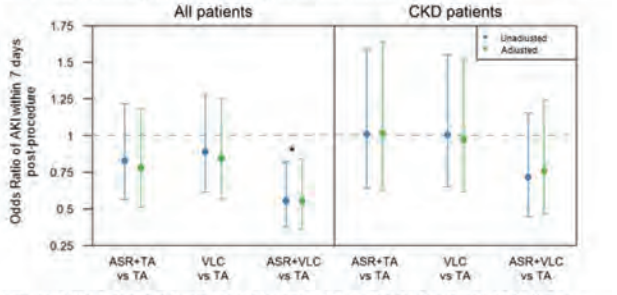
Methods: We conducted a 2x2 factorial cluster-randomized trial that randomized 20 hospitals to receive TA, TA+ASR, VLC, or VLC+ASR for 18-months. All sites received an AKI Prevention Toolkit that included AKI preventive strategies. We fit multilevel logistic models for AKI with site-level random effects to account for the clustered design.

Results: Across 20 randomized Veterans Administration medical centers, there were 4,517 patients including 1,153 patients with pre-existing chronic kidney disease (CKD) during the 18-month intervention phase of the trial. There were 510 AKI events (214 among CKD patients). In all patients, the VLC+ASR intervention cluster had a substantial reduction in AKI when compared to TA alone (aOR=0.55; 0.36, 0.84) mirrored by a strong yet non-significant effect among CKD patients (aOR: 0.76; 0.46, 1.24).

Conclusions: This implementation trial estimates that the combination of VLC with ASR reduces AKI by a highly significant 45% at an institution and is suggestive of a reduction among CKD patients. Therefore, the combined VLC with ASR team-based coaching intervention is an effective, scalable framework to establish aggressive prevention protocols to prevent AKI.

Funding: NIDDK Support

Figure 1. Multilevel logistic models for acute kidney disease with site-level random effects for all cardiac catheterization patients and those patients with chronic kidney disease.



Footnote: ASR: Automated Surveillance Reporting, TA: Technical Assistance, VLC: Virtual Learning Collaborative. The following patient features were included for adjustment: age, race, tobacco use, anemia, heart failure, CKD, diabetes, hypertension, and prior percutaneous coronary intervention. *In all patients, the VLC+ASR intervention cluster compared to TA alone showed a statistically significant reduction in AKI with an adjusted and unadjusted odds ratio of 0.55 [0.36, 0.84] and 0.56 [0.38, 0.82], respectively.

TH-OR09

Properties of Proenkephalin (penKid) in Septic AKI

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Background: Acute kidney injury (AKI) remains a serious complication in critically ill patients. The current definition of AKI continues to be based on changes in serum creatinine (SCr) and diuresis. However, neither SCr nor changes in diuresis provide an accurate estimate of true renal function. Proenkephalin (penKid) is a small and stable peptide derived from the same precursor molecule as encephalins. Recent evidence suggests that plasma PenKid concentrations more accurately reflect the true glomerular filtration rate than SCr. We therefore investigated the kinetic and diagnostic properties of penKid in critically ill patients with septic AKI.

Methods: In a secondary analysis of a prospective observational study, penKid levels were measured longitudinally in 200 patients with positive Sepsis-3 criteria. Plasma penKid levels were analyzed in relation to the severity and course of AKI and under renal replacement therapy. Area under the receiver-operating characteristic curve (AUC-ROC) analyses were performed.

Results: Sixty-two patients had no or mild AKI, 96 patients developed moderate or severe AKI without requiring RRT, and 42 patients developed RRT criteria or died within seven days after inclusion. Thirty-nine patients had transient AKI and 92 patients experienced persistent AKI or required RRT. Overall, penKid kinetics were more dynamic than SCr, and penKid courses preceded corresponding SCr courses by 48 h to 72 h. In patients without AKI, penKid levels generally remained below 50 pmol/L. Moreover, penKid levels discriminated well between transient and persistent AKI or the need for RRT. After 24 hours of sepsis therapy, the combination of SCr and penKid showed an improved AUC of 0.82 (95% CI 0.76-0.88) for predicting RRT or death compared with SCr or penKid alone (SCr: AUC 0.78, 95% CI 0.70-0.86; penKid: AUC 0.80, 95% CI 0.73-0.87). Interestingly, penKid courses were hardly affected by RRT and in some cases even increased under RRT.

Conclusions: Plasma penKid appears to indicate changes in renal function more dynamically than SCr and seems to provide additional diagnostic information on renal function. Remarkably, RRT appears to have little effect on plasma concentrations of penKid. Thus, penKid could allow assessment of renal function under RRT. Further research is needed to verify these results.

TH-OR10

Renal Outcomes After Chimeric Antigen Receptor T Cell (CAR-T) Therapy: A Single-Center Perspective

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Background: Recently chimeric antigen receptor T-cell immunotherapy (CAR-T) has shown promise for refractory non Hodgkin lymphoma. While involving genetically engineered self T cells to express a synthetic receptor binding to tumor antigens, a great concern is the development of cytokine release syndrome (CRS). The release of cytokines can lead to vasodilation, decreased cardiac output, and intravascular volume depletion which may potentiate renal injury. Unfortunately a paucity of data exists of renal outcomes in patients treated with CAR-T, especially with chronic kidney disease (CKD). We aim to further elucidate renal outcomes in patients treated with CAR-T at our institution.

Methods: We reviewed the course of 39 adults who received CAR-T at our institution between July 2018 and May 2021. Baseline demographics (age, gender, comorbidites), and serum laboratory values were obtained. Primary outcomes compared the incidence of acute kidney injury (AKI), death and CRS between patients with and without CKD as defined by KDIGO (kidney disease improving global outcomes). Fisher's exact tests were used to calculate associations of univariate risk ratios. Multivariate survival analysis (COX model) was conducted for all outcomes, adjusting age, gender and death between patients with and without CKD.

Results: With an average age of 58.7 years (SD=10.5), 24 males and 15 females, 14/39 had mild CKD (GFR <90 ml/min/1.73 m^2) and 4/39 had moderate CKD (GFR <60 ml/min/1.73 m^2). CRS was observed in 22/39 (56%) and ICU care in 6/39 (15%) cases. Of the 9 AKI cases (6 class 1, 1 class 2, 2 class 3), 5 resolved, 2 progressed and 2 patients expired. There were a total of 10 deaths (8-678 days after CAR-T). Univariately, there was a correlation between underlying hypertension and AKI with death (RR (95% CI) = 3.4 (1.2, 9.8), P=0.04; RR (95% CI) = 5.0 (1.8, 13.9), p=0.004). ICU correlated with AKI (RR (95% CI) = 4.4 (1.6, 11.8), P=0.02), but there was no association between CRS and the development of AKI. Multivariate survival analysis didn't find any difference between patients with and without CKD.

Conclusions: Our findings did not show an increased risk of AKI or death in CKD patients treated with CAR-T. This supports the use of CAR-T in CKD patients, but with our small sample size, and lack of diverse ethnicities, more studies are needed to determine the safety of CAR-T therapy.

TH-OR11

Treatment of Osteoporosis in CKD5D Patients Based on Bone Turnover: A Randomized Controlled Trial Showing Better Survival in Patients with Non-High Turnover

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Background: Bone turnover in osteoporotic CKD5D patients (pts.) may be elevated (HTO), normal or low (Non-high turnover, NHTO). There is no information on a tailored approach to treatment based on bone turnover. In HTO, characterized by excessive resorption, it makes sense to use antiresorbers, while they should be avoided in NHTO.

Methods: 119 adult CKD-5D pts. with DXA t-scores < -1.0 were enrolled into this 12 month trial. Pts. were classified as NHTO or HTO based on race specific cutoff values of serum PTH. NHTO pts. were randomized into treatment (Trx) with teriparatide or standard of care (Ctrl) and HTO pts. into treatment with Alendronate or Ctrl. Demographic and clinical data, lab values, DXA and QCT total hip BMD, and MSQCT measurements of aortic calcium were obtained at baseline and 12 months. Outcomes were changes in BMD and aortic calcification (ΔAC). Declaration of Helsinki was followed. There were 48 NHTO and 71 HTO pts. The median total PTH was 183 (IQR 138-337) in the NHTO group and 669 (IQR 502-1068) in the HTO group. Treatment groups and turnover arms were well balanced relative to patient race (34% AA), sex (57% m), age (61.0 ±SD 12.5 y), dialysis vintage (4.7 ± 4.0 y) and DXA t-score (-2.9 ± 0.7). Throughout the study, 37 pts. withdrew due to transplantation and personal reasons.

Results: Bone loss was improved in treated NHTO pts. (Trx: +5.7 g/cm^3 ±SE 4.7 vs. Ctrl:-10.7 ±SE 4.7, p=.019) but not significantly in HTO pts. (Trx: +0.2 g/cm3 ±SE 5.7 vs. Ctrl: -3.5 ±SE 3.4, p=.577). ΔAC was higher in the HTO arm (NHTO: 4.5 ±SE 1.6 vs. HTO: 8.7 ±SE 1.4, p=.049) and lower in African Americans (AA: 3.6 ±SE 1.7 vs. White: 8.8 ±SE 1.4, p=.017). The multiv. ΔAC regression coefficient for HTO vs. NHTO was 5.0 HU (95% CI 0.9-9.2, p=.019) and for AA vs. Whites was -5.4 (95% CI -9.6–1.1, p=.013). In the NHTO group there were 0 deaths compared to 18% deaths in the HTO group (11 deaths, p = .005).

Conclusions: We demonstrate a benefit to teriparatide for management of osteoporosis in CKD5D pts. with PTH between 138-337 pg/mL. These same pts. had a significant survival benefit relative to the HTO pts. and had less progression of aortic calcification. African American CKD5D pts. experienced less progression of aortic calcification regardless of turnover status or treatment modality.

Funding: NIDDK Support, Private Foundation Support

TH-OR12

The Calcified Vasculature in CKD Secretes Signal Proteins That Inhibit Bone Mineralization

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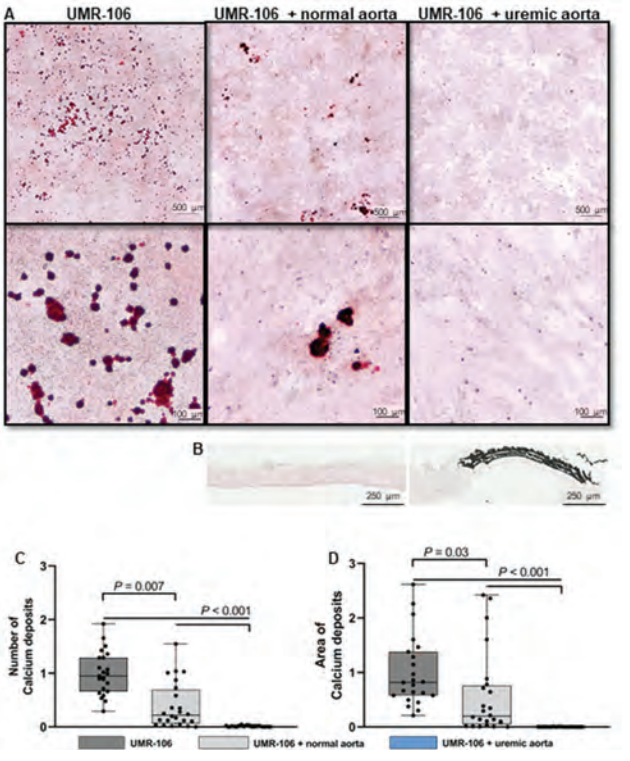
Background: Our group has recently demonstrated that CKD-induced vascular calcification impairs bone formation & mineralization in an *in vivo* model by transplanting calcified aortas from CKD rats into healthy recipients. Aim was to confirm our hypothesis of a direct crosstalk between the vasculature & bone in *in vitro* experiments.

Methods: Vascular calcification was induced in uremic Wistar rats. Normal aortas (NA) & uremic calcified aortas (CA) were incubated *ex vivo* or co-incubated with UMR-106 cell line (UMR). Media was measured for Wnt inhibitors sclerostin (Scl), Dkk1, SFRP4 & activin A (Act A). UMR-106 cell mineralization stained with Alizarin red. Signal pathways were analyzed by PCR and WB.

Results: CA completely inhibited mineralization in UMR-106 cells (Figure 1). Mineralization inhibitor osteopontin (OPN) mRNA & protein were highly upregulated in UMR+CA (OPN mRNA UMR+CA 25.50 [5.53-51.00], UMR+NA 2.78 [1.20-7.85], UMR 0.80 [0.39-5.49], p<0.001). Induction of OPN was abolished by LiCl. ANKH was upregulated in UMR+UA (2.95 [1.87-7.32], UMR+NA 1.75 [0.51-2.46], UMR 0.96 [0.49-2.15], p<0.01), whereas same levels of *Alpl* were found. Similar expressions of β-catenin protein & Wnt target genes *c-Myc* & *Ccnd1* were found. However, *Jun* was upregulated in UMR+NA & UMR+CA (UMR 0.94 [0.61-2.83] vs. UMR+NA 1.58 [1.18-2.29] vs. UMR+CA 1.98 [1.08-3.44], p< 0.01). The CA secreted large amounts of Scl (1936 [495-4400] vs. NA 31 [7-88] pg/ml, p=0.002), Dkk1 (353 [110-686] pg/ml vs. none in NA), and Act A (12158 [4712-18000] vs. NA 1838 [250-4146] pg/ml, p=0.002). NA & CA secreted SFRP4.

Conclusions: The present study confirms our hypothesis on a direct crosstalk between vasculature and bone. The uremic calcified aorta secretes signal molecules that inhibit bone mineralization.

Funding: Private Foundation Support



TH-OR13

HIF-PHI Have Direct Actions in Osteocytes: Implications for Anemia Treatment in CKD

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Background: Patients with CKD manifest overlapping oxygen sensing/endocrine dysfunction as osteocyte-produced FGF23 is highly elevated under prevailing anemia, however the cellular mechanisms driving FGF23 production are not understood. Our goal was to test the molecular context of osteocyte oxygen sensing, and the roles of these systems in FGF23 induction which can have severe effects on CKD bone disease.

Methods: A hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI; FG-4592, 'Roxadustat') was used to treat parent undifferentiated MSCs ('MPC2', mesenchymal progenitor cell clone 2) and 3-week differentiated osteocytes (Ocy), to mimic changes in cellular oxygen status *in vitro*, followed by ATACseq and RNAseq. Conditional Fgf23-KO mice were treated with FG-4592 *in vivo*.

Results: Following FG-4592 (50μM) treatment of MSCs and Ocy, unbiased RNAseq and Gene Ontology analysis validated Ocy enrichment for bone ossification/mineralization processes as well as revealed unforeseen pathways critical for oxygen and iron utilization. ATACseq showed that FG-4592 acutely (48 h) increased genome-wide chromatin accessibility, with HOMER motif analysis identifying highly significant enrichment in Ocy HIF-1α/β and -2α transcription factor binding motif accessibility (p<1e-33). In contrast, HIF motif accessibility in FG-treated MSC was unchanged, revealing a predisposition of Ocy to mediate oxygen responses. RNAseq (confirmed by qPCR) also showed significant upregulation of Fgf23 in FG-4592-treated Ocy cultures (logFC 5.8; FDR<0.001) but not in MSCs (logFC 0.08; FDR NS), and HIF1α inhibition completely suppressed Ocy Fgf23. Further, the iron chelator DFO increased Fgf23 (80-fold), which was dose-dependently reduced by holo-transferrin (p<0.001), underscoring direct effects of oxygen/iron on Ocy. In normal mice, FG-4592 injections induced plasma iFGF23 (450-900 pg/mL, p<0.001). In contrast, conditional *Fgf23* deletion from Ocy (flox-Fgf23/Dmp1-cre+) completely abolished this response despite similarly elevated plasma EPO (8,000-77,000 pg/mL, p<0.001) in both genotypes.

Conclusions: These data show Ocy are poised to respond to oxygen/iron via rapid genomic accessibility and transcriptional mechanisms, which together may drive Ocy biomineralization potential through FGF23 and thus have important implications for CKD-MBD.

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

TH-OR14

Association of Genetically Predicted FGF23 with Heart Failure: A Mendelian Randomization Study

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Background: Multiple observational studies provide evidence of the role of FGF23 in the pathophysiology of heart failure, among individuals with CKD and in the general population. However, these studies suffer from many potential biases, e.g.confounding and reverse causation, limiting their ability to robustly identify causal associations. Mendelian randomization (MR) has emerged as a powerful study design to provide evidence supporting or refuting causality.

Methods: We performed a two-sample MR study to assess the causal association of FGF-23 with overall heart failure and heart failure subtypes. Instrumental variables were defined as independent SNPs associated with FGF23 genome-wide: rs17479566, rs11741640, rs9925837, rs17216707, and rs2769071. Summary-level data from the HERMES consortium and individual-level data from BioVU, was used to examine associations of the 5 SNPs with incident heart failure and subtype. We additionally developed an eGFR polygenic risk score based on CKD-GEN summary statistics, composed of SNPs associated with eGFR at $p<5 \times 10^{-3}$, and dichotomized the eGFR PRS at one SD below the mean.

Results: We found that genetically increased circulating FGF23 was significantly associated with higher risk of heart failure overall and with heart failure with preserved ejection fraction among individuals with genetically-predicted low eGFR (Table). Elevated FGF23 was not associated with reduced ejection fraction heart failure or preserved ejection fraction among individuals with higher genetically-predicted eGFR.

Conclusions: Our results provide evidence supporting a causal association between FGF23 and heart failure, particularly preserved ejection fraction heart failure, among individuals with low eGFR.

Funding: NIDDK Support

Mendelian Randomization Estimates for the Effect of FGF23 on Heart Failure and Subtypes

Outcome and data source	Number of HF Events	MR Estimate	
		Hazard Ratio (95%CI)	P-value
Heart failure, HERMES	47,309	1.25 (1.01, 1.55)	0.039
Preserved EF, BioVU			
Overall	12,900	1.23 (0.88, 1.72)	0.236
eGFR PRS <-1 SD	2,188	2.98 (1.31, 6.77)	0.009
eGFR PRS > -1 SD	10,712	1.02 (0.71, 1.48)	0.908
Reduced EF, BioVU			
Overall	2,928	0.89 (0.44, 1.83)	0.760
eGFR PRS <-1 SD	486	0.43 (0.08, 2.34)	0.326
eGFR PRS > -1 SD	2,442	1.04 (0.47, 2.28)	0.923

TH-OR15

The Spatial-Temporal Heterogeneity Dictating Kidney FGF23 Bioactivity as Identified by Single-Cell RNA Sequencing

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Background: FGF23 is critical for maintaining phosphate balance via interactions with renal FGFRs and Klotho (KL), and its effects on gene expression have been described at tissue levels. However, KL is expressed in multiple nephron cell types thus the full spectrum and spatial-temporal mechanisms dictating FGF23 bioactivity remain undefined.

Methods: A single cell RNA-seq approach was used to identify the dynamics of FGF23-mediated bioactivity. Kidneys were isolated from FGF23 (400ng/g)-injected C57BL/6 mice at 1, 4 and 12h, and single cell transcriptomics were analyzed.

Results: From libraries of 10,000 male/female kidney cells, 21 UMAP cluster enriched markers distinctly identified epithelial, endothelial, and immune cells. At baseline, *KL* mRNA had diffuse expression in proximal tubule (PT) S1-S3 cells, overlap in loop of Henle, and was more concentrated in distal/connecting tubule (DT/CNT). In response to FGF23, at 1h *Egr1*, other MAPK genes, and eIF2 signaling were increased, tracking with 80% of KL-positive PT and DT cells. The vitamin D 24-OHase (*Cyp24a1*) was the most up-regulated gene in PT-S1/S2 at 4h, whereas KL was reduced, and *Egr1* and vitamin D 1-alpha-OHase (*Cyp27b1*) were completely suppressed out to 12h. Pathway Analysis showed that most expressional changes were not cell type unique, including PT and DT up-regulation (8-20 fold) of TNF pathway member *Tnfrs12a*, supporting that FGF23 initially signals via common mechanisms but its function is defined by nephron-site specific gene expression. To segregate KL-dependent FGF23 responses in PT-S1, a critical FGF23 target, KL+ and KL- cells were subsetted. Of note, in response to FGF23, KL+ cells showed distinct clustering at each time point, whereas KL- cells remained indistinguishable, highlighting that temporal FGF23 responses drive unique and transient cellular identity. At later time points, PXR signaling was specific to PT, and Epithelial Remodeling and Actin-based Motility signaling to DT.

Conclusions: Kidney KL distribution was pinpointed at the single cell level, and we demonstrated that FGF23 bioactivity controls nephron segment-unique and -general transcriptional events that regulate mineral metabolism. Identification of these pathways is critical for the isolation of novel disease targets.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-OR16

Distinct Effects of FGF23, Iron and Phosphate on Mineral Metabolism and Kidney Function in Mice with CKD

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Background: Elevated levels of fibroblast growth factor 23 (FGF23), hyperphosphatemia and iron deficiency are common complications of chronic kidney disease (CKD) and strong predictors of disease progression and death. We have previously found that administration of ferric citrate (FC), an iron-based, oral phosphate binder, to mice with CKD reduced dietary phosphate absorption and FGF23, increased iron stores, slowed CKD progression and prolonged survival. This suggests that FGF23, phosphate and/or iron play a major role in CKD progression.

Methods: To distinguish between the individual and combined effects of FGF23, phosphate and iron in CKD, we fed WT and Col4a3^{KO} mice (CKD model) from 4-10wks either control (Ctr), low iron (LI), low phosphate (LP), 1% carbonyl iron (CI) or ferric citrate (FC) diets. To further study the role of iron in CKD, we compared the effects of these diets to mice receiving iv ferric derisomaltose (FD) using biochemical, histological and RNAseq analyzes.

Results: CKD mice showed higher serum FGF23, PTH, phosphate and low calcitriol levels and administration of LI diet further accentuated these differences. Surprisingly, phosphate restriction in LP-CKD mice minimally reduced hyperphosphatemia and PTH levels and had no effect on FGF23. In sharp contrast, all iron containing diets reduced PTH and FGF23 levels. Surprisingly, similar effects were observed in mice receiving iv iron, suggesting that iron deficiency is a stronger predictor of FGF23 excess in CKD than hyperphosphatemia. Compared to Ctr-CKD mice, FC enriched diets showed the strongest potential to reduce FGF23 (-68%), and serum phosphate (-37%) and the only treatment to increase calcitriol (+220%). Biochemical, histological and RNAseq analyses also showed that only the combined reductions of phosphate and FGF23, and iron repletion, achieved by FC treatment, improved kidney function and slowed CKD progression. These benefits were fully reversed when FC-treated mice received a daily dose of 30ng/g of rFGF23 during 28 days. FGF23 administration increased renal inflammatory signaling and further accentuated CKD progression.

Conclusions: Our results suggest that combined corrections of FGF23, phosphate and iron slows CKD progression and suggest that FGF23 plays a major role in CKD progression independently of other disease modifiers.

Funding: NIDDK Support, Commercial Support - Akebia, Private Foundation Support

TH-OR17

Critical Role of Osteopontin in Maintaining Urinary Phosphate Solubility in CKD

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Background: The loss of functional nephrons dramatically increases tubular phosphate concentrations in residual nephrons to levels that exceed supersaturation. Osteopontin (OPN), a SIBLING protein expressed by epithelial cells of the distal nephron, is known to enhance calcium-phosphate solubility *in vitro*; however, the role of OPN in maintaining tubular mineral solubility in CKD remains undefined.

Methods: We used CKD mouse models to determine: (1) the expression and timing of kidney/urine OPN changes in relation to mineral metabolism and kidney function markers, (2) the differential effects of tubular injury and acute nephron reduction on OPN expression, (3) how OPN deficiency alters kidney mineral deposition in CKD, and (4) how neutralization of the mineral-binding (ASARM) motif of OPN alters kidney mineralization and injury in phosphaturic mice.

Results: OPN protein expression is markedly increased in all tubular segments in mouse models of cystic kidney disease (*pcy/pcy*), glomerulonephritis (*Col4a3*$^{-/-}$), and chronic tubulointerstitial injury (aristolochic acid). In *Col4a3*$^{-/-}$ mice with slowly progressive CKD, kidney OPN expression and urinary OPN:Cr increased before gross histologic changes in the kidney or a rise in BUN, serum Cr, FGF23 and PTH. Unilateral nephrectomy studies in wild-type mice proved that nephron reduction alone was sufficient to increase tubular OPN production. Induction of CKD in OPN-null mice fed a high phosphate diet led to severe nephrocalcinosis (**Figure 1**). Lastly, pharmacologic neutralization of the ASARM motif of OPN in phosphaturic (*Hyp*) mice resulted in severe nephrocalcinosis that mimicked OPN-null CKD mice.

Conclusions: Tubular OPN expression is increased in very early CKD and nephron loss alone is sufficient to induce these changes. OPN serves a key biological function to maintain tubular phosphate solubility in CKD.

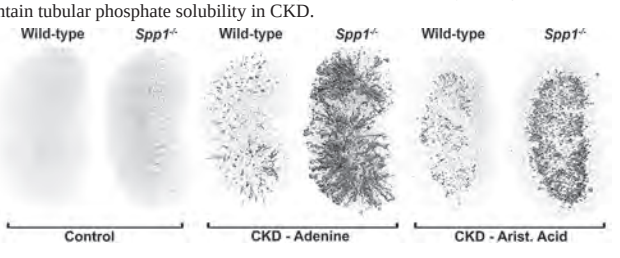

Figure 1. Induction of CKD in *Spp1*$^{-/-}$ (OPN-null) mice results in severe nephrocalcinosis. Whole kidney μCT images demonstrating severe nephrocalcinosis in *Spp1*$^{-/-}$ mice fed a high phosphate (1.1%) diet following CKD induction by either ingestion of 0.2% adenine or IP injections of aristolochic acid.

TH-OR18

Tenapanor Controls Serum Phosphorus and Reduces PTH and FGF-23 in Patients on Dialysis with Severe Secondary Hyperparathyroidism

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Background: Secondary hyperparathyroidism (sHPT) is common in patients with chronic kidney failure, and most nephrologists treat parathyroid hormone (PTH) values >600 pg/mL. Hyperphosphatemia may directly contribute to sHPT, making the glands less responsive to therapy. Tenapanor is a first-in-class phosphate absorption inhibitor (PAI) that targets the paracellular pathway, the primary pathway of phosphate absorption.

Methods: The phase 3 PHREEDOM trial evaluated the safety and efficacy of tenapanor in patients on dialysis with hyperphosphatemia. Following washout from binders, patients whose serum phosphorus (sP) increased by 1.5 to ≥6.0 mg/dL were randomized. Those randomized to the tenapanor arm received tenapanor 30 mg PO BID for 26 weeks. Serum calcium (sCa), sP, PTH, and FGF23 were measured per protocol. This post-hoc analysis evaluates changes in PTH, FGF23, sP, and sCa among tenapanor-treated patients with baseline PTH >600 pg/mL and at least one post-baseline PTH measure (n=73).

Results: For the 73 participants with severe sHPT (defined as >600 pg/mL), the median baseline PTH was 766 pg/mL with a median absolute (percent) reduction of 280 pg/mL (34.0%) at week 26. Of these 73 patients, 31 had a recorded change in PTH-modifying medication during the treatment period, whereas 42 did not have any recorded change. Among those with medication changes, median PTH reduction was 231 pg/mL (26.9%); among those without changes, PTH reduction was 300 pg/mL (35.4%). Median baseline FGF23 was 15,275 ng/L with a median reduction of 3165 ng/L (40.7%) at the end of the treatment period. The magnitude of the median reductions was similar in the medication change and non-change subgroups (4278 ng/L [40.9%] and 2730 ng/L [38.7%], respectively). On average, sP decreased by 1.8 mg/dL (from 8.0±1.5 mg/dL at baseline), with similar changes in medication change and non-change subgroups (1.9 mg/dL and 1.8 mg/dL, respectively). sCa remained unchanged overall (0.2 mg/dL) and in the medication change and non-change subgroups (0 mg/dL and 0.3 mg/dL, respectively).

Conclusions: Tenapanor effectively lowers sP in patients on maintenance dialysis with severe sHPT and demonstrates that effective sP control with tenapanor improves both PTH and FGF23 concentrations.

Funding: Commercial Support - Ardelyx, Inc.

TH-OR19

Initial Evaluation of High-Dose Extended-Release Calcifediol (ERC) in Patients with Stage 5 CKD on Hemodialysis (HD)

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Background: ERC has been approved since 2016 for treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3-4 CKD and vitamin D insufficiency at weekly doses of 210 or 420 mcg (30 or 60 mcg/day). Conversion of calcifediol to calcitriol by CYP27B1 is thought to occur primarily in the kidney despite expression elsewhere, supporting a belief that normal serum levels of 1,25-dihydroxyvitamin D (1,25D) cannot be maintained with advancing CKD. A phase 2a study explored treatment of end-stage renal disease patients with SHPT requiring regular HD with high strength ERC (150 mcg/capsule). The goals of the study were to: (1) evaluate whether these patients could tolerate a high dose of ERC (900 mcg/week); (2) ascertain whether ERC could normalize serum total 1,25D in the absence of functional kidneys; and (3) determine whether ERC could reduce intact parathyroid hormone (iPTH).

Methods: Adults with stage 5 CKD on regular HD with iPTH ≥150 and <600 pg/mL and serum total 25-hydroxyvitamin D (25D) <30 ng/mL were enrolled from U.S. dialysis centers. Subjects underwent an 8-week washout from previous iPTH-lowering therapies and were randomized to 26 weeks of open-label treatment with ERC (300 mcg thrice weekly during HD) or matching placebo. Serum 25D, 1,25D, calcium (Ca) and phosphorus (P) and plasma iPTH were monitored at the start of HD on a weekly or bi-weekly basis.

Results: A total of 44 subjects were enrolled (33 on ERC and 11 on placebo). ERC-treated subjects attained mean (±SE) steady-state levels of 25D of 161±11 ng/mL vs 30±5.6 with placebo treatment without significant increases in serum Ca or P or the incidence of adverse events compared to placebo. Serum total 1,25D rose into the normal range (62.0±8.3 pg/mL) from undetectable or low baseline levels (10.6±1.5 pg/mL) in direct proportion to elevation of serum total 25D above 50 ng/mL. Significant decreases in iPTH were observed, in particular in patients reaching 25D levels exceeding 50 ng/mL.

Conclusions: ERC was well tolerated at 900 mcg/week, readily activated to calcitriol despite the lack of functional kidneys, and capable of suppressing elevated iPTH levels. These data suggest that extra-renal production of 1,25D can be sufficient to lower iPTH when serum 25D is gradually raised to high levels exceeding 50 ng/mL.

Funding: Commercial Support - OPKO Health

TH-OR20

Parathyroid-Specific Knockout of Core Circadian Clock Gene Bmal1 Increases Proliferation of the Parathyroid Gland in CKD

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Background: Proper rhythms in metabolism, hormone secretion and cell cycle are maintained by a molecular circadian clock (CC) in the CNS as well as in peripheral tissues. The transcription factor *Bmal1* is a major component of the CC. We have previously shown that an internal CC operates in the parathyroid gland (PTG) and that it is disturbed in uremia. We constructed a PTG-specific *Bmal1* knockout mouse to investigate the function of the PTG clock in health and in CKD.

Methods: PTG-specific knockout of *Bmal1* was generated by crossing *PTHcre* mice with *Bmal1$^{flox/flox}$* mice (WT) giving rise to *PTHcre*; *Bmal1$^{flox/flox}$* (KO). Blood samples and PTGs were harvested at 4h interval. CKD was induced by feeding mice an adenine diet for 3 weeks. Gene expression was examined by qPCR, protein expression by western blot and proliferation by Ki-67 labeling. Circadian rhythmicity was assessed by cosinor analysis.

Results: BMAL1 protein was reduced by 77% in the PTGs of KO mice and circadian rhythmicity of *Bmal1* gene expression was abolished along with abolishment of rhythmicity of clock genes *Cry1* and *Cry2* and significant upregulation of clock genes *Per2* (p=0.01), *Cry1* (p<0.0001) and *Cry2* (p=0.0001), compared to WT. The disturbed clock in KO resulted in abrogated rhythmicity of clock-controlled cell cycle regulator *Wee1* (KO p=0.16, WT p=0.0016) and of regulators of parathyroid proliferation *Gcm2* (KO p=0.63, WT p=0.03) and *Gata3* (KO p=0.84, WT p=0.01). *Gata3* was upregulated compared to WT (p=0.01). Plasma PTH was significantly rhythmic in both KO and WT mice. In a basal condition the phenotype of KO mice was similar to WT, regarding weight, femur length, basal PTH levels and secretory response to hypocalcemia. Uremia significantly increased the PTG KI-67 labeling index in KO compared with WT (7.0% vs. 2.4%, p=0.036).

Conclusions: *Bmal1* knockout in the PTG resulted in disrupted rhythm of CC genes and a clock-controlled cell cycle regulator. The significant rhythms of regulators of parathyroid proliferation; *Gcm2* and *Gata3* found in PTGs of WT mice was absent in KO mice suggesting CC regulation of these genes. Increased KI-67 expression was found when PTGs of KO mice were challenged by CKD as compared to WT mice, indicating a key role of the CC in regulating the proliferation in the PTGs.

TH-OR21

mTOR-Activating Mutations in RRAGD Cause Kidney Tubulopathy and Cardiomyopathy (KICA) Syndrome

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Background: Over the last decades, advances in genetic techniques have resulted in the identification of rare hereditary disorders of renal magnesium and salt handling. Nevertheless, ±20% of all tubulopathy patients remain without genetic diagnosis. Here, we explore a large multicentric patient cohort with a novel inherited salt-losing tubulopathy, hypomagnesemia and dilated cardiomyopathy (DCM).

Methods: Whole exome and genome sequencing were performed with various subsequent functional analyses of identified *RRAGD* variants in vitro.

Results: In 8 children from unrelated families with a tubulopathy characterized by hypomagnesemia, hypokalemia, salt-wasting, and nephrocalcinosis, we identified heterozygous missense variants in *RRAGD* that mostly occurred *de novo*. Six of these patients additionally suffered from DCM and a heart transplantation was performed in 3 of them. A dominant variant in *RRAGD* was simultaneously identified in eight members of a large family with a similar renal phenotype. *RRAGD* encodes GTPase RagD mediating amino acid signaling to the mechanistic target of rapamycin complex 1 (mTORC1). RagD expression along the mammalian nephron include the thick ascending limb and the distal convoluted tubule. The identified *RRAGD* variants were shown to induce a constitutive activation of mTOR signaling *in vitro.*

Conclusions: Our findings establish a novel disease phenotype combining kidney tubulopathy and cardiomyopathy (KICA) caused by an activation of mTOR signaling suggesting a critical role of Rag GTPase D for renal electrolyte handling and cardiac function.

TH-OR22

Gitelman Syndrome Phenocopy Caused by Pathogenic Variants in Mitochondrial DNA

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Background: Gitelman syndrome (GS) is the most frequent hereditary salt-losing tubulopathy and is characterized by hypokalemic alkalosis and hypomagnesemia. GS is caused by biallelic pathogenic variants in *SLC12A3*, encoding the Na^+-Cl^- cotransporter (NCC) expressed in the distal convoluted tubule. Pathogenic variants in *CLCNKB, HNF1B, FXYD2* or *KCNJ10* may result in renal phenocopies of GS, as they can lead to reduced NCC activity. Nevertheless, ±10% of patients with a GS phenotype remain genetically unsolved.

Methods: After identification of mitochondrial DNA (mtDNA) variants in three families with GS-like electrolyte abnormalities, 155 families were investigated for variants in *MT-TI* and *MT-TF*, encoding the transfer RNAs for phenylalanine and isoleucine. Mitochondrial respiratory chain function was assessed in patient fibroblasts. In NCC-expressing HEK293 cells, mitochondrial dysfunction was induced to assess the effect on thiazide-sensitive $^{22}Na^+$ transport.

Results: Genetic investigations revealed four mtDNA variants in 12 families: m.591C>T (*n*=7), m.616T>C (*n*=1), m.643A>G (*n*=1) (all in *MT-TF*) and m.4291T>C (*n*=3, in *MT-TI*). Variants segregated with the phenotype and were near homoplasmic in affected individuals. Importantly, affected members of six families with an *MT-TF* variant additionally suffered from progressive chronic kidney disease (CKD). Kidney biopsies in two affected individuals showed abnormal mitochondria, especially in the distal tubule. Maximal mitochondrial respiratory capacity was reduced in patient fibroblasts, caused by dysfunction of oxidative phosphorylation complex IV. *In vitro* pharmacological inhibition of complex IV, mimicking the effect of the mtDNA variants, demonstrated an inhibitory effect on NCC phosphorylation and NCC-mediated sodium uptake.

Conclusions: Pathogenic mtDNA variants in *MT-TF* and *MT-TI* can cause a GS phenocopy. Genetic investigation of mtDNA should be considered in patients with unexplained GS-like tubulopathies. Moreover, pathogenic variants in *MT-TF* confer a significant risk for the development of CKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-OR23

KS-WNK1 Translates the Potassium Ingestion State to NCC Activity and Expression

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Background: The physioilogical role of KS-WNK1 in the distal convoluted tubule is not yet elucidated. KS-WNK1 upregulates NCC through activation of WNK4-SPAK pathway. Under low potassium diet, in which NCC activity is increased, KS-WNK1 is required for the formation of WNK bodies. However, changes in plasma K^+ has not been observed in KS-WNK1 mice when compare to WT mice. We have recently shown that KS-WNK1 is highly sensitive to the CUL3-KLHL3 complex (JCI 2020) and its expression under control conditions is negligible, but it is increased under low potassium diet (AJP Renal 2021). In wild life, mammalians are exposed to cycles of no food and thus no K^+ consumption for days, followed by a vast meet and thus K^+ ingestion of in few hours. Because of the high sensitivity of KS-WNK1 expression to K^+ intake, we assessed the expression of KS-WNK1 and NCC-SPAK modulation using a model to imitate what occurs in wild life.

Methods: We exposed wild type (WT) and KS-WNK1-KO (KS-KO) mice to 10 days of zero K^+ diet (0KD), followed by high K^+ diet (5 %) to imitate what occurs in the wild. Groups of mice were sacrificed before the HKD and at 12 or 24 hours of HKD. Blood was taken for electrolyte analysis and renal proteins were subjected to western blot using anti NCC, phospho-NCC, SPAK, phospho-SPAK, WNK4, WNK1 and actin antibodies.

Results: At the end of 10 days of 0KD, serum K^+ was significantly lower in KS-KO mice than in WT mice (2.62±0.28 vs 3.40±0.22 mEq/L, $p<0.05$), while NCC phosphorylation was higher in the WT mice (1.00±0.32vs 0.58±0.06 a.u., $p<0.05$). At this point expression of KS-WNK1 was detected in WT, but not in KS-KO mice. In contrast, 24 hours after HKD, NCC expression and phosphorylation was not reduced in KS-KO mice, as ocurred in WT mice (WT 1.00±0.20 vs KS-KO 2.44±0.31, a.u., $p<0.01$ and 1.00±0.24 vs 3.07±0.56 mEq/l, $p<0.05$, respectively) and WT mice K^+ excretion was higher, since the plasma K^+ concentration was lower in WT than in KS-KO mice (6.02±0.62 vs 6.75±0.714 mEq/l, $p<0.001$).

Conclusions: Our data show that in WT mice during 0KD, activation of NCC was higher and after HKD, downregulation of NCC was more effective than in KS-KO mice. Thus, wild type mice are better suited to respond to extreme changes in potassium diet as those that probably occurs in wild life in mammals.

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

TH-OR24

Role of WNK1 and WNK4 in Sensing Extracellular Potassium in Principal Cells to Modulate mTORC2-Dependent Activation of Epithelial Sodium Channel

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Background: mTORC2 phosphorylation of SGK1 and consequent activation of ENaC is essential in the regulation of ion transport by principal cells (PCs) of the distal tubular system. We recently demonstrated that local K^+ concentration could be sensed by PCs to activate ENaC through mTORC2-SGK1 signaling, and suggested a role for WNK1 in this mechanism. However, the mechanistic basis of this regulation has not been explored. In DCT, WNK4 modulates NCC activity in response to extracellular K^+ in a kinase-dependent manner. Here we have explored the role of WNK1 and 4 in local sensing of extracellular K^+ and ENaC regulation in the mpkCCD cultured PC model.

Methods: We used CRISPR to generate $WNK1^{-/-}$ and $WNK4^{-/-}$ mpkCCD cells. WT and KO cells were grown on Transwell filters and adapted to 1 or 3 mM [K^+] on the basolateral side, followed by raising [K^+] to 5 mM in the presence or absence of WNK kinase inhibitor. Amiloride-sensitive current was measured by volt-ohmmeter as well as by patch clamp. Cells were processed for co-IP and immunoblot analysis.

Results: In WT mpkCCD cells, extracellular K^+ stimulated ENaC current concomitant with mTORC2-dependent SGK1 phosphorylation, Nedd4-2 phosphorylation and expression of cleaved ENaC. In WT cells, inhibition of WNK kinase activity by WNK463 had no significant effect on K^+-stimulated ENaC current or SGK1 phosphorylation, although SPAK phosphorylation was markedly reduced. In contrast, WNK1 deletion blocked the effect of extracellular K^+ on ENaC and SGK1 phosphorylation. Transfection of $WNK1^{-/-}$ mpkCCD cells with either WT or kinase-dead WNK1 restored K^+-stimulated SGK1 phosphorylation and ENaC activity. Furthermore, this effect was accompanied by greater association of SGK1 with both mTORC2 and WNK1 (WT or kinase-dead). WNK4 deletion and the recovery of WNK4 expression, had similar effects to WNK1 on SGK1 phosphorylation and ENaC current.

Conclusions: Our data support a scaffolding role for WNK1 and 4 that promotes mTORC2-SGK1 interaction and hence phosphorylation through a mechanism that does not require its kinase activity. Extracellular K^+, which has a well-established role to inhibit WNK-dependent SPAK phosphorylation, stimulates WNK1/4-SGK1 interaction, and assembly of an mTORC2-SGK1-WNK complex, resulting in enhanced SGK1 activity and ENaC activation in PCs

Funding: NIDDK Support, Private Foundation Support

TH-OR25

Comparative Effectiveness of Patiromer and RAAS Inhibitor Continuation vs. No Potassium Binder and Discontinued RAAS Inhibitors on Healthcare Resource Utilization and Cost Outcomes in Hyperkalemia

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Background: Patiromer (PAT) is a sodium-free, non-absorbed potassium (K^+) binder approved for treatment of hyperkalemia (HK). The objective of the study was to estimate relative cost of treating Medicare Advantage patients (pts) with HK with different therapeutic strategies.

Methods: This retrospective, propensity score–matched cohort study utilized the de-identified Optum Clinformatics® Data Mart (from 2016 to 2019). Two HK cohorts were identified: 1) pts exposed to PAT+RAASi therapy; and 2) pts who discontinued RAASi therapy (DC RAASi). All pts had serum K^+ ≥5.0 mEq/L, HK diagnosis, and ≥6 mos insurance enrollment. Pts were propensity score matched on baseline characteristics. Relative healthcare spending rate (exposure contrast: PAT+RAASi vs DC RAASi [reference]) was analyzed at 3 mos using zero-inflated negative binomial regression. Cost outcomes included: total, inpatient, emergency department (ED), outpatient services, and outpatient pharmacy.

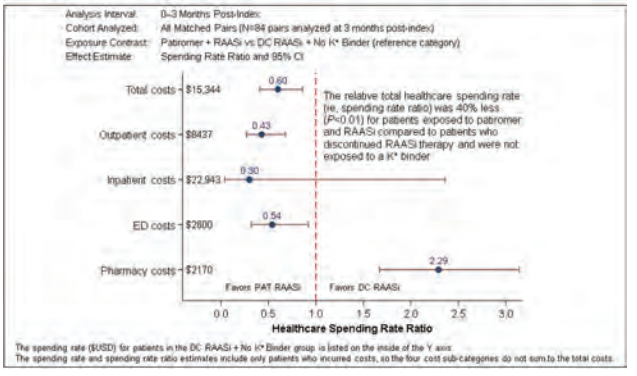
Results: Study cohorts included 464 pts (232 matched pairs). Overall, mean age was 74 yrs, 59% male, and 31% Hispanic. Pts had a mean of 5 comorbidities: CKD (95%), diabetes mellitus (73%), chronic heart failure (32%), cardiac arrhythmias (33%), and coronary artery disease (39%). At 3 mos, 168 pts (84 matched pairs) remained uncensored and were analyzed. Total healthcare spending rate for DC RAASi cohort was $15,344 vs $9135 (95% confidence interval, $6303, $13,241) for PAT+RAASi cohort over 3 mos ($P<0.01$; Figure) and was driven by marked reductions in outpatient and ED costs.

Conclusions: After 3 mos of PAT+RAASi therapy, relative total healthcare spending rate was 40% lower compared with pts not exposed to a K^+ binder who discontinued RAASi to manage HK in matched Medicare Advantage pts. Study Limitation: Potential exposure misclassification via RAASi dispensings from generic pharmacy programs.

Funding: Commercial Support - Vifor Pharma, Inc.

Outcome	DC RAASi ($) (reference)	PAT RAASi ($)	LCL ($)	UCL ($)	*P*-value
Total healthcare costs	15,344	9135	6303	13,241	0.006
Outpatient medical costs	8437	3852	2319	5752	0.000
Inpatient facility costs	22,943	6888	901	54,178	0.255
Emergency department costs	2600	1414	839	2385	0.022
Outpatient pharmacy dispensing costs	2170	4974	3635	8806	0.000

LCL, lower confidence level; UCL, upper confidence level



TH-OR26

Dietary Anion Prioritizes Pendrin Activation over Aldosterone

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Background: It is well established that the bicarbonate-chloride exchanger, Pendrin, is physiologically modulated in intercalated cells to maintain acid-base balance. Because Pendrin is also upregulated by aldosterone and angiotensin II to preserve intravascular fluid volume but is inhibited in high aldosterone states of dietary potassium-chloride loading, it has been suggested pendrin may be differentially regulated to help sculpt the distinct adaptive responses of aldosterone to volume contraction and hyperkalemia. Here, we challenge this hypothesis by investigating how Pendrin is modulated by dietary potassium salts.

Methods: C57/Bl6J male mice (2 month old) were randomized to matched control (2% KCl), high potassium bicarbonate (13.4% KHCO3), or high potassium chloride (10% KCl) diets (4 days). A separate cohort of mice was randomized to a switch anion diet protocol, whereby mice were first adapted to the high KHCO3 or the high KCl diet (4 days), and the response to changing the anion in the context of high potassium, high aldosterone was assessed at 24 and 48 hours. Aldosterone and plasma electrolytes were measured by standard methods. Kidney Pendrin mRNA and protein abundance were assessed by qRT-PCR and western blot, respectively.

Results: Dietary KCl and KHCO3 loading increased plasma potassium and aldosterone to the same extent but had opposite effects on pendrin abundance. KHCO3 loading increased pendrin, while dietary KCl loading inhibited it. Pendrin protein and transcript abundance decreased within 24 hours of switching the high KHCO3 diet to high KCl, and the response was coincident with an increase in plasma chloride and a decrease in bicarbonate. Switching the high KCl diet to high KHCO3 had the opposite response, increasing pendrin protein and transcript as plasma bicarbonate increased and chloride decreased. Neither anion switch protocol changed the extent of hyperaldosterone or hyperkalemia.

Conclusions: Pendrin regulation is prioritized by the dietary anion. Ingestion of an alkaline-rich, high potassium diet drives pendrin expression to prevent metabolic alkalosis, while pendrin is rapidly downregulated to limit hyperchloremic acidosis with consumption of a high KCl diet. We conclude pendrin is differently regulated depending on the potassium salt to control acid-base balance rather than to maintain K+ homeostasis.

Funding: NIDDK Support, Private Foundation Support

TH-OR27

Intracellular Water Shift and Disturbed Osmoregulatory Responses to High Sodium in Patients with Hereditary Multiple Exostosis

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Background: Tissue Na^+ accumulation plays an important role in Na^+ homeostasis. During high Na^+ diet, negatively charged glycosaminoglycans (GAGs) facilitate extracellular Na^+ accumulation in various tissues. Patients with Hereditary Multiple Exostosis (HME) have a heterozygous loss of function mutation in a gene involved in heparan sulfate (HS) synthesis. HME patients may therefore respond differently to high Na^+ conditions with regard to Na^+ and water homeostasis.

Methods: We performed a randomized cross-over study in 7 male HME patients and 12 healthy controls, matched for age, body mass index, blood pressure and eGFR. All subjects followed randomized both an 8-day low Na^+ diet (LSD, <50mmol/d) and high Na^+ diet (HSD, >200mmol/d). After each diet, blood and urine samples were collected. Also, body fluid compartments measurements were performed by using the distribution curve of iohexol and ^{125}I-albumin.

Results: After LSD, body fluid volume distribution over total body water (TBW) was equal (Fig 1A). HSD resulted in a different distribution between groups (Fig 1B), while absolute TBW increase was not different (1.4 L vs 1.5 L, p=0.91). HME patients showed 3.9% ICFV expansion without concurrent changes in plasma effective osmolality (p=0.18). Whereas, in healthy controls, 23.0% IFV expansion was accompanied by increased plasma effective osmolality (p<0.01). HSD-induced changes in HS excretion were associated with ICFV change in healthy controls (Fig 1C).

Conclusions: HME patients, characterized by defective HS, show distinct body fluid composition and altered osmoregulation after HSD when compared to controls. The incapacity to expand IFV may reflect reduced extracellular Na^+ accumulation with reduced commensurate water. As a consequence, water shifts to the ICFV after hypertonic stress, indicating disturbed maintenance of a stable milieu intérieur. Our results underscore that intact HS synthesis is crucial for Na^+ homeostasis and fluid balance.

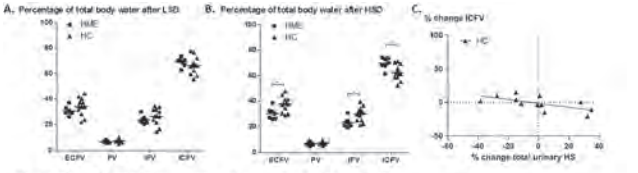

Fig 1.A. After LSD, body fluid compartments are similar divided over TBW.
B. After HSD the proportion of ICFV to TBW became higher in HME patients as compared to healthy controls (69.8L vs 62.5L ,p=0.01). Whereas, in healthy controls the proportion of ECFV to TBW was higher when compared to HME patients (30.2L vs 37.5L, p=0.01), which mainly resulted from a larger IFV compartment (23.2L vs 29.7L, p=0.01)
C. Linear regression graph showing the correlation between percentage change in total urinary NS and percentage change of ICFV in healthy controls, showed a significant negative correlation (r=-0.76, p<0.01).

TH-OR28

Renal Lymphatic Pumping Involves Interstitial Sodium Regulation of NKCC1 Transporter

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Background: Sodium-potassium-chloride cotransporter 1 (NKCC1) is regulated by extracellular sodium and has recently been shown to modulate vascular dynamics contributing to hypertension. Previously, we showed that NKCC1 is expressed in renal lymphatic vessels of rats and in cultured human lymphatic endothelial cells (LECs). Since interstitial sodium retention is a hallmark of proteinuric injury and nephrotic syndrome, we examined whether high interstitial sodium environment affects expression of the NKCC1 transporter and alters pumping dynamic function of renal lymphatic vessels.

Methods: Puromycin aminonucleoside injected rats (PAN) served as a model of nephrotic syndrome and saline-injected rats served as control. *In vivo*, MRI was used to assess the renal sodium and water content. Renal lymph, which reflects the interstitial composition, was collected and sodium concentration analyzed. *Ex vivo*, contractile dynamics of isolated renal collection lymphatic vessels were studied in a perfusion chamber. Cultured LECs were used to assess the effects of high sodium on NKCC1.

Results: MRI revealed a significant elevation in the renal sodium and water content in PAN vs control rats. The renal lymph of PAN contained significantly higher sodium vs controls although the plasma sodium concentration was not different between the groups. *Ex vivo* studies revealed that high sodium environment decreased contractility of renal collecting lymphatic vessels. Immunostaining and PCR studies showed PAN injury increased NKCC1 expression in renal lymphatic vessels vs control. In cultured LECs, high sodium concentration increased mRNA and reduced phosphorylated NKCC1 protein as well as SPAK, an upstream activating kinase of NKCC1, and eNOS, a downstream link between LECs and smooth muscle cells. Like high sodium environment, furosemide, an NKCC1 inhibitor, showed a weaker effect on amplitude and ejection fraction in isolated renal lymphatics of PAN vs controls.

Conclusions: High sodium within the renal interstitium following proteinuric injury impairs the pumping function of renal lymphatic vessels through SPAK-NKCC1-eNOS pathway that may contribute to sodium and water retention and reduces lymphatic responsiveness to furosemide. We propose this dysfunctional pathway in lymphatic vessels is a novel mechanism of progressive edema in proteinuric kidney disease.

Funding: NIDDK Support

TH-OR29

A Novel Model of Hyperuricemia via Inducible Uricase Knock-Out

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Background: Hyperuricemia contributes to the development of kidney stones, chronic kidney disease, cardiovascular disease, metabolic syndrome, and gout. Classically, hyperuricemia was viewed as caused by an overproduction of urate (UA), underexcretion, or a combination of the two. Creating genetic animal models for overproduction type hyperuricemia is complicated because, unlike humans, mice express the enzyme uricase (*Uox*), which metabolizes UA. Previous models using germline *Uox* knock out resulted in significant juvenile mortality related to crystal induced nephropathy making longitudinal and transcriptional investigations difficult. Here we describe a novel inducible model of *Uox* inactivation (UOX-iKO) that surmounts previous challenges to begin to elucidate renal consequences of overproduction type hyperuricemia.

Methods: CRISPR-Cas9 was used to insert LoxP sites into the *Uox* gene of C57BL6J mice, then crossed with mice harboring a tamoxifen inducible Cre (*Gt(ROSA)26Sor*$^{tm1(cre/ERT2)Tyj}$). Male (M) and female (F) mice were induced at 9 weeks with tamoxifen or vehicle control and sacrificed after 2 weeks or followed longitudinally. RNA-Seq was performed on kidneys of 2 week induced and control mice, followed by DESeq2 and pathway analysis.

Results: Induced animals of both sexes showed significant increases in serum UA and urinary UA excretion 2 weeks after induction, increases that persisted for 10 weeks with no increase in mortality. RNA-Seq analysis revealed both sexes showed differential expression of inflammatory and other immune associated genes including renal injury markers *Lcn2* and *Stc1*, indicating subtle acute renal injury, even without changes in BUN. M mice demonstrated significant decreases in expression of UA transporter genes *Slc17a1* and *Slc17a3*, while F mice showed a significant increase in UA associated transcription factor *Hnf4a*. M but not F mice also had differential expression of genes involved in metabolic processes, while F but not M mice showed differential expression in signal transduction pathways including phospholipase C and toll-like receptor signaling.

Conclusions: The UOX-iKO mice cannot metabolize UA, and thus are an excellent model for overproduction of UA. These mice provide significant insights into the acute transcriptional changes occurring after UA increases, mechanisms of renal UA homeostasis *in vivo*, and new insights into hyperuricemia treatment.

Funding: NIDDK Support

TH-OR30

Factors Associated with Sex Differences in the Risk of Kidney Stones

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Background: Kidney stone disease is a highly prevalent condition. Men are at higher risk of developing stones compared with women, however recent data suggest a changing epidemiology with women being relatively more affected than in the past. The reasons for such differences and changes over time are not clear.

Methods: We analyzed the association between sex and incident kidney stones using data from three large cohorts. Kidney stone incidence rates for men and women overall and across categories of age and calendar time were computed and hazard ratios (HRs) and 95% confidence intervals (CIs) generated with age-adjusted Cox proportional hazards regression models. Mediation analysis was performed to estimate the amount of excess risk for men explained by established risk factors, including waist circumference, history of high blood pressure, history of diabetes, use of thiazides, dietary intakes. Twenty-four hour urine composition was also examined.

Results: The analysis included data from 268,553 participants, contributing 5,872,249 person-years of follow-up, during which 10,302 incident stone events were confirmed. The incidence rate of kidney stones was 271 and 159 per 100,000 person-years for men and women, respectively. The age-adjusted HR for men compared with women was 2.32 (95% CI 2.20, 2.45). Part of the difference in rates was explained by the risk factors included in the analysis, mainly waist circumference and fluid intake. The risk of stones was consistently higher across categories of age among men compared with women (HRs ranging from 2.02 to 2.76). Regarding calendar time, the risk remained higher among men, but tended to decrease over time while it increased among women, resulting in a 48.1% decrease for after 2009 compared with before 1990. Supersaturations for calcium oxalate and uric acid were higher among men, primarily because of 26.3% higher urine oxalate, 16.3% higher urine uric acid, 23.5% higher urine phosphate and more acidic urine. Urine volume, citrate, oxalate and pH contributed significantly toward an increased risk among men.

Conclusions: The risk of kidney stones is higher among men compared with women. This difference is only partly explained by modifiable lifestyle risk factors; however, differences in urine chemistries explain a substantial fraction of the excess risk.

Funding: Other NIH Support - DK094910, DK91417, CA186107, CA176726, and CA167552

TH-OR31

Deconvolution of Genetic Variation Using High-Quality Cis-Regulatory Elements Map of Kidney Cells

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Background: Genome-wide association studies (GWAS) have facilitated the discovery of disease- or trait-associated genetic variants that can ultimately lead to improved precision of clinical diagnosis and/or molecular pathogenesis in a translational medicine framework. However, identifying specific cell types within organs in which the GWAS variants exert their function remains a significant challenge, especially for the complex and heterogeneous kidney.

Methods: To tackle this, we constructed high-quality maps of *cis*-regulatory elements (CREs) for kidney cells to deconvolute GWAS variants for kidney-relevant phenotypes. Specifically, we devised a computational framework using a sequence-based predictive model that maximally detects CREs by identifying open-chromatin regions with marginal read-mappings but harboring CRE sequence features. We applied this method to kidney ATAC-seq data.

Results: Our high-quality CRE maps have enabled us to detect >100,000 CREs for podocytes, a key rare (<1%) cell type involved in kidney filtration function. Newly found CREs explained the significant proportion of SNP-heritability for a major kidney trait (Urinary Albumin-to-Creatinine Ratio (UACR); Pr[h_g^2]=9.3%). Heritability analysis using these CRE maps uncovered the differential contribution of specific cell types to two major kidney functional traits, UACR and estimated glomerular filtration rate (eGFR). As would be predicted from physiologic understanding, CREs for podocytes and proximal tubule cells (PT) had enriched proportion of SNP-heritability for UACR and eGFR, respectively (UACR: Pr[h_g^2]/Pr[SNPs]=6.8 for podocyte, 2.3 for PT; eGFR: Pr[h_g^2]/Pr[SNPs]=-1.9 for podocyte, 4.3 for PT. Moreover, we found the podocyte relevance of a known GWAS variant (rs17831251; OR=2.25, P=4.7×10^{-103}) on *PLA2R1* associated with Membranous Nephropathy. Our CRE map showed strong podocyte-unique CRE that overlaps with the index variant, suggesting that the index SNP is potentially the causal variant perturbing podocyte-specific transcriptional regulation of *PLA2R1*.

Conclusions: Taken together, we expect that the deconvolution of GWAS variants using the high-quality kidney CRE maps will provide cell-type relevance of GWAS variants on genetic effects not captured by single-cell RNA-seq alone.

Funding: NIDDK Support, Private Foundation Support

TH-OR32

Epistatic Interactions of APOL1 Modify the Association Between APOL1 and CKD in African and Hispanic Americans

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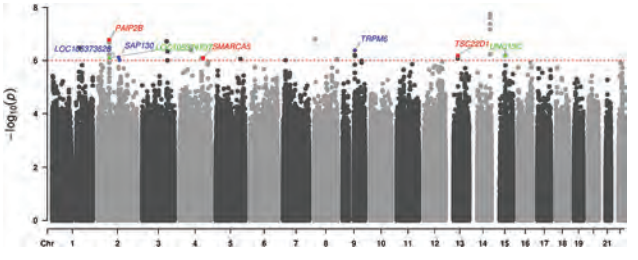
Background: Chronic kidney disease (CKD) is a major public health problem, and disproportionately effects racial and ethnic minorities. While the *Apolipoprotein L1 (APOL1)* locus has been identified as a significant genetic contributor to the disparities, only a minority of individuals with *APOL1* high-risk genotype develop kidney disease suggesting a major role for genetic and environmental modifiers. Prior genetic association studies studying gene/genetic variants interacting with *APOL1* were limited by small sample sizes and detected very few significant interactions.

Methods: In this study, we conducted a genome-wide single nucleotide polymorphism (SNP)x*APOL1* interaction analysis to identify SNPs that modify the association of *APOL1* high-risk genotypes with CKD in the largest minority cohort to date. Interaction analyses were conducted separately for four independent cohorts, 12,145 African Americans (AAs) and 16,580 Hispanic Americans (HAs) from the Population Architecture through Genomics and Environment (PAGE) Study and 6,827 AAs and 10,314 HAs from the Bio*Me* Biobank, followed by sample size based meta-analysis.

Results: Among the four cohorts, CKD cases and *APOL1* high-risk genotypes were observed with higher frequencies in AA (8.48% CKD and 11.99% *APOL1* in PAGE; 18.21% CKD and 13.90% *APOL1* in Bio*Me*) than in HA (3.40% CKD and 0.45% *APOL*1 in PAGE; 14.14% CKD and 1.69% *APOL1* in Bio*Me*). We tested about 28 million SNPs in our interaction analyses and identified 51 significant SNPs (P value < 1.0 x 10^{-6}) interacting with the *APOL1* locus across the genome (Figure 1). Of these, 28 SNPs were within a gene, and 14 out of the 28 SNPs were within the gene *PAIP2B* which has been showed to be involved in controlling translation and glucose homeostasis.

Conclusions: Although further biological validation is needed, our results provide early insights on the impact of genetic interaction on the association between *APOL1* and kidney disease.



Manhattan Plot of the results from the meta-analysis of SNPx*APOL1* interaction

TH-OR33

Phenotypic Spectrum of COL4A3 Variants: The Geisinger MyCode/ DiscovEHR Study

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Background: Patients with heterozygous *COL4A3* variants have been shown to be at increased risk of kidney disease, ranging from microscopic hematuria to focal segmental glomerulosclerosis (FSGS) and end-stage kidney disease (ESKD). Most studies of patients with *COL4A3* variants have focused on individuals presenting with more severe manifestations, and thus the full phenotypic spectrum remains unclear.

Methods: We used data from 174,418 participants in the Geisinger MyCode/ DiscovEHR study, an unselected health system-based cohort with whole exome sequencing and EHR data. We identified participants with *COL4A3* variants listed as pathogenic or likely pathogenic (P/LP) in ClinVar at minor allele frequency <0.01. Phenotypes were assessed using ICD diagnosis codes, linkage to the US Renal Data System, blood and urine laboratory data, and targeted chart review. Associations between

COL4A3 P/LP variants and Alport syndrome-related phenotypic features were assessed using logistic regression. Additional analyses were done comparing carriers and related non-carriers for the most common variant (p.Gly695Arg) observed in our cohort.

Results: There were 329 (0.2%) participants with a previously reported P/LP rare *COL4A3* variant. Individuals with a *COL4A3* variant (mean age 58.8 years) were at increased risk of ESKD (OR 3.79, 95% CI: 2.36-6.08), hematuria (OR 1.99, 95% I: 1.37-2.88), FSGS/renal sclerosis (OR 7.46, 95% CI: 3.31-16.84), and eGFR <60 ml/min/1.73m^2 (OR 1.46, 95% CI: 1.07-1.99) but not hearing loss. The most common P/LP variant was p.Gly695Arg with 161 heterozygous individuals in 58 families **(Table).** Compared to 123 related non-carriers, those with the p.Gly695Arg variant were at increased risk of hematuria (OR 3.44, 95% CI: 1.34-8.86), and ESKD (OR 12.39 (1.59-96.33; P=0.02). Two patients had a known family history of Alport Syndrome, and only 1 patient had been diagnosed using clinical genetic testing.

Conclusions: In an unselected health system cohort, we demonstrate that rare P/LP variants in *COL4A3* increase risks of hematuria, FSGS, and ESKD, and are undiagnosed in the vast majority of individuals.

Funding: NIDDK Support

Renal phenotype	Any P/LP *COL4A3* variant (n=329)	No P/LP *COL4A3* variant (n=174438)		*COL4A3* p.Gly695Arg variant (n=161)	No P/LP *COL4A3* variant, relatives of p.Gly695Arg probands (n=123)	
	Percent	Percent	Chi square P value	Percent	Percent	Chi square P value
Hematuria ICD code	9.40%	5.10%	<0.001	10.60%	7.30%	0.3
Hematuria (chart review)	N/A	N/A	N/A	19.30%	6.50%	0.002
eGFR <60	20.10%	27.10%	0.002	51.70%	27.10%	0.4
FSGS or renal sclerosis ICD code	1.80%	0.30%	<0.001	3.10%	0%	0.05
Glomerular disease ICD code	3.70%	1.20%	<0.001	5.60%	0%	0.008
ESKD ICD code or USRDS	5.80%	1.60%	<0.001	8.10%	0.80%	P=0.02

TH-OR34

The Genetic and Clinical Spectrum of Tubulointerstitial Kidney Disease and Associated Syndromes Revealed Through Whole-Genome Sequencing in the UK 100,000 Genomes Project

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Background: Tubulointerstitial kidney disease (TKD) is a heterogeneous group of monogenic disorders with progressive chronic kidney disease characterised by interstitial fibrosis, tubular atrophy and variable clinical manifestations. TKD includes recessive ciliopathies, autosomal dominant tubulointerstitial kidney diseases (ADTKD) and mitochondrial diseases. The Genomics England (GEL) project offered a unique opportunity to apply a novel discovery approach, synthesising the effect of common and rare variants using a whole-gene-based pathogenicity score (GenePy). This scoring system results in per gene-per person pathogenicity scores, with higher scores representing a higher mutational burden.

Methods: We applied the GenePy scoring system integrating patient zygosity, allele frequency, and deleteriousness metrics. We identified unrelated Europeans for a phenotype-genotype approach of 232 cases with TKD and 8,282 controls with no documented kidney phenotype. GenePy scores were generated for a discrete set of candidate genes for each individual. The highest decile GenePy scores were compared using a one-tailed Mann-Whitney U-test. We then took an unbiased genotype-phenotype approach by calculating GenePy scores for all 78,050 germline genomes. Individuals were ranked by gene score, and individuals with the highest scores were assessed for their phenotype.

Results: The difference in top decile scores between cases and the same proportion of controls was statistically significant for *PKD2* ($p=2.81\times10^{-6}$), *DNAJB11* ($p=3.56\times10^{-5}$), *XPNPEP3* (p=0.0083), *UMOD* (p=0.0015) and *CEP290* (p=0.034). Novel variants consistent with TKD were identified. The unbiased genotype-phenotype approach additionally revealed variants consistent with monogenic TKD in participants recruited for diverse reasons, including cancer.

Conclusions: Using a novel gene-level scoring system, we describe new gene variants associated with TKD and associated phenotypes. Patients were identified in non-kidney disease recruits demonstrating the benefit of an unbiased 'gene first' approach in large scale datasets such as the 100,000 Genomes Project.

TH-OR35

A Glomerular Transcriptomic Landscape of APOL1 in Black Patients with Focal Segmental Glomerulosclerosis

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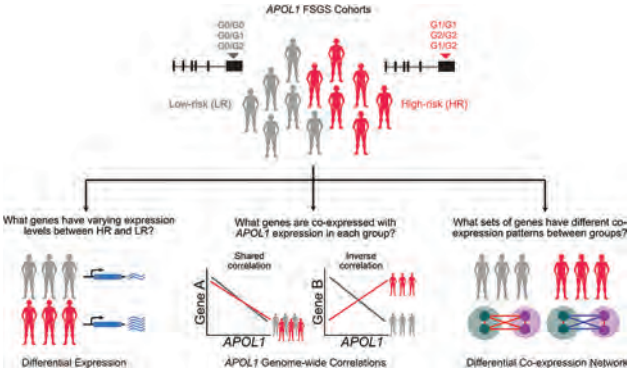
Background: Apolipoprotein L1 (APOL1)-associated focal segmental glomerulosclerosis (FSGS) is the dominant form of FSGS in Black people. There are no targeted therapies for this condition, in part because the molecular mechanisms underlying APOL1's pathogenic contribution to FSGS are incompletely understood. Studying the transcriptomic landscape of APOL1 FSGS in patient kidneys is an important way to discover genes and molecular behaviors that are unique or most relevant to the human disease.

Methods: With the hypothesis that the pathology driven by the high-risk (HR) APOL1 genotype is reflected in alteration of gene expression across the glomerular transcriptome, we compared expression and co-expression profiles of 15,703 genes in 16 Black FSGS patients with a HR vs 14 with a low-risk ("LR") APOL1 genotype. Expression data from APOL1-inducible HEK293 cells and normal human glomeruli were used to pursue genes and molecular pathways illuminated in these studies.

Results: We discovered (1) increased expression of APOL1 in HR and nine other significant differentially expressed genes, including stanniocalcin (STC1), which has a role in mitochondrial and calcium-related processes, (2) differential correlations between HR and LR APOL1 and metabolism pathway genes, but similar correlations with extracellular matrix- and immune-related genes, (3) significant loss of co-expression of mitochondrial genes in HR FSGS, and (4) an NF-kB -down-regulating gene, NKIRAS1, as the most significant hub gene with strong differential correlations with NDUF family and immune-related genes.

Conclusions: Overall, differences in mitochondrial gene regulation appear to underlie many differences observed between HR and LR FSGS. All data are available for secondary analysis through the "APOL1 Portal" (http://APOL1portal.org).



TH-OR36

Therapeutic Potential of a CFTR Corrector to Mitigate Slowly Progressing Adult-Onset Polycystic Kidney Disease

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Background: Autosomal dominant kidney disease is the most common dominant genetic renal disorder in humans leading to significant health care costs. It is associated with the slow but relentless formation of multiple renal cysts driven by cAMP-dependent fluid secretion leading to considerable patient morbidity.

Methods: We used a combination of MRI, Immunoblotting and Immunostaining to test VX-809 in a slowly progressing RC/RC mouse model, bearing the R3277C mutation

Results: At 6 months of age the RC/RC mice develop large renal cysts and impaired renal function. However, when treated with VX-809 between the ages of 6-8 months cyst area is reduced suggesting that VX-809 has shrunk already existing cysts (Fig. 1). Importantly, after 2 months of treatment their cyst size is approximately 50% less compared to untreated animals of the same age (8 months). The reduction in cyst size was accompanied by improved renal function. Colocalizations studies confirm that CFTR is localized predominately at the apical membrane in the 8-month-old untreated animals consistent with its role in Cl^- secretion. However, after treatment CFTR localization with the basolateral membrane increases approximately 4-fold, accompanied by an approximately 2-fold decrease in its apical colocalizing indicating that VX-809 alters the phenotype of the cysts to favor fluid absorption.

Conclusions: Demonstration of cyst reduction, improved renal function and generation of an absorptive phenotype increases the therapeutic potential of VX-809 as a treatment of ADPKD.

Funding: NIDDK Support

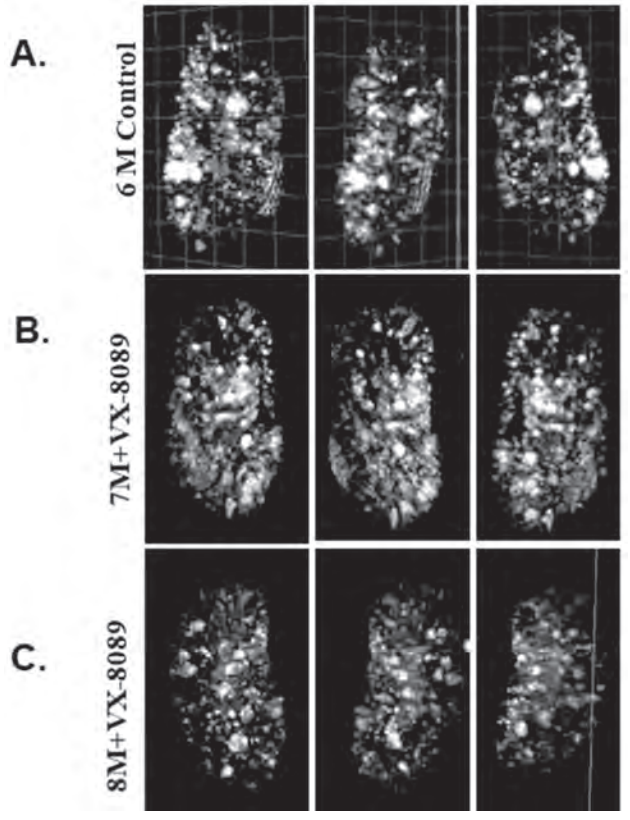

Fig 1: MRI images of mice kidneys Three sequential images are depicted. The animal depicted here (6M-Control) was allowed to develop cysts slowly over 6 months and then injected for one (B) and two months (C) with VX-809 (30 mg/kg) (8M+VX-809). **Note that** VX-809 shrinks the cysts between 6 and 8 months of age

TH-OR37

Comparative PKD1 and PKD2 Missense Variant Profiling Aids Molecular Diagnoses Across the ADPKD Spectrum and Reveals Common Pathomechanisms

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and growth of fluid-filled renal cysts, often leading to kidney failure. Typically, monoallelic *PKD1* or *PKD2* variants cause ADPKD, however, complex inheritance and a broad phenotypic spectrum also exist. The advent of genomewide variant screening has emphasized the importance of ADPKD molecular diagnostic methods to reliably determine the pathogenicity of variants of unknown significance (VUS).

Methods: Here, we developed a cell-based flow cytometry assay to assess the pathogenicity of *PKD1* and *PKD2* VUS. This assay utilizes localization of polycystin 1 (PC1; encoded by *PKD1*) to the apical plasma membrane, where formation of the PC1/PC2 complex (PC2; encoded by *PKD2*) is required for proper PC1 trafficking. Employing this assay, we have assessed 48 *PKD1* and 44 *PKD2* variants with predicted pathogenicity ranging from fully penetrant monoallelic, to incompletely penetrant biallelic, and likely benign variants.

Results: The majority of likely pathogenic monoallelic *PKD1* and *PKD2* missense variants perturb PC1 trafficking by >80%, with a correlation between the predicted penetrance (determined bioinformatically) and surface PC1. *In cis* monoallelic *PKD1* variants have an additive effect and perturb PC1 trafficking by 60-98%, whereas proposed biallelic *PKD1* variants exhibit variable impacts (0-70% perturbation; majority <60%). In contrast, likely benign variants have little or no impact. To understand mechanisms underlying aberrant PC1 trafficking, we evaluated defective protein folding under enhanced folding conditions (reduced culture temperature; 30°C). The majority of *PKD1* and *PKD2* monoallelic, and all *PKD1* and *PKD2* complex variants impact PC1 or PC2 folding, and can be partially or fully rescued at 30°C.

Conclusions: These studies describe a novel *in vitro* assay for determining *PKD1* and *PKD2* VUS pathogenicity, and highlight a continuum of allele penetrance across the ADPKD spectrum. This firmly establishes PC1 trafficking as a common *PKD1*/*PKD2*-mediated ADPKD pathomechanism, but suggests that other mechanisms account for a minority of variants. Further, demonstrated aberrant PC1 or PC2 folding suggests a role for chaperone therapy in ADPKD.

Funding: NIDDK Support

TH-OR38

The C-Terminal Tail of Polycystin 1 Rescues Cystic Phenotype in a Mitochondrial Enzyme-Dependent Fashion

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Background: Approximately 85% of Autosomal Dominant Polycystic Kidney Disease (ADPKD) cases are caused by mutations in *PKD1*, which encodes polycystin-1 (PC1). PC1 is a large transmembrane protein that undergoes C-terminal cleavage, generating fragments (PC1-CTT) that translocate to mitochondria and nucleus. We find that PC1-CTT expression in an inducible PC1 KO ADPKD mouse model substantially rescues cystic phenotype and we elucidate mechanisms involved in this effect.

Methods: We generated BAC transgenic mice expressing a Flox-Stop 2HA-PC1-CTT inserted in the Rosa26 locus and crossed it with the inducible *Pax8rtTA; TetO-Cre; Pkd1$^{fl/fl}$* ADPKD mouse model. Doxycycline induction of these mice (*PC1-CTT*; *Pax8rtTA; TetO-Cre; Pkd1$^{fl/fl}$* on the C57BL6N background) leads to PC1-CTT expression in renal epithelial cells that lack full-length PC1. We applied MS-based proteomics and Co-IP techniques to identify PC1-CTT interactors and used MS-based metabolomics to identify mitochondrial differences associated with the observed phenotype.

Results: Compared to PC1 KO mice, PC1 KO mice expressing PC1-CTT have 3-fold lower kidney weight/body weight ratio (5.10% vs 14.85%, $p<0.0001$) and 3.6-fold lower BUN (32.7mg/dL vs 120.7mg/dL, $p=0.0008$), with both groups presenting comparable gender distributions. BUN levels in PC1-CTT-expressing ADPKD mice are comparable to those in WT controls. We show that PC1-CTT interacts with mitochondrial enzyme Nicotinamide Nucleotide Transhydrogenase (NNT) and confirm the importance of this interaction by crossing the same PC1-CTT expressing PC1 KO mice with NNT-deficient C57BL6J mice. These mice do not exhibit an improved cystic phenotype. Both *in vivo* and *in vitro*, PC1-CTT re-expression in the presence of NNT leads to increased mitochondrial mass, altered redox modulation, increased assembly of ATP synthase at a "per mitochondria" level as well as decreased tubular proliferation, suggesting potential mechanisms for the observed rescue. Finally, unbiased metabolomics reveals that PC1-CTT's ability to rescue the ADPKD metabolic profile is tied to the presence of NNT.

Conclusions: Expression of PC1-CTT and its interaction with NNT significantly rescues ADPKD renal phenotype. Considering its small size, PC1-CTT could be explored as a gene therapy approach for ADPKD.

Funding: NIDDK Support, Private Foundation Support

TH-OR39

Read-Through Therapeutics Reduce Cystogenesis in a Novel Cohort of CRISPR Base Edited ADPKD Organoids

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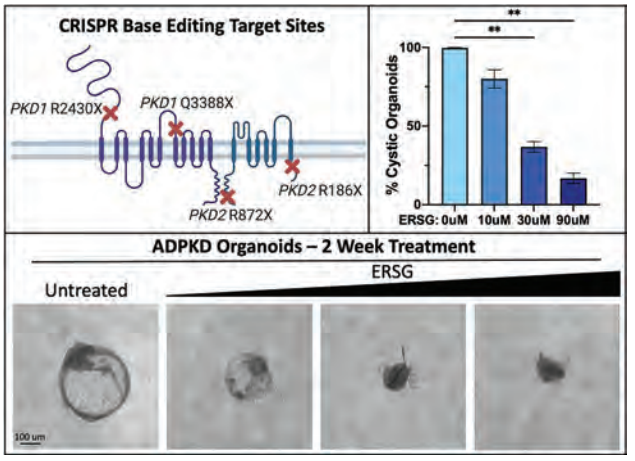
Background: In autosomal dominant polycystic kidney disease (ADPKD), truncating nonsense mutations are responsible for 40-50% of cases, with increased disease severity and limited treatment options. Eukaryotic ribosomal selective glycosides (ERSGs) allow read-through of premature stop codons to restore full-length proteins as a novel therapeutic approach. However, existing animal and kidney organoid models of ADPKD lack mutations amenable to read-through.

Methods: Human pluripotent stem cells were CRISPR base edited to introduce four specific nonsense mutations previously documented in ADPKD patients – *PKD1* R2430X and Q3838X and *PKD2* R186X and R872X. Mutations were confirmed by sequencing and protein changes by immunoblot. Mutant and isogenic control stem cells were differentiated into kidney organoids to determine if nonsense mutations conferred a cystic phenotype. Premature stop codon read-through potential was evaluated for impact on cyst formation and toxicity (live/dead staining and LDH release) over a period of two weeks using two unique ERSGs.

Results: Nonsense mutant clones of each targeted genotype were obtained with the desired single base pair mutation and lacked expression of full-length protein. Fewer than 5% of isogenic control organoids formed cysts compared to > 80% in untreated mutant organoids. Treatment of mutant organoids with ERSGs reduced cystogenesis to < 20% and slowed the rate of cyst expansion in a dose-dependent manner. Treatment associated toxicity was not significantly detected at efficacious doses.

Conclusions: CRISPR base editing enabled rapid generation of an ADPKD organoid cohort with patient targeted nonsense mutations. The data suggest that read-through by ERSGs is a viable therapeutic approach for reducing cystic burden in a large subpopulation of patients with ADPKD, supporting the advancement of ERSGs in human clinical trials.

Funding: NIDDK Support, Commercial Support - Eloxx Pharmaceuticals



TH-OR40

Whole-Genome Sequencing Reveals the Genetic Architecture of Posterior Urethral Valves

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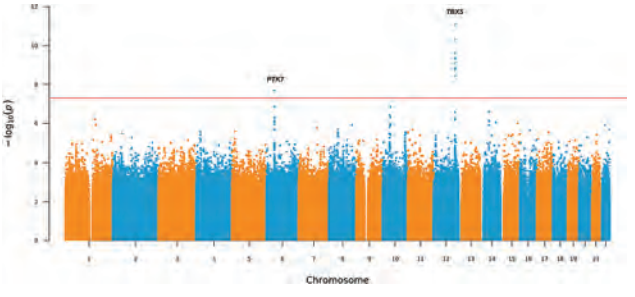
Background: Posterior urethral valves (PUV) are the commonest cause of childhood kidney failure and a major unmet clinical problem in pediatric nephrology. While usually sporadic, familial clustering and twin studies suggest a genetic component that is as yet unidentified. Using large-scale whole genome sequencing (WGS) we sought to understand the genetic architecture of PUV and identify key contributing genes.

Methods: We analysed WGS data from 132 unrelated PUV patients and 23,727 ancestry-matched unaffected controls from the 100,000 Genomes Project, seeking enrichment of common and rare single-nucleotide and structural variation (SV) on a genome-wide, per-gene, and cis-regulatory element basis.

Results: Exome-wide there was no significant enrichment of rare coding variation in any one gene. SV analysis identified an increased burden of rare inversions affecting CTCF-only cis-regulatory elements (P=2.0x10^{-5}; OR 2.1), but these did not affect any single genomic locus recurrently. GWAS of 17 million variants with minor allele frequency [MAF] > 0.001 revealed significant (P<5x10^{-8}) associations at two loci: 12q24.21 (P=7.8x10^{-12}; OR 0.4; MAF 0.37) and 6p21.1 (P=2.0x10^{-8}; OR 7.2; MAF 0.007), both of which replicated in an independent cohort of 398 European PUV patients. Bayesian fine mapping and *in silico* functional annotation mapped these loci to the transcription factor *TBX5* and planar cell polarity gene *PTK7*, respectively. Both are highly expressed in the embryonic mouse urethra and known to regulate development.

Conclusions: This work demonstrates that non-specific perturbations of broad regulatory networks and chromatin looping may be important in the pathogenesis of PUV. Furthermore, for the first time, two genetic loci for PUV are identified which map to the genes *TBX5* and *PTK7*, providing novel insights into the biological mechanisms underlying this complex disorder.



Manhattan plot for GWAS of 132 PUV patients and 23,727 unaffected controls.

TH-OR41

Role of Hypertension in the Risk of Heart Failure in CKD

Sydney E. Hartsell,[1] Guo Wei,[1] Robert E. Boucher,[1] Adhish Agarwal,[1,2] James C. Fang,[1] Adam Bress,[1] Alfred K. Cheung,[1,2] Srinivasan Beddhu.[1,2] *[1]The University of Utah School of Medicine, Salt Lake City, UT; [2]VA Salt Lake City Health Care System, Salt Lake City, UT.*

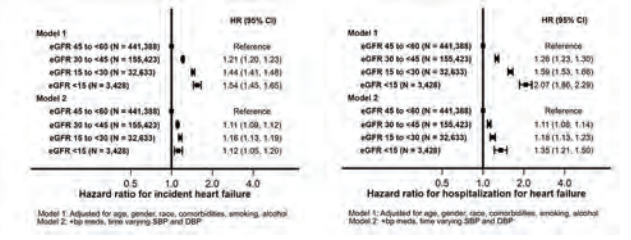
Background: Chronic kidney disease (CKD) is a risk factor for heart failure (HF), but the extent to which hypertension (HTN) contributes to development of HF in CKD is unclear.

Methods: We used the VA Informatics and Computing Infrastructure (VINCI) platform to identify a national cohort of veterans with prevelant CKD (two or more outpatient CKD-EPI eGFR <60 ml/min/1.73m^2 taken 60 days apart from January 2010 to December 2015). We used inpatient and outpatient ICD 9/10 codes to define HF admissions and incident HF through August 2018. We first related CKD stages at baseline with the time to HF hospitalizations and incident HF with adjustment for demographics and baseline comorbidity in a multivariable Cox regression. Next, we adjusted for baseline blood pressure (BP) and BP-lowering medications (BP meds). Finally, we conducted a time varying Cox regression model with 3-month averages of BP values and BP meds.

Results: Of the 915,038 veterans with prevelant CKD, we included 632,872 (69%) without known HF at baseline. Over about 3.5 million patient-years of follow up, 111,549 (18%) patients developed HF and 29,597 (5%) were hospitalized for HF. Compared to stage 3A CKD, more advanced CKD stages were significantly associated with HF incidence and admissions (Fig 1). Results were similar when adjusted for demographics only (incident HR 1.63 (95%CI 1.52-1.74); admission HR 2.28 (95%CI 2.05-2.53)) or with addition of comorbidities and atherosclerotic risk factors (Fig 1). Controlling for time-varying BP and BP meds significantly attenuated these hazard ratios (Fig 1). Results were similarly attenuated using baseline BP and BP meds (incident HR 1.06 (95% CI 0.99-1.13); admission HR 1.24 (95%CI 1.12-1.38).

Conclusions: Adjusting for HTN to a large degree attenuates the increased risk of HF observed in patients with CKD. Interventional trials targeting BP are needed to establish whether intensive BP control can reduce the risk of HF in CKD.

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



Hazard of HF incidence and admissions in CKD

TH-OR42

Prediction of Incident Heart Failure in CKD

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Background: Heart failure (HF) is common in patients with chronic kidney disease (CKD); identifying high risk patients would guide clinical care. We assessed prognostic value of cardiac biomarkers and echocardiographic (echo) variables for HF prediction compared to a published clinical equation in the Chronic Renal Insufficiency Cohort (CRIC).

Methods: Among 2,146 CRIC participants without prior HF and with complete clinical, cardiac biomarker and echo data, we compared the discrimination of the 11-variable Atherosclerosis Risk in Communities (ARIC) HF prediction equation to cardiac biomarkers (N terminal brain natriuretic peptide, NT-proBNP, and high sensitivity troponin T, hsTnT) and echo measures (left ventricular mass, LVM, and ejection fraction, LVEF) to predict 10-year risk of HF hospitalization using Cox regression. We separately evaluated prediction of HF with preserved and reduced LVEF (LVEF ≥50% and <50%, respectively). We assessed discrimination with internally valid, 10-fold cross-validated C-indices.

Results: Participants had mean (SD) age 59 (11), eGFR 44 (16) mL/min/1.73m2, 53% men, and 43% Black; 268 incident HF hospitalizations occurred during 6.7 (SD 2.5) years of follow-up. The ARIC HF model with clinical variables had a C-index of 0.68 (**Table**). hsTnT alone (C-index 0.69) and LVM+LVEF (C-index 0.71) were comparable to the ARIC model, while NT-proBNP alone had better discrimination (C-index 0.72,

p=0.04). A model including cardiac biomarkers, echo, and clinical variables had a C-index of 0.78. Discrimination of HF with preserved LVEF was lower than for HF with reduced LVEF for most models (**Table**).

Conclusions: The ARIC HF prediction model for 10-year HF risk had modest discrimination among adults with CKD. NT-proBNP alone discriminated better than the ARIC model, and was comparable to models with echo variables. HF clinical prediction models specifically in adults with CKD are needed. Until then, use of NT-proBNP may be a low burden approach to predict HF in this population, and offers moderate discrimination.

Funding: NIDDK Support

Table. Discriminatory ability of models to predict incident heart failure (HF), compared with the published ARIC model

	Incident HF		Incident HFpEF		Incident HFrEF	
Number of events	268		107		88	
	C-index (95% CI)	Difference from ARIC clinical model C-index (95% CI)	C-index (95% CI)	Difference from ARIC clinical model C-index (95% CI)	C-index (95% CI)	Difference from ARIC clinical model C-index (95% CI)
ARIC clinical model	0.69 (0.64, 0.71)	NA	0.69 (0.65, 0.74)	NA	0.72 (0.67, 0.78)	NA
NT-proBNP alone	0.72 (0.69, 0.75)	**0.04 (0.00, 0.08)**	0.72 (0.67, 0.77)	0.03 (-0.01, 0.08)	0.77 (0.72, 0.81)	**0.04 (+0.01, 0.10)**
hsTnT alone	0.69 (0.64, 0.73)	0.01 (-0.03, 0.05)	0.72 (0.67, 0.77)	0.03 (-0.01, 0.08)	0.71 (0.65, 0.76)	-0.01 (-0.07, 0.04)
LVM+ cVEP	0.71 (0.68, 0.74)	0.03 (-0.01, 0.07)	0.73 (0.68, 0.79)	0.02 (-0.04, 0.08)	0.77 (0.71, 0.82)	0.04 (+0.02, 0.11)
Clinical variables + NT-proBNP	0.77 (0.74, 0.80)	**0.08 (0.05, 0.12)**	0.78 (0.73, 0.82)	**0.09 (0.04, 0.13)**	0.81 (0.77, 0.86)	**0.09 (0.04, 0.14)**
Clinical variables + hsTnT	0.74 (0.70, 0.77)	**0.05 (0.02, 0.08)**	0.73 (0.72, 0.81)	**0.07 (0.03, 0.12)**	0.75 (0.68, 0.83)	0.03 (-0.02, 0.09)
Clinical variables + LVM + LVEF	0.75 (0.72, 0.78)	**0.07 (0.04, 0.10)**	0.75 (0.70, 0.80)	**0.08 (0.03, 0.13)**	0.80 (0.75, 0.85)	**0.08 (0.03, 0.13)**
Clinical variables + NT-proBNP + hsTnT + LVM + LVEF	0.78 (0.75, 0.81)	**0.10 (0.06, 0.13)**	0.79 (0.74, 0.85)	**0.09 (0.05, 0.14)**	0.83 (0.79, 0.87)	**0.11 (0.06, 0.16)**

Entries for ARIC clinical model are C-index and 95% bootstrap confidence intervals. All other entries are 10-fold cross-validated C-indices or difference in C-indices compared with ARIC clinical model, and 95% bootstrap confidence intervals. Bolded entries indicate statistical significance at the 5% level. ARIC clinical model predicts 10-year risk of HF from age, Black race/ethnicity, sex, heart rate, systolic blood pressure, use of antihypertensive medications, diabetes, coronary heart disease, current and former smoking, and BMI. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

TH-OR43

Risk of Subclinical-Cardiovascular Outcomes in Children with Ambulatory Hypertension: A Systematic Review and Meta-Analysis

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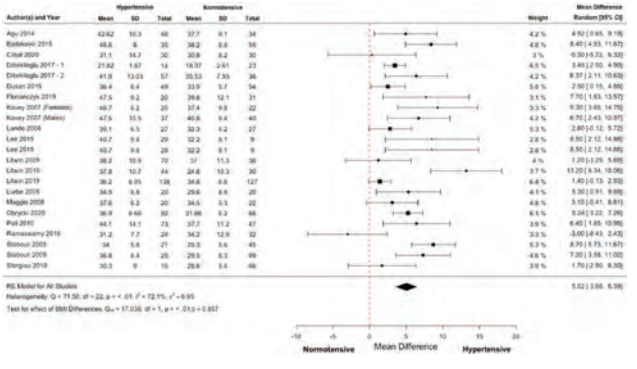
Background: Several studies have shown associations between childhood hypertension (HTN) and subclinical-cardiovascular outcomes (SCOs) such as left ventricular hypertrophy (LVH), increased pulse wave velocity (PWV) and increased carotid intima media thickness (cIMT). These data support the effect of elevated blood pressure (BP) in children leading to cardiovascular risk in adults; however, the association is not consistent in all studies. In this review, we investigate the prevalence of SCOs in children with HTN, diagnosed by ambulatory blood pressure monitoring (ABPM).

Methods: A systematic literature search was conducted on four electronic databases to include relevant full-length publications in English language, published abstracts and conference proceedings from Jan 1974 to Mar 2020. Article screening, data extraction and quality assessment were independently completed and verified by two reviewers. Primary outcomes included SCOs such as LVH, left ventricular mass index (LVMI), PWV and cIMT as per standard definitions. Meta-regression was done to adjust for the effect of body mass index (BMI) on LVMI.

Results: Of 8996 studies, 38 were included for analysis. SCO indices were significantly greater in those with HTN than those with normotension (NTN). Mean difference between the HTN and NTN group was 0.03mm (95% CI: 0.01, 0.05) for cIMT, 0.42 m/sec (95% CI: 0.25-0.6) for PWV, and 5.02$gm^{-2.7}$ (95% CI: 3.66-6.39) for LVMI. HTN group had 3-times higher odds of LVH (3.10 [95% CI: 1.65-5.82]). Meta regression showed that BMI had a significant influence on the mean differences in LVMI, with the mean difference in LVMI increasing by 0.81$gm^{-2.7}$ (95% CI [0.42, 1.19], $p < 0.001$) per unit increase in BMI.

Conclusions: Children with ambulatory HTN have a greater risk of SCOs. These findings emphasize the importance for children to have their BP within normal values.



TH-OR44

Renal Revascularization Attenuates Myocardial Mitochondrial Damage and Improves Diastolic Function in Pigs with Metabolic Syndrome and Renovascular Hypertension

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Background: Percutaneous transluminal renal angioplasty (PTRA) may improve renal and cardiac function in renovascular hypertension (RVH), but its effect on the biological mechanisms implicated in cardiac damage remains unknown. We hypothesized that restoration of kidney function by PTRA ameliorates myocardial mitochondrial damage and preserves cardiac function in pigs with metabolic syndrome (MetS) and RVH.

Methods: Pigs were studied after 16 weeks of MetS+RVH, MetS+RVH treated 4 weeks earlier with PTRA, and Lean and MetS Sham controls (n=6 each). Cardiac and renal function was assessed by multi-detector CT, whereas cardiac mitochondrial morphology and function, and injury pathways were assessed ex vivo.

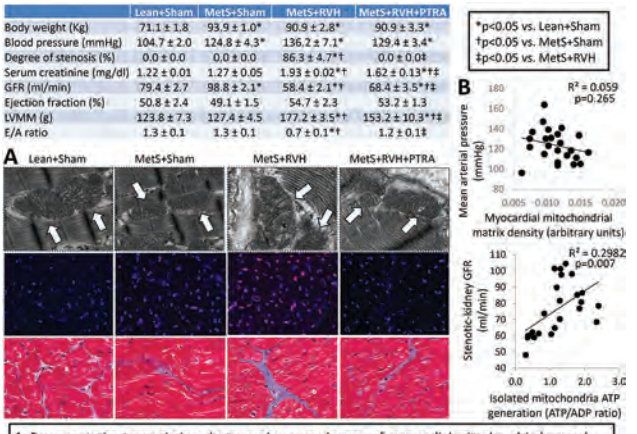
Results: RVH induced renal and cardiac diastolic (albeit not systolic) dysfunction (Table). PTRA improved renal function but not RVH. It preserved myocardial mitochondrial structure and function, ameliorated oxidative stress and fibrosis (Fig.A), attenuated left ventricular remodeling (LVMM), and restored diastolic function (E/A ratio). Myocardial mitochondrial damage did not correlate with blood pressure but correlated directly with renal dysfunction (Fig.B).

Conclusions: Improved renal function by PTRA preserves myocardial mitochondria and enhances cardiac recovery regardless of RVH, underscoring reno-cardiac crosstalk in experimental MetS+RVH.

Funding: NIDDK Support

	Lean+Sham	MetS+Sham	MetS+RVH	MetS+RVH+PTRA
Body weight (Kg)	71.1 ± 1.8	93.9 ± 1.0*	90.9 ± 2.8*	90.9 ± 3.3*
Blood pressure (mmHg)	104.7 ± 2.0	124.8 ± 4.3*	136.2 ± 7.1*	129.4 ± 3.4*
Degree of stenosis (%)	0.0 ± 0.0	0.0 ± 0.0	86.3 ± 4.7*†	0.0 ± 0.0‡
Serum creatinine (mg/dl)	1.22 ± 0.01	1.27 ± 0.05	1.93 ± 0.02*†	1.62 ± 0.13*†‡
GFR (ml/min)	79.4 ± 2.7	98.8 ± 2.1*	58.4 ± 2.1*†	68.4 ± 3.5*†‡
Ejection fraction (%)	50.8 ± 2.4	49.1 ± 1.5	54.7 ± 2.3	53.2 ± 1.3
LVMM (g)	123.8 ± 7.3	127.4 ± 4.5	177.2 ± 3.5*†	153.2 ± 10.3*†‡
E/A ratio	1.3 ± 0.1	1.3 ± 0.1	0.7 ± 0.1*†	1.2 ± 0.1‡

*p<0.05 vs. Lean+Sham
†p<0.05 vs. MetS+Sham
‡p<0.05 vs. MetS+RVH



A: Representative transmission electron microscopy images of myocardial mitochondria (arrows), dihydroethidium (DHE, red), and fibrosis (Trichrome, blue) in all groups. **B:** Myocardial mitochondrial matrix density did not correlate directly with mean arterial pressure, but myocardial mitochondrial ATP generation correlated directly with stenotic kidney GFR.

TH-OR45

Baseline and Time-Updated Systolic Blood Pressure and Incident Cognitive Impairment in the Chronic Renal Insufficiency Cohort

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Background: A linear relationship exists between systolic blood pressure (SBP) and cognitive impairment in the general population. Patients with chronic kidney disease (CKD) are at higher risk for hypertension and cognitive impairment. We therefore sought to investigate the relationship between SBP and cognitive impairment in patients with CKD.

Methods: Using data from the Chronic Renal Insufficiency Cohort Study, we investigated the association between baseline and time-updated SBP and incident cognitive impairment, defined as a mini-mental state (3MS) score < 80, during annual assessments using discrete hazards models that adjusted for demographics as well as cardiovascular and kidney disease risk factors.

Results: Mean (SD) age and eGFR (SD) by the CKD-Epi equation of the 3753 participants were 58 years (11), and 44 mL/min/1.73m^2 (15), respectively. Baseline cognitive impairment was present in 10.1% of overall participants (n = 365), and 5.4%, 9.5%, and 16.4% of participants with baseline SBP <120, 120-140, and ≥140 mm Hg, respectively ($p < 0.01$). There were 314 individuals who developed cognitive impairment during a median 6 years of follow-up. After multivariable adjustment, participants with higher baseline SBP were more likely to have incident cognitive impairment (hazard ratio (HR) [95%CI] = 1.09 [1.03, 1.16] per 10 mmHg higher SBP); this relationship was attenuated when using time-updated SBP (HR [95%CI] = 1.04 [0.99, 1.10]) (Table 1).

Conclusions: Among patients with CKD, elevated baseline SBP but not time-updated SBP was associated with incident cognitive impairment.

Funding: NIDDK Support

Table 1. Association of Systolic Blood Pressure with Incident Cognitive Impairment by 3MS Score <80

Exposure		Unadjusted HR (95% CI)	Model 1* HR (95% CI)	Model 2** HR (95% CI)
Baseline	SBP <120 mmHg	0.39 (0.30, 0.53)	0.56 (0.42, 0.76)	0.69 (0.50, 0.95)
	SBP 120-140 mmHg	0.62 (0.47, 0.81)	0.72 (0.55, 0.95)	0.82 (0.62, 1.10)
	SBP >140 mmHg	*ref*	*ref*	*ref*
	Continuous SBP	1.22 (1.16, 1.28)	1.14 (1.08, 1.20)	1.09 (1.03, 1.16)
Time-updated	SBP <120 mmHg	0.48 (0.36, 0.63)	0.74 (0.56, 0.98)	0.88 (0.65, 1.18)
	SBP 120-140 mmHg	0.53 (0.40, 0.88)	0.67 (0.50, 0.88)	0.75 (0.57, 1.00)
	SBP >140 mmHg	*ref*	*ref*	*ref*
	Continuous SBP	1.17 (1.11, 1.22)	1.08 (1.03, 1.14)	1.04 (0.99, 1.10)

n = 2,928, after excluding individuals with cognitive impairment at baseline and those missing blood pressure measures
*Adjusted for age, sex, race, education
** Adjusted for age, sex, race, education, cardiovascular disease, stroke, body mass index, diabetes mellitus, eGFR, and urine albumin to creatinine ratio

TH-OR46

Influence of Baseline Diastolic Blood Pressure on the Effect of Lowering Systolic Blood Pressure on Mild Cognitive Impairment and Probable Dementia

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Background: Lowering of systolic blood pressure (SBP) with already low diastolic blood pressure (DBP), can potentially decrease cerebral perfusion and worsen cognition. We examined the influence of baseline DBP on the effect of lowering SBP on incident mild cognitive impairment (MCI) and probable dementia (PD).

Methods: In this post-hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) study (N = 8562), we examined the effects of intensive (<120 mmHg) vs standard (<140 mmHg) SBP control on a composite, adjudicated outcome of MCI/PD across the range of baseline DBP in a spline Cox regression model. We also tested for interactions of baseline DBP on the effect of SBP goal on MCI/PD.

Results: Mean age was 68±9 years, 35% were women and 66% White. There were 640 MCI/PD events over 39,022 participant-years. Compared to standard SBP, intensive SBP control further lowered the DBP in those in the lowest baseline DBP tertile (Figure 1A) but also lowered the risk of MCI/PD (Table 1). While lower baseline DBP was associated with higher risk of MCI/PD (Table 1), there was no evidence that intensive SBP lowering increased the risk of MCI/PD in those with low baseline DBP (Figure 1B) with with baseline DBP x SBP goal interaction p = 0.37.

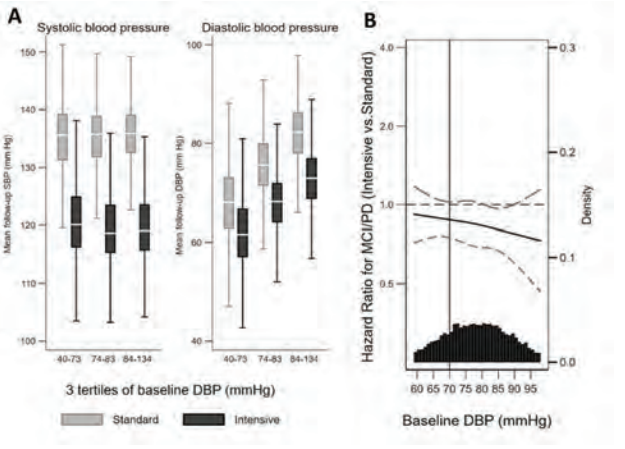
Conclusions: Intensive SBP lowering that further lowered DBP did not increase the risk of MCI/PD in those with low baseline DBP. The association of low baseline DBP with greater risk of MCI/PD is unlikely to be causal.

Funding: Other NIH Support - NIA

Table 1: Cox proportional hazard models for hazard ratios for MCI/PD for each 5 mmHg decrease in DBP and intervention.

	SBP intervention alone	DBP alone	Joint model
SBP intervention	0.80 (0.69, 0.94)		0.81 (0.69, 0.95)
Each 5 mmHg decrease in DBP		1.17 (1.13, 1.20)	1.17 (1.13, 1.20)

There was no interaction between baseline DBP and MCI/PD with the SBP intervention p=0.36



TH-OR47

Changes in Aortic Compliance During Individualized Hypertension Management in CKD

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Background: The prevalence of hypertension (HTN) in chronic kidney disease (CKD) patients ranges from 60% to 90% with up to 50% having drug resistant hypertension.

Methods: Using a prospective pragmatic CQI initiative, we evaluated the effectiveness of a novel hypertension management (Study) with standard care (Control) in a cohort of patients with uncontrolled hypertension with and without chronic kidney disease. A pre-determined Study group algorithm, guided by hemodynamic data obtained using noninvasive bioimpedance-derived stroke volume measurements, was used for selecting and titrating antihypertensive medications based on state: vasoconstricted, hyperdynamic, and mixed. Hypertensive patients were assigned to groups at baseline, then followed for 4-6 months (endpoint). Aortic compliance was computed as the ratio of stroke volume (SV) over central pulse pressure (PP).

Results: There were 73 patients in Study group and 20 in Control. Baseline demographics and BP were similar in both groups (Table 1). Individualized hemodynamic guided management resulted in significantly greater reductions in mean SBP (24.2 vs. 14.5 mmHg, p = 0.010), DBP (12.8 vs. 7.3 mmHg, p = 0.031), and a greater proportion of patients achieving target BP (57.5% vs. 25.0%, p = 0.010). This was associated with more normalization of physiology at endpoint in the Study group (68.5% vs. 35.0%, p = 0.006). The change in compliance (endpoint-baseline) was statistically different only in Study Group A (Table 2). The correlation between the change in compliance and the change in SV was significantly different between groups (p= 0.021). In contrast, the changes in central PP were similarly correlated in both groups.

Conclusions: Hypertension management is more effective when guided by hemodynamic state. Greater decrease in BP is strongly associated with both hemodynamics normalization and compliance improvement, with the latter associated with increase in SV.

Funding: Commercial Support - NIMedical, Israel

Variable at Baseline	Study Group (N = 73)	Control Group (N = 20)	P-value
Age, mean (SD) years	60.5 (16.4)	63.3 (10.7)	0.490
Female, N (%)	36 (49)	13 (65)	0.213
CKD 1-5, N (%)	54 (74)	13 (65)	0.139
SBP, mean (SD) mmHg	161.2 (15.6)	163.4(16.4)	0.588
DBP, mean (SD) mmHg	89.8 (12.0)	88.4 (12.9)	0.977
MAP, mean (SD) mmHg	113.3 (9.9)	113.9 (9.1)	0.815
Central SBP, mean (SD) mmHg	140.7 (21.4)	144.8 (14.8)	0.413
Central DBP, mean (SD) mmHg	90.3 (15.9)	91.3 (11.7)	0.790

Table 1: Baseline demographics and BP

	Compliance (ml/mmHg)		
	Baseline (Mean, SD)	Endpoint (Mean, SD)	P-value
Study Group	1.6 (0.7)	2.0 (0.7)	<0.001
Control Group	1.5 (0.5)	1.7 (0.5)	0.063

Table 2: Compliance at Baseline and Endpoint

TH-OR48

Regulation of Sodium Excretion and Blood Pressure by the Nuclear Factor of Activated T Cells 5 (NFAT5) in Renal Tubular Cells

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Background: NFAT5 is an osmoprotective transcription factor, which is crucial for cell survival under hypertonic conditions such as those encountered in the renal medulla. Physiological role of NFAT5 in the kidney, however, is still obscure. We investigated the role of NFAT5 in renal tubules using renal tubular cell-specific NFAT5-knockout (KO) mice.

Methods: We crossed NFAT5 floxed mice with Pax8-rtTA/LC-1 mice to obtain mice with inducible and specific deletion of NFAT5 in renal tubular cells. To characterize the mice, urine and blood parameters and blood pressure of wild type (WT) and KO mice were examined at basal condition. Then, WT mice and KO mice were fed either a high-salt diet (HSD) or a regular-salt diet (RSD) for 4 weeks. The mRNA expression of sodium transporter-related genes in the kidney was examined by real-time PCR. Protein expression of the epithelial sodium channel (ENaC) in the membrane fraction was examined by Western blotting. Concentrations of urea and sodium in the renal medulla were measured.

Results: Compared to WT mice, KO mice exhibited polyuria (WT vs. KO: 2.0 ± 0.08 vs. 5.2 ± 0.18 ml/day) at basal condition. The serum sodium level was increased (151.8 ± 0.78 vs. 156.6 ± 0.45 mEq/L) and the urinary sodium excretion was decreased (498.7 ± 25 vs. 368.9 ± 15 mEq/gCr) in KO mice. Interestingly, the systolic blood pressure was significantly elevated in KO mice (97.4 ± 2.4 vs.114.9 ± 1.1 mmHg). mRNA expressions of AQP2 and UT-A1, a water channel and a urea transporter, respectively, were significantly decreased, while the expressions of ENaC were increased in KO mice. There was no significant difference in the plasma renin activity or aldosterone levels. The systolic blood pressure of KO mice fed HSD was significantly elevated earlier compared to WT mice fed HSD. ENaC protein levels were increased in KO mice fed HSD compared to WT. The urea concentration was lower and the Na concentration was higher in the medulla of KO mice than those of WT mice. HSD significantly increased the medullary Na concentration, but not the urea concentration in KO mice.

Conclusions: These results suggest that NFAT5 can regulate the urine concentration and sodium reabsorption in renal tubules, which could be important for body fluid homeostasis and blood pressure regulation.

Funding: Government Support - Non-U.S.

TH-OR49

Fluid Overload, 24-Hour Blood Pressure Patterns, and Their Association with Cardiovascular and Kidney Outcomes in CKD

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Background: Fluid overload is well-known risk factor for adverse cardiovascular and kidney outcomes in chronic kidney disease (CKD) patients. However, it is unclear whether fluid overload is associated with blood pressure (BP) patterns and their relationship to adverse clinical outcomes in CKD patients.

Methods: A total of 1,147 CKD (stage 1 to 5) patients were enrolled from the prospective observational cohort of CMERC-HI (Cardiovascular and Metabolic Disease Etiology Research Center-High Risk). The patients were classified into tertile based on fluid status defined as the extracellular water to total body water ratio (ECW/TBW) measured by bioelectrical impedance analysis; hypovolemic, euvolemic, and hypervolemic groups. BP patterns were assessed by 24-h BP measurements; dipper (nighttime BP fall 10-20%), extreme dipper (nighttime BP fall >20%), non-dipper (nighttime BP fall 0-10%), and reverse dipper (nighttime BP fall <0%). Primary outcome was composite of nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality. The secondary outcome was progression of CKD (composite of at least 50% decrease in eGFR> 50% from baseline or eGFR <60 ml/min/1.73 m^2, or end-stage kidney disease).

Results: The mean age of study subjects was 59.9±12.2 years and 615(53.6%) were male. The hypervolemic group was associated with increased risk of reverse-dipping pattern (OR, 2.46; 95% CI, 1.30-4.64; *P*=0.01). During a median follow-up of 42.1 (41.3-42.9) months, the composite of cardiovascular events and CKD progression occurred in 42 (3.7%) and 345 (30.1%), respectively. The Kaplan-Meier analysis showed that hypervolemic group was associated with increased risk of cardiovascular events and CKD progression compared to hypovolemic group. In multivariable Cox analyses, hypervolemic group was associated with increased risk of cardiovascular events (HR, 4.44; 95% CI, 1.16-17.0; *P*=0.03). Moreover, hypervolemic group was associated with increased risk of CKD progression (HR, 2.47; 95% CI, 1.77-3.45; *P*<0.001). This increased risks of cardiovascular events and CKD progression with hypervolemic status were still consistent in patients with reverse-dipping pattern.

Conclusions: The increased risk of cardiovascular events and kidney disease progression in CKD patients with fluid overload can be explained by an association with a reverse-dipping BP pattern.

TH-OR50

Galectin 3 and Air Pollution in Hypertensive Patients with and Without CKD

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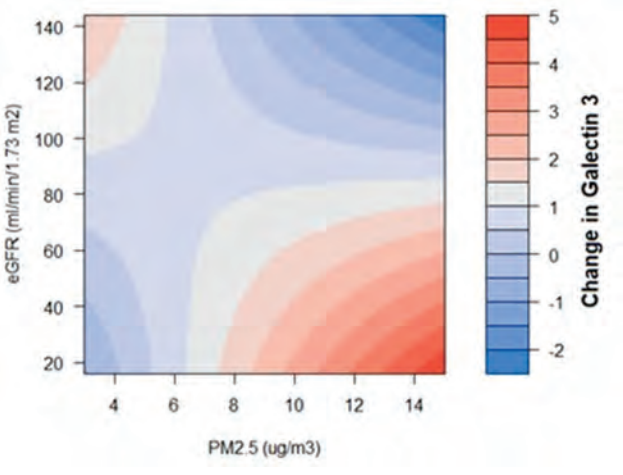
Background: Air pollution is a major contributor to cardiovascular and kidney complications. The mechanisms linking air pollution with cardiorenal events are not well understood. We sought to assess whether Galectin 3 level, a marker of myocardial fibrosis and remodeling is associated with air pollution exposure in hypertensive patients with and without chronic kidney disease.

Methods: Satellite-derived PM2.5 measurements were linked with participants in the Systolic Blood Pressure Intervention Trial (SPRINT, Clinicaltrials.gov NCT01206062). A total of 1019 SPRINT participants with available Galectin 3 levels at study baseline and 24 months follow-up were included in these analyses. Multivariable linear regression models, adjusted for age, sex, race, eGFR, Framingham risk score, body mass index, and randomization assignment were built to assess the association between air pollution and Galectin 3 at baseline and longitudinal change at 2 years.

Results: The mean $PM_{2.5}$ was 9.6 μg/m^3, and the median (IQR) Galectin 3 level was 14.4 (11.5-18.0) ng/mL. In multivariable models, we found no association between $PM_{2.5}$ and baseline (β=-0.02, P=0.46) or longitudinal change (β=0.05, P=0.12) in Galectin 3. In the subgroup of participants with CKD (n=201), $PM_{2.5}$ was associated with change in Galectin 3 (β=0.21, P=0.002), which remained statistically significant after multivariable adjustments (β=0.23, P=0.003). In the overall cohort (n=1019), there was a significant interaction between $PM_{2.5}$ and eGFR with change in Galectin 3 (p-value for interaction=0.02), (Figure).

Conclusions: Air pollution may be associated with worsening myocardial fibrosis as evidenced by increasing levels of Galectin 3 in individuals with preexisting CKD. Further studies are needed to corroborate these findings with rigorous cardiac imaging studies.

Funding: Other NIH Support - MD is supported by R01HL141846



Change in Galectin 3 and PM2.5 exposure by eGFR

TH-OR51

Diagnostic Application of NanoString Gene Scores in Transplant Biopsies with Suspicious Features of Antibody-Mediated Rejection

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Background: Antibody-mediated rejection (AMR) is the leading cause of renal allograft loss, a diagnosis which is reached using the Banff Classification for Allograft Pathology. Biopsies that only partially fulfil the histological criteria for AMR, those with 'incomplete phenotypes', provide a challenge for diagnosis, prognosis and management. The Banff Molecular Diagnostics Working Group has designed a 758-gene panel for use with NanoString with the aim of developing a gene transcript signature to improve the diagnosis of AMR, but this has not been validated in biopsies with features suspicious for AMR, where its use may distinguish between cases that represent AMR from those that do not.

Methods: RNA was extracted from a retrospective cohort of 147 FFPE biopsies that were divided into three groups: biopsies that fulfilled the 2019 Banff Criteria for AMR ('AMR', n=34), those that would meet the criteria for AMR only in the presence of a validated gene signature ('AMRsusp', n=41), and biopsies that showed no features of AMR ('No AMR', n=72). Gene expression analysis of 758 genes in the Banff Human Organ Transplant panel was carried out using Nanostring® analysis. Gene expression was normalised using twelve housekeeper genes and internal positive-control normalisation

Results: Of the 758 genes, 134 were significantly different (with FDR set at 0.01) in biopsies which fulfilled the full Banff Criteria for AMR, compared to biopsies without features of AMR. Lasso regression was used to define a set of 37 up-regulated genes that were strongly predictive of AMR, and used to create an AMR Gene Score. A Reciever-Operating Characteristic demonstrated that the Gene Score was able to differentiate

between AMR and No AMR Cases (AUC 0.8742 ,95% CI 0.8095-0.9388, p<0.0001) and was used to develop a gene score cut-off, maximising sensitivity and specificity. In biopsies suspicious for AMR, but which did not complete the full diagnostic criteria, a high Gene Score was predictive of allograft loss, compared to biopsies with a low gene score (p=0.0065)

Conclusions: Nanostring analysis of gene expression in FFPE biopsy samples can be used to identify biopsies suspicious for AMR that are at higher risk of allograft loss, and may have a role in characterising cases that represent AMR, even in the abscence of full diagnostic criteria.

TH-OR52

Proteomics Reveals Extracellular Matrix Injury in the Glomeruli and Tubulointerstitium of Kidney Allografts with Early Antibody-Mediated Rejection

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Background: Antibody-mediated rejection (AMR) accounts for >50% of kidney allograft losses. AMR is caused by donor-specific antibodies (DSA) against HLA and non-HLA antigens in the glomeruli and the tubulointerstitium, which together with interferon gamma and tumor necrosis factor-alpha (TNFα), trigger graft injury. The reasons behind cell-specific injury in AMR remain unclear. Identifying compartment-specific proteome alterations may help uncover mechanisms of early antibody-mediated injury.

Methods: We studied 30 for-cause kidney biopsies with early AMR, acute cellular rejection (ACR) or acute tubular necrosis (ATN). We laser-captured microdissected glomeruli and tubulointerstitium and subjected them to unbiased proteome analysis.

Results: We found 107 glomerular and 112 tubulointerstitial proteins significantly differentially expressed in AMR vs. ACR. Similarly, 112 (glomeruli) and 124 (tubulointerstitium) proteins were regulated in AMR vs. ATN. Basement membrane and extracellular matrix (ECM) proteins were decreased in both compartments in AMR, compared with ACR and ATN. We verified decreased glomerular and tubulointerstitial LAMC1 expression, and decreased glomerular NPHS1 and PTPRO expression in AMR. Cathepsin-V (CTSV) was predicted to cleave ECM-proteins in the AMR glomeruli. We identified galectin-1, an immunomodulatory protein upregulated in AMR glomeruli and linked to the ECM. Examination of publicly available data revealed that galectin-1 is increased at the gene level in AMR. Anti-HLA class-I significantly increased CTSV expression, and galectin-1 expression and secretion, in human glomerular endothelial cells. We also studied glutathione S-transferase omega-1 (GSTO1), an ECM-modifying enzyme, increased in the AMR tubulointerstitium. GSTO1 expression was significantly increased in TNFα-treated proximal tubular epithelial cells.

Conclusions: Basement membranes are often remodeled in chronic AMR, and we demonstrated that this remodeling begins early in glomeruli and tubulointerstitium. Targeting ECM-remodeling in AMR may represent a new therapeutic avenue.

TH-OR53

Single-Cell Profiling Reveals Sex-Based Transcriptional Programs in Healthy Human Kidney

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Background: Single-cell transcriptomics provide unprecedented insight into disease states in the kidney, yet our understanding of the transcriptional programs of human kidney cells at homeostasis is limited by difficulty accessing healthy, fresh tissue. Sex-based dichotomy in human kidney cells remains unaddressed, but may underpin acute and chronic kidney diseases e.g. progressive diabetic kidney disease and IRI which exhibit a male preponderance.

Methods: We sequenced single-cell suspensions of 19 pre-implantation living donor biopsies (9 male, 10 female)(10X Genomics). Analyses were performed with Cellranger and Seurat in R. Sex-based transcriptomic differences were examined using varimax-rotated principal component analysis, machine learning approaches and differential expression analysis.

Results: 27677 high-quality cells forming 23 clusters were identified with several immune populations and all anticipated parenchymal populations. Individual kidney populations were examined for separation due to donor sex, with clear separation observed for the PT population alone using varimax-rotated principal component analysis (Fig1a). Machine learning identified the most discriminant subset of genes (Model1: 80 genes) that could correctly classify cell sex (AUC 0.98). 75 genes were differentially expressed between males and females (p-value <0.05, LogFC>0.25). Anti-oxidant metallothionein genes were increased in females. Pathway analysis revealed metabolism-related processes (oxidative phosphorylation, and the TCA cycle) as increased in males (Fig1B).

Conclusions: We report striking sex-based transcriptional differences in PT cells, suggesting higher baseline metabolic activity in males, and increased anti-oxidant metallothionein genes in females. These sex-based differences in PT gene expression may provide insights into the well-recognized, but previously unexplained sexual dimorphism observed in kidney diseases.

Figure 1: Identifying sex-biased gene expression in proximal tubule cells. (A) Varimax rotation of PCA components shows clear separation between PT cells from males and females **(B)** Depiction of top-ranking terms identified by GSEA analysis as being enriched in males and females respectively. Abbreviations: GSEA: Gene Set Enrichment Analysis; PT, proximal tubular NES, normalized enrichment score.

TH-OR54

Vaccination with Class-Ib MHC Binding Synthetic Superagonist and Adoptive Transfer of Antigen-Specific CD8 Tregs Prolong Cardiac Allograft Survival in Alloantigen-Sensitized Hosts

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Background: Previously, we showed Qa-1 (HLA-E in human) restricted regulatory CD8 T cells (CD8 Treg) are highly suppressive of follicular helper T cells (Tfh), and play a critical role in suppressing donor-specific antibodies (DSA) and antibody-mediated rejection (AMR). Alloreactive CD4 T cells upregulate Qa-1 in association with stress peptides such as FL9 that are recognized by CD8 Treg. Therefore, we hypothesized that vaccinating hosts with a superagonist that mobilizes CD8 Treg, and adoptive transfer of antigen-specific CD8 Treg may protect heart allografts from antibody-mediated injury.

Methods: We used a tetramer to sort FL9-Qa-1 specific CD8 T cells and sequenced their T cell receptors (TCR). We screened over 100 peptides synthesized with FL9 backbone and identified a superagonist that induces the strongest CD8 T cell response. We also generated FL9-Qa-1 TCR Transgenic mice (FL9-Tg mice). We then sensitized B6 hosts with Balb/c skin allograft with or without vaccinating with superagonist, AND with or without transferring CD8 T cells isolated from FL9-Tg. Following the sensitization with different treatments, each group received BALB/c heart allografts and was monitored for graft survival.

Results: The superagonist induced a strong CD8 Treg response that suppresses Tfh, activated B cells, plasma cells and DSA in vivo. Allograft retrieved from the treatment group showed less C4d deposit and attenuated graft injury. The treatment group also showed prolonged allograft survival; the superagonist and the adoptive transfer showed a synergistic effect.

Conclusions: Allo-sensitized, cardiac transplantation is a stringent model in which allografts undergo a robust process of AMR. While antibody-mediated graft injury in clinical transplantation is a major barrier to long-term kidney allograft survival, we believe the graft protection using the superagonist and antigen-specific CD8 Treg is biologically significant with a high translational potential. Further investigation is needed to maximize the efficacy of CD8 Treg therapy, such as co-administration of CD8 Treg-specific co-stimulator. In addition, we are investigating the human equivalent of FL9 peptide, and examining the potential unwanted toxicity of FL9-Qa-1 specific CD8 T cells on allografts.

Funding: Other NIH Support - NIAID

TH-OR55

Sodium-Glucose Cotransporter 2 Inhibitors in Kidney Transplant Recipients

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Background: The effect and safety of sodium-glucose cotransporter 2 inhibitors (SGLT2i) have not been investigated in kidney transplant recipients (KTRs) with diabetes. We evaluated the impact of SGLT2i in a multicenter cohort of diabetic KTRs.

Methods: A total of 2083 KTRs with diabetes were enrolled from six transplant centers in Korea. Among them, 226 (10.8%) patients prescribed with SGLT2i for more than 90 days. The primary outcome was a composite outcome of all-cause mortality, death-censored graft failure, and serum creatinine doubling. An acute dip in estimated glomerular filtration rate (eGFR) over 10% was surveyed after SGLT2i use.

Results: During the mean follow-up of 62.9 ± 42.2 months, the SGLT2i group had a lower risk of primary composite outcome than the control group in the multivariate and propensity score-matched models (Figure 1; adjusted hazard ratio [aHR], 0.52; 95% confidence interval [CI], 0.29–0.94; P = 0.031 and aHR, 0.46; 95% CI, 0.24–0.89; P = 0.022, respectively). Multivariate analyses consistently showed a decreased risk of serum creatinine doubling in the SGLT2i group. The overall eGFR remained stable without the initial dip after SGLT2i use. A minority (15.6%) of the SGLT2i users showed

acute eGFR dip during the first month, but the eGFR recovered thereafter (Figure 2). The risk factors for the eGFR dip were time from transplantation to SGLT2i usage and mean tacrolimus trough level.

Conclusions: SGLT2i improved a composite of all-cause mortality, death-censored graft failure, or serum creatinine doubling in KTRs. SGLT2i can be used safely and have beneficial effects on preserving graft function in diabetic KTRs.

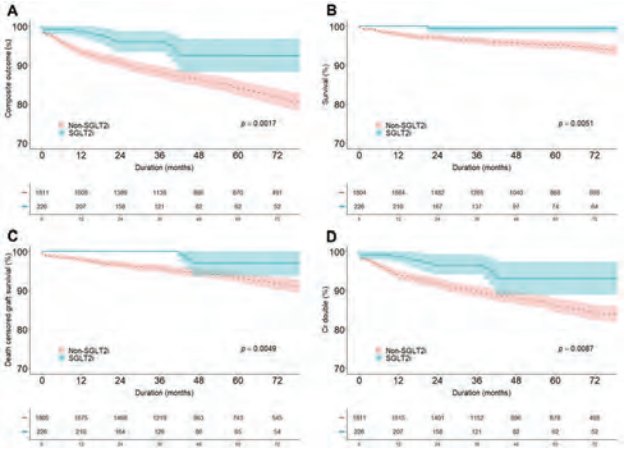

Figure 1. Kaplan–Meier curves for the outcomes

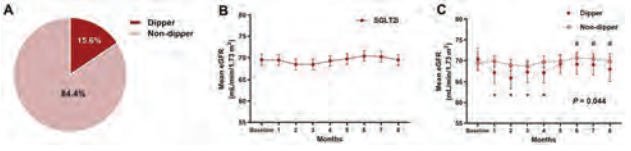

Figure 2. Temporal changes in the eGFR of SGTL2i users due to eGFR dip.

TH-OR56

The Role of Combined Gene Expression Profiling and Donor-Derived Cell-Free DNA to Diagnose Acute Rejection in Patients with Acute Allograft Dysfunction

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Background: Gene expression profiling (GEP) has been used to monitor for subclinical acute rejection. Conversely, the majority of data with donor-derived cell-free DNA (dd-cfDNA) has been in patients with allograft dysfunction. We hypothesized that combining GEP and dd-cfDNA could improve the diagnostic performance to detect acute rejection in patients with acute allograft dysfunction.

Methods: We analyzed a total of 131 blood samples paired with kidney biopsies from patients (n=96) with 'for cause' biopsies in the CTOT 08 study. Blood samples were analyzed with the GEP and the dd-cfDNA assay. The area under the receiver operating characteristics (AUROC) was used for GEP and dd-cfDNA separately based on their continuous output variables, and for combining two assays with logistic regression.

Results: Of 131 blood samples, 50 and 81 cases were biopsy-proven clinical acute rejection and acute allograft dysfunction without rejection, respectively. In binary analysis, GEP showed a lower positive predictive value (PPV) at 0.54 to 0.64 from dd-cfDNA, but a higher negative predictive value (NPV) at 0.80 to 0.70. When both tests were positive, PPV increased to 0.68 (95% CI, 0.50-0.88). In cases when both tests were negative, NPV increased to 0.88 (95% CI< 0.78-0.96) (Table 1). Performance of GEP and dd-cfDNA on detection of antibody-mediated rejection and acute cellular rejection shown in Figure 1. The combined use of two assays showed similar AUROC, to 0.75 than GEP (0.74, p-value = 0.26) and dd-cfDNA (0.72, p-value=0.69).

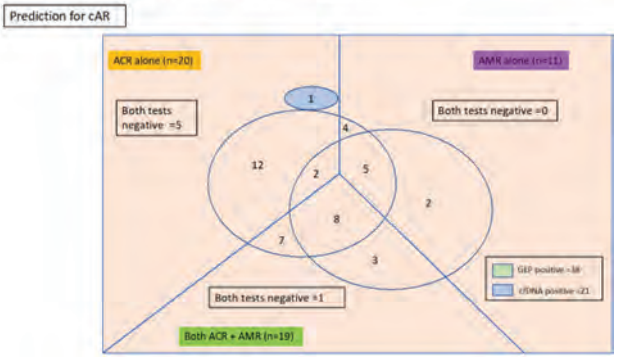
Conclusions: Combined GEP and dd-cfDNA assay might improve the diagnostic performance of acute rejection in patients with acute renal allograft dysfunction.

Funding: Commercial Support - Viracor-Eurofins

Table 1) Diagnostic performance of a gene expression profile and donor-derived cell-free DNA for acute rejection

	GEP alone (>50)	dd-cfDNA alone (>0.7%)	Positive = GEP+ or dd-cfDNA	Positive = GEP+ AND dd-cfDNA+
Sensitivity (95% CI)	0.76 (0.62-0.88)	0.42 (0.27-0.57)	0.88 (0.77-0.96)	0.3 (0.18-0.43)
Specificity (95% CI)	0.58 (0.47-0.69)	0.85 (0.77-0.93)	0.52 (0.41-0.63)	0.91 (0.84-0.97)
PPV (95% CI)	0.54 (0.41-0.64)	0.64 (0.46-0.80)	0.53 (0.41-0.64)	0.68 (0.50-0.88)
NPV (95% CI)	0.80 (0.69-0.90)	0.70 (0.61-0.80)	0.88 (0.78-0.96)	0.68 (0.59-0.77)

Figure 1) GEP and dd-cfDNA performance by rejection types



TH-OR57

Phase 3 Study of Maribavir (MBV) vs. Investigator-Assigned Therapy (IAT) for Refractory/Resistant (R/R) Cytomegalovirus (CMV) Infection Post-Transplant: Analysis of Kidney Recipients and Renal Safety

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Background: Risk of nephrotoxicity limits antiviral use for treatment (tx) of transplant recipients with CMV infection. We report efficacy (including sub-analysis of kidney recipients) and renal safety data from a phase 3 study of MBV vs IAT in patients (pts) with R/R CMV infection (NCT02931539).

Methods: Transplant recipients (≥12y) with CMV infection (screening plasma DNA≥910IU/mL) R/R to prior tx (failure to achieve>1$\log_{10}$ decrease in CMV DNA after≥14days±genotyped resistance) were randomized 2:1 MBV (400mg BID):IAT (val/ganciclovir, foscarnet[FOS], cidofovir) for 8wks. Primary endpoint:confirmed CMV clearance at end of Wk8 (plasma DNA<137IU/mL in 2 consecutive tests≥5days apart). Key secondary endpoint:CMV clearance and symptom control at end of Wk8 maintained through Wk16. Group differences were adjusted for baseline CMV DNA level+solid organ/hematopoietic cell transplant where applicable. Subgroup analysis of kidney recipients was conducted. Tx-emergent adverse events (TEAEs) were assessed (safety set).

Results: More MBV (randomized set: 235 MBV, 117 IAT[47 FOS]) pts achieved the primary (55.7% vs 23.9% IAT; adjusted difference[AD] 32.8%, 95% CI 22.8–42.7; **p<0.001**) and key secondary endpoint (18.7% vs 10.3% IAT; AD 9.5%, 95%CI 2.0–16.9; **p=0.013**). For kidney recipients (74 MBV, 32 IAT), 59.5% MBV vs 34.4% IAT pts achieved CMV clearance (AD 26.7%, 95%CI 7.5–45.9). Rates of TEAEs were similar between MBV and IAT (**Table**). Dysgeusia was the most frequent TEAE with MBV (37.2%, IAT 3.4% pts). Tx-related TEAE of increased immunosuppressant drug level was reported in 6% pts treated with MBV (IAT 0% pts). Renal and urinary TEAE rates were lower for MBV (17.1% pts) than IAT (26.7% pts[FOS 44.7% pts]). A lower proportion of pts had tx-related acute kidney injury (AKI) with MBV (1.7%) than IAT (7.8%[FOS 19.1%]). Pts in the IAT arm discontinued tx due to AKI (5.2% [FOS 12.8%]); no pts treated with MBV discontinued tx due to renal TEAEs.

Conclusions: Maribavir was superior to IAT for achievement of clearance of R/R CMV infection among transplant recipients, with consistent benefit in kidney recipients. Rates of renal TEAEs were lower with MBV than IAT.

Funding: Commercial Support - Funding: Shire ViroPharma, Incorporated, a Takeda company

Overall and renal TEAEs and tx-related TEAEs occurring in ≥5% of patients in the MBV or IAT arms (safety set)

n (%) of patients	TEAE		Tx-related TEAE	
	MBV (n=234)	IAT (n=116)	MBV (n=234)	IAT (n=116)
Any TEAE or tx-related TEAE	228 (97.4)	106 (91.4)	141 (60.3)	57 (49.1)
Any renal and urinary TEAE[a]	40 (17.1)	31 (26.7)	4 (1.7)	15 (12.9)
Acute kidney injury[b]	20 (8.5)	11 (9.5)	4 (1.7)	9 (7.8)

[a]System organ class. Included adverse events coded using MedDRA, version 23.0; [b]Preferred term.
IAT, investigator-assigned therapy; MBV, maribavir; TEAE, treatment-emergent adverse event; tx, treatment.

TH-OR58

Living in High Minority, Less English-Proficient Communities May Facilitate Living Donor Kidney Transplantation Among Asian Americans and Pacific Islanders

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Background: Living donor kidney transplantation (LDKT) racial disparities have increased. Living in linguistically isolated communities or areas with large minority populations has been associated with decreased access to transplant, but LDKT recipient-donor pairs are 95% racially concordant. The contemporary relationship between LDKT access and living in high minority, less English proficient communities is unknown.

Methods: The Scientific Registry of Transplant Recipients was utilized to identify adult, kidney-only transplant recipients (1/1/2018-12/31/2018). The Minority Status and Language Theme of the Centers for Disease Control and Prevention 2018 Social Vulnerability Index was linked to recipients' zip codes. Modified Poisson regression was utilized to evaluate likelihood of LDKT.

Results: Of the 18,950 kidney transplant recipients included in this study, 32% achieved LDKT. Black (adjusted relative risk (aRR): 0.60, 95% confidence interval (CI): 0.49-0.74) and Asian American and Pacific Islander (AAPI) recipients (aRR: 0.52, 95%CI: 0.39-0.70) were less likely to receive LDKT compared to White recipients. Overall, community minority status and language proficiency was not associated with LDKT (aRR: 1.01, 95%CI: 1.00-1.02), but the effect of this vulnerability measure varied by race. Among AAPI recipients only, living in higher minority, less English proficient communities was associated with increased likelihood of LDKT (ratio of aRR: 1.66, 95%CI: 1.12-2.47; Figure 1).

Conclusions: While all minority recipients had lower likelihood of LDKT, living in higher minority, less English proficient communities may be paradoxically advantageous for AAPI patients. Given LDKT racial concordance, living in areas with shared culture or language may facilitate LDKT access among AAPI.

Funding: NIDDK Support

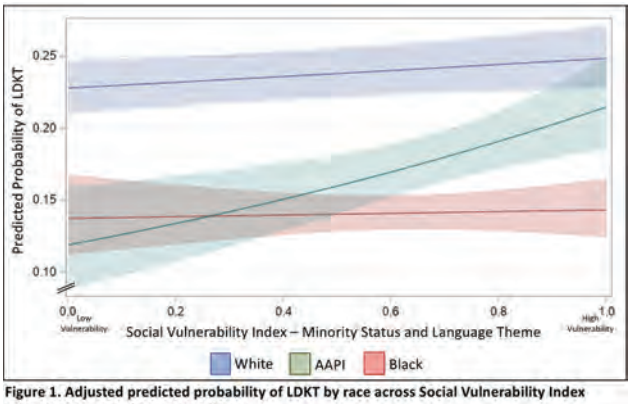

Figure 1. Adjusted predicted probability of LDKT by race across Social Vulnerability Index Minority Status and Language Theme.

TH-OR59

Modifiable Risk Factors for New-Onset Hypertension After Live Kidney Donation

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Background: Hypertension is a common comorbidity and also a risk factor for the development of end-stage kidney disease in living kidney donors. Herein, we aimed to evaluate the impact of exposure to overweight after donation on the development of new-onset hypertension.

Methods: A total of 6,581 donors and 13,350 controls were extracted from the national health insurance database between 2001 and 2018. Subjects took national health check-up 2 times and more were included. Controls were randomly extracted after matching with age, sex, date of donation, underlying hypertension and diabetes in the general population. Exposure to overweight and obesity was defined by body mass index (BMI) ≥23 kg/m^2 and ≥25 kg/m^2 during follow-up period. Overweight/obesity status was divided into 4 groups; 1) persistently no exposure, 2) exposure at only last health check-up, 3) persistently exposure in two times of health check-up, and 4) recovered from exposure at last health check-up. We used a multivariate logistic regression model to identify risk factors for new-onset hypertension.

Results: A total of 1,642 donors and 3,655 controls were finally included in the study. During 7.3±3.2 years, there were 142 (8.6%) and 253 (6.9%) subjects newly diagnosed with hypertension, respectively. After adjusted such variables showed significance in univariate analysis, kidney donation significantly increased risk for the development of hypertension (adjusted odds ratio [aOR] 1.53, 95% confidence interval [CI] 1.21-1.93). Persistent overweight significantly increased risk for the development of hypertension (aOR 3.53, 95% CI 2.07-6.35 vs. aOR 1.69, 95% CI 1.19-2.43), whereas recovered from overweight did not increase risk (aOR 1.61, 95% CI 0.36-5.1 vs. aOR 0.87, 95% CI 0.35-1.87) in kidney donor and controls, respectively. Exposure to persistent obesity significantly increased the risk for hypertension in both groups, but recovered from obesity still increased the risk in kidney donors (aOR 2.51, 95% CI 1.03-5.45) in contrary to the control (aOR 1.60, 95% CI 0.88-2.76).

Conclusions: Both exposures to overweight or obesity increased the risk for new-onset hypertension, but recovered from overweight or obesity showed different results in donors. Physicians need to be focused on counseling for reducing the modifiable risk factor such as for overweight during the follow-up period.

TH-OR60

A Mate Kidney Analysis to Determine the Impact of Preemptive Transplantation on Outcomes of High Kidney Donor Profile Index Deceased Donor Transplants

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Background: There is an inadequate supply of kidneys for transplant. The kidney donor profile index (KDPI) combines donor factors into a percentile that summarizes the likelihood of deceased donor transplant failure. High KDPI kidneys are frequently discarded. Pre-emptive transplantation is associated with improved patient and graft survival, but it is unknown if this benefit is preserved with high KDPI kidneys.

Methods: Using the SRTR database, N = 7,232 donors were identified where one donor kidney was transplanted pre-emptively (before the recipient required dialysis) and the other was used non-pre-emptively (after the recipient has initiated dialysis). We compared all cause graft loss (ACGL), death censored graft loss (DCGL), and death with function (DWF) between the pre-emptive and non-pre-emptive recipients using univariable and multivariable time to event analyses adjusted for differences in recipient factors.

Results: Pre-emptive transplantation was associated with improved outcomes of ACGL, DCGL, and DWF (Fig 1). These results were consistent in the subgroup where the donor KDPI was >= 91%. Furthermore, the risk of ACGL with a pre-emptive transplant from a KDPI >= 91% donor (HR: 1.65, CI: 1.51 – 1.81) was similar to the risk of ACGL from a non-pre-emptive transplant from a KDPI 51-80% donor (HR: 1.57 CI: 1-48 – 1.66) (Fig 2).

Conclusions: In this mate kidney analysis, outcomes after a pre-emptive transplant were superior compared to a non-pre-emptive transplant, even among kidneys from donors with very high KDPI. Pre-emptive transplantation of high KDPI kidneys is an opportunity to safely increase the number of kidney transplants from the limited supply of deceased donor kidneys.

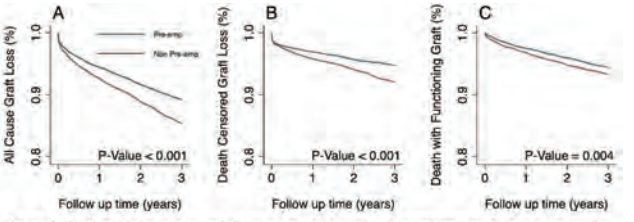

Figure 1: Kaplan-Meier curves of all cause graft loss, death censored graft loss and death with a functioning graft in a mate kidney cohort.

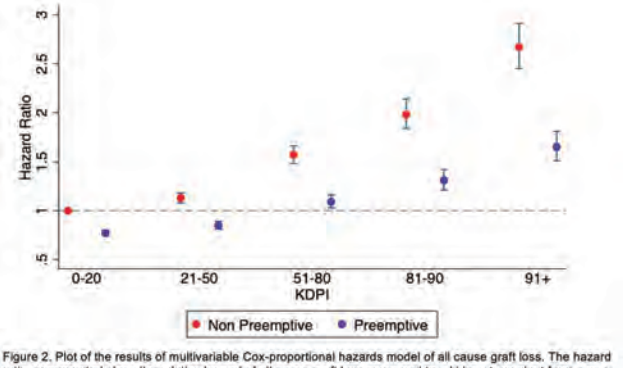

Figure 2. Plot of the results of multivariable Cox-proportional hazards model of all cause graft loss. The hazard ratios represented show the relative hazard of all cause graft loss compared to a kidney transplant from a non-pre-emptive donor with a KDPI of 0-20% (horizontal dotted line). The hazard ratios in blue represent the hazard ratio for a pre-emptive kidney transplant, while the hazard ratios in red represent the hazard ratio for a non-pre-emptive kidney transplant. The 95% confidence intervals are represented by the error bars.

TH-OR61

Quantifying Individual-Level Uncertainty in GFR Estimation

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Background: Although the differences between estimated GFR (eGFR) and measured GFR (mGFR) are well-recognized, the magnitude and potential clinical implications of these differences at the individual level are not fully appreciated.

Methods: Using data from four US community-based cohorts with mGFR (total N=3,223), we calculated eGFR from serum creatinine alone ($eGFR_{CR}$) and cystatin and creatinine ($eGFR_{CYS-CR}$) using the CKD-EPI equations without race coefficients. Using quantile regression, we assessed eGFR's individual-level reliability by calculating a 95% prediction interval (PI), defined as the distribution of 95% of the observed mGFR values at a given eGFR. We also assessed eGFR's population-level reliability using standard metrics, including median difference (eGFR-mGFR). All GFR results are presented as ml/min/1.73m^2.

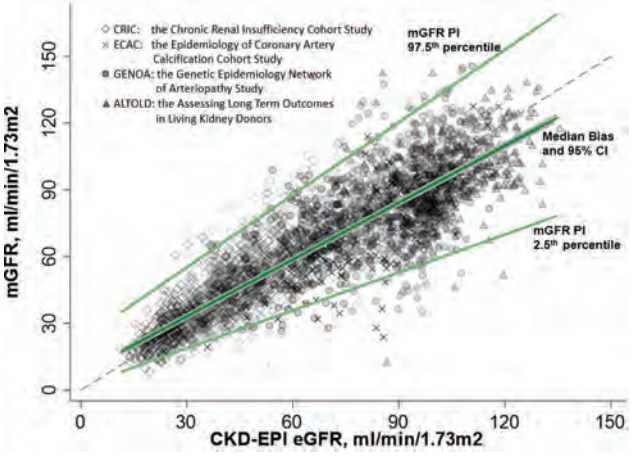
Results: The participants' median age was 61 years, 32% were Black, and 55% were female. The median mGFR was 68 (IQR, 46 to 88). At the population level, the median difference between $eGFR_{CR}$ and mGFR was small (1.4; 95% CI: 0.9 to 1.9). In contrast, the individual-level 95% PI of the $eGFR_{CR}$ was large, ranging from 53 to 120 at $eGFR_{CR}$ 90 and from 19 to 55 at $eGFR_{CR}$ 30 (Figure and Table). Substantial individual misclassification was also noted using $eGFR_{CR}$: 16% of individuals with $eGFR_{CR}$ <60 and 28% of those with $eGFR_{CR}$ <30 had mGFR above those thresholds. Results were similar for $eGFR_{CYS-CR}$.

Conclusions: A substantial individual-level discrepancy exists between eGFR and mGFR. The eGFR PI should be included with eGFR reporting. Some clinical decisions may need to be based on mGFR rather than eGFR.

Funding: Other NIH Support - NINR, NHLBI

Table 1

eGFR, ml/min/1.73 m2	15	20	30	45	60	90	110
95% Confidence Interval (of median)	19, 21	24, 26	32, 34	45, 46	58, 59	83, 85	100, 102
95% Precision Interval (of mGFR)	10, 39	13, 44	19, 55	27, 71	36, 88	53, 120	64, 142



TH-OR62

Kidney Function Biomarkers Among American Indians (AI) and Hispanic Americans (HA)

Monica Moya Balasch, Christos Argyropoulos, Maria-Eleni Roumelioti. *University of New Mexico School of Medicine, Albuquerque, NM.*

Background: The NKF-ASN Task Force recommends that kidney function be estimated by an approach that is accurate introducing bias through racial adjustments. Use of multiple biomarkers may offer such an approach which we explored in a prospective community cohort of HA and AI in rural New Mexico.

Methods: Markers of kidney function, IDMS-Creatinine (SCr), chemiluminescence Beta-2 Microglobulin (B2M), Nephelometry-calibrated ELISA Cystatin C (CysC), inflammation, glucose tolerance, demographics, BUN/UACR from the baseline visit of the COMPASS cohort (PMID: 29486722), were analyzed by kernel-based machine learning methods.

Results: Cohort consisted of 172 individuals, 61% female, 30.2% AI, 54.7% HA, age 51.1 ± 18, SBP/BP 128 ±14.4/77.4 ± 11.5 mmHg, Height 1.7 ±0.1m, Weight 83 ± 20 kg, BUN 14±5 mg/dl, SCr 0.9 ±0.3 mg/dl, B2M 1.8 ± 0.5 mg/L, CysC 0.7 ± 0.2 mg/dl, UACR 43.8 ± 231 mg/g, hs-CRP 4.8 ± 6.7 mg/L, HbA1c ± 1.7 %. B2M was not associated with race/ethnicity/anthropometrics. CysC had the most non-kidney determinants [Table]. 75% of all log10 transformed values culustered together [Figure, yellow]. Ethnicity (p=0.02), HbA1c (p=0.03), hs-CRP (p=0.04) predicted discordance among the biomarkers (mauve).

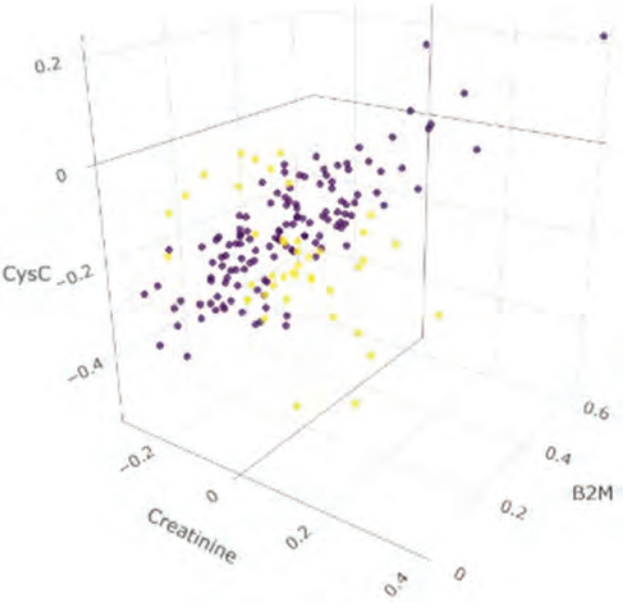
Conclusions: Ethnicity, inflammation and diabetes increase discordance among kidney biomarkers. B2M was affected the least and should be strongly considered as a measure fulfilling the criteria for the NKF-ASN because its eGFR equation does not need adjustment for race or sex(PMID: 26362696)

Funding: Other NIH Support - CTSC Grant Number: UL1TR001449, Commercial Support - Dialysis Clinic Incorporated

Predictors of kidney biomarkers

	Age	Sex	Ethnicity (HI)	Race (AI)	Albumin (serum)	UACR	BUN	SBP	Weight x Height x Gender response surface
SCr	0.99	0.44	0.33	0.03	0.13	0.90	<10^-10	0.001	0.02
B2M	0.01	0.88	0.78	0.21	0.03	0.57	10^-3	0.01	0.66
CysC	0.02	0.85	0.04	0.74	0.80	0.02	0.001	0.04	10^-4

p-values (ANOVA) from null-space kernel regression. DBP & hs-CRP were not predictive of any biomarker



TH-OR63

Decline in Estimated Glomerular Filtration Rate (eGFR) Among Black Veterans After Removing the Race Coefficient: Results of the US Veterans Health Administration Electronic Health Records

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Background: In the US, Black Americans with CKD have faster kidney function decline than White peers. We examined whether this faster decline was also observed when the race coefficient was removed from eGFR calculation among US veterans.

Methods: eGFRs were calculated from serum creatinine measurements (excluding acute care settings) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) and the CKD-EPI without the race coefficient (CKD-EPI-RACEout). We estimated eGFR slopes using quarterly averages of eGFRs for up to 8 years or until May 31, 2018 starting from the first quarter after CKD incidence (i.e., first eGFR<60 mL/min/1.73m^2 for >3 months). We used linear mixed-effects models with random intercept and slope, adjusting for age, sex, eGFR at CKD incidence, and CKD incidence year.

Results: From 2003-2017, 139,921 Black veterans had incident CKD defined by CKD-EPI-RACEout and 100,510 by CKD-EPI; and 636,598 White veterans by CKD-EPI, with median number of quarterly averages of eGFRs per patient of 8, 8, and 7, respectively. Overall, eGFR decline was greater among Blacks defined by CKD-EPI than Whites (-1.37 vs -0.84 mL/min/1.73m^2 per year, Table), consistent with prior findings. eGFR decline among Blacks by CKD-EPI-RACEout was attenuated (-1.07), but still greater than among Whites. In the two youngest groups, Blacks by CKD-EPI-RACEout still had about 2-fold larger decline versus Whites (Table).

Conclusions: Black veterans with CKD defined by eGFR without race coefficient still had faster kidney function decline following CKD incidence compared to White veterans, but the difference was attenuated. Use of eGFR without race coefficient may pick up earlier, less aggressive cases of CKD among younger Blacks and promote earlier prevention.

Funding: NIDDK Support

Slopes as eGFR decline per year (95% CI) with CKD-EPI with and without race coefficient

	Black, eGFR defined by CKD-EPI	Black, eGFR defined by CKD-EPI without race coefficient	White
Overall	-1.37 (-1.40, -1.35)	-1.07 (-1.09, -1.06)	-0.84 (-0.85, -0.83)
Age 18-45	-2.45 (-2.66, -2.25)	-1.26 (-1.38, -1.15)	-0.59 (-0.74, -0.45)
Age 46-55	-1.92 (-1.99, -1.85)	-1.16 (-1.20, -1.11)	-0.60 (-0.64, -0.55)
Age 56-65	-1.47 (-1.52, -1.44)	-1.10 (-1.13, -1.07)	-0.73 (-0.75, -0.71)
Age 66-75	-1.18 (-1.21, -1.14)	-1.04 (-1.07, -1.00)	-0.84 (-0.86, -0.83)
Age 76-85	-0.97 (-1.01, -0.92)	-0.92 (-0.96, -0.87)	-0.93 (-0.94, -0.91)
Age 86-100	-0.82 (-0.94, -0.71)	-0.82 (-0.95, -0.67)	-1.00 (-1.04, -0.97)

TH-OR64

Race, Genetic Ancestry, and GFR Estimation: Findings from the CRIC Study

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CRIC *[1]University of California San Francisco, San Francisco, CA; [2]Tulane University, New Orleans, LA; [3]Johns Hopkins University School of Medicine, Baltimore, MD; [4]Kaiser Permanente Northern California, Oakland, CA; [5]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [6]University of Illinois at Chicago, Chicago, IL; [7]The University of Mississippi Medical Center, Jackson, MS; [8]Boston University School of Medicine, Boston, MA; [9]Wayne State University, Detroit, MI; [10]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [11]The University of Chicago Medicine, Chicago, IL; [12]Duke University, Durham, NC.*

Background: Inclusion of race in GFR estimating equations is undesirable. Prior studies have not examined replacing race with genetic ancestry.

Methods: We studied 1248 Chronic Renal Insufficiency Cohort (CRIC) Study participants with urinary ^{125}I-iothalamate clearance GFR (iGFR) measurements and complete data on self-reported race, genetic ancestry, serum creatinine (SCr) & cystatin C. Genotyping was conducted using the Illumina HumanOmni1-Quad v1.0 microarray. The cohort was split into development (2/3) and validation (1/3) samples. Using linear regression, we derived GFR estimating equations for iGFR using SCr or cystatin C, age, sex, and self-reported race or African ancestry. The derived equations were then applied to the validation sample. Equation performance was assessed using root mean squared error (RMSE), adjusted R^2, bias (iGFR - eGFR), and proportion of eGFR within 10% (P10) and 30% (P30) of iGFR.

Results: 539 participants were female and 458 self-identified as Black. Mean±SD age was 55.9±12.1 yr, iGFR 48±20 ml/min/1.73m^2, median [IQR] SCr was 1.5 [1.3-2.0] mg/dL, cystatin C 1.35 [1.09-1.71] mg/L. Median % African ancestry was 82.6% [74.5-88.3%] among those who self-identified as Black and 0.2% [0.1-2.0%] in those who did not. When using SCr to estimate GFR, incorporating vs omitting self-reported race yielded better performing estimates (**Table**). Incorporating genetic ancestry provided estimates of GFR similar to those incorporating self-reported race. Incorporation of race or ancestry was unnecessary when estimating GFR using cystatin C. A GFR estimating equation using cystatin C, age and sex performed comparably to an equation using SCr, age, sex, and race or ancestry.

Conclusions: Switching from SCr to cystatin C to estimate GFR yields comparably valid without needing to include either race or genetic ancestry.

Funding: NIDDK Support

Model for iGFR	RMSE	Adjusted R2	Median (IQR) Bias, mL/min/1.73m2 (iGFR - eGFR)		P30		P10		% Higher iGFR (95% CI)
			Black	Non-Black	Black	Non-Black	Black	Non-Black	
SCr, age, sex	11.39	0.667	3.99 (-1.90, 10.13)	-0.91 (-7.17, 6.05)	86	81	31	34	
SCr, age, sex, race	11.22	0.677	1.11 (-4.48, 6.73)	1.01 (-5.16, 7.81)	86	82	42	37	13.6 (9.9 to 17.3)% if Black vs. non-Black race
SCr, age, sex, % African ancestry	11.21	0.678	1.33 (-4.98, 6.18)	1.07 (-5.30, 7.78)	86	83	42	37	1.6 (1.2 to 2.1)% per 10% higher African ancestry
Cystatin C, age, sex	10.76	0.704	0.33 (-4.50, 6.53)	0.29 (-4.69, 6.91)	85	83	41	39	
Cystatin C, age, sex, race	10.76	0.703	0.85 (-3.98, 6.92)	0.03 (-4.99, 6.71)	85	83	42	39	-1.6 (-4.7% to 1.4)% if Black vs. non-Black race
Cystatin C, age, sex, % African ancestry	10.75	0.704	0.90 (-4.05, 6.74)	0.04 (-4.97, 6.72)	85	83	42	39	-0.2 (-0.6% to 0.2)% per 10% higher African ancestry

TH-OR65

Comparison of Estimated Glomerular Filtration Rate with and Without Race Adjustment on Associations with ESRD: The CRIC Study

Joshua D. Bundy,[1] Katherine T. Mills,[1] Amanda H. Anderson,[1] Wei Yang,[2] L. Lee Hamm,[3] Jing Chen,[1,3] Jiang He.[1,3] *[1]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]Tulane University School of Medicine, New Orleans, LA.*

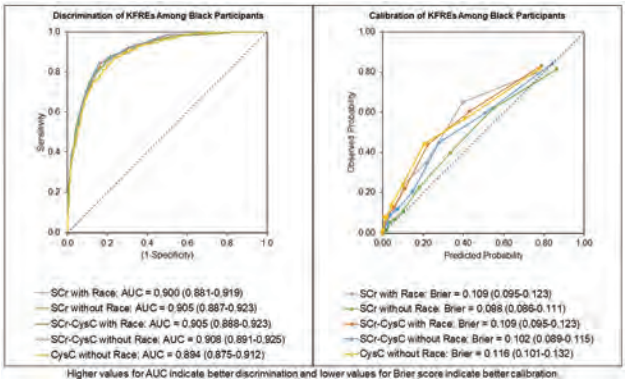
Background: Lower estimated glomerular filtration rate (eGFR) is strongly associated with higher risk of end-stage renal disease (ESRD). eGFR equations typically include adjustment for Black race, but this practice is controversial and the impact of its removal on associations with ESRD are unknown.

Methods: We included 3786 participants (mean age 57.8 years; 45.2% women; 41.8% Black) from the CRIC Study. ESRD was defined as initiation of dialysis or transplantation. We evaluated five CKD-EPI equations for calculating eGFR based on serum creatinine (SCr), cystatin C (CysC), and with or without race adjustment. We estimated associations and predictions of 5-year ESRD risk using Cox proportional hazards regression and the 4-variable Kidney Failure Risk Equation (KFRE), which includes age, sex, eGFR, and urinary albumin-to-creatinine ratio. Models were evaluated using measures of discrimination (AUC) and calibration (Brier score).

Results: Within 5 years after baseline, 642 participants developed ESRD and the cumulative incidence among Black and white/other participants was 22.5% and 15.4%, respectively. Across all eGFR equations, the KFRE was superior for prediction of 5-year risk of ESRD compared with eGFR alone among all participants (AUC range, 0.899-0.915 vs. 0.816-0.837 for eGFR alone; P<0.001). Among Black participants, the KFRE using creatinine-based eGFR without race adjustment improved calibration compared with the other equations (Figure).

Conclusions: The KFRE has superior discrimination for 5-year risk of ESRD compared with eGFR alone, regardless of whether race adjustment is employed. Removing the race adjustment for the creatinine-based CKD-EPI equation may improve prediction of 5-year risk of ESRD.

Funding: NIDDK Support



TH-OR66

How Removing the Race Coefficient from eGFR Equations Impacts Racial Differences in CKD Progression Among People with HIV

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NA-ACCORD *[1]University of California San Francisco, San Francisco, CA; [2]Northern California Institute for Research and Education, San Francisco, CA.*

Background: The impact of removing the race coefficient from eGFR equations on racial differences in CKD progression in people with HIV (PWH) is unknown.

Methods: We included 69,125 PWH enrolled in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) from Jan 1, 2005-Dec 31,2014. Baseline date was defined as the date of enrollment in NA-ACCORD or beginning of cohort eGFR observation window, whichever came last. Reported race was categorized as Black, White, or Other. We defined CKD stages in 2 ways: 1) Serum creatinine-based CKD-EPI eGFR equation, which assigns higher eGFR for Black persons; and 2) CKD-EPI eGFR without the race coefficient. We created Markov models to estimate 5-year probabilities of transitioning from the initial stage to worse CKD stages, with death as a competing event; the associations of race (Black vs White) with progression across CKD stages were evaluated.

Results: 31,298 PWH were Black, in whom baseline antiretroviral use and HIV suppression were less prevalent and hepatitis C infection, hypertension and diabetes were more prevalent compared with White participants (N=27,542). eGFR without the race coefficient reclassified 25% of Black PWH into a worse CKD stage at baseline. Those reclassified had a higher prevalence of CKD risk factors compared with Black PWH who were not reclassified. When modeled with the race coefficient, Black PWH had 23% lower risk of progressing from CKD stage 1 to 2, similar risk of progressing from stage 2 to 3 and 3-fold increased risk of progressing from stage 3 to 4, compared with White PWH. When CKD progression was modeled using race-free eGFR, Black PWH consistently had a higher risk of CKD progression compared with White PWH **(Table).**

Conclusions: Prior studies suggesting that Black PWH have lower risk than White individuals for early CKD progression but higher risk at later stages were likely biased by the race coefficient. Assigning higher kidney function for all Black individuals based on race systematically masks a subgroup of Black PWH who are at higher risk of CKD progression.

Funding: NIDDK Support

CKD progression	With Race Coefficient Hazard Ratio (95% CI)	Without Race Coefficient Hazard Ratio (95% CI)
Stage 1 to 2	0.77 (0.73,0.82)	1.26 (1.20,1.33)
Stage 2 to 3	0.99 (0.92,1.07)	1.08 (1.01,1.16)
Stage 3 to 4	2.93 (2.50,3.44)	1.61 (1.36,1.88)

Hazard ratio adjusted for calendar period (2005-2009 and 2010-2015), age, sex, History of AIDS, Hepatitis C, Diabetes, Hypertension, Cardiovascular disease, baseline viral load, and baseline eGFR.

TH-OR67

GFR in the Era of Precision Medicine: The Importance of a Measured GFR in Onco-Nephrology

Francesco Trevisani,[1] Giulia Pegoraro,[2] Daniele Pugno,[2] Giulia Quattrini,[1] Federico Di marco,[1] Alessandra Cinque,[1] Arianna Bettiga,[1] Umberto Capitanio,[1] Andrea Salonia,[1] Giorgio Pizzagalli,[1] Francesco Montorsi.[1] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Biorek S.R.L., Milano, Italy.*

Background: An accurate assessment of renal function in nephrological patients (pts) is of paramount importance Unfortunately, the most used method to measure GFR is represented by the estimated GFR(eGFR) which harbours a significant error in comparison to gold standards(mGFR). Aim of this study was to determine the extent of the error of eGFR compared to the mGFR in onco-nephrological pts.

Methods: A total consecutive cohort of 200 pts was collected to compare the eGFR formulas (MDRD, CKD-EPI 2012) with mGFR method(Iohexol Plasma Clearance). Cohort composition: 116 oncological pts(cases) and 84 functional diseases pts(controls) matched for baseline variables. The agreement between eGFR and mGFR was evaluated using bias, precision, accuracy, and total deviation index. The differences between cohorts were evaluated with Fisher's exact test and Chi-squared test and Wilcoxon rank sum test for continuous variables.

Results: Clinical data are reported in Table 1. The two matched cohorts displayed no statistical differences in term of clinical variables and agreement parameters(TDI, CCC and P30). Surprisingly, both groups harboured a non negligible errors in each CKD class with a huge discrepancy between the eGFR formulas and the gold standard method (Figure 1, 2), suggesting the great relevance of mGFR in the clinical decision making algorithm, both with two and one kidney.

Conclusions: The error in the classification of CKD stages using eGFR by formulas was too common in case and controls, with a poor agreement with mGFR in all CKD classes. The use of mGFR should be mandatory to obtain a tailored management in onco-nephrology.

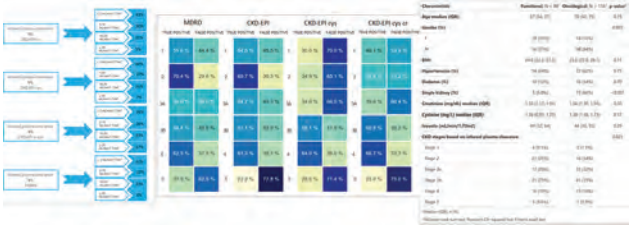

Figure on the left represent the percentages of pts with four different intervals of error. Figure on the right represent the classification of pts in CKD stages by eGFR. True positive represent subjects that were correctly classified from eGFR and false positive represent the cases that were not classified in the corresponding class. Table shows the clinical data of the population divided in two cohorts: functional and oncological pts.

TH-OR68

The Effect of Age on Performance of the Kidney Failure Risk Equation in Advanced CKD

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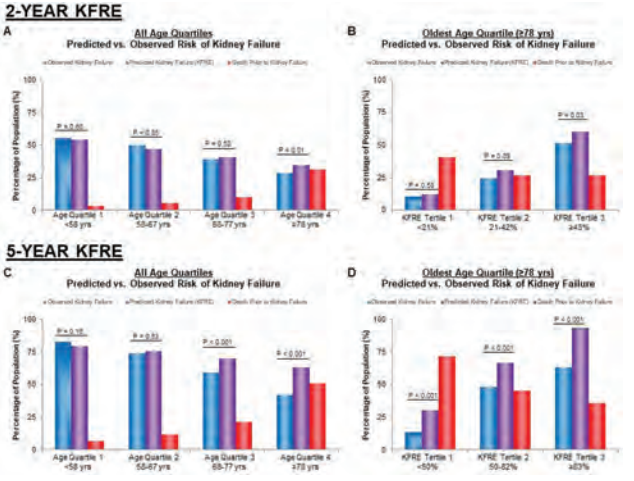
Background: The Kidney Failure Risk Equation (KFRE) is a validated clinical tool used to predict progression from CKD to kidney failure. Concerns over risk overestimation have been raised with prediction models, such as the KFRE, where death is not treated as a competing event. Herein, we evaluated the effect of age (with which the competing risk of death would be anticipated to increase) on KFRE performance in advanced CKD.

Methods: All patients referred to the advanced CKD clinic at the Ottawa Hospital from 2010-2018 were divided into age quartiles: <58, 58-67, 68-77, and ≥78 years. Predicted vs observed rates of kidney failure were compared over 2- and 5-years. Predictive performance of the KFRE was determined by ROC curves (discrimination) and calibration plots. Cumulative incidence of kidney failure was compared between models that accounted for the competing risk of death and those that did not.

Results: The mean (SD) age and eGFR were 66 (15) years and 17 (6) mL/min/1.73m^2. The median (IQR) 2- and 5-year KFRE scores were 41% (22-64%) and 81% (55-96%), respectively. The KFRE overestimated the risk of kidney failure among the oldest age quartile (≥78 years) with absolute differences of 5.8% (P=0.01) and 21.6% (P<0.001) between predicted and observed risks over 2- and 5-years, respectively. The 2-year KFRE discrimination was reduced among patients ≥78 years compared with patients 58-67 years (P=0.03) and 68-77 years (P=0.03) though the difference was non-significant when compared with patients <58 years (P=0.06). The KFRE displayed adequate calibration across all age quartiles. The cumulative incidence of kidney failure was overestimated in models that did not account for the competing risk of death and this overestimation was more prominent with older age.

Conclusions: In older patients with advanced CKD at high risk of kidney failure, the KFRE overestimates risk and this overestimation relates to the increasing competing risk of death with older age.



TH-OR69

A Prediction Equation for Incident CKD Using Routinely Collected Data: The Kidney Disease Risk Equation (KDRE)

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Background: The identification of individuals at risk for incident CKD (eGFR < 60 ml/min, stage 3a) is an important first step for disease surveillance, monitoring, education and allocation of key therapies to reduce CKD progression. Despite recommendations, albuminuria measurements in appropriate individuals remains poor. As such, we set out to develop and validate a prediction equation for new onset CKD with and without an albumin creatine ratio (ACR).

Methods: Population-level administrative data cohort of 1,109,905 adults (>66 years old) from Ontario, Canada April 1, 2008 and December 31, 2017 with a minimum of 2 eGFR measures (one for baseline > 70 ml/min, one for outcome) were included. Prediction equations stratifying individuals with (n=191,690) and without (n=998,825) ACR were derived, internally validated by bootstrapping and externally validated in 122,144 (22,809 ACR, 99,335 non-ACR) individuals in Manitoba, Canada. The study outcome was a single eGFR measure < 60 mls/min/1.73 m^2 with up to 10 years follow-up. In additional analyses, we examined two eGFR measures < 60 mls/min and a single eGFR < 45 ml/min as study outcomes.

Results: Among individuals (54.5% women, mean age 64 SD 7, mean baseline eGFR 82 SD 8, median ACR 1 IQR 1-3), an eGFR < 60 ml/min occurred in 37.2% during the follow-up. The final model including up to 6 variables (age, sex, baseline eGFR, hemoglobin, time from hypertension and diabetes mellitus diagnosis) yielded a 5-year c-statistics of 0.77 (no ACR) and 0.78 (with ACR) with excellent calibration. Model performance was similar in additional analyses and in an external validation.

Conclusions: An equation incorporating readily available and routinely collected administrative data variables can accurately predict the onset of CKD with or without ACR.

TH-OR70

Tubular Secretion of Creatinine and Clinical Outcomes: The AASK Trial

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Background: Tubular secretion is a critical kidney function that is not routinely assessed. We evaluated the association of tubular secretion of creatinine calculated using the difference between either measured glomerular filtration rate (mGFR) or estimated GFR (eGFR) and 24-hour urine creatinine clearance (CrCl) with long-term clinical outcomes.

Methods: This prospective analysis of the African American Study of Kidney Disease (AASK) included 999 participants with baseline measures of iothalamate mGFR, creatinine based eGFR and 24-hour urine CrCl. Tubular secretion of creatinine was calculated in two ways as the difference between 1) CrCl and mGFR (mTS_{cr}); and 2) CrCl and eGFR (eTS_{cr}). The associations between mTS_{cr} and eTS_{cr} with incident end-stage kidney disease (ESKD) and cardiovascular disease (CVD) and all-cause mortality were evaluated using Cox regression.

Results: At baseline, the mean mGFR was 45.3 ml/min/1.73 m^2, and the mean CrCl was 49.3 ml/min/1.73 m^2. The mean (SD) mTS_{cr} and eTS_{cr} were 4.0 (14) and 6.5 (14) ml/min/1.73/m^2 respectively. Over 4.2 years of follow up there were 149 ESKD, 82 all-cause mortality, and 132 incident CVD events. Each 10 ml higher mTS_{cr} (HR 0.73, 95% CI 0.58-0.93) and each 10 ml higher eTS_{cr} (HR 0.59, 95% CI 0.44, 0.79) were associated with lower risk of ESKD, after adjustment for mGFR or eGFR, proteinuria, and other potential confounding factors (Table). Associations between mTS_{cr} or eTS_{cr} with lower risk of all-cause mortality or CVD events were not detected.

Conclusions: eTScr provides a measure of creatinine secretion similar to mTScr and is strongly associated with risk of ESKD, independent of GFR, proteinuria, or other risk factors. This allows for the incorporation of eTScr into epidemiological studies which may not have collected mGFR.

Funding: NIDDK Support

Multivariable Association of mTScr and eTScr with End-Stage Kidney Disease

	Events (N)	HR, 95% CI Model 1	HR, 95% CI Model 2	HR, 95% CI Model 3	HR, 95% CI Model 4
	mTScr and End-Stage Kidney Disease				
Per 10ml higher	149	0.9 (0.8, 1), 0.055	0.92 (0.82, 1.03),	0.93 (0.83, 1.04),	**0.73 (0.58, 0.93)**
Q1	29	3.17 (1.6, 6.29),	3.01 (1.51, 5.98),	2.97 (1.49, 5.91),	1.77 (0.86, 3.61),
Q2	66	5.73 (3.01, 10.92),	5.48 (2.86, 10.47),	5.66 (2.95, 10.86),	1.04 (0.52, 2.09),
Q3	41	4.69 (2.44, 9.04),	4.72 (2.45, 9.11),	5 (2.59, 9.68), 0	0.76 (0.37, 1.54),
Q4	12	Ref	Ref	Ref	Ref
	eTScr and End-Stage Kidney Disease				
Per 10ml higher	149	**0.89 (0.79, 0.99),**	0.91 (0.81, 1.02),	0.91 (0.82, 1.02),	**0.59 (0.44, 0.79), 0**
Q1	29	1.83 (0.97, 3.46),	1.72 (0.91, 3.27),	1.7 (0.89, 3.23),	1.9 (0.79, 4.57),
Q2	66	4.87 (2.77, 8.55),	4.59 (2.6, 8.1), 0	4.92 (2.77, 8.72),	1.27 (0.59, 2.75),
Q3	41	3.15 (1.76, 5.66),	3 (1.67, 5.4), 0	3.16 (1.75, 5.72),	0.67 (0.31, 1.48),
Q4	12	Ref	Ref	Ref	Ref

Model 1: unadjusted, Model 2: adjusted for age, sex, BMI, randomization arm, Model 3: Model 2+ smoking, CVD, systolic BP, antihypertensive medications
Model 4: Model 3+ urine protein/creatinine + baseline mGFR
mTScr: Tubular secretion of creatinine using measured glomerular filtration rate (mGFR)

FR-OR01

Role of Off-Target Ferrochelatase Inhibition in Vemurafenib Nephrotoxicity

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Background: Complications linked with both cancer and anti-cancer therapeutics can trigger kidney injury. For targeted anti-cancer therapeutics, nephrotoxicity may occur because of on- or off- target mechanisms. In melanoma and other cancers with BRAF kinase activating mutations, targeted small molecule therapeutics such as vemurafenib, and dabrafenib have shown remarkable clinical benefits. However, recent clinical studies have shown that a significant number of patients that receive vemurafenib develop AKI through mechanisms that remain unknown. Here we have developed cell culture and murine models of vemurafenib nephrotoxicity to understand the causal mechanisms.

Methods: We established a murine model of vemurafenib toxicity through oral administration of 20 mg/kg vemurafenib in C57B6/J mice. We confirmed kidney damage and toxicity in these mice through measurement of blood urea nitrogen, serum creatinine, histological analysis, and TUNEL staining. Using the GGT-Cre strain we have also generated BRAF conditional knockout mice. To understand the role of ferrochelatase we used a hydrodynamic siRNA injection approach or heterozygous (+/fch) mutant mice. Control and gene knockout mice were treated with vemurafenib to examine the role of BRAF and FECH in vemurafenib nephrotoxicity.

Results: We found that BRAF gene deletion in tubular epithelial cells had no influence on vemurafenib-associated AKI. Instead, we found that inhibition of ferrochelatase (FECH), an enzyme involved in heme biosynthesis contributes to vemurafenib nephrotoxicity. FECH overexpression mitigated and conversely FECH knockdown increased the sensitivity to vemurafenib nephrotoxicity.

Conclusions: In the present study, we demonstrate that the mechanism for vemurafenib nephrotoxicity is not through the BRAF kinase inhibition, but instead occurs through off-target inhibition of FECH. Furthermore, these findings suggest that along with vemurafenib, other drugs that inhibit FECH activity might cause nephrotoxicity. Together, the present study describes the development of novel experimental models of vemurafenib nephrotoxicity and reveals the underlying off-target mechanisms that contribute to renal injury.

Funding: Other NIH Support - NCI

FR-OR02

Kidney Tubule Polyploidization Is an Evolutionary Conserved Mechanism Required to Survive AKI

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Background: Acute Kidney Injury (AKI) is characterized by a rapid deterioration of kidney function. Recently, we showed that tubular epithelial cells (TEC) respond to AKI by triggering polyploidy, a condition in which a normally diploid cell acquires additional sets of chromosomes. Polyploidy offers several advantages, but in the kidney the biological significance of polyploidization remains unclear. In this study we hypothesized that polyploidy 1) is the predominant cellular response during AKI and 2) is an adaptive stress response required to maintain a residual kidney function to assure survival.

Methods: To address these hypotheses, we employed in vivo transgenic models based on the Confetti reporter and the Fluorescence Ubiquitin Cell Cycle Indicator (FUCCI) technology in combination with YAP1 downregulation. Mice were subjected to unilateral ischemia reperfusion injury (IRI) or glycerol-induced rhabdomyolysis to induce AKI. Polyploid cells have been then characterized by single cell-RNA sequencing analysis, cell sorting, FACS analysis, super-resolution and transmission electron microscopy.

Results: After AKI, YAP1 is activated driving TEC polyploidization. Polyploid TEC increase in parallel to massive cell death triggered by AKI suggesting that polyploidization could be a means to escape cell death. Indeed, we found that polyploid TEC tend to accumulate genome instability and survive, while diploid TEC do not. Of note, virtually all dying cells were cycling cells based on the FUCCI reporter suggesting that TEC death occurred during the S or G2/M phase. As polyploid TEC increase immediately following AKI, they may be required to survive injury and damage by sustaining renal function. In order to evaluate the functional role of polyploid cells during AKI, we generated YAP1*ko* mice, where YAP1 is knocked-out specifically in TEC. Indeed, after AKI, YAP1*ko* mice showed a reduced number of polyploid cells, worsened kidney function and a dramatic reduction of mouse survival, proving that polyploidization is required to survive AKI.

Conclusions: In conclusion, we demonstrated that after AKI: 1) TEC accumulate genome instability and die or become polyploidy; 2) TEC polyploidy is essential to preserve residual kidney function allowing survival.

FR-OR03

Single-Cell and Spatial Transcriptomics Reveal Distinct Subpopulations of Kidney Resident Macrophages in AKI

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Background: Macrophages are important in renal homeostasis and the response to acute kidney injury (AKI). Kidney resident macrophages (KRMs) are a unique, self-renewing $F4/80^{Hi}CD11b^{Int}$ population that originate from the fetal yolk sac and fetal liver during embryogenesis. Preliminary data suggests that the KRM population consists of a number of undescribed subpopulations with distinct functions, but the transcriptional signatures and spatial organization of these subsets in the kidney tissue remain unknown. Here, we combined scRNAseq and spatial transcriptomics to identify and localize KRM subpopulations during homeostasis and injury.

Methods: Fluorescence activated cell sorting was used to isolate KRMs from C57BL/6J mice without treatment and at one and six days after bilateral ischemia-reperfusion injury (BIRI). Single-cell RNA sequencing was performed using the 10X Genomics platform. For spatial transcriptomics, kidney sections were placed on 10X Visium Spatial Gene Expression slides, imaged, and then sequenced. scRNAseq and spatial gene expression data were integrated and analyzed using the R package, Seurat 4.0.

Results: UMAP plots of integrated data from injured and control mice revealed 6 major clusters of KRMs with unique transcriptional profiles. Spatial transcriptomics revealed that these clusters reside in distinct cellular compartments within the kidney. Following IRI, these subpopulations appear in cellular compartments distinct from those occupied in the controls. Gene ontology analysis (Biologic Process) indicated that the largest subpopulations changing location expressed transcripts associated with locomotion and chemotaxis. It also indicated that the transcriptomic profiles of each subpopulation were associated with distinct functions.

Conclusions: Transcriptionally distinct subpopulations of KRMs reside within specific kidney microenvironments and change location as a function of injury. Gene expression data suggests that they are physically migrating from one compartment to another. This indicates that resident macrophages in the kidney are not static with respect to transcriptional profiles and location. Therefore, further study of the temporal and spatial characteristics and signaling pathways of these subpopulations in the context of homeostasis and injury is warranted.

Funding: NIDDK Support, Other NIH Support - NIGMS T32-GM008361, Veterans Affairs Support

FR-OR04

Proximal Tubule Pannexin 1 Channel Regulates Mitochondrial Function and Cell Death During AKI

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Background: Pannexin 1 (Panx1) channel serves as a conduit for release of small metabolites upon activation during cellular stress and injury. We have previously shown that pharmacological inhibition or genetic deletion of *Panx1* in mice prior to injury is protective against renal ischemia-reperfusion injury (IRI). How Panx1 contributes to acute kidney injury (AKI) is unknown. We hypothesized that Panx1 induces cell death by mediating both intracellular and extracellular events.

Methods: We performed IRI or cisplatin-induced AKI in a novel human Panx1 overexpressing mouse (*hPANX1*-Tg) and in proximal tubule specific Panx1 overexpressing mice (*hPANX1-Tg*^{PTEC}) and assessed plasma creatinine, renal expression of neutrophil gelatin associated lipocalin (*Ngal*), and acute tubular necrosis scoring. We challenged *PANX1* overexpressing murine proximal tubule-derived TKPTS cells with cisplatin and assessed cell death and mitochondrial changes. We next assessed the changes in mitochondria of kidneys from cisplatin challenged *hPANX1-Tg* animals.

Results: *hPANX1-Tg* mice had significant rise in plasma creatinine and expression of *Ngal* in the kidneys in both models of AKI compared to their littermate controls. Proximal tubule specific overexpression of hPANX1 also resulted in overt injury following IRI or cisplatin-induced AKI compared to littermate controls. *In vitro* studies showed that overexpression of PANX1 in TKPTS cells resulted in significantly higher cell death compared to controls during cisplatin challenge, which was associated with reduced mitochondrial biogenesis, mitochondrial function, increased mitochondrial ROS production, and altered mitochondrial quality control. Assessment of mitochondria in kidneys showed a significant reduction in Drp1 levels in kidneys from *hPANX1-Tg animals* compared to littermate controls after cisplatin challenge.

Conclusions: PANX1 overexpression results in overt renal injury during AKI that is in part mediated by reduced mitochondrial function and quality control in proximal tubules that facilitates proximal tubule cell death. These results provide strong rationale for the development of selective strategies to inhibit Panx1 in the prevention or treatment of AKI.

Funding: NIDDK Support, Private Foundation Support

FR-OR05

The Long Noncoding RNA GSTM3P1 Is Induced to Exacerbate Ischemic AKI by Antagonizing MicroRNA-668

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Background: Long non-coding RNAs (lncRNAs) are a group of epigenetic regulators that may play important roles in kidney diseases, but the specific LncRNAs involved and the underlying mechanisms are poorly understood. We recently unveiled miR-668 as a potent protective microRNA in ischemic AKI (Wei Q et al. J Clin Invest 128:5448, 2018). By deep sequencing of mir-668-induced silencing complex, we have identified GSTM3P1, a lncRNA, as a potential interactor and regulator of mir-668.

Methods: The expression of GSTM3P1 and its mouse homologue gstm2-ps1 were examined in hypoxia-treated HK2 cells and in mouse kidneys after ischemic AKI. GSTM3P1 was overexpressed in renal cells for functional examination. Proximal tubule-specific gstm2-ps1 knockout mouse model was established to test its role in ischemic AKI in vivo.

Results: GSTM3P1/gstm2-ps1 was markedly induced in the early phase of ischemic AKI models both in vitro and in vivo. In HK2 cells, qPCR indicated a significant increase of GSTM3P1 at 3 hours after 1% O_2 treatment. In C57BL/6 mice, gstm2-ps1 was significantly induced in kidneys after 30 minutes of ischemia and 3 hours of reperfusion, which was also accompanied with the suppression of mir-668. In vitro, overexpression of GSTM3P1 led to more renal proximal tubular cell death after ATP depletion. GSTM3P1 overexpression in HEK cells caused significant decrease of the mature form of mir-668. A mir-668 binding site in GSTM3P1 was also confirmed by luciferase assay. We further generated kidney proximal tubule-specific gstm2-ps1 knockout (KO) mouse model. Compared to wild type littermates (WT), the conditional gstm2-ps1 KO mice were significantly protected from renal ischemia-reperfusion injury. Both blood urea nitrogen level [268.18±47.97 mg/dL (WT) vs 174.42±28.65 mg/dL (KO)] and the serum creatinine level [2.45±0.36 mg/dL (WT) vs 1.41±0.27 mg/dL (KO)] were remarkably decreased. Consistently, renal tubular damage and apoptosis were significantly suppressed in KO kidneys. KO kidneys also had lower tubular NGAL.

Conclusions: These results indicate that GSTM3P1/gstm2-ps1 is induced in ischemic AKI, and following induction it mediates tubular cell injury and death by interacting and antagonizing mir-668.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR06

Novel Immune Checkpoint Molecule TIGIT Is Upregulated on Kidney CD4 T Cells and Mediates AKI in Mice

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Background: T cells play important roles in acute kidney injury (AKI) but the molecular mechanisms are largely unknown. Our unbiased RNAseq analysis initially demonstrated increased mRNA expression of novel immune checkpoint molecule T cell immunoreceptor with Ig and ITIM domains (TIGIT) on kidney CD4 T cells after AKI. Here, we validated TIGIT expression on kidney T cells at protein level and investigated its effect on kidney T cell activation, function and AKI outcome.

Methods: C57BL/6J wild type (WT) mice underwent bilateral ischemia reperfusion (IR). TIGIT expression and effect on kidney T cell activation and cytokine expression was studied at baseline and after IR injury by flow cytometry in WT mice. TIGIT knockout (TIGIT KO) mice were used to assess effects on AKI. Human kidney at baseline and post ischemia for nephrectomy had CD4 TIGIT measured by flow cytometry.

Results: TIGIT expression increased significantly ($p<0.001$) on CD4 T cells in post IR kidneys compared to controls (15.0±1.5% vs 3.8±0.2%). Furthermore, TIGIT+ CD4 T cells from WT kidneys showed significantly increased expression of activation markers, CD25 (10.9±1.7% vs 2.4±0.2%, $p<0.001$), CD69 (14.5±1.4% vs 8.8±1.0%, $p<0.01$) and CD44 (93.9±1.5% vs 74.5±1.7%, $p<0.001$) compared to TIGIT- CD4 T cells. Intracellular cytokine analysis showed significantly increased IFNγ (50.4±3.4% vs 20.3±3.3%, $p<0.001$) and TNFα (55.7±5.0% vs 35.4±4.9%, $p<0.02$) expression by TIGIT+ CD4 T cells compared to TIGIT- CD4 T cell after IR injury in WT mice. TIGIT KO mice had significantly reduced SCr at 24h (2.1±0.2 vs 2.6±0.1 mg/dL; $p=0.03$) and 72h (1.3±0.3 vs 2.7±0.4 mg/dL; $p=0.02$) post IR compared to WT mice. At baseline, TIGIT KO mouse kidneys had significantly ($p=0.03$) reduced CD4 T cells compared to WT kidneys (59.2±1.7% vs 54.0±0.5%). CD4 T cells from ischemic human kidney had increased TIGIT expression compared to non-ischemic kidney (236.5±127.9 vs 24.75±19.4; $p=0.15$).

Conclusions: These data show that TIGIT expression increases on kidney CD4 T cells after ischemia in mice and humans. This correlates with increased CD4 activation and proinflammatory phenotype. Importantly, absence of TIGIT in mice reduced kidney dysfunction after AKI. TIGIT is a promising novel therapeutic target for AKI therapy and could also mediate other immune mediated kidney diseases.

FR-OR07

Compartment-Specific Role of Retinoic Acid Receptor Activation in AKI

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Background: Retinoic acid receptors (RARs) are activated in proximal tubules (PT), collecting duct (CD), and renal macrophages (Møs) after ischemia reperfusion AKI (IR-AKI), and systemic RAR inactivation increases Mø-dependent injury after IR-AKI. However, the functional roles of RAR activation in different cellular compartments are unknown.

Methods: RARE-LacZ (RAR reporter); PEPCK-CRE; R26R-Dominant Negative RAR (PT-DNRAR); AQP2-CRE; DNRAR (CD-DNRAR); LysM-CRE; DN-RAR (Mø-DNRAR) underwent bilateral IR- and/or rhabdomyolysis-AKI (rhabdo-AKI). Injury and RARE-LacZ localization were evaluated by BUN, LacZ staining and IF. Renal Mø activation determined by FACS; primary PTEC proliferation and metabolic activity using Seahorse.

Results: RARs are more widely activated after rhabdo- vs. IR-AKI: ~90% in LTL or Kim1+ PTECs; ~5% in AQP2+ CD; ~2-3% in F4/80+ Møs; and <2% in THP1+ thick ascending limb. To evaluate RAR function, we performed IR- and rhabdo-AKI in PT-, CD- and Mø-DNRAR mice. AKI was less severe in PT-DNRAR mice: day 3 BUN in CRE- vs. +; rhabdo-AKI: 52.9 (11.2) vs. 29.1 (1.8); IR-AKI: 71.7 (8.8) vs. 38.4 (8.3) mg/dl, $p<0.005$. In contrast, Mø-DNRAR had more severe injury: IR-AKI, day 3 BUN CRE- vs. + 37.0 (2.9) vs. 63.1 (10.6), $p<0.05$. There was no difference in IR- or rhabdo-AKI severity in CD-DNRAR mice. Despite decreased injury, there was increased Kim1 and F4/80+ Møs after AKI, associated with decreased MLKL (necrosis) and increased Sox9 and Ki67 (de-differentiation and repair) in PT-DNRAR mice. FACS also showed decreased Ly6C inflammatory renal Møs after AKI. Uninjured PT-DN-RAR mice also had patchy increase in Kim1/Sox9+ PTECs; increased F4/80+ CD206+ reparative Møs; and PTECs from PT-DNRAR CRE+ mice were more metabolically active and proliferative than CRE- mice.

Conclusions: Inhibition of RAR in PTs protects against AKI by increasing reparative, metabolically active PTECs, and suppresses Mø activation, while inhibition of RAR in Møs exacerbates AKI. In contrast, inhibition of RARs in CDs does not affect the severity of injury. These findings indicate that RAR activation in different cellular compartments exert opposing effects on the severity AKI through distinct mechanisms, and provides the first evidence that dedifferentiated and inflammatory PTECs, recently described molecular signatures of failed repair, may be protective in AKI.

Funding: NIDDK Support

FR-OR08

Gasdermin D-Deficient Mice Are Hypersensitive to Necroptosis-Mediated AKI

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Background: Within the last decade, a central role for regulated necrosis (RN) in the pathophysiology of renal ischemia/reperfusion injury (IRI) has been established. RN is an umbrella term for several RN subtypes. With respect to the kidney, necroptosis and ferroptosis are the best studied pathways. However, the role of pyroptosis, a highly inflammatory RN type dependent on the protein GSDMD (gasdermin D), during IRI remains unclear.

Methods: Acute kidney injury was induced by IRI or cisplatin application in wild type and GSDMD-ko mice. Furthermore, GSDMD/GSDME-dko mice were utilized in these models to broaden the biological understandings. Mechanistically, MLKL/GSDMD-dko mice (deficient for both necroptosis and pyroptosis) were generated and tested as l. Additionally, immunohistochemistry in murine and human kidney samples as well as experimental work in freshly isolated murine kidney tubules and cell culture were performed.

Results: We investigated gasdermin D- and gasdermin E-deficient mice in a well-established model of moderate IRI. Both strains showed more severe AKI than matched wildtypes as demonstrated by higher levels of serum creatinine and urea as well as more severe tubular damage. This effect was neither dependent on increased tubular cell death as measured by LDH release from freshly isolated murine tubules nor on increased infiltration by $CD3^+$ or $CD68^+$ cells. Based on previous studies, we speculated that pyroptosis-deficiency might promote necroptosis during AKI. To test this hypothesis, we generated MLKL/GSDMD-dko. In IRI, co-deletion of MLKL ameliorated the effects of pyroptosis-deficiency and led to reduced levels of serum creatinine and urea as well as reduced tubular damage compared to both wildtype and pyroptosis-deficient mice. Furthermore, we investigated whether this interaction of pyroptosis and necroptosis is transferable to other forms of AKI by utilizing cisplatin-induced tubular injury as a second model. Again, pyroptosis-deficient mice were more sensitive to AKI and could be protected by co-deletion of MLKL.

Conclusions: In summary, Gasdermin D and E appear to have protective roles in murine AKI as they help to reduce MLKL-mediated necroptosis. Our data are in striking contrast to previously published data (Miao et al., Kidney International 2019).

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR09

ZFP24 Drives Sox9 Upregulation During AKI

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Background: Sox9 is a member of the Sox family of transcription factors that have essential roles in cell-fate determination. In the normal adult kidneys, Sox9 expression is very low. During AKI, Sox9 is transcriptionally upregulated. Functionally, Sox9 plays a cytoprotective role during the early phase of AKI and facilitates repair during the recovery phase. Interestingly, the identify of transcription factor(s) that drive Sox9 upregulation during AKI remains unknown. Zinc finger protein ZFP24 belongs to the superfamily of SCAN-domain containing transcription factors. Outside the nervous system, ZFP24 is expressed in several tissues such as kidney, liver, heart, and spleen. However, its role in the kidney or its contribution to transcriptional regulation of Sox9 remains unknown.

Methods: To identify upstream transcriptional regulators of Sox9, we used RNAi mediated silencing of transcription factors and related genes (siRNA libraries from Dharmacon and Sigma, ~1900 genes) in BUMPT cells, followed by high-throughput-qPCR based examination of stress-induced (cisplatin) Sox9 gene induction. The primary and secondary screens in BUMPT and HK-2 cells identified ZFP24 as the key Sox9 regulatory gene. We then generated a conditional knockout mouse by crossing ZFP24 floxed mice with GGT1-Cre mice. The severity of renal injury (bilateral ischemia and cisplatin nephrotoxicity) was monitored in control and knockout littermates through measurement of blood urea nitrogen, serum creatinine, histological analysis, and biomarker analysis. To test promoter binding, we performed ZFP24 chromatin immunoprecipitation studies in renal tissues. Sox9 and its target gene upregulation was also monitored through qPCR and western blot analysis.

Results: We found that ZFP24 gene deletion in tubular epithelial cells increases the severity of ischemia and cisplatin-associated AKI. Importantly, ZFP24 gene ablation significantly suppresses injury induced Sox9 upregulation in tubular epithelial cells. Chromatin immunoprecipitation studies also demonstrated direct binding of ZFP24 to the Sox9 promoter region.

Conclusions: In the present study, we demonstrate that the transcription factor ZFP24 drives injury induced Sox9 upregulation. These studies establish ZFP24 as a critical regulator of kidney injury and recovery.

Funding: Other NIH Support - NCI

FR-OR10

Cysteine Catabolism Is a Central Player in Diet-Induced Renal Stress-Resistance

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Background: Caloric restriction (CR) protects from acute kidney injury (AKI) in rodents. Translation of CR to the clinic is complex. Novel targeted dietary regimens modulating the dietary composition of macro- and micronutrients promise similar protective effects and increased translatability.

Methods: Six targeted dietary preconditioning protocols - fasting mimicking diet (FMD), ketogenic diet (KD), dietary restriction of branched chain amino acids (BCAA), SR80/100, two dietary regimens restricting sulfur containing amino acids (SAA) by 80 percent (SR80) or entirely (SR100), and CR - were systematically examined in a murine model of renal ischemia-reperfusion injury (IRI) to quantify diet-induced kidney protection. Shared mechanisms of dietary achieved renal resilience were deciphered using targeted metabolite and proteome profiling and confirmed in a human cohort of cardiac surgery patients adhering to a low-SAA diet.

Results: FMD, SR80/100 and CR efficiently protected from IRI-induced AKI quantified by kidney function, tissue damage and survival rates in mice. Preconditioning with KD yielded moderate benefits after IRI, whereas BCAA failed to protect from renal ischemic damage. Targeted metabolite and proteome profiling revealed overlapping changes in oxidative and hydrogen sulfide (H_2S)-dependent cysteine catabolism as a pivotal mechanism of kidney protection in response to FMD, SR80/100 and CR identifying sulfite as its central component. These diet-induced metabolic adaptions were confirmed in humans consuming a low-SAA diet.

Conclusions: FMD, SR80/100 and CR protect from IRI-induced AKI and show common metabolic patterns regarding cysteine catabolism. Importantly, these metabolic changes can be recapitulated in patients undergoing a low-SAA diet indicating a conserved metabolic response. Since FMD and low-SAA diets are feasible in humans our findings provide an important outlook towards novel protective strategies in the patient setting.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR11

Deep Learning Uncovers Clinical Subphenotypes of Diabetic Kidney Disease Driven by Genetic Variation in Rac1 Pathway

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Background: Although diabetic kidney disease (DKD) is a leading cause of end stage renal disease, therapeutic development targeting causal pathways has been limited by disease heterogeneity. Integration of clinical data and genomics may uncover hidden DKD subphenotypes.

Methods: DKD patients from the Mount Sinai Bio*Me* Biobank were included. Using laboratory measurements, vitals, and clinical notes in a deep leaning framework (Fig 1 A,B) we performed unsupervised clustering, accounting for population structure. We then performed a genome wide association study comparing patients in each cluster with healthy controls.

Results: We identified two clusters (Fig 1C), M (mild, N = 972) and S (severe, N = 390). Cluster M had greater ESKD prevalence (16% vs 5%; p <0.001) and higher baseline serum creatinine (1.2 vs 1.1; p<0.001). Using exome sequencing, a missense variant in *ARHGEF18*, rs117824875, was significantly associated with DKD in cluster S, but not cluster M (OR = 7.7; $p = 9.56x10^{-8}$). This variant was also associated with DKD in an external cohort, UK Biobank (OR = 2.4, p =0.044). *ARHGEF18* knockdown in a diabetic zebrafish model induced whole body edema (Fig 1D). Stable overexpression of the rs117824875 mutant *ARHGEF18* transcript in a human podocyte cell line led to decreased cell viability (Fig 1E), actin cytoskeleton reorganization (Fig 1F) and induced *RhoA* and *Rac1* activation (Fig 1G). Mutant *ARHGEF18* transcripts exhibited slower ubiquitin mediated degradation (Fig 1H).

Conclusions: Integration of electronic health records with exome sequencing using deep learning uncovered DKD heterogeneity driven by a gain of function variant in *ARHGEF18. ARHGEF18* knockdown caused kidney failure in a zebrafish model. Mutant *ARHGEF18* was resistant to degradation and activated the *Rac1* pathway, suggesting pharmacological inhibition of *ARHGEF18* may be a therapeutic target by preventing *Rac1*mediated podocyte damage (Fig 1I).

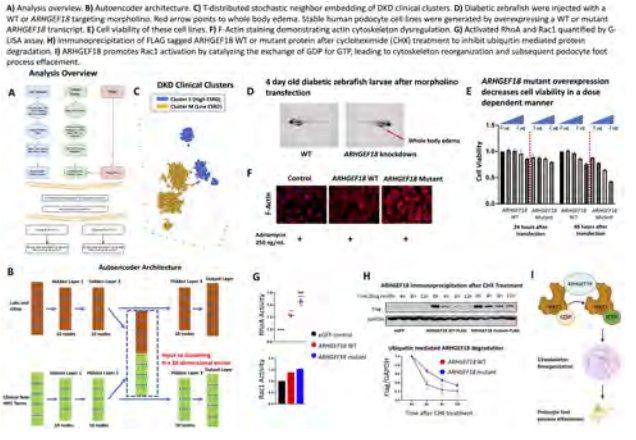

Figure 1

FR-OR12

Identifying Diabetic Kidney Disease Signatures in the Nuclei of the Tubular Epithelium Using a Novel Deep Learning Approach

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Background: Diabetic nephropathy (DN), a leading cause of end stage kidney disease (ESKD) is generally viewed as a glomerular disease. However, progression of DN towards ESKD correlates best with tubular pathology and fibrosis. Due to the spatial complexity of the human kidney, which includes many cell types, it is a challenge to capture the biology at the single cell level. While there is a growing body of information on the molecular phenotype of DN at the single cell level using omics approaches on dissociated tissue, there is little information on cellular changes in intact kidney tissue.

Methods: We used a 3D nuclei image-based deep learning approach to uncover spatially resolved single cell signatures of DN. 3D Imaging datasets were collected from fluorescently labeled human reference nephrectomy samples and biopsies from patients with DN. Using Volumetric Tissue Exploration and Analysis (VTEA) and cell-type markers, a 3D nuclei image dataset was generated from reference nephrectomies and used to train a custom Convolutional Neural Network (CNN). A second 3D nuclei image dataset was generated from images of biopsies taken from patients with DN and classified with the trained CNN.

Results: We generated a 3D nuclei image library from DN tissue secured from the NIDDK/Kidney Precision Medicine Project. We used our nuclei-based CNN classification of renal cells to uncover unique classes of renal epithelium and identify novel single cell image-based signature in DN. Using VTEA, we were able to spatially localize these novel classes of renal epithelium and assess correlation with injury and renal structures for a spatially resolved 3D nuclei image-based signature of DN.

Conclusions: Our work demonstrates that 3D nuclei images from renal cells allows for the identification of DN signatures. These data further suggest that in addition to glomeruli, the tubular epithelium plays a role in DN. Our work underlines the potential of using machine learning and deep learning approaches to automatically uncover new cell types which may emerge due to changes occurring in diabetes, while maintaining their spatial context. Thus, our work can provide insight into the cellular changes in intact kidney tissue during progression in DN.

Funding: NIDDK Support

FR-OR13

Multi-Omics Identifies CERS6 and C16:0 Ceramide in Podocytes as Novel Therapeutic Targets for Diabetic Kidney Disease

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Background: Dysregulated renal ceramide (Cer)/sphingomyelin (SM) metabolism has been reported in human and animal models of diabetic kidney disease (DKD). However, there have been limited investigations in understanding the roles of Cer/SM in the pathogenesis of podocyte dysfunction. To understand the role of sphingolipid metabolism in normal and diabetic kidneys, we integrated matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) data to single nucleus Droplet-based sequencing (snDrop-Seq) and single-cell RNA sequencing (scRNA-Seq) data for a network analysis of a tabulated list of 48 Cer/SM metabolism-related gene/enzymes.

Methods: Two MALDI-MSI platforms (QE-HFX and FTICR) were employed to characterize the lipid profile in normal human kidney tissues (n = 6; U. Michigan) *in situ* (spatial resolution: 20-30 μm). Same tissues were also processed by snDrop-Seq analysis for multi-omics data integration. To compare kidney scRNA-Seq profiles between DKD patients and healthy controls, patient kidney biopsies (n = 44) from an early DKD cohort were collected and 18 living donor (LD) biopsies were used as reference healthy tissues.

Results: Among 30 different cell types identified by snDrop-seq, we found that *CERS6* was specifically expressed in podocytes of the normal human kidney. Fluorescence microscopy analysis showed that CERS6 protein is co-localized with synaptopodin (a podocyte marker). In addition, MALDI-MSI data showed that the downstream C16:0 ceramide of CERS6 was specifically enriched in podocytes of normal human kidney biopsy tissues. scRNA-seq data of kidney biopsy tissues from LD controls and DKD patients showed that *CERS6* gene was exclusively enriched in podocytes of normal human kidney biopsies (LD), while no *CERS6* expression was detected in DKD biopsies, suggesting the potential role of CERS6 in regulating kidney functions.

Conclusions: This highlights the value of kidney atlas for healthy and diseased kidneys on the single cell levels of genes and metabolites in the kidney precision medicine. Multi-omics techniques could help identify novel therapeutic targets for different types of kidney diseases.

Funding: NIDDK Support

FR-OR14

Integrated Multi-Omics Reveal the Complexity of TGF-β Signalling to Chromatin in Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: Critical pathological features of diabetic kidney disease are now accepted to include dysregulation of epigenetic processes as evidenced by the observed differential methylation in patients with or without progressive disease. TGFβ resides at the centre of therapeutic approaches for the treatment of renal fibrosis, but few intervention studies have demonstrated clinical efficacy. Recently, we demonstrated a novel direct interaction between Smad3 and EZH2, the enzymatic component of the polycomb repressive complex 2 (PRC2) during cell fate specification.

Methods: Using the 10X Genomics platform, we performed single cell RNA-seq and -ATAC-seq on human iPSC-derived kidney organoids treated with the EZH2 inhibitor, GSK343, for 1 hour prior to treatment with TGFβ1 for 48 hours.

Results: Single cell RNA-seq analysis revealed that TGFβ1 treated organoids exhibited a similar fibrotic response to what is observed in human diabetic kidneys. Furthermore, TGFβ1 induced the differentiation of resident stromal cells into activated myofibroblasts, and this was accompanied by the upregulation of fibrotic genes such as α-smooth muscle actin and transgelin, consistent to what is observed *in vivo*. Single cell ATAC-seq of iPSC-derived kidney organoids treated with TGFβ1 revealed that TGFβ increases chromatin accessibility at all promoters, DNase I hypersensitive, and transcription start sites in all cell types present within the organoid. Furthermore, TGFβ1 increased chromatin accessibility at some enhancers and this was cell-type dependent. We have shown that pre-treatment with EZH2 inhibitor, GSK343, prevents TGFβ mediated increase in chromatin accessibility and inhibits the expression of the fibrotic marker, α-smooth muscle actin.

Conclusions: We propose that that the enzymatic function of the polycomb repressive complex is necessary for TGFβ1 induced increase in chromatin accessibility and its subsequent gene regulatory functions. Understanding the exact nature of how TGFβ cooperates with epigenetic complexes at the chromatin level will allow for a more comprehensive understanding of how changes in cell fate occur in developmental and pathological contexts. Manipulation of the association between Smad3 and EZH2 may be a useful therapeutic strategy for the resolution of renal fibrosis.

FR-OR15

Spatial Mapping of Murine Diabetic Kidney Disease (DKD) Transcriptomics at Single-Cell Resolution

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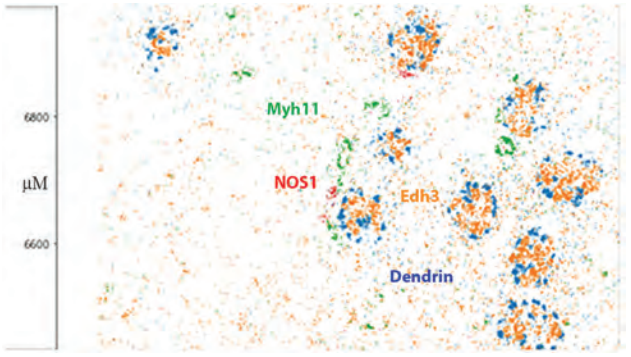
Background: DKD is the major cause of kidney failure in the USA, yet the molecular pathogenesis of DKD and the spatial distribution of the transcriptomic response to injury is poorly characterized. Single cell RNA sequencing and cell clustering has been used on a limited basis in DKD to explore distinct cell-type transcriptomic responses. Here we applied *Multiplexed error-robust fluorescence in situ hybridization* (MERFISH) to anatomically validate snRNAseq cell clustering in diabetic mouse kidney.

Methods: MERFISH was used to localize a panel of 260 cell selective markers derived from single nuclear RNAseq clustering in frozen kidney sections from 3 murine models: C57BLKS db/m, db/db LacZ and db/db Renin-AAV.

Results: Each section contained ~100,000 cells. Single-cell gene expression profiling and cell identification by MERFISH allowed us to map the spatial organization of 11 major cell types: PTS1, PTS3, EC, DCT, Podo, DTL, injPT, PC, mTAL, cTAL, and fibroblasts. Podocyte cluster transcripts Cdkn1c, Dendrin, Sema3g, and EphA6 were specifically expressed in glomeruli and EphA6 and Sema3g were significantly increased in diabetes. Top PTS1 markers including Ppara, Slc7a9 and Slc5a2 exhibited superficial cortical localization whereas PTS3 markers Slc22a19, Acox2 and Kcnc3 were in the cortical/medullary region. Myh11 selectively labled JGA while Nos1 marked the macula densa. Endothelial (EC) markers including Egfl7, Cdh5, Ehd3, Plxnd1, Pi16, EphB4, exhibited distinct anatomic expression, with Ehd3 most highly expressed in glomeruli (**figure**), while Cdh5 and Plvap were low to absent in glomeruli and rather predominated in peri-tubular interstitium.

Conclusions: This application of MERFISH single cell spatial transcriptomics to murine diabetic kidney identified nephron specific cell clusters and confirmed anatomically separate gene expression patterns in PT and EC subpopulations.

Funding: Commercial Support - Janssen R&D LLC



mRNA expression in Glomeruli

FR-OR16

Set7 Lysine Methyltransferase Influences Endothelial to Mesenchymal Transition in Experimental Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the number one cause of renal failure with therapeutic options to prevent its progression limited. In response to hyperglycaemia, the lysine methyltransferase Set7 is known to regulate inflammation and fibrosis, however, its role in DN remains poorly understood. This study defines unique endothelial to mesenchymal transition in experimental diabetic nephropathy.

Methods: Set7$^{-/-}$ constitutive knockout mice were back crossed with ApoE$^{-/-}$ to accelerate DN. Streptozotocin (STZ) administration was used to induce diabetes with subsequent renal injury in Set7$^{-/-}$ApoE$^{-/-}$ mice over five consecutive days (referred now as diabetic Set7KO). Single cell RNA-seq (scRNA-seq) was used to identify the major renal cell types modified by hyperglycaemia. The selective inhibitor of the Set7 methyltransferase, PFI-2, was used to determine the generalizability in human proximal tubule cells (PTC), glomerular endothelial (GEN) and podocyte (PDC) cells.

Results: Diabetic Set7KO mice had improved urinary albumin excretion and glomerular pathology. Assessments of the transcriptome revealed endothelial-to-mesenchymal transition was predictive of diabetic injury using scRNA-seq. Gene expression changes dependent on Set7 regulation were identified in PTC, GEN, PDC and mesenchymal (MSC) cells. Network analyses of diabetic renal injury identified pathways dependent on Set7 involve respiratory electron transport (RET), rRNA processing, extracellular matrix organisation (EMO) and peroxisome proliferator activated receptor alpha (PPARa). Because scRNA-seq identified GEN, PDC and PTC populations as major cell types regulated by Set7 involved in diabetic injury, we extended studies to hyperglycaemic human renal cells using PFI-2, a pharmacological Set7 inhibitor. Pathways associated with diabetic injury in mice which are improved by genetic Set7 deletion closely correspond with Set7 inhibition using PFI-2 in human PTC, GEN and podocyte cells.

Conclusions: These findings support the rationale of targeting Set7 activity as a strategy for developing reno-protective therapies in diabetes. Our studies also show the MSC gene markers upregulated by diabetes in mice were attenuated in human GEN cells by PFI-2 and implicate Set7 in endothelial to mesenchymal transition.

Funding: Government Support - Non-U.S.

FR-OR17

PTEN-Induced Kinase 1 Exerts a Protective Effect in Diabetic Tubulopathy by Attenuating Necroptosis

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Background: Mitochondria are cell generators that are critical to cell metabolism, survival, and homeostasis. Necroptosis, a programmed form of cell death mimicking features of apoptosis and necrosis, has emerging significance in various human disease. PTEN-induced serin/threonine kinase 1 (PINK1) is one of the core organizer of mitochondria quality control and contributes to mitochondrial homeostasis. We designed this study to explore the relationship of PINK1 and tubular cell necroptosis under high glucose conditions and investigate its effects on the progression of diabetic kidney disease.

Methods: Diabetes was induced with streptozotocin (STZ, 50mg/kg i.p. for 5 days) in male PINK1$^{+/+}$ and PINK$^{-/-}$ mice. Human renal proximal tubular epithelial cells (hRPTCs, HKC8) were subjected to low or high-glucose conditions (5mM, or 30mM D-glucose). PINK1-overexpressed (OE) HKC8 and primary renal tubular epithelial cells from kidneys of PINK1$^{+/+}$ and PINK$^{-/-}$ mice were used.

Results: PINK1$^{-/-}$ mice developed severer diabetic tubulopathy accompanied with much more albuminuria than PINK1$^{+/+}$ mice after induction of diabetes using STZ injection. More inflammatory and profibrotic cytokines were produced in the kidneys of diabetic PINK1$^{-/-}$ mice, eventually culminating in aggravated interstitial fibrosis. Dysmorphic and fissional mitochondria increased in the renal tubular cells of diabetic PINK$^{-/-}$ mice and lower levels of mitochondrial ROS and increased mitophagy were observed in PINK1 OE HKC8. We found that upregulation of PINK1 reduced necroptosis of renal tubular cells under high glucose conditions and mitigated the expressions of profibrotic markers. However, PINK1 deficiency was associated with amplified mitochondrial ROS production, exacerbated expressions of necroptosis regulator proteins, and profibrotic markers in hRPECs. Inhibitor of necroptosis and antioxidant attenuated the expressions of profibrotic and inflammatory proteins in HKC8 during treatment with high glucose media.

Conclusions: Our data suggest that PINK1 has roles in suppression of tubular cell necroptosis under high glucose conditions and exerts a protective effect in diabetic tubulopathy.

Funding: Government Support - Non-U.S.

FR-OR18

RTNA1 Mediates the Diabetic Kidney Disease Progression Through Endoplasmic Reticulum (ER) Mitochondrial Contacts in Renal Tubular Epithelial Cells

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Background: Renal tubular epithelial cell (RTEC) injury contributes to kidney fibrosis and the progression of diabetic kidney disease (DKD), but the major risk factors contributing to RTEC injury in early DKD remain unclear. We previously showed that expression of reticulon 1A (RTN1A), an ER-associated protein, increases in RTEC in human and mice with DKD and contributes RTEC injury in vitro and in vivo through activation of ER stress. Here, we will further dissect the role and mechanism of RTA1A in RTEC injury in early DKD.

Methods: To assess the RTEC-specific role of RTN1A in the progression of DKD, we generated transgenic mice with tetracycline-inducible, RTEC-specific RTN1A overexpression (Pax8-rtTA;TRE-RTN1A). To assess the role of RTN1A in tubular injury in the setting of DKD, diabetes was induced in 8-week old transgenic mice with low-dose injections of streptozotocin (STZ). Also, we crossed the Pax8-RTN1A mice with diabetic OVE26. To delineate the molecular mechanisms of RTN1A-induced RTEC injury, we examined the RTN1A-interacting proteins by mass spectrometry. The role of RTN1A in regulation of ER-mitochondrial contacts (EMC) was assessed by measurement of both mitochondrial function and ER stress markers in the cultured RTEC and mice with RTN1A overexpression.

Results: We found that increased RTN1A expression in the RTEC induced significantly tubule-interstitial fibrosis and decline of renal function in both STZ and OVE26 diabetic mice with early DKD. We also demonstrated in vitro that RTN1A interacted with several mitochondrial proteins and RTN1A was enriched in the EMC. We showed that RTN1A overexpression in RTECs not only worsens ER stress but also induces mitochondrial dysfunction in RTEC in vitro and in vivo. As a novel mechnanism, we demonstrated that RTN1A interacts with mitochondrial hexokinase-1 (HK1) and competing for its interaction with voltage-dependent anion channel-1 (VDAC1). Disengagement of VDAC1 from HK1 subsequently results in the activation of apoptosis and inflammasome pathways, leading to RTEC injury and loss.

Conclusions: Our findings highlight the previously unrecognized role of ER-mitochondrial crosstalk in RTEC injury and progression of DKD and the importance of RTN1A-mediated EMC regulation in DKD pathogenesis.

Funding: NIDDK Support

FR-OR19

Advanced Light Sheet Microscopy and 3D Image Analyses of Kidney Injury, Glomerulosclerosis, and Fibrosis in a Mouse Model of Diabetic Kidney Disease

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Background: Development of novel therapies for diabetic kidney disease (DKD) and other glomerulopathies is challenged by poor translatability of preclinical animal models. Novel biomarkers are sought to close this translational gap. Using 3D imaging techniques and advanced image analyses, we aimed to develop a method for quantification of kidney injury and fibrosis in a preclinical mouse model of progressive DKD.

Methods: Kidneys from hypertensive uninephrectomized db/db mice (reninAAV UNx db/db) and healthy controls were fixed and processed for whole-mount immunohistochemistry and light sheet microscopy (LSM) to assess and quantify tubular injury by KIM-1, and fibrosis and glomerulosclerosis by tenascin in the intact kidney. Using 3D image analysis, the distribution and intensity of KIM-1 and tenascin were determined. To correlate 3D imaging endpoints with DKD severity, kidney fibrosis and injury was characterized using standard methodologies including 2D histology.

Results: In reninAAV UNx db/db mice, tenascin was present in glomeruli as showed by its overlap with podocin. A sub-population of glomeruli with augmented tenascin intensity, but with no overlap of podocin was identified indicating that these glomeruli have global glomerulosclerosis and loss of podocytes. Tubulointerstitial tenascin was limited. These findings correlated with traditional histopathological assessment of glomerulosclerosis scoring and fibrosis quantification in PAS and collagen 3 stained kidney section, respectively. KIM-1 positive tubuli were also visualized in intact kidneys from reninAAV UNx db/db mice and showed a heterogenous pattern across the kidney.

KIM-1 was clearly localized to the proximal tubules and was also present in parietal cells in a subpopulation of glomeruli. These observations correlated with 2D IHC stains of KIM-1. Kidneys from healthy controls were KIM-1 negative in both 3D and 2D.

Conclusions: Development of advanced microscopy and 3D imaging technologies allows for assessment of kidney fibrosis and injury in the intact mouse kidney. Thereby, this 3D imaging technique can be used to support functional and 2D histological readouts in mouse models to improve their translatability in the study of disease mechanisms and drug discovery for DKD.

FR-OR20

Long Noncoding RNA lncMGC Mediates TGF-β-Induced Effects Related to Diabetic Kidney Disease via Nucleosome Remodeling Factors

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Background: microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) play key roles in diabetic kidney disease (DKD). miR-379 megacluster of miRNAs and its host transcript lncMGC (lnc-megacluster) are regulated by transforming growth factor-β (TGFβ), increased in glomeruli of diabetic mice and promote features of early DKD. However, biochemical functions of lncMGC are unknown. Here we screened lncMGC-interacting proteins by in vitro-transcribed lncMGC RNA-pull down followed by mass spectrometry (MS). We also created lncMGC knockout (KO) mice by CRISPR-Cas9 editing and used mouse mesangial cells (MMC) from the KO mice to examine the effects of lncMGC on gene expression related to DKD, changes in promoter histone modifications and chromatin remodeling.

Methods: In vitro transcribed lncMGC RNA was mixed with lysates from HK2 cells (human kidney cell line). lncMGC interacting proteins were identified by MS. Candidate proteins were confirmed by RNA immunoprecipitation (RIP) and qPCR. Cas9 and guide RNAs were injected into mouse eggs to create lncMGC-KO mice. Wild type (WT) and lncMGC-KO MMC were treated with TGF-β and RNA expression (by RNA-seq and qPCR) and histone modifications (by chromatin immunoprecipitation) and chromatin remodeling/ open chromatin (by Assay for Transposase-Accessible Chromatin, ATAC-seq) were examined.

Results: Several nucleosome remodeling factors including SMARCA5 and SMARCC2 were identified as lncMGC interacting proteins by MS, and confirmed by RIP-qPCR. MMC from lncMGC-KO mice showed no basal or TGF-β-induced expression of lncMGC. Interestingly, several miRNAs in the miR-379 cluster were also reduced in lncMGC-KO MMC compared to WT MMC. Enrichment of histone H3K27 acetylation and SMARCA5 at the lncMGC promoter was increased in TGF-β-treated WT MMC but significantly reduced in lncMGC-KO MMC. ATAC peaks at the lncMGC promoter region as well as many other loci including *Col1a2*, *Col4a3*, *Col4a4* and *CTGF* were significantly lower in lncMGC-KO MMC than WT MMC.

Conclusions: lncMGC RNA interacts with several nucleosome remodeling factors to promote chromatin relaxation and enhance the expression of lncMGC itself and other genes including pro-fibrotic genes. Its epigenetic regulation in target kidney cells may contribute to DKD pathogenesis.

Funding: NIDDK Support

FR-OR21

Impact of Medicare Bundled Dialysis Payment on Regional Racial Disparities in Home Dialysis Utilization

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Background: The 2011 Medicare prospective payment system (PPS) for dialysis modestly increased access to home-based peritoneal dialysis (PD) and home hemodialysis (HHD) treatment modalities. To examine whether racial disparities in home dialysis use (PD and HHD) were affected, we compared regional change in home dialysis use by White and non-White dialysis patients over time.

Methods: We conducted a retrospective cohort study of dialysis facilities offering home dialysis to 1,098,579 patients with end-stage kidney disease (ESKD) in 2006-2016. Health care region was defined as hospital referral regions (HRR). Patients of non-Hispanic Black/African American, Hispanic, non-Hispanic Asian or Pacific Islander, or other race/ethnicity were grouped into a general category of non-White due to small numbers of home dialysis patients and small samples in some HRRs. For each HRR-year, we computed home dialysis utilization rates for White patients by dividing counts of home dialysis users by White users of any dialysis modality. We repeated this procedure to compute rates for non-White patients, and compared these rates using a generalized estimating equation (GEE) model with a negative binomial distribution, adjusting for regional ESKD provider and patient characteristics.

Results: The mean number of facilities offering home dialysis in each HRR increased from 15.6 in 2006 to 22.1 in 2016, with for-profit ownership (79.8% in 2006, 87.1% in 2016) and chain affiliation (82.3% in 2006, 91.7% in 2016) increasing over time. While average regional home dialysis utilization rates increased over time, disparities persisted with White patients having consistently higher home dialysis utilization than non-Whites in every year (19.5% vs. 12.9% in 2006, 26.2% vs. 17.8% in 2016, on average across HRRs). In adjusted analysis, region-level home dialysis use was one-third lower among non-White patients compared to White patients. Home dialysis disparities did not change following the 2011 Medicare payment reform (incidence rate ratio (IRR)=0.97, 95% CI=0.92, 1.02; p=0.29).

Conclusions: Racial disparities in home dialysis use persist after Medicare payment reform despite modest increases in dialysis facility availability and patient utilization. Targeted policy efforts are needed to reduce disparities in the use of home dialysis.

Funding: Other U.S. Government Support

FR-OR22

Real-World Analysis of Timing of Dialysis Transition and Mortality in a Nationally Representative Cohort of Advanced CKD Patients

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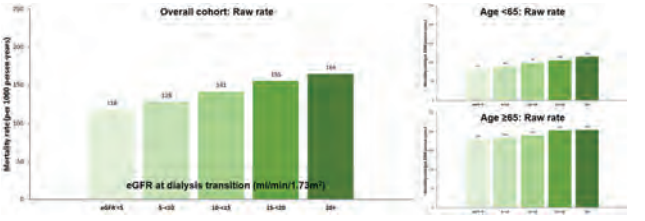
Background: While there is substantial variation in the timing of the dialysis initiation in advanced CKD patients transitioning to ESRD, large population-based studies have observed a trend towards earlier dialysis transition over time. We sought to conduct a real-world analysis of the impact of timing of dialysis transition on mortality rates in a nationally representative cohort of advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days).

Methods: In advanced CKD patients transitioning to dialysis over 1/1/07-6/30/20, we examined the impact of timing of dialysis transition (defined by eGFR at the time of dialysis initiation) on mortality rates. Patients were identified from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were granularly categorized according to novel time-intervals of dialysis transition, defined as CKD stages 4B, 4C, 5A, 5B, and 5C (eGFRs 20-<25, 15-<20, 10-<15, 5-<10, and <5 at the time of dialysis transition, respectively). Poisson regression was used to compare mortality rates across exposure groups.

Results: Among 97,320 advanced CKD patients who transitioned to dialysis, 6%, 11%, 31%, 43%, and 9% initiated treatment at CKD stages 4B, 4C, 5A, 5B, and 5C. Patients who underwent incrementally earlier dialysis transitions experienced increasingly higher raw mortality rates: 118, 128, 141, 155, and 164 deaths per 1000 person-yrs for CKD stages 5C, 5B, 4C, and 4B. A similar trend was observed for Poisson model-based mortality rates in the overall cohort, as well as raw and model-based mortality rates stratified by age (<65 vs. ≥65 yrs).

Conclusions: In a real-world analysis of a nationally representative US cohort, incrementally earlier dialysis transitions demonstrated increasingly higher mortality rates. Further studies are needed to identify strategies optimizing survival in advanced CKD patients transitioning to dialysis.

Funding: NIDDK Support



FR-OR23

Associations of Local Area Deprivation Index with Outcomes During the First Year of Maintenance Dialysis

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Background: Clinical outcomes among patients undergoing maintenance dialysis are typically ascribed to non-modifiable patient characteristics and treatments. However, outcomes may be highly influenced by local socioeconomic conditions. We assessed whether the Area Deprivation Index (ADI), a composite measure of income, education, employment, and housing quality within 9-digit ZIP Code areas, is associated with the incidence of death and kidney transplantation during the first year of maintenance dialysis.

Methods: We analyzed United States Renal Data System Standard Analysis Files. The cohort included patients who initiated outpatient dialysis in 2014-2017; we retained patients with a 9-digit ZIP Code of residence, according to the Medicare Enrollment Database, as that code facilitated linkage to the ADI. Patients were followed from the initiation of outpatient dialysis to the earlier of death or kidney transplantation; patients were censored after one year of follow-up. We fit Cox models of death and kidney transplantation, including ADI decile (higher = more disadvantaged) and adjustment for age, sex, race/ethnicity, primary cause of end stage kidney disease, comorbidity, and dialysis modality.

Results: The cohort included 381,623 patients. Over 14% of patients resided in 9-digit ZIP Codes in the highest ADI decile. ADI deciles were linearly associated with adjusted hazards of death and kidney transplantation (table). The highest versus lowest ADI decile was associated with 20% higher rate of death and 72% lower rate of transplantation.

Conclusions: Increasing socioeconomic disadvantage in the local area was associated with higher rates of death and markedly lower rates of transplantation during the first year of dialysis.

Funding: NIDDK Support

	AHR of death	AHR of kidney transplant
ADI decile 1	1.00 (referent)	1.00 (referent)
ADI decile 2	1.01 (0.97-1.05)	0.83 (0.75-0.93)
ADI decile 3	1.04 (1.00-1.08)	0.77 (0.69-0.85)
ADI decile 4	1.06 (1.02-1.10)	0.73 (0.66-0.81)
ADI decile 5	1.09 (1.05-1.13)	0.70 (0.63-0.78)
ADI decile 6	1.10 (1.06-1.15)	0.57 (0.51-0.63)
ADI decile 7	1.12 (1.08-1.16)	0.50 (0.44-0.56)
ADI decile 8	1.14 (1.09-1.18)	0.42 (0.37-0.47)
ADI decile 9	1.18 (1.14-1.23)	0.38 (0.34-0.43)
ADI decile 10	1.20 (1.16-1.25)	0.28 (0.25-0.32)

Abbreviations: ADI, area deprivation index; AHR, adjusted hazard ratio.

FR-OR24

Ultrafiltration Rate and Mortality in Hemodialysis: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

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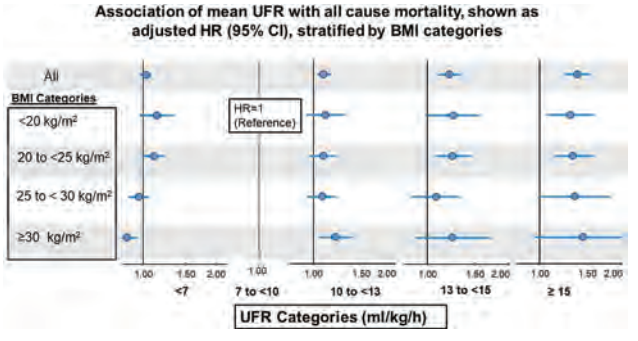
Background: Fluid management is an essential component of hemodialysis (HD) practice. Both insufficient fluid removal and rapid ultrafiltration rate (UFR) are associated with higher cardiovascular and all-cause mortality risk, particularly in US populations, but it is uncertain whether adhering to a single UFR limit will mitigate this risk.

Methods: This retrospective cohort study includes 47,640 adult in-center HD patients from phases 4-6 of DOPPS (2009-2018) from the US, Japan, Australia, New Zealand, Russia, 7 European and 6 GCC countries. Mean UFR was calculated over one week occurring during the first four-month DOPPS data collection interval. Follow-up for all-cause mortality began after this interval. Risk was estimated using Cox models adjusting for DOPPS phase, country, years on dialysis, age, sex, race, 7 comorbidities, body mass index (BMI), catheter use, 5 labs, Kt/V, residual urine volume, and pre-HD session systolic BP.

Results: Mean UFR for the entire cohort was 8.3 (SD 3.8) ml/hr/kg and median follow up time was 1.3 (IQR 0.7-2.3) years. In adjusted analyses, compared to patients with mean UFR of 7 to <10 ml/hr/kg, those with higher UFR had greater risk of mortality: HR 1.09 (95% CI 1.03-1.17) for UFR 10 to <13 ml/hr/kg, HR 1.21 (1.09-1.33) for UFR of 13 to <15 ml/hr/kg, and HR 1.38 (1.24-1.55) for UFR >15 ml/hr/kg). Higher UFR was associated with a greater mortality risk for patients with higher weight or BMI (p-value <0.001 for both). DOPPS region did not modify the relationship between UFR and mortality despite differences in patient characteristics and HD practices across regions (p-value 0.67).

Conclusions: In a large international cohort, higher mean UFR, was associated with an increased risk of mortality. Patients with higher weight or BMI have a greater mortality risk from higher UFR, suggesting that a single UFR threshold to identify risk may not be equally beneficial for all patients.

Funding: Commercial Support - Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical CO., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torii Pharmaceutical Co.,Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd



FR-OR25

Outcomes and Predictors Associated with Skin Sodium Concentration in Dialysis Patients

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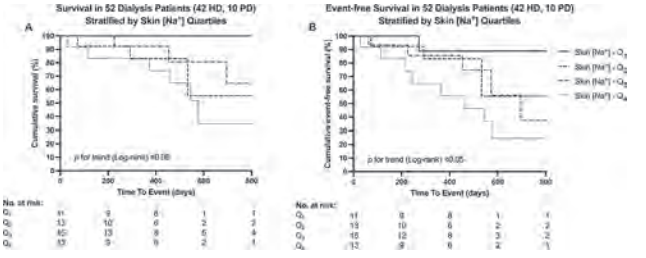
Background: Sodium-23 magnetic resonance imaging (^{23}Na MRI) allows the measurement of skin sodium concentration ([Na^+]). In patients requiring dialysis no data are available relating to the clinical outcomes associated with skin sodium accumulation or the determinants of increasing deposition.

Methods: This was an exploratory, observational study of adult hemodialysis (HD) and peritoneal dialysis (PD) patients. Participants underwent skin [Na^+] quantification with leg ^{23}Na MRI at the study beginning. Outcomes of interest were all-cause mortality and composite all-cause mortality and major cardiovascular adverse events (MACE) and were assessed. Cumulative total and event-free survival were assessed using the Kaplan-Meier survival function after stratification into Skin [Na^+] quartiles. Cox proportional hazards regression was used to model the association between Skin [Na^+] and outcomes of interest. Multiple linear regression was used to model the predictors of Skin [Na^+].

Results: 52 participants (42 HD, 10 PD) underwent the study procedures. Median follow-up was 423 days (*IQR*: 290-550). As shown in Figure 1, increasing Skin [Na^+] quartiles were associated with significantly shorter composite event-free survival (log-rank $\chi^2(1) = 4.733$, $p < 0.05$). Skin [Na^+] was significantly associated with all-cause mortality (univariate *HR* 1.059, *95% CI*: 1.014-1.107; sex-adjusted *HR*: 1.063, *95% CI*: 1.019-1.109) and composite all-cause mortality and MACE (univariate *HR* 1.054, *95% CI*: 1.017-1.092; sex-adjusted *HR*: 1.055, *95% CI*: 1.019-1.093). In multiple regression models, dialysate [Na^+], serum albumin and congestive heart failure were significantly associated with Skin [Na^+] in HD patients (R^2_{adj}=0.62).

Conclusions: Higher Skin [Na^+] was associated with worse clinical outcomes in dialysis patients and may represent a direct therapeutic target.



Kaplan Meier curves for overall survival (A) and event-free survival as a composite of all-cause mortality and major adverse cardiovascular events (B), after skin [Na^+] quartile stratification.

FR-OR26

Itch Reduction with Difelikefalin Correlates with Improved Sleep Quality in Hemodialysis Patients with Pruritus

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Background: CKD–associated pruritus (CKD-aP) may impair sleep of hemodialysis (HD) patients. This analysis of a Phase 3 open-label study evaluated if itch reduction in HD patients treated with the investigational, peripherally restricted kappa opioid receptor agonist, difelikefalin (DFK), correlated with improved sleep quality.

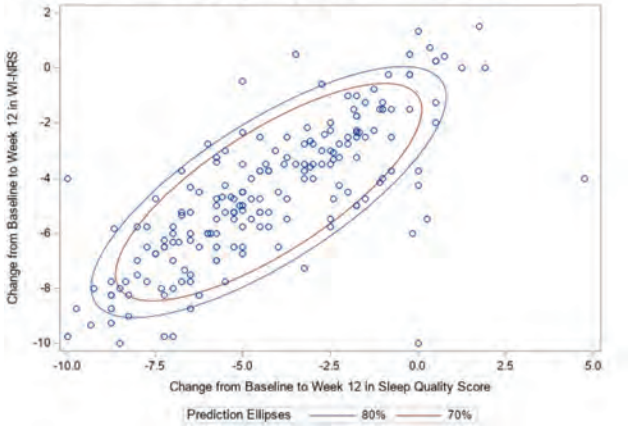
Methods: 222 patients with moderate-to-severe CKD-aP received intravenous DFK 0.5 mcg/kg thrice weekly for up to 12 weeks. Change in itch intensity from baseline to week 12 was evaluated by weekly mean of the 24-hour Worst Itching Intensity Numerical Rating Scale (WI-NRS) score (range 0 [no itch] to 10 [worst itch imaginable]). Impact of pruritus on sleep quality was evaluated by the change from baseline to week 12 in weekly mean of the 24-hour Sleep Quality Questionnaire (SQQ) score (0 [did not interfere] to 10 [completely interfered]), and the sleep disability question score from the 5-D Itch (1 [never affects sleep] to 5 [delays falling asleep and frequently wakes me up at night]) at baseline and week 12. Spearman's correlation analysis was performed.

Results: At week 12, most patients achieved a ≥3-point reduction in WI-NRS (74%) and SQQ score (66%). Patients with a ≥3-point (vs <3-point) reduction in WI-NRS had greater reductions in mean SQQ score (–5.22 vs –1.53) and 5-D Itch sleep question score (–1.83 vs –0.78) from baseline to week 12. There was a strong correlation between changes in WI-NRS and SQQ scores from baseline to week 12 (r=0.78) (**Figure**) and a moderate correlation between changes in WI-NRS and 5-D Itch sleep question scores during this period (r=0.48). Week 12 SQQ and 5-D Itch sleep disability question scores were strongly correlated (r=0.64).

Conclusions: Itch reduction with DFK correlated with improvements in sleep quality as evaluated by the SQQ and 5-D Itch sleep disability question.

Funding: Commercial Support - Vifor Pharma

Figure: Correlation between change from baseline to Week 12 in WI-NRS and Sleep Quality Questionnaire scores



FR-OR27

Fluid-Related Risk Factors of Peritoneal Dialysis Technique Failure

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Background: Inadequate fluid management in peritoneal dialysis (PD) patients is associated with a higher risk of cardiovascular morbidity and mortality and may result in shortened PD technique survival (Van Biesen et al, 2019). In this analysis, we evaluated the associations between fluid-related clinical factors and PD technique failure within 1 year of treatment initiation.

Methods: Adult, ESKD patients who were newly prescribed PD for ≥ 120 days at Fresenius Kidney Care (FKC) facilities between 2017-2019 were included. Deidentified data were extracted from the FKC clinical data warehouse and evaluated within 120 days of treatment initiation. Crude and case-mix adjusted Cox regression models with competing risks (patient transfer to HD, death, and loss to follow-up) were used to evaluate the associations between fluid-related risk factors and PD technique failure.

Results: 15,854 automated PD patients (APD; age: 58 years; K_{RU}: 4.5 mL/min) and 1,547 manual PD patients (CAPD; age: 58 years; K_{RU}: 4.8 mL/min) were included. 53% of APD patients and 56% of CAPD patients had a PD technique survival ≥ 1 year, and all patients with urine volume ≤ 100 mL, systolic BP > 160 mmHg, history of cardiovascular events and hospitalizations, or weight change ≥ 2 kg between day 1 and day 120 of PD treatment had a higher risk of 1-year PD technique failure (Figure 1). Significant patient-reported risk factors included shortness of breath (APD only) and edema (APD and CAPD). Patients with a weekly Kt/V > 2 had half the risk of PD attrition at 1 year.

Conclusions: APD and CAPD patients with fluid-related complaints (shortness of breath and edema), history of cardiovascular morbidity and hospitalizations, hypertension, or weight change ≥ 2 kg within 120 days of PD initiation had a higher risk of technique failure within 1 year of PD initiation.

Funding: Commercial Support - Fresenius Medical Care North America

Fluid-Related Risk Factors of 1-Year PD Technique Failure	Automated PD (N=15,854)		Manual PD (n=1,547)	
	N (%)	Adjusted HR* [95% CI]	*N* (%)	Adjusted HR* [95% CI]
Clinical Characteristics				
Urine volume > 100 mL, Yes (vs No)	14649 (92%)	0.48 [0.42, 0.55]	1411 (91%)	0.37 [0.26, 0.55]
Systolic BP > 160 mmHg, Yes (vs No)	3062 (19%)	1.25 [1.13, 1.39]	294 (19%)	1.52 [1.1, 2.1]
Weight change between PD day 1 & day 120				
Increased by > 2kg (vs Change ≤ ± 2kg)	3051 (20%)	1.26 [1.12, 1.41]	334 (22%)	0.87 [0.59, 1.27]
Decreased by > 2kg (vs Change ≤ ± 2kg)	4480 (29%)	1.25 [1.13, 1.38]	391 (26%)	1.11 [0.79, 1.55]
Serum albumin > 3.5 g/dL, Yes (vs No)	2857 (18%)	0.72 [0.63, 0.82]	327 (21%)	0.75 [0.52, 1.1]
(Renal + PD) Kt/V > 2, Yes (vs No)	13337 (84%)	0.51 [0.46, 0.57]	1360 (89%)	0.66 [0.44, 0.99]
Cardiovascular Morbidity/Events				
Congestive heart failure, Yes (vs No)	624 (4%)	1.98 [1.66, 2.36]	79 (5%)	2.16 [1.33, 3.51]
Ischemic heart disease, Yes (vs No)	595 (4%)	2.14 [1.79, 2.54]	56 (4%)	1.61 [0.85, 3.05]
Peripheral vascular disease, Yes (vs No)	1064 (7%)	1.2 [1.02, 1.42]	106 (7%)	1.03 [0.6, 1.78]
Fluid-related hospitalizations, Yes (vs No)	970 (6%)	3.29 [2.89, 3.73]	97 (6%)	3.2 [2.14, 4.78]
Other cardiovascular hospitalizations, Yes (vs No)	1212 (8%)	2.46 [2.17, 2.79]	116 (8%)	1.48 [0.92, 2.37]
Patient-Reported Signs and Symptoms				
Shortness of Breath, Yes (vs No)	5230 (33%)	1.27 [1.16, 1.39]	539 (35%)	1.34 [1, 1.79]
Edema, Yes (vs No)	9790 (62%)	1.39 [1.26, 1.53]	953 (62%)	1.54 [1.12, 2.11]

*Multivariable models were adjusted for calendar year of PD initiation, residual kidney function[A,M], age[A], gender, race/ethnicity[A], dialysis vintage[A,M], PD training time, body surface area[A], Charlson Comorbidity Index[A,M], diabetes[A,M], dialysis facility region[A], dialysis facility size of PD program[A], primary payor[A], employment status[A], marital status[A], and patient's primary language of communication[A]

A - Significant case-mix variables in the automated PD models. M - Significant case-mix variables in the manual PD models

Figure 1

FR-OR28

Mass Spectrometry-Based Proteomic Analysis of Adsorbed Molecules in a Hexadecyl-Immobilized Cellulose Beads Column for the Treatment of Dialysis-Related Amyloidosis

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Background: Dialysis-related amyloidosis (DRA) is a serious complication in CKD patients undergoing long-term hemodialysis (HD). β_2-microglobulin (β_2-m)-related amyloid deposition induces osteoarticular disorders including carpal tunnel syndrome. Direct hemoperfusion with a column containing hexadecyl-immobilized cellulose beads (HICB) is used to adsorb circulating β_2-m to inhibit the progression of DRA. As use of the column improves joint pain and physical functions; it is possible that the column adsorbs not only β_2-m but also other molecules associated with amyloidogenesis and inflammation.

Methods: We included 14 HD patients with DRA. Proteins were extracted from the HICB-containing column after treatment and identified using liquid chromatography-linked mass chromatography. We measured the adsorption rate of the proteins detected by proteomics, and compared it with those in the patients undergoing HD and hemodiafiltration (HDF). The amyloid tissue deposition in the carpal tunnel in the HD patients (n = 8) was corrected using laser microdissection and examined on liquid chromatography-linked mass chromatography. The protein profiles were compared between the HICB-containing column and the amyloid lesions.

Results: With high confidence criteria, 200 proteins adsorbed by the HICB were identified (e.g., β_2-m SIN, 193.8 ± 143.4; lysozyme SIN, 156.5 ± 47.8). After passing the HICB-containing column, the serum levels of several proteins were decreased as compared with those in the HD dialyzer and HDF hemofilter (e.g., adsorption rate of β_2-m, 80.5 ± 9.8% vs 38.0 ± 25.5% [HD] and 25.0 ± 14.6% [HDF], $p < 0.01$; lysozyme, 79.2 ± 10.9% vs 15.8 ± 18.8% [HD] and 10.0 ± 13.4% [HDF], $p < 0.01$). In the amyloid deposited in the carpal tunnel, 143 proteins were identified, of which 54 were also found in the HICB-containing column. Cellular protein metabolic process was one of major Gene Ontology pathways in the common proteins ($p = 1.05E-10$).

Conclusions: The HICB-containing column adsorbed various proteins in the HD patients with DRA, of which some were found in the lesions with amyloid deposition. The results suggest that direct hemoperfusion with the HICB-containing column contributes to the improvement of DRA by reducing the levels of related proteins.

Funding: Commercial Support - Kaneka Medix Co

FR-OR29

Effects of NOS3 and Nitric Oxide Releasing Bionanomatrix Gel on Reducing Intimal Hyperplasia and Vascular Remodeling

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Background: An arteriovenous fistula (AVF) is the preferred type of vascular access in hemodialysis patients. However, nearly 60% of AVFs created develop AVF maturation failure due to venous intimal hyperplasia (IH) formation and poor vascular remodeling (VR). We hypothesize that the endothelial nitric oxide synthase (NOS3) system is critical for reduction of IH and outward VR and local nitric oxide (NO) delivery at the time of AVF creation can enhance AVF maturation

Methods: To explore the role of NOS3, AVFs were created in NOS3 -/-, NOS3 +/+ and NOS3 overexpression mice. To investigate the efficacy of NO gel, rat femoral AVFs were created and immediately after, therapy was applied on the anastomosis. Animals were sacrificed at 7 days following AVF creation to evaluate histomorphological changes. MRI based computational fluid dynamic simulations were performed to investigate hemodynamic changes

Results: As compared to the controls, overexpression of NOS3 can significantly 1) reduce venous IH 2) promote hemodynamic adaptation and VR by increasing venous cross-sectional area, reducing wall shear stress and vorticity through elevating cGMP levels. NO gel therapy had similar significant effects, including reduction of IH (P <0.0091, 70%). In addition, the NO treated group showed significant reduction in intimal α-SMA, vimentin, desmin and MCP-1 levels. Furthermore, slow degradation of NO-releasing gel resulted in prolonged release of NO during the AVF maturation process

Conclusions: NOS3-NO-cGMP system is a critical regulator of AVF remodeling. Thus NO-releasing gel has great potential to promote clinically successful AVF maturation

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

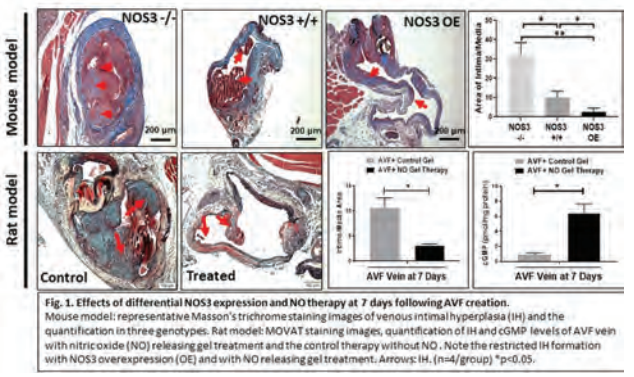

Fig. 1. Effects of differential NOS3 expression and NO therapy at 7 days following AVF creation.
Mouse model: representative Masson's trichrome staining images of venous intimal hyperplasia (IH) and the quantification in three genotypes. Rat model: MOVAT staining images, quantification of IH and cGMP levels of AVF vein with nitric oxide (NO) releasing gel treatment and the control therapy without NO . Note the restricted IH formation with NOS3 overexpression (OE) and with NO releasing gel treatment. Arrows: IH. (n=4/group) *p<0.05.

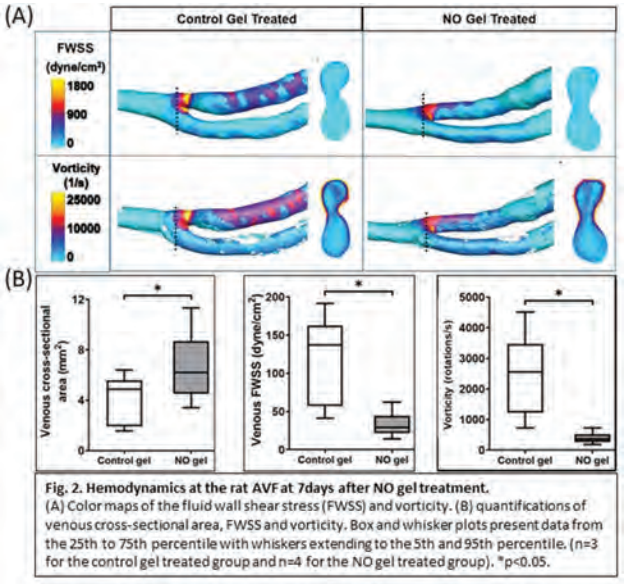

Fig. 2. Hemodynamics at the rat AVF at 7days after NO gel treatment.
(A) Color maps of the fluid wall shear stress (FWSS) and vorticity. (B) quantifications of venous cross-sectional area, FWSS and vorticity. Box and whisker plots present data from the 25th to 75th percentile with whiskers extending to the 5th and 95th percentile. (n=3 for the control gel treated group and n=4 for the NO gel treated group). *p<0.05.

FR-OR30

The Transcriptomic Landscape of the Arteriovenous Fistula: The Postoperative Genetic Signature of Maturation Failure

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Background: The molecular mechanisms contributing to arteriovenous fistulas (AVF) maturation or failure remain elusive, in part due to the scarcity of human postoperative biological data that may guide mechanistic and translational studies. The brachiobasilic AVF created in two stages overcomes this limitation and allows to collect vascular tissues representative of both outcomes at the time of transposition.

Methods: In this study, we compared the transcriptomic profiles of 40 postoperative AVF samples (20 matured and 20 failed) collected 4-6 weeks after access creation by bulk RNA sequencing.

Results: We identified 156 differentially expressed genes (DEG) between both outcomes (log_2FoldChange>1, FDR<0.05), including 101 protein-coding genes downregulated with failure and 11 protein-coding genes with higher expression in this group compared to AVF that matured. Gene set enrichment analysis (GSEA) indicated a suppression of responses to stress/stimuli and signal transduction pathways in AVF that failed. The main downregulated players include G protein-coupled receptors, metalloproteinases, and immunoregulatory chemokines. In contrast, upregulated transcripts in AVF that failed include a urea cell-surface transporter, a serotonin biosynthesis enzyme, and various extracellular matrix and cell adhesion proteins. A supervised machine learning algorithm (XGBoost) was applied to gene expression normalized counts to identify the best discerning features of AVF failure. The highest contributors to the decision tree by total gain were IL-10 and GPR183 (each downregulated 2.6 folds in AVF that failed and with an FDR significance level of $2x10^{-5}$). The area under the curve (AUC) in the logistic regression models for each of these genes is >90%.

Conclusions: In conclusion, this study identified for the first time a postoperative molecular fingerprint of AVF failure. These findings may allow us to pinpoint venous remodeling deficiencies that are responsible for this outcome and potentially correct them using targeted therapies.

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

FR-OR31

Human PLA2R-Antibodies Induce Membranous Nephropathy in Minipigs

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Background: PLA_2R is the main target antigen in patients with membranous nephropathy (MN). The pathogenicity of PLA_2R-antibodies (ab) in MN patients have so far not been proven. This study aimed to prove the pathogenicity of human PLA_2R-ab in MN, and to induce an active PLA_2R-dependend model of MN in minipigs.

Methods: In a first model, plasma and purified IgG from patients with PLA_2R-ab positive MN and healthy donors (negative control) were transferred into minipigs. In a second model, human PLA_2R-protein was used for active immunization of a minipig. We analyzed the PLA_2R-ab in serum, development of proteinuria as well as kidney tissues using immunohistochemistry, immunofluorescence, electron microscopy and "podocyte exact morphology measurement (PEMP)".

Results: After transfer into minipigs, the human PLA_2R-ab bound specifically to minipig PLA_2R in the glomeruli and induced all morphologic characteristics of human MN. Human PLA_2R-ab of the IgG4 subclass could be eluted from minipig glomeruli, showing that the antibodies were able to bind to PLA_2R in the absence of other human serum components. The active immunization of minipigs with human PLA_2R-protein led to the development of PLA_2R-ab, which recognized the N-terminal CysR-CTLD1-region, as well as the C-terminal CTLD7-8-region. Analyses of the kidney tissue revealed all morphologic characteristics of human MN, including a granular deposition of pig IgG and C3 along the glomerular basement membrane, as well as electron dense immune deposits, which were associated with effacement of podocyte food processes. Antibodies eluted from isolated glomeruli were able to bind human and minipig PLA_2R. The minipig developed moderate proteinuria. In contrast, no morphologic or clinical characteristics of MN were detectable in the control animal.

Conclusions: Human PLA_2R-ab induce MN in minipigs. Immunization of minipigs with PLA_2R-protein leads to the development of autoimmune PLA_2R-induced MN, which presents with activation of the complement system and all morphologic and clinical characteristics of human MN. These findings prove the pathogenicity of human PLA_2R-ab and fulfill Koch's postulate.

Funding: Government Support - Non-U.S.

FR-OR32

Chimeric Autoantibody Receptor (CAAR) T Cells as a Precision Therapy for Antigen-Specific B Cell Depletion in PLA2R Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) is an autoimmune disease caused by autoantibodies against podocyte antigens, leading to glomerular damage, nephrotic syndrome, and potentially end-stage renal disease requiring dialysis or transplant. Phospholipase A2 receptor (PLA2R) autoantibodies are found in 70-80% of primary MN patients, co-localize with PLA2R and IgG4 glomerular immune deposits, and correlate with disease activity, supporting their causative role in disease pathogenesis. B cell depletion with rituximab is an effective strategy for treatment of primary MN. However, patients often require repeat treatments for disease relapse or maintenance of remission, and infectious serious adverse events are observed in up to 6.2% of rituximab-treated patients, highlighting the need for therapy that induces durable disease remission without generalized immunosuppression. Chimeric antigen receptor T cells have proven clinical ability to induce long-term remission of B cell cancers. We have shown that autoantigen-based chimeric autoantibody receptor (CAAR) T cells cause DSG3-specific B cell depletion in animal models of mucosal pemphigus vulgaris (mPV) without detectable off-target toxicity, which has led to a phase 1 trial of DSG3-CAART in mPV (NCT04422912). This study extends the CAART approach to PLA2R MN.

Methods: CAARs comprising PLA2R immunodominant epitopes linked to CD137-CD3ζ cytoplasmic domains were expressed in primary human T cells and evaluated for specific cytotoxicity against anti-PLA2R target cells, adsorption of anti-PLA2R MN IgG, and potential off-target binding using luciferase assays, ELISA, and commercial membrane proteome arrays.

Results: PLA2R CAARs directed specific cytolysis of anti-PLA2R cell lines targeting major PLA2R MN epitopes in the cysteine-rich and C-type lectin 1 and 7 domains. PLA2R-CAART cells adsorbed 95-99% of anti-PLA2R IgG from MN patient plasma, indicating that PLA2R CAARs encompass the major autoantibody-binding epitopes in MN patients. Membrane proteome arrays screened with PLA2R CAAR extracellular domains did not identify off-target interactions.

Conclusions: CAAR T cells represent a novel strategy for targeted B cell depletion in PLA2R MN and may ultimately prove to be valuable for the treatment for a broad range of antibody-mediated diseases.

Funding: Commercial Support - Cabaletta Bio

FR-OR33

New Insights on the Role of C3a/C3aR1 Signaling in Membranous Nephropathy

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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults worldwide. MN is characterized by the deposition of anti-podocyte-antibodies within the glomerular subepithelial space. While complement deposition and formation of membrane-attack-complex (MAC) are thought to play a crucial pathogenic role, the exact mechanism of injury in MN is still unclear. We have developed a novel glomerulus-on-a-chip system (GOAC) using human primary podocytes and glomerular endothelial cells (GEC) to study MN and assessed functional response to human MN serum, role of MAC formation and C3a/C3aR1 signaling in MN pathogenesis in addition to in vivo studies.

Methods: GOACs were cultured with serum containing either anti-PLA2R+ or THSD7A+ MN patients and from healthy individuals (as control). Functional response was assessed by albumin permeability assay. The mechanistic role of MAC and C3a/C3aR1 signaling pathway was assessed by immunofluorescence, functional analysis, PCR arrays and Western Blotting. Results were further confirmed in GOAC using podocytes$^{C3aR1-/-}$ and in vivo using THSD7A induced MN in balb/c mice.

Results: Following exposure to sera from MN patients, we have confirmed deposition of human lgG on podocytes and formation of MAC complex, accompanied by albumin leakage. MAC inhibition did not prevent albumin leakage while GOAC supplemented with C3aR1 antagonists as well as GOAC using podocytes$^{C3aR1-/-}$ were able to prevent glomerular filtration damage and albumin leakage. Efficacy of C3aR1 antagonists in preventing proteinuria was confirmed in mice injected with serum from patients with anti-thrombospondin Ab, substantiating our findings.

Conclusions: Using our microfluidic GOAC system in combination with in vivo animal models, we have found evidence that C3a/C3aR1 plays a dominant role in complement-mediated MN pathogenesis. Our results not only shed some light on the injury mechanisms in complement-mediated damage but could provide new avenues for the development of glomerulus-specific treatments.

Funding: NIDDK Support, Private Foundation Support

FR-OR34

C3d-Targeted Factor H Achieves Potent Renal Complement Inhibition and Reduced Glomerular Injury Without Affecting Systemic Complement

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Background: Complement is critical to both the innate and adaptive immune systems, serving an essential role in pathogen response and as an effector of humoral immunity. This system is tightly controlled, and inappropriate activation can cause inflammation and organ injury. Consequently, inhibition has been pursued as a therapeutic strategy for rare complement-driven diseases. However, complement proteins exist in high abundance systemically and undergo rapid turnover, making effective chronic inhibition challenging. Furthermore, because of the complement system's essential role in immunity, systemic blockade raises the risk of infection in patients. As a result, substantial unmet need remains for safer and more effective anti-complement therapies, particularly for chronic diseases.

Methods: We designed a targeted fusion protein to inhibit complement activation in tissue while minimizing systemic blockade. ADX-097 is a humanized anti-C3d monoclonal antibody linked to five N-terminal consensus repeats of the complement inhibitor factor H (fH_{1-5}). We evaluated tissue targeting and both circulating and tissue PK and PD of a mouse ADX-097 surrogate, ADX-118, in $fH^{-/-}$ mice, which exhibit robust glomerular complement activation. We also examined disease-modifying efficacy of ADX-097 in the rat Passive Heymann Nephritis (PHN) model of membranous nephropathy.

Results: We demonstrate that our anti-C3d antibody binds high-density glomerular C3d deposits across a range of renal diseases, indicating that this binding could deliver fH_{1-5} locally. In $fH^{-/-}$ mice, a single subcutaneous dose of 1 mg/kg ADX-118 achieves >75% complement inhibition in glomeruli for at least 7 days post-dose while avoiding systemic complement blockade. A lower, 0.3 mg/kg dose achieves approximately 50% inhibition in glomeruli. In the rat PHN model, a single 1 mg/kg dose of ADX-097 inhibits glomerular complement and significantly reduces urine protein- and albumin-creatinine ratios, indicating potent disease-modifying efficacy.

Conclusions: These data provide proof-of-concept that targeting fH_{1-5} to deposited C3d results in potent, durable, and efficacious complement blockade in kidney while avoiding systemic complement inhibition.

Funding: Commercial Support - Q32 Bio

FR-OR35

Differentiating Steroid-Sensitive Minimal Change Disease and Primary and Secondary Focal Segmental Glomerulosclerosis: A Proteomics-Based Approach

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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are common causes of nephrotic syndrome. Whether distinct molecular mechanisms are involved in the pathogenesis of MCD and FSGS remains unclear. We used proteomic studies in human kidney biopsies to characterize the differentiating molecular phenotype of steroid-sensitive MCD and primary and secondary FSGS.

Methods: Formalin-fixed paraffin-embedded kidney biopsies from patients with steroid-sensitive MCD (n=9), primary FSGS (pFSGS, n= 3), and secondary FSGS (sFSGS, n=4) were included. Patients with pFSGS had nephrotic syndrome and diffuse foot process effacement (FPE) in kidney biopsy. Patients with sFSGS were obese and had non-nephrotic range proteinuria, normal serum albumin and evidence of hyperfiltration and <80% FPE in kidney biopsy. Glomeruli were isolated using laser capture microdissection and HPLC MS/MS were performed using Orbitrap eclipse mass spectrometer. Paired *t*-test in the normalized data was used to compare the groups.

Results: 733 and 701 significant differentially expressed proteins were detected between MCD, and pFSGS and sFSGS respectively. Proteins regulating cell-cell and cell-matrix adhesion and differentiation (THY1, TRIP6, ACTN3, ACTN1, ITGA7, ITGB2, COL6A1, MMP9, FN1) were significantly upregulated in glomeruli of pFSGS compared to MCD. In the glomeruli of sFSGS, immune regulatory pathways predominantly from the complement system (C3, C5, C6, C8A, C8B, C8G, C9, CFHR1, CFHR5, CFH) were upregulated compared to MCD (**Figure 1**). FN1, EIF2AK4, MAP2K3, PHKB, INTS12, BET1 were the most significantly overexpressed proteins in pFSGS compared to MCD.

Conclusions: Proteomic signatures of glomeruli from primary and secondary FSGS are distinct from MCD. The differential upregulation of cell-cell, cell-matrix interacting proteins in pFSGS and immune regulatory proteins in sFSGS suggest distinct underlying pathogenic mechanisms. The causal role of novel molecules dysregulated in pFSGS compared to MCD needs to be investigated. A larger cohort of patient samples needs to be interrogated to validate the observation.

Funding: Clinical Revenue Support

FR-OR36

Association of HLA-DPB1*04:01 and Maintenance of Remission in ANCA-Associated Vasculitis

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Background: Genome wide association studies identified HLA-DPB1*04:01 in ANCA vasculitis and observational studies suggest a biological role. We explored the interaction between HLA/PR3 peptide and association with clinical disease remission.

Methods: Peripheral blood mononuclear cells from patients with ANCA vasculitis and healthy controls with HLA-DPB1*04:01 were utilized for mRNA and protein expression assays. PR3 peptides associating with HLA-DPB1*04:01 were identified via *in silico* and *in vitro* assays. Antigen-presenting cells were analyzed for co-fluorescence of HLA-DPB1 and fluorescently tagged PR3 peptide. HLA/peptide multimers were used to identify autoreactive T cells.

Results: Carriers of HLA-DPB1*04:01 were less likely to maintain remission in PR3-ANCA vasculitis (adjusted hazard ratio for leaving remission 2.06 (1.01,4.20)), though similar effect was not observed in MPO-ANCA or the combined cohort. *In silico* predictions of HLA and PR3 peptide interactions showed strong affinity between $PR3_{225-239}$ and HLA-DPB1*04:01 and confirmed by *in vitro* assays. Expression of HLA-DPB1 did not differ among patients and controls. Circulating APCs analyzed by flow cytometry demonstrated higher fluorescence overlap between peptide and HLA among patients on therapy compared to healthy controls or patients in long-term remission off therapy (Figure). We also found that there is a dynamic autoreactive CD4+ T cell response.

Conclusions: Affinity between $PR3_{225-239}$ and HLA-DPB1*04:01 is reduced among patients in long-term clinical disease remission. These data suggest that the interaction is dynamic and that it could determine the subsequent immune response of T cell activation and maintenance of immunological remission. When HLA-DPB1*04:01 does present $PR3_{225-239}$ as an antigen, it is recognized by autoreactive T cells. The peptide-HLA interaction may be the link explaining why patients with PR3-ANCA and HLA-DPB1*04:01 are unable to maintain disease remission.

Funding: NIDDK Support

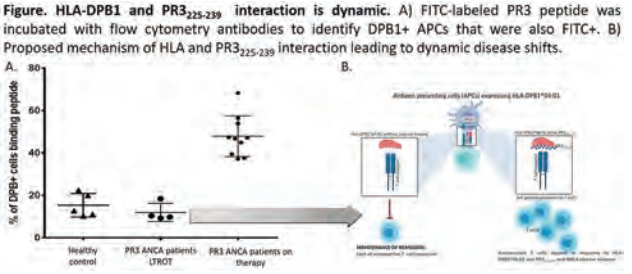

Figure. HLA-DPB1 and $PR3_{225-239}$ interaction is dynamic. A) FITC-labeled PR3 peptide was incubated with flow cytometry antibodies to identify DPB1+ APCs that were also FITC+. B) Proposed mechanism of HLA and $PR3_{225-239}$ interaction leading to dynamic disease shifts.

FR-OR37

Leukotriene B4-BLT1 Axis Controls Neutrophil Accumulation via Fcγ Receptor-Dependent Leukotriene B4 Production in Experimental Glomerulonephritis

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Background: Eicosanoids are biologically active lipid mediators generated rapidly at sites of inflammation. Leukotrienes are one of the eicosanoids generated through the metabolism of arachidonic acid by 5-lipoxygenase and LTA_4 hydrolase. Although it is generally known that leukotriene B_4 (LTB_4) functions as a potent chemotactic factor for neutrophils via its receptor BLT1, the role of LTB_4-BLT1 axis on glomerulonephritis has not been clarified.

Methods: We used the nephrotoxic serum nephritis model, which mimics human glomerulonephritis. To investigate the effect of LTB_4-BLT1 axis on glomerulonephritis, we used BLT1-knock out (KO) mice. Specifically, serological and histological analyses were performed in acute and chronic phases. We used LC/MS/MS to measure LTB_4 in the kidney. To confirm LTB_4 production by neutrophils, we activated the Fcγ receptor of neutrophils by cross-linking with IgG.

Results: On day 7 after onset of nephritis, wild-type (WT) mice showed severe proteinuria, crescent formation accompanied by macrophage infiltration, which was markedly attenuated in BLT1-KO mice. Next, we examined neutrophil infiltration in glomeruli in acute phase; the number of neutrophils in glomeruli peaked at 6 hours after onset both in WT and BLT1-KO mice, but was markedly lower in BLT1-KO mice. Complement activity and chemokines were comparable in both groups. Then, we measured LTB_4 in the kidney and found that LTB_4 production occurred within an hour of onset, indicating a dominant effect of the LTB_4-BLT1 axis on early neutrophil infiltration. In vitro studies demonstrated that LTB_4 production was dependent on activation of Fcγ receptors. On day 1 after onset, BLT1-KO mice exhibited reduced proteinuria and attenuated endothelial damage. Furthermore, administration of BLT1 receptor antagonists after onset relieved nephritis, strongly indicating its therapeutic effect. Finally, BLT1-positive cells infiltrated glomeruli of patients with ANCA-associated vasculitis, suggesting that the LTB_4-BLT1 axis might play important roles in human glomerulonephritis.

Conclusions: Our results revealed that blockage of initial neutrophil infiltration by inhibition of the LTB_4-BLT1 axis mitigated nephritis and could counteract subsequent macrophage infiltration. The LTB_4-BLT1 might be a promising therapeutic target for glomerulonephritis.

FR-OR38

mTOR Activity of Macula Densa (MD) Cells Is a Major Determinant of Glomerular Structure and Function

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Background: Macula densa (MD) cells are paracrine regulators of renal hemodynamics and renin and were recently reported to feature a high rate of protein synthesis. Since the central regulator of protein synthesis is the mTOR pathway, the purpose of the present study was to examine the role of MD mTOR signaling in the maintenance of glomerular structure and function.

Methods: Inducible MD-specific mTOR gain-of-function (MD-mTOR^{gof}) mice were generated by crossing nNOS/CreERT2-mTmG and TSC2/fl mice. Protein synthesis activity *in vivo* at the single-cell level was quantified using O-propargyl-puromycin (OPP) fluorescence imaging and histological analysis in Sox2-tdTomato and MD-GFP mice. Glomerular filtration rate (GFR) was measured via transdermal detection of FITC-sinistrin plasma decay (MediBeacon) and renal blood flow (RBF) was quantified via intravital microscopy.

Results: Sox2-tdTomato mice and the OPP assay showed the highest protein expression in the MD among all renal cell types. Immunolabeling validated MD-specific TSC2 KO and upregulated pS6K in MD-mTOR^{gof} mice. MD-mTOR^{gof} significantly increased the overall rate of protein synthesis in MD cells (1.300±0.057) vs control (0.944±0.039). Physiological activation of MD cells by low salt diet further enhanced MD protein synthesis in both WT (1.365±0.055) and MD-mTOR^{gof} (1.482±0.056) mice, which was blocked by Rapamycin treatment. MD-enriched proteins such as CCN1, CCN3, Pappa2 and CxCl14 had significantly higher expression in response to MD-mTOR^{gof}. GFR was significantly elevated in MD-mTOR^{gof} mice compared to WT (1981±121.30 vs 1444±99.48 μL/min/100 g BW) with similar changes observed with respect to RBF based on single afferent (AA)/efferent arteriole (EA) blood flow, vessel diameter and glomerular tuft area measurements. COX2, mPGES1, renin, the length of basal MD cell processes (maculapodia) and MD cell number/plaque were also significantly increased in MD-mTOR^{gof} vs WT mice.

Conclusions: mTOR signaling is an important regulator of MD cell protein synthesis, proliferation, differentiation and paracrine signaling to the glomerulus via classic hemodynamic and novel, non-traditional glomerular tissue remodeling elements that may be therapeutically targeted to increase RBF, GFR and endogenous tissue remodeling in kidney diseases.

Funding: NIDDK Support

FR-OR39

Extracellular Vesicles and Alport Syndrome: The Role of miR-93 in Modulating Glomerular Cell Biology

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Background: miRNAs play important roles in the pathogenesis of various renal diseases miR-93 is a potent regulator of pathways responsible for glomerular damage like VEGF, TGFb, and Msk2. We have evidence that miR-93 is altered in the glomeruli of mice with Alport syndrome (AS, Col4a5-/-), and in glomeruli of AS patients. Here, we investigated the role of miR-93 in mesangial cells, podocytes, and glomerular endothelial cells (GEC) of mouse and human origin. We also used extracellular vesicles (EVs) derived from human amniotic fluid stem cells to assess their disease-modifying activity in vitro and in vivo by regulation of miR-93.

Methods: miR-93 expression was evaluated by qRT-PCR in mesangial cells, podocytes and GEC sorted from glomeruli of male and female WT and homozygous and heterozygous AS mice at different stages of disease (2m, 3.5m, and 5.5m) and in biopsies of AS patients. The role of miR-93-EVs was evaluated in vitro in human glomerular cells using $EV^{miR93-/-}$. The therapeutic effect of EVs was tested in vivo. RNA-seq analysis was performed in isolated glomeruli of EV-injected mice vs. controls.

Results: miR-93 expression differs between male and female mice along disease progression. In AS males, miR-93 level was significantly lower in GEC, but not in podocytes or mesangial cells vs. WT cells. miR-93 expression was downregulated in glomeruli and urine of AS patients. Expression of WT1 in PAN damaged human podocytes, of fibronectin and VEGF in damaged human GEC, and expression of PDGFRb in TGFb damaged mesangial cells were restored by miR-93 EV cargo transfer, unlike $EV^{miR93-/-}$. EVs showed amelioration of proteinuria and increased lifespan of treated mice. Transcriptomic analysis showed that WT male and female present differences in respiratory and metabolic pathways, extracellular matrix, and cell adhesion molecules. AS males injected with EVs showed improved gene modulations in metabolic function, extracellular matrix interaction, angiogenesis and fibrosis, important miR-93 targeted pathways.

Conclusions: Gender-specific variation in miR-93 expression in glomerular cells might indicate important differences in response to injury in progressive disease. EVs demonstrate great potential to restore lost miR-93 expression and its targets, thus presenting a targeted approach for the treatment of CKD.

Funding: NIDDK Support

FR-OR40

Intravital Imaging Reveals Glomerular Capillary Enlargement and Endothelial/Immune Cell Activation Early in Alport Syndrome

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Background: Alport syndrome (AS) is a rare genetic disorder caused by mutations in type IV collagen that lead to defective glomerular basement membrane, damage of the glomerular filtration barrier (GFB), and progressive kidney disease. While the genetics of AS is well known, the molecular and cellular mechanistic details of disease pathogenesis have been elusive, hindering the development of effective, specific, and mechanism-based therapies. Here we aimed to obtain direct visual clues on the major drivers of AS pathology by performing high-power intravital multiphoton microscopy (MPM) of the local kidney tissue microenvironment in a mouse model of AS, with translation to the human condition.

Methods: In vivo kidney MPM imaging of transgenic Alport mice (Col4α5 mutation) at 2 and 5 months of age was combined with urinalysis and histology. Endothelial glycocalyx was labeled with FITC-WGA, T cells with anti-CD3-Alexa594/CD44-Alexa488 antibodies, and plasma with Albumin-Alexa680. Animals received hyaluronidase (50U iv). AS patient renal biopsy specimens with minimal change disease controls were used for semithin and immunofluorescence histological analysis and single glomerular spatial proteomics (Nanostring).

Results: Severely distended glomerular capillaries and aneurysms were found in AS mice accompanied by numerous microthrombi, increased glomerular endothelial glycocalyx and immune cell homing, albumin leakage through the GFB, glomerulosclerosis and interstitial fibrosis by 5 months of age with an intermediate phenotype at 2 months. Histological and single glomerular spatial proteomics analysis of AS patient biopsies confirmed the presence of dilated glomerular capillaries, activated T cells, endothelial

injury and inflammation. Acute treatment of AS mice with hyaluronidase reduced excess glomerular endothelial glycocalyx and blocked immune cell homing and albumin leakage through the GFB.

Conclusions: We identified the central roles of glomerular capillary mechanical strain, endothelial and immune cell activation early in AS in both mice and humans that may be therapeutically targeted to reduce local tissue injury and improve kidney function.

Funding: NIDDK Support

FR-OR41

Comparative Human and Mouse Kidney Transcriptomics Identify ELF4 as Potential Therapeutic Target

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Background: Mouse models provide an excellent tool to study kidney disease pathogenesis, but little is known how well mouse models recapitulate molecular changes of human CKD.

Methods: Here we created four different mouse kidney disease models a) unilateral ureteral obstruction, b) folic acid injection c) tubular specific overexpression of Notch1 and d) podocyte specific overexpression of risk variant APOL1. We performed detailed phenotyping and molecular profiling by RNA Sequencing of mouse models. We also generated RNA Sequencing for 95 human kidney samples. We used the CRISPR technology to generate mice with ELF4 deletion. We used antisense oligonucleotides for test the therapeutic potential of ELF4 inhibition.

Results: Using comparative bioinformatics approaches we identified 1256 genes and 47 transcription factors that were commonly regulated in all mouse CKD and in patients with CKD. In particular we identified ELF3 and ELF4 transcription factors as they were elevated both in all mouse models and patient samples. Mice with genetic deletion of Elf4 was healthy at baseline and showed protection from FA and cisplatin induced kidney fibrosis and disease. We found that ELF4 is mostly expressed in immune cells and influenced inflammation. Therapeutic inhibition of ELF4 was tested by injection of Elf4, which showed similar protection of kidney disease.

Conclusions: Comparative transcriptomics identified Elf4 as one of the key conserved transcription factor in human and mouse CKD. Genetic deletion or pharmacological inhibition of Elf4 protected mice from fibrosis.

FR-OR42

Proteome-Wide and Transcriptome-Wide Association Studies of Kidney Function

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Background: Large-scale genome-wide association studies (GWAS) have implicated 424 loci associated with eGFR based on creatinine (eGFRcr), including 320 also associated with eGFR based on cystatin C (eGFRcys). However, the mechanisms by which genetic variation in these loci lead to differences in kidney function remain largely unknown. Combining genetic association statistics from GWAS of eGFR with those from the plasma proteome and gene expression in multiple tissues can reveal potentially causal genes and proteins affecting kidney function.

Methods: We applied proteome-wide association studies (PWAS) for eGFRcr and eGFRcys using summary-statistics from the CKDGen Consortium (EA, N_{eGFRcr}=1,004,041; $N_{eGFRcys}$=460,826) and 1,318 genetic plasma protein level prediction models developed in the Atherosclerosis Risk in Communities (ARIC) study (N=7,213 European American (EA) participants). Similarly, we conducted transcriptome-wide association studies (TWAS) based on prediction models developed in 49 human tissues (GTEx) and from 121 kidney tubule samples.

Results: We identified 62 proteins which were associated with eGFRcr and 42 with eGFRcys ($p<0.05/1,318$). Of these, 19 were associated with both kidney function measures in a directionally consistent manner, nominating novel gene annotations in 18 of the 19 genetically associated regions. The enzyme isopentenyl-diphosphate delta isomerase 2 (IDI2) showed the strongest associations (p_{eGFRcr}=4.8e-37, $p_{eGFRcys}$=1.0e-15). TWAS identified 1,799 and 845 transcripts for eGFRcr and eGFRcys, respectively ($p<0.05/235,763$). Of these, 544 were associated with both kidney function measures, including 13 of the 19 PWAS genes. There were also 27 identified in kidney tubule expression, including *DACH1* and *MANBA*, which were recently identified as contributors to kidney fibrosis.

Conclusions: We were able to consistently implicate 13 genes/proteins for eGFRcrea and eGFRcys across both PWAS and TWAS. Based on our human *in vivo* data these proteins are excellent candidates for downstream functional studies and for potential drug repurposing in the context of chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-OR43

CTGF Aggravates the Oxidative Stress-DNA Damage-Cellular Senescence Sequence Following Renal Ischemia-Reperfusion Injury

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Background: Recent data suggest that AKI to CKD progression may be driven by cellular senescence evolving from prolonged DNA damage response following oxidative stress. Connective tissue growth factor (CTGF; CCN2) is a major contributor to CKD development and was found to aggravate DNA damage and the subsequent DNA damage response (DDR)-Cellular Senescence-Fibrosis sequence following renal ischemia reperfusion injury (IRI). Here, we investigated the impact of CTGF inhibition on the immediate (4 hours) and early (3 days) renal response to IRI.

Methods: We induced AKI by bilateral IRI in wild type and conditional CTGF-KO mice and euthanized the mice 4 hours and 3 days after reperfusion. We performed full transcriptome RNA sequencing to identify major dysregulated pathways and validated the findings by qPCR and immunohistochemistry.

Results: IRI resulted in upregulation of CTGF 4 hours and 3 days after reperfusion (Figure 1A,C). Four hours after reperfusion, CTGF-dependent differentially regulated genes were enriched in multiple signaling pathways related to oxidative stress and DNA damage. Consistently, decreased staining for γH2AX and p-p53 (Figure 1B) indicated reduced DNA damage response in tubular epithelial cells of CTGF-KO mice, although decline in kidney function, acute tubular damage score, and KIM1- and NGAL expression were not different. Three days after IRI, oxidative stress response markers (4HNE, nitrotyrosine, and Nrf2 target genes HMOX1 and NQO1), DDR markers (γH2AX-, p-p53, p21), and anti-apoptotic factors (Bcl-xL, HMGB1) were less elevated in CTGF-KO than in wild type mice.

Conclusions: Together, our observations suggest that CTGF inhibition might mitigate AKI to CKD progression by reducing oxidative stress induced DNA damage and the subsequent DDR-cellular senescence-fibrosis sequence response.

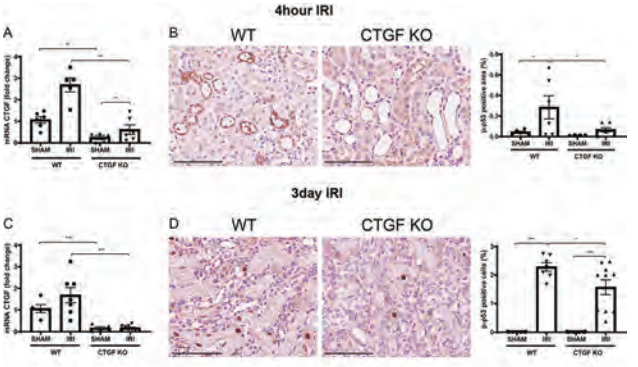

Figure 1. Near total deletion of CTGF resulted in reduced DNA damage induced p53 activation 4 hours and 3 days after IRI. (A, C) qPCR analysis showed that CTGF mRNA upregulation 4 hours (A) and 3 days (C) after IRI was decreased in CTGF KO mice compared with WT mice. (B, D) Cytoplasmic/membranous staining for phosphorylated p53 (p-p53) in the 4hour IRI model (B) and nuclear staining for p-p53 in the 3day IRI model (D) indicates that increased DNA damage induced p53 activation in IRI kidneys was decreased in CTGF KO mice compared with WT mice.

FR-OR44

Urinary mRNA Expression of Glomerular Podocyte Markers in Glomerular Disease and Renal Transplant

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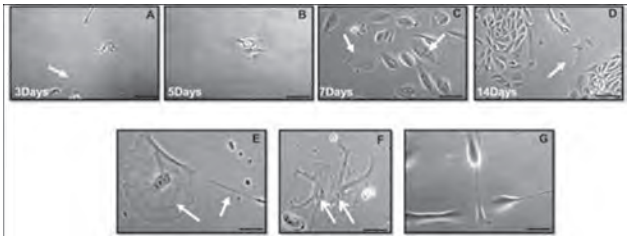
Background: The search for urinary markers to monitor the progression of kidney disease is still ongoing and previous works have demonstrated the useful of quantifying mRNA expression of urinary cells. It is well known that in podocytes the slit diaphragm integrity and the function of the molecules shared with neuronal signaling pathways are essential for the maintenance of cell physiology. Our study focuses on the identification of the urinary mRNA expression of a panel of podocytes genes useful to identify possible biomarkers of glomerular pathology.

Methods: We studied the urine obtained from patients, native and renal transplant, affected by renal disease and undergone, with clinical indication, to renal biopsy (Rbx). We investigated the presence and the morphology of podocytes by immunocytochemistry and measured the expression of genes responsible for their structure and function by RTqPCR. We considered and applied possibly alternative methods to correct gene expression in respect to the total number of podocytes to compare different groups of patients.

Results: Our results demonstrate in urine the presence of podocytes with cytoskeletal alterations. Furthermore, we detected the increase of WT1 mRNA in the urine of both groups. After all kinds of normalization for the number of podocytes, there was a tendency to increase, compared to healthy controls, of the most of the tested genes; in particular, we obtained a significant rise of TRPC6 expression.

Conclusions: We suggest the expression of WT1 mRNA as a surrogate for quantifying podocytes in urine. We propose the increase of TRPC6 and GRM1 mRNA in urinary podocytes as a marker helpful to provide complementary information to Rbx. These genes are useful for monitoring actin cytoskeleton remodeling in podocytes that contributes to glomerular damage in course of renal disease.



Urinary cells culture. Podocytes are recognizable by their processes (A-E), a large cytoskeleton (A-C-D-E), by low duplication capacity (B) other than double nucleus (C-F) and processes trying to connect with those of other cells by synaptic-like structures (G)

FR-OR45

FKBP12 Interacts with 14-3-3 and Synaptopodin to Maintain Actin Cytoskeleton and Processes in Podocytes

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Background: FKBP12 is identified as a binding protein of Tacrolimus (Tac). We reported that FKBP12 is highly expressed in podocytes in kidney, and FKBP12 in podocytes is localized along the actin cytoskeleton. We also reported that FKBP12 is decreased in injured podocytes, and Tac ameliorates podocyte injury by restoring FKBP12 at the actin cytoskeleton (ASN 2019). However, the interaction of FKBP12 with actin-associated proteins and the molecular function of FKBP12 in podocyte are not elucidated yet.

Methods: The localization of FKBP12 with actin-associated proteins was analyzed by dual label immunostaining in glomeruli and human cultured podocytes. The subcellular distribution of FKBP12 was analyzed by western blot in the cultured podocytes. The interaction of FKBP12 with F-actin was analyzed by actin-binding assay with the cell lysate. The interaction of FKBP12 with the actin-associated proteins was analyzed by immunoprecipitation (IP) assay with the lysate of cultured podocytes and HEK293 transfected cells. The effect of FKBP12 siRNA and Tac treatment was analyzed in cultured podocytes.

Results: FKBP12 staining was co-localized with the actin-associated proteins 14-3-3β and synaptopodin (Synp) in glomeruli. The subcellular distribution of FKBP12 was similar to that of 14-3-3 in cultured podocytes. FKBP12 was co-localized and associated with F-actin in the podocytes. FKBP12 interacted with 14-3-3β in cultured podocytes. The IP assay with the HEK expression system also showed FKBP12 interacted with endogenous 14-3-3β. FKBP12 interacted with Synp in the HEK cells co-transfected with FKBP12 and Synp. The interaction of FKBP12 with Synp was not altered by the treatment of 14-3-3β siRNA. Tac enhanced the interaction of FKBP12 with Synp. The expression of 14-3-3β was decreased (63.0% to normal, $P<0.01$), the structure of F-actin is deranged (staining score, 2.0 vs. 2.9 of normal, $P<0.05$), and the process formation was impaired (40.4% to normal, $P<0.005$) in the podocytes treated with FKBP12 siRNA. Tac treatment to normal cells increased the expression of FKBP12 at F-actin in processes and enhanced process formation.

Conclusions: FKBP12 interacts with 14-3-3 and Synp to maintain the actin cytoskeleton and processes in podocyte. The enhanced interactions of FKBP12 with Synp and 14-3-3 by Tac treatment restores FKBP12 at actin cytoskeleton in podocyte.

Funding: Government Support - Non-U.S.

FR-OR46

Soluble Flt1 Binds to Anti-Inflammatory Macrophages in the Kidney

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Background: Soluble Flt1 (sFlt1), a decoy receptor of VEGF ligands, is a key regulator of angiogenesis. High systemic levels of sFlt1 have been linked to the pathogenesis of preeclampsia. However, we have previously reported that treatment with low concentrations of sFlt1 ameliorates kidney damage and inflammation. Specifically, sFlt1 targets macrophages, suggesting that sFlt1 has nephroprotective immunomodulating effects. Here, we studied the presence of sFlt1 in human kidney diseases and investigated the expression and direct binding of sFlt1 to macrophages.

Methods: Renal biopsies of patients with various kidney diseases (IgA, LN, DN, FSGS, MCD) and pre-transplant control biopsies were stained for sFlt1, CD163 and CD68. Cultured macrophages were incubated with increasing concentrations of sFlt1-His, after which membrane binding was measured using flow cytometry. For this, THP-1 monocytes were differentiated with PMA and activated with IFN-γ+LPS or IL-4; primary macrophages were differentiated using GM-CSF or M-CSF.

Results: A patchy pattern of sFlt1 staining colocalizes with CD163/CD68-positive cells in tubulointerstitial areas and with CD68-positive cells in glomeruli. No quantitative differences in renal sFlt1 levels were observed in patients with kidney disease and controls. Flow cytometric analysis revealed that sFlt1 binds to PMA-differentiated THP-1 macrophages but does not bind to THP-1 monocytes. Activation with IFN-γ and LPS decreases sFlt1 binding to THP-1 macrophages. However, IL-4 activation of THP-1 macrophages strongly increases membrane sFlt1 binding. Furthermore, IL-4 activation upregulates sFlt1 mRNA expression in THP-1 macrophages. In primary macrophages, sFlt1 binding was higher in macrophages differentiated with GM-CSF compared to M-CSF.

Conclusions: Our results suggest that sFlt1, while typically associated with angiogenesis, binds to anti-inflammatory macrophages in the human kidney. Alternative activation of macrophages by IL-4 strongly induces sFlt1 production and increases direct binding of sFlt1 to the cell surface membrane. We infer that sFlt1 functions as an autocrine stimulus of anti-inflammatory macrophages, independent of its antiangiogenic properties. Since anti-inflammatory macrophages mediate repair after kidney injury, our work suggests the potential of sFlt1 as a therapeutic tool.

FR-OR47

Cytokines of Kidney Origin Are Retained in the Heart and Induce Cardiac Injury in CKD: A Renal-Cardio Axis

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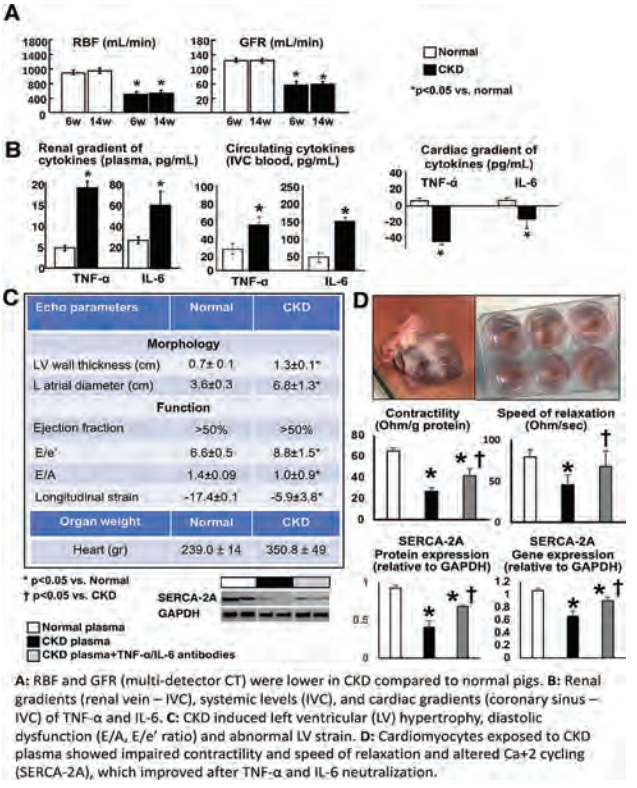
Background: Chronic kidney disease (CKD) is a major contributor to heart failure (HF), but the mechanisms underpinning CKD-induced HF remain to be fully elucidated. We hypothesize that inflammatory signaling from the kidney drives the development of cardiac injury in CKD.

Methods: CKD was induced in 4 pigs (bilateral renovascular disease and dyslipidemia) and observed for 14 weeks. Normal pigs served as controls. Renal hemodynamics (RBF, GFR) were quantified by multi-detector CT, and cardiac morphology and function by echocardiography. Renal vein, coronary sinus, and systemic blood was collected to quantify renal and cardiac gradients of TNF-α and IL-6. In a biomimetic heart culture system, pig heart slices were exposed to plasma from CKD or normal pigs and contractile/relaxation kinetics and sarcoplasmic-reticulum Ca^{+2} dynamics were investigated.

Results: Loss of renal function in CKD was accompanied by positive renal (renal release) and negative cardiac (cardiac retention) cytokine gradients, left ventricular (LV) hypertrophy, diastolic dysfunction (E/A, E/e' ratio) and abnormal LV strain. Cardiomyocytes exposed to CKD plasma showed impaired contractility and speed of relaxation, and altered Ca^{+2} cycling, which improved after TNF-α and IL-6 neutralization **(Figure)**.

Conclusions: This study supports a link between TNF-α/IL-6 inflammatory signaling from the kidney in causing cardiac dysfunction in CKD. Cardiac impairment *in vivo* was mirrored by altered cardiomyocytes kinetics and Ca^{+2} cycling after exposure to CKD plasma *in vitro*, supporting an inflammatory renal-cardio axis in CKD-to-HF pathophysiology.

Funding: Other NIH Support - NHLBI



A: RBF and GFR (multi-detector CT) were lower in CKD compared to normal pigs. **B:** Renal gradients (renal vein – IVC), systemic levels (IVC), and cardiac gradients (coronary sinus – IVC) of TNF-α and IL-6. **C:** CKD induced left ventricular (LV) hypertrophy, diastolic dysfunction (E/A, E/e' ratio) and abnormal LV strain. **D:** Cardiomyocytes exposed to CKD plasma showed impaired contractility and speed of relaxation and altered Ca+2 cycling (SERCA-2A), which improved after TNF-α and IL-6 neutralization.

FR-OR48

Computational Quantification of Interstitial Fibrosis and Tubular Atrophy (IFTA) for CKD Cases of the Kidney Precision Medicine Project

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Background: Quantification of interstitial fibrosis and tubular atrophy (IFTA) is critical in the evaluation of kidney diseases. In this study, our previously developed computational IFTA segmentation model was tested on an independent dataset of renal biopsy whole slide images (WSI) from Kidney Precision Medicine Project (KPMP) and compared to visual assessment.

Methods: A computational model for the IFTA segmentation was trained using 48 PAS stained WSIs from kidney biopsies obtained at three non-KPMP institutions. Twenty-six PAS WSIs from the KPMP chronic kidney disease (CKD) cohort were used as independent testing dataset. Quality control (QC) of the KPMP WSIs was performed using HistoQC, a previously developed QC tool for digital pathology images. Computationally derived percent IFTA scores were calculated using morphological processing to segment IFTA tissue regions in WSIs. Three KPMP pathologists independently estimated the percent IFTA on the same KPMP dataset. The pathologists' estimates and the computationally predicted percent IFTA values were compared pairwise using Pearson correlation.

Results: Computationally derived IFTA segmentations from select cases are shown in ***Fig. 1a.*** The Pearson correlation showed a high degree of agreement between both pathologists and the computational model. The pairwise correlations are shown in the confusion matrix in ***Fig. 1b.***

Conclusions: Computational segmentation of IFTA has the potential to add enhanced reproducibility, precision, and efficiency to clinical tasks such as the estimation of percent IFTA.

Funding: NIDDK Support

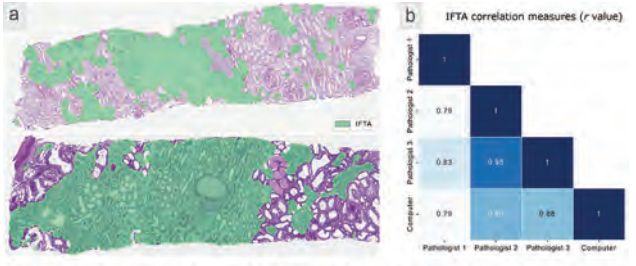

Figure 1. IFTA quantification results for KPMP renal biopsies. (a) Qualitative performance depicting segmented IFTA region in green overlaid on top of select KPMP CKD renal biopsies. (b) Pearson correlation measures comparing pathologists' visual assessment of IFTA and computationally quantified IFTA scores.

FR-OR49

Complement Convertases in Glomerulonephritis: An Explainable Artificial Intelligence-Assisted Renal Biopsy Study

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Background: Complement activation is crucial in the pathogenesis of C3 glomerulopathy (C3GP). It is likely also involved in other forms of glomerulonephritis (GN), however, here, intensity, significance, and predominant activation pathways are less clear.

Methods: Proximity ligation assays (PLA) were used to visualize C3/C5 complement convertases in renal biopsies. Close proximity of C3b and Bb or C2 and C4b was interpreted as assembled alternative or classical/lectin C3/C5 convertases, respectively. For quantification we used deep learning based on explainable artificial intelligence (xAI) in a two-stage workflow: 1. detection of the glomeruli and 2. detection of the PLA signals. Signal densities were calculated as numbers of signals per glomerular area [signals/sqmm]. Cases of C3GP (n=10), immune complex-mediated membranoproliferative GN (IC-MPGN; n=10), IgA nephropathy (IgAN; n=10), postinfectious GN (PIGN; n=10), and membranous nephropathy (MN; n=10) were analyzed and compared with thin basement membrane disease (n=10) as control group, in which no local complement activity is expected.

Results: In C3GP and PIGN a clear predominance of the alternative convertase (mean 8410 and 14483 signals/sqmm) was detected as compared to the control group (mean 798 signals/sqmm) whereas IC-MPGN and MN cases showed higher densities of the classical/lectin convertase (3039 signals/sqmm and 5015 signals/sqmm) as compared to the control group (mean 176 signals/sqmm). Interestingly, cases with IgAN revealed increased densities for the alternative convertase (mean 2088 signals/sqmm) but only very slightly increased densities for the classical/lectin convertase (225 signals/sqmm).

Conclusions: This work shows the applicability of human-machine collaboration based on xAI to characterize and quantify local complement activity. The results reveal insights into the role of complement in the pathogenesis of different forms of glomerulonephritis. Moreover, it opens up the possibility to assess the local activity of the alternative and the classical/lectin pathway C3/C5 convertases in individual patients. Since several novel anti-complement agents are under clinical investigation, this method might become helpful for a more individual complement targeting therapy.

Funding: Government Support - Non-U.S.

FR-OR50

Cubilin Is a Novel Target Antigen in Anti-Brush Border Disease

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Background: Anti-brush border antibody disease (ABBA) is an autoimmune kidney disease that frequently progresses to kidney failure. It is characterized by proximal tubule damage, IgG-positive immune deposits along the tubular basement membrane (TBM), and circulating autoantibodies directed against the brush border. To date, the multiligand receptor megalin (also known as LDL receptor-related protein 2, LRP2) is the only target antigen associated with ABBA.

Methods: Here, we investigated a patient with LRP2-negative ABBA and applied mass spectrometry and confocal microscopy to identify a novel target antigen.

Results: A 75-year-old European female patient with past history of hypertension, type 2 diabetes and stage G3/A1 CKD was referred for rapid decline in kidney function (decrease in CKD-EPI estimated glomerular filtration rate from 37 to 16 ml/min per 1.73 m^2 over a few months). This was associated with new onset proximal tubule dysfunction, as attested by low molecular weight proteinuria and aminoaciduria. There was no evidence of monoclonal gammopathy, systemic autoimmune disease or exposure to environmental toxins, and serum cobalamin level was normal. The kidney biopsy revealed a protracted pattern of tubular injury, granular IgG deposits along the TBM, with a predominance of IgG1 subclass, and electron-dense deposits in the TBM on ultrastructural analysis. There was no light chain restriction. Although indirect immunofluorescence showed reactivity of the patient's serum against normal kidney brush border, consistent with the diagnosis of ABBA, immunofluorescence failed to detect LRP2 within TBM deposits. Protein G immunoprecipitation followed by mass spectrometry revealed cubilin (CUBN), another multiligand, endocytic-membrane glycoprotein of the proximal tubule, to be uniquely present within immune complexes eluted from frozen biopsy tissue. Confocal microscopy confirmed CUBN specifically colocalized with IgG in the TBM. Such colocalization was specific to the disease and not observed in other immune complex-mediated tubulointerstitial diseases, including LRP2 nephropathy, IgG4-related kidney disease, idiopathic hypocomplementemic interstitial nephritis, lupus nephritis, or polyomavirus nephritis.

Conclusions: CUBN is a novel target antigen in ABBA.

FR-OR51

The Effect of Dapagliflozin on Rate of Kidney Function Decline in Patients with CKD: A Prespecified Analysis from the DAPA-CKD Trial

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Background: Dapagliflozin reduced the risk of kidney failure in patients with chronic kidney disease (CKD) with and without type 2 diabetes in the DAPA-CKD trial (NCT03036150). This pre-specified analysis assessed the effect of dapagliflozin on the rate of change in estimated glomerular filtration rate (eGFR) slope.

Methods: DAPA-CKD randomized 4304 participants with urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g and eGFR 25–75 mL/min/1.73m^2 to dapagliflozin 10 mg or placebo once daily, added to standard care. We analysed eGFR slope using

mixed effect models with different slopes from baseline to Week 2 (acute change); Week 2 to end-of-treatment (chronic eGFR slope); and baseline to end-of-treatment at median 2.3 years (total eGFR slope).

Results: In the overall cohort, dapagliflozin compared to placebo slowed mean eGFR decline from baseline to end-of-treatment by 0.9 mL/min/1.73m^2/year (95% CI 0.6–1.3). Dapagliflozin compared with placebo caused an acute eGFR decline of 2.6 mL/min/1.73m^2 (95%CI 2.2–3.1) and 2.0 mL/min/1.73m^2 (95%CI 1.4–2.7), in patients with and without type 2 diabetes, respectively. Thereafter, dapagliflozin compared to placebo reduced the mean rate of eGFR decline by a greater amount in patients with type 2 diabetes (chronic eGFR slope mean difference 2.3 mL/min/1.73m^2/year [95% CI 1.9–2.6]) than in those without type 2 diabetes (1.3 mL/min/1.73m^2/year [95% CI 0.7–1.8]; interaction p=0.005). The effect of dapagliflozin compared to placebo on total slope in patients with and without type 2 diabetes was 1.2 mL/min/1.73m^2/year (95%CI 0.8–1.6) and 0.5 mL/min/1.73m^2/year (95%CI –0.1–1.0; interaction p=0.04), respectively. The total eGFR slope was steeper in patients with higher baseline HbA1c and UACR; the beneficial effect of dapagliflozin on eGFR slope was also more pronounced in patients with higher baseline HbA1c and UACR.

Conclusions: Dapagliflozin significantly slowed long-term eGFR decline in patients with CKD. The mean difference in eGFR slope between dapagliflozin- and placebo-treated patients was greater in patients with type 2 diabetes, with higher baseline HbA1c and higher UACR.

Funding: Commercial Support - AstraZeneca

FR-OR52

Phenome-Wide Association Study of Common Genetic Variants in SGLT2 and Health Disparities in Kidney Outcomes

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Background: SGLT2 inhibition represents one of the greatest therapeutic achievements of the last two decades, improving cardiovascular outcomes and slowing the progression of CKD to ESRD by 30% in patients with diabetes. Whether common genetic variants in *SGLT2* gene contribute to kidney disease progression and to health disparities in kidney disease is unknown.

Methods: We tested the association of two SNPs in the *SLC5A2* gene encoding SGLT2 with clinically diagnosed phenotypes in a phenome-wide association study in 428,438 whites and 114,536 non-Hispanic blacks (NHB)s from the Million Veteran Program. Using logistic regression adjusted for age, sex, and 10 principal components of ancestry, we regressed 250 phenotypes against the two SNPs (rs9934336; rs3116150), stratified by race and diabetes status. Minor allele frequencies for rs9934336 were 0.26 and 0.20 and for rs3116150 were 0.24 and 0.04 in White and non-Hispanic Black participants, respectively.

Results: The rs9934336 variant was associated with multiple kidney phenotypes in NHBs as shown in the table, while no associations of rs9934336 and kidney phenotypes were observed in whites. When stratified by diabetes, renal failure NOS remained significantly associated in diabetics, and anemia of CKD in non-diabetics. The rs3116150 variant was also associated with several kidney phenotypes in NHBs, while no associations were observed in whites. When stratified by diabetes, most of the associations of rs3116150 and kidney phenotypes remained.

Conclusions: Our study shows that SGLT2 variants are associated with CKD and ESRD in non-Hispanic blacks. This novel association with health disparities needs to be further evaluated. Mendelian randomization studies for *SLC5A2* variants are underway

Funding: Veterans Affairs Support

Table 1. SGLT2 Variants and Renal Disease ICD Codes in Non-Hispanic Blacks (odds ratio with unadjusted p-value)

	rs9934336	rs3116150
Anemia in CKD	All: 0.89, p=6.25 x10-5 Non-DM: 0.83, p=1.17 x10-3	All: 1.18, p=2.67 x10-4 DM: 1.18, p=1.49 x10-3
Renal failure NOS	All: 0.88, p=2.44 x10-4 DM: 0.88, p=1.28 x10-3	All: 1.17, p=1.56 x10-3
Hyperpotassemia	All: 0.92, p=4.33 x10-3	
Renal dialysis	All: 0.91, p=5.76 x10-3	
ESRD	All: 0.92, p=7.57 x10-3	All: 1.14, p=5.07 x10-3 DM: 1.16, p=5.09 x10-3
Disorders resulting from impaired renal function	All: 0.92, p=9.69 x10-3	All: 1.15, p=3.96 x10-3 DM: 1.17, p=6.08 x10-3
Renal osteodystrophy		All: 1.36, p=1.46 x10-3 DM: 1.36, p=4.88 x10-3
Acute glomerulonephritis NOS		All: 2.28, p=5.12 x10-3

FR-OR53

Effects of Daprodustat on Hemoglobin and Quality of Life in Patients with CKD: Results of the ASCEND-NHQ Randomized, Double-Blind, Placebo-Controlled Trial

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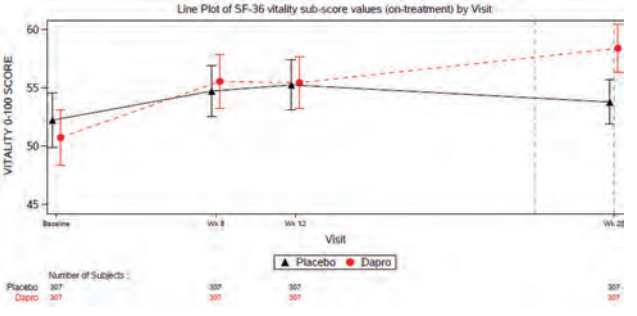
Background: Daprodustat (dapro) is a hypoxia-inducible factor prolyl hydroxylase inhibitor being developed for treating anemia of chronic kidney disease (CKD). In a Phase 3 trial in non-dialysis dependent (ND) CKD patients, we evaluated the effect of dapro vs placebo (PBO) on hemoglobin (Hb) and the SF-36 quality of life Vitality score (fatigue) over 28 weeks.

Methods: Adults with CKD stage 3–5, Hb 8.5–10.0 g/dL, transferrin saturation ≥15%, ferritin ≥50 ng/ml without recent rhEPO use were randomized 1:1 to dapro or PBO to maintain Hb 11–12 g/dL (NCT03409107). Primary endpoint was mean change in Hb between baseline (BL) and the evaluation period (mean over Wk 24–28). Principal secondary endpoints were 1) proportion with ≥1 g/dL increase in Hb, 2) mean change in SF-36 Vitality (fatigue) between BL and Wk 28. SF-36 Vitality responder (≥6 point increase) and blood pressure (BP) elevations were secondary endpoints. Superiority for all endpoints was tested (1-sided α=0.025).

Results: 614 ND-CKD patients were randomized. BL demographic characteristics were balanced; Hb was similar (9.73 g/dL dapro, 9.71 g/dL PBO). The adjusted mean difference (AMD) in change in Hb was 1.40 g/dL (95% CI 1.23, 1.56; P<0.001). A greater proportion on dapro had a ≥1 g/dL increase in Hb from BL (77% vs 18%; P<0.001). Adjusted mean (SE) SF-36 Vitality score increased by 7.3 (1.1) points (dapro) vs 1.9 (1.2) points (PBO); AMD at Wk 28 was 5.4 (95% CI 2.2, 8.6; P<0.001, Figure). 58% on dapro vs 40% on PBO were SF-36 Vitality responders (difference 13%; 95% CI 4%, 22%). While more BP elevations occurred in dapro vs PBO (32% vs 26%, p=0.07), dapro's overall effect on BP was similar to PBO. Rates of adverse events were similar (dapro 69% vs PBO 71%).

Conclusions: In patients with ND-CKD, dapro effectively increased Hb, significantly improved the vitality score (fatigue) and was well tolerated.

Funding: Commercial Support - GlaxoSmithKline



FR-OR54

Integrated Efficacy and Safety of Bardoxolone Methyl in CKD

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Background: Bardoxolone methyl (Bard), an Nrf2 activator, has been studied in multiple CKD trials. To further characterize the safety and efficacy of Bard, we performed integrated analyses across all studies conducted with Bard in CKD.

Methods: Data from the following placebo-controlled trials, CARDINAL Phase 3 (NCT03019185) in 157 patients with Alport syndrome, TSUBAKI (NCT02316821) in 120 patients with T2DM and CKD, and BEACON (NCT01351675) in 2185 patients with T2DM and CKD, were pooled in a CKD Placebo-Controlled Set. An Overall Integrated Analysis Set included additional data from open-label Phase 2 studies.

Results: The CKD Placebo-Controlled Set included 2462 patients (1232 placebo, 1230 Bard). The median and maximum duration of exposure for the Bard group was 0.5 years and 1.9 years, respectively. The Overall Integrated Analysis Set included 3448 patients (1340 placebo, 2108 Bard) with a maximum Bard exposure of 4.8 years. In the CKD Placebo-Controlled Set, Bard significantly increased eGFR from baseline by 6.4±0.2 mL/min/1.73m^2 ($p<0.0001$) at the last on-treatment assessment while the placebo group had a significant decrease in eGFR (mean±SE:-1.1±0.2 mL/min/1.73m^2; $p<0.0001$). The eGFR increases with Bard were sustained four weeks after treatment withdrawal (1.5±0.2 mL/min/1.73m^2; $p<0.0001$ vs baseline and vs placebo). Fewer events in a composite of ESKD, ≥30% decline in eGFR, and eGFR <15 mL/min/1.73m^2 were seen in the Bard group (111 [9%]) compared to placebo (274 [22%]). The Overall Integrated Analysis Set showed similar results. Common adverse events (AEs) in both integrated sets included muscle spasms, decreased appetite, hypomagnesaemia and decreased weight. No serious AEs of cardiac failure were reported with Bard in CKD trials conducted after BEACON.

Conclusions: Across all studies in CKD, Bard preserved kidney function with on- and off-treatment eGFR benefits and was generally well tolerated. Studies in persons with CKD conducted after BEACON mitigated the risk for heart failure previously observed in patients with type 2 diabetes and Stage 4 CKD.

Funding: Commercial Support - Reata Pharmaceuticals

FR-OR55

Renal Outcomes Associated with Direct Acting Antiviral Therapy in Patients with Hepatitis C Virus Infection

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Background: Direct Acting Antiviral (DAA) agents are effective treatments for chronic Hepatitis C virus (HCV) infection, leading to sustained viral response in the majority of treated individuals. While HCV infection is associated with poorer renal outcomes in observational studies, the effect of DAA therapy on long term renal outcomes remains unclear.

Methods: We identified a national cohort of US Veterans with HCV infection based on positive quantitative RNA viral load testing and extracted data on any DAA therapy using pharmacy dispensation data. We examined the association of DAA therapy (compared to no DAA therapy) with the incidence of end stage kidney disease (ESKD) and the composite of ESKD or death, using time dependent Cox models adjusted for demographic characteristics, socio-economic characteristics including alcohol and illicit substance use, comorbid conditions and baseline kidney function and proteinuria.

Results: We identified 114,358 patients with HCV infection, of whom 58,045 (51%) received a course of DAA therapy between 2013-2018. The overall mean (SD) age at HCV diagnosis was 55.0 (7.5) years, 97% were male, 38% were African American, the mean (SD) eGFR was 92 (17) ml/min/1.73 m^2 and 8% had proteinuria. There were 497 ESKD events and 26,684 composite events over a median follow-up of 11.5 years. DAA therapy was associated with lower risk of ESKD and the composite event (multivariable adjusted HRs and 95%CI: 0.43, 0.31-0.61 and 0.62, 0.60-0.65) [table].

Conclusions: In a large national cohort of US veterans DAA therapy was associated with significantly lower risk of ESKD and the composite of ESKD or death, supporting the long term benefit on kidney function of HCV cure.

Funding: Veterans Affairs Support

	N (%)	ESKD event rate	Multivariable adjusted hazard ratio (95% CI)	ESKD or death event rate	Multivariable adjusted hazard ratio (95% CI)
No DAA	56,313 (49%)	0.44/1000 PY	Referent	22.3/1000 PY	Referent
DAA	58,045 (51%)	0.31/1000 PY	0.43 (0.31-0.61)	22.9/1000 PY	0.62 (0.60-0.65)

FR-OR56

The Comparative Effectiveness and Safety of Direct Oral Anticoagulant (DOAC) and Warfarin Initiation in Adults with Atrial Fibrillation (AF) by eGFR Category

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Background: There is ongoing uncertainty regarding the risk-benefit ratio of DOACs in patients with AF and CKD.

Methods: We conducted an international multicenter cohort study(2011-2018) using healthcare data from 5 jurisdictions across Australia (666 participants of the 45 and Up Study [among 267153 recruited in 2006-09] with data linked to hospital/laboratory data [by CHeReL] and the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data provided by Services Australia; all linked data accessed via SURE) and Canada (73876 patients in AB,BC,MB,ON; record linkage of provincial administrative/ laboratory data). We propensity score matched adults with a new dispensation of a DOAC (rivaroxaban, apixaban, dabigatran) or warfarin, who had AF and a recorded eGFR grouped as ≥60,45-59,30-44, <30ml/min/1.73m^2. Chronic dialysis or kidney transplant recipients were excluded. We assessed 2 composite outcomes within 1 year of initiating either therapy: ischemic (all-cause death, ischemic stroke or TIA) and bleeding (intracranial, gastrointestinal or other). We used Cox regression to estimate the hazard ratios (HRs[95%CI]) of outcomes across eGFR categories and summarized centre data in random effects meta-analysis.

Results: A total of 74542 eligible patients were included, among whom there were 6923(9.2%) ischemic and 1572(2.1%) bleeding events recorded. Across eGFR groups, DOAC initiation was associated with lower or similar risk for the ischemic outcome compared with warfarin initiation (pooled HRs[95%CI] for eGFR groups: 0.74[0.69-0.79], 0.76[0.54-1.07], 0.68[0.61-0.75] and 0.86[0.76-0.98], respectively). Similar results were observed for bleeding (0.75[0.65-0.86], 0.81[0.65-1.01], 0.82 [0.66-1.02], 0.71[0.52-0.99], respectively). There was no evidence of heterogeneity across jurisdictions except for eGFR 45-59ml/min/1.73m^2 for the ischemic outcome (I^2=77%).

Conclusions: In this cohort of AF patients initiating DOAC or warfarin, compared to warfarin, DOAC use was associated with lower or similar risk of both ischemic and bleeding outcomes independent of eGFR. Our results suggest DOAC therapy may have a favourable risk-benefit ratio in AF patients with non-dialysis dependent CKD that is similar to that seen in AF patients with preserved kidney function. Adequately powered randomized trials are needed to confirm these findings.

Funding: Government Support - Non-U.S.

FR-OR57

Adiposity and Obesity-Related Metabolomics: The CRIC Study

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Background: Obesity and adiposity are associated with progression and complications of CKD, partially by altering lipid metabolism and homeostasis. However, the phenotypic- and molecular-level mechanisms underlying these associations are not well understood. We identified adiposity/obesity related (AOR) CKD subgroups and examined potential mediation of CKD progression by plasma metabolites.

Methods: Among 1,529 CRIC participants with metabolomics data (Broad Institute) we applied consensus clustering with K-means on 20 adiposity-obesity and comorbidity parameters to identify CKD subgroups. We examined mediation effects by 634 plasma metabolites on the associations of patient subgroups with CKD progression using Aalen additive hazards models. For those statistically significant mediators, we estimated the HRs of CKD progression for each 2-fold increment in metabolite level using Cox model.

Results: We discovered 3 AOR CKD subgroups (groups with low obesity/diabetes risk, high obesity risk, and high diabetes risk) associated with CKD progression. 79 metabolites were significant mediators ($p<0.05$) for this subgroup-outcome association. After Bonferroni correction ($p<6.33\times10^{-4}$) and adjusting for eGFR, 11 metabolites were associated with a lower hazard and 9 with an increased hazard of CKD progression (**Table**). After additional adjustment for covariates, 4 metabolites remained statistically significantly associated with CKD progression.

Conclusions: We identified 3 clinically meaningful CKD subgroups driven by participant adiposity/obesity profiles and metabolites that mediated the association with the risk of CKD progression. Our findings provide insights into the pathophysiological link between obesity and CKD progression and may indicate potential therapeutic targets. Replication in other populations is needed.

Funding: NIDDK Support

Table. The associations [a] of individual mediator metabolites with CKD progression [b] using Cox proportional hazard model

	Adjusted for eGFR		Fully adjusted [c]	
Metabolite	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
C34:3 phosphatidylcholines	0.33 (0.25, 0.45)	1.54E-12	**0.49 (0.34, 0.70)**	**7.61E-05**
C50:3 triacylglycerols *	0.71 (0.59, 0.86)	3.59E-04	**0.65 (0.52, 0.81)**	**8.24E-05**
C34:3 phosphatidylcholines *	0.67 (0.58, 0.79)	5.12E-07	**0.71 (0.59, 0.86)**	**4.43E-04**
C32:2 phosphatidylcholines	0.72 (0.63, 0.83)	6.12E-07	0.78 (0.67, 0.90)	1.07E-03
C36:3 phosphatidylcholines *	0.67 (0.54, 0.83)	2.24E-04	0.68 (0.53, 0.88)	3.35E-03
C32:2 phosphatidylcholines *	0.78 (0.70, 0.87)	3.99E-06	0.83 (0.73, 0.94)	4.18E-03
C30:0 phosphatidylcholines *	0.84 (0.77, 0.93)	1.02E-04	0.87 (0.79, 0.97)	8.77E-03
C34:4 phosphatidylcholines *	0.79 (0.71, 0.89)	4.69E-05	0.85 (0.75, 0.96)	0.011
Myristoleate	0.63 (0.57, 0.69)	6.17E-21	0.89 (0.79, 1.01)	0.077
Tyrosine	0.54 (0.43, 0.68)	1.24E-07	0.83 (0.64, 1.08)	0.172
Phenylalanine	0.57 (0.44, 0.75)	5.84E-05	0.91 (0.67, 1.24)	0.557
Creatinine	4.35 (2.86, 6.64)	8.14E-12	**4.40 (2.22, 8.73)**	**2.28E-05**
Urate	1.59 (1.23, 2.05)	3.45E-04	1.55 (1.16, 2.08)	2.96E-03
4-Acetamidobutanoate	1.66 (1.39, 1.99)	2.52E-08	1.32 (1.07, 1.62)	8.85E-03
C-glycosyltryptophan	1.43 (1.19, 1.71)	1.04E-04	1.14 (0.94, 1.40)	0.183
N-acetyltryptophan	1.31 (1.17, 1.45)	1.38E-06	1.08 (0.96, 1.23)	0.208
C16:0 Ceramide (D18:1) *	1.41 (1.18, 1.70)	2.15E-04	1.10 (0.89, 1.36)	0.392
N2, N2-Dimethylguanosine	1.63 (1.29, 2.06)	3.72E-05	1.11 (0.87, 1.43)	0.412
Choline	1.78 (1.29, 2.45)	3.98E-04	0.89 (0.63, 1.26)	0.508
C16:0 sphingomyelins	1.57 (1.22, 2.03)	4.60E-04	1.09 (0.82, 1.46)	0.556

[a] The significance of individual mediator metabolite association with CKD progression is based on the Cox model adjusted for eGFR, with Bonferroni corrected cut off of **p<0.05/79=6.33E-04**; (significant association in the fully adjusted model is bolded)
[b] CKD progression was defined as incident ESRD or ≥ 40% eGFR decline from baseline
[c] Model adjusted for age, gender, race/ethnicity, smoking status, eGFR, log(UPCR), systolic blood pressure, diabetes status, BMI, and CVD history
* Asterisk indicates that metabolites were measured with C8-pos liquid chromatography-mass spectrometry lipids measurement, otherwise metabolites were measured with hydrophilic interaction liquid chromatography for metabolites in positive ionization mode (HILIC-pos)

Abbreviation: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; UPCR, 24-hour urine protein-to-creatinine ratio

FR-OR58

Association Between the Gut Microbiota and Kidney Function

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Background: The human gut microbiota is composed of the bacteria, fungi and other microorganisms that live in the lower intestines in a symbiotic relationship with the host. Disruption of the gut microbiota has been associated with cardiovascular and metabolic diseases, but the association with kidney disease is still largely unknown.

Methods: We studied the composition and predicted function of the gut microbiota based on shotgun whole-genome sequencing of microbial DNA in fecal samples collected from 9,788 adults enrolled in the longitudinal, population-based Swedish SCAPIS cohort study. Linear regression adjusted for technical variables, age, sex, Shannon diversity index and (in sensitivity analysis) established kidney disease risk factors was used to identify associations between the log(x+1)-transformed relative frequencies of 1,900 metagenomic species and estimated glomerular filtration rate (eGFR). Additional sensitivity analyses included stratified analyses for gender, hypertension and diabetes mellitus. The Benjamini-Hochberg false discovery rate (FDR) multiplicity correction was used.

Results: We included 5,130 women (57.5±4.3 years) and 4,658 men (57.6±4.4 years). The mean eGFR was 86.5±11.3 for men, and 85.5±12.1 for women. Amongst all participants, 42% had an eGFR above 90, 39% had an eGFR between 75-90, 17% had an eGFR between 60-75, 2% had an eGFR between 45-60, and less than 0.1% had an eGFR below 45. In the age- and sex-adjusted model, we identified four bacteria that were associated with eGFR at an FDR < 0.05. Additional adjustment for kidney disease risk factors rendered one of the associations no longer significant. The kidney function-associated bacteria could be identified down to the species level and belonged to the Orders of *Eubacteriales* (two bacteria), *Coriobacteriales*, and *Veillonellales*. Gene set enrichment analysis indicated significant (FDR < 0.05) enrichment in 48 metabolic pathways.

Conclusions: In the largest gut microbiome association study of kidney function on healthy adults to date, we discovered four bacteria whose abundance was associated with glomerular filtration rate. The functional enrichment of kidney function-associated microbiota provides further insights into its possible role in kidney health.

FR-OR59

Genetic Determinants of Serum Calcification Propensity and Mortality Risk in CKD

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Background: Serum calciprotein particle maturation time (T_{50}), a measure of calcification propensity, is associated with cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD). Here, we aimed to identify genetic loci for serum T_{50} and examine whether these loci are linked with adverse outcomes.

Methods: We performed a genome-wide association study (GWAS) of serum T_{50} in 2,739 community-dwelling individuals of mostly European descent. Subsequently, we used the community-based Rotterdam study (RS) to examine the association between the identified variants and all-cause mortality in the general population and in a subgroup of CKD patients, applying multivariate logistic regression analysis.

Results: We identified three independent genome-wide significant single nucleotide polymorphism (SNPs), rs4917 ($p=1.72 \times 10^{-101}$), rs2077119 ($p=3.34 \times 10^{-18}$), and rs9870756 ($p=3.10 \times 10^{-8}$) in the *AHSG* gene encoding fetuin-A. The three SNPs together explained 18.3% of the variation in serum T_{50}. Quantitative trait locus analysis revealed that all three SNPs have effects detectable at blood protein level of fetuin-A. Associations with outcomes were studied in 8,556 RS participants (age 65.1±9.9 y, 57% female, 63% hypertension, BMI 27.3±4.2 kg/m^2), of whom 833 had CKD (age 75.5±8.7 y, 59% female, 85% hypertension, BMI 27.7±4.1 kg/m^2). The minor allele of rs9870756, linked with a reduced T_{50} and thus a higher calcification propensity, was significantly associated with a higher risk of all-cause mortality, both in the general population [OR (95% CI)=1.14 (1.00-1.30)] and in the CKD subgroup [OR (95% CI)=1.60 (1.05-2.42)]. In the fully adjusted model, the minor allele of rs9870756 was only associated with all-cause mortality in the CKD subgroup [OR (95% CI)=1.93 (1.21-3.08)]. The other two variants were not associated with all-cause mortality.

Conclusions: We identified three independent SNPs in the fetuin-A gene as strong genetic determinants of calcification propensity. The minor allele of rs9870756 was significantly associated with a higher risk of all-cause mortality in CKD patients. Our findings connect genetic susceptibility to calcification with adverse outcome in CKD patients.

Funding: Commercial Support - Sanofi Genzyme

FR-OR60

Decision Aid for Renal Therapy (DART) Reduces Decisional Conflict and Improves Knowledge Among Older Adults with Advanced CKD: A Randomized Clinical Trial

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Background: For older adults, making decisions about kidney failure treatments is challenging, and dialysis may be inconsistent with life goals. Greater decisional conflict is associated with regret, poor outcomes, and worse satisfaction. The DART trial assessed the effectiveness of an interactive, web-based decision aid on decisional conflict and knowledge among older CKD patients facing dialysis decisions.

Methods: Randomized trial evaluating the web-based DART versus usual education, enrolling adults age 70+, English-fluent, with CKD stage 4-5 from 4 US sites. The primary outcome was change in decisional conflict scale (DCS) score from baseline to first follow-up (~ 3 months) compared using ANCOVA. The validated 16-question DCS (100 point scale; lower score indicates less decisional conflict) measures personal perception of uncertainty in choosing among treatment options and modifiable factors contributing to uncertainty. Twelve knowledge questions about CKD and treatment options were assessed at both visits.

Results: Among 363 participants, 180 were randomized to education and 183 to DART; 162 (89%) completed DART. Mean age was 78 years, mean eGFR was 23 mL/min/1.73 m2, 78% were white and 48% had diabetes. Groups were balanced at baseline. At first follow-up, DCS score improved significantly more among the DART group [mean difference 8.7 (5.2, 12.2)]. Results were similar across DCS subscales (Table). DART was also associated with a 7.2% (3.7, 10.7) greater improvement in knowledge.

Conclusions: DART reduced decisional conflict and improved knowledge among older adults facing kidney failure treatment decisions, emphasizing that the decision-making process for older adults with advanced CKD can be improved with use of this effective educational intervention. Funded by PCORI, CDR-2017C1-6297

Funding: Private Foundation Support

Decisional Conflict by Randomization Group

	DART			Usual Education				
Scale	N	Baseline	Follow-Up	N	Baseline	Follow-Up	Mean Difference	p-value
Overall	158	46.6 (22.6)	30.5 (17.7)	159	44.7 (24.4)	38.3 (20.6)	8.7 (5.2, 12.2)	<0.001
Informed	157	52.0 (27.8)	27.5 (19.5)	157	49.6 (30.1)	37.5 (23.4)	10.9 (6.6, 15.1)	<0.001
Values Clarity	155	49.1 (27.2)	31.2 (20.3)	157	48.9 (29.9)	41.0 (24.2)	9.8 (5.6, 14.1)	<0.001
Support	158	31.1 (21.3)	24.7 (18.4)	159	31.2 (23.4)	28.3 (21.0)	3.5 (-0.2, 7.3)	0.07
Uncertainty	154	55.1 (26.3)	38.6 (24.8)	156	52.7 (29.6)	47.1 (26.9)	9.7 (4.8, 14.6)	<0.001
Effective Decision	113	40.4 (23.9)	27.3 (17.9)	122	39.2 (26.2)	34.9 (23.4)	8.0 (3.2, 12.8)	0.001

N (%) or mean (95% CI)

SA-OR01

Identification of a Special Cell Type as a Determinant of the Kidney Tropism of SARS-CoV-2

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Background: Coronavirus disease-2019 (COVID-19) is an infectious disease caused by a novel discovered coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The kidney tropism of SARS-CoV-2 has been well-validated clinically and often leads to various forms of renal damage in COVID-19 patients. However, the underlying mechanisms and diagnostic approaches remain to be determined.

Methods: We interrogated the expression of virus-related host factors in single-cell RNA sequencing (scRNA-seq) datasets of normal human kidneys and kidneys with pre-existing diseases. We validated the results with immunohistochemistry and urinary proteomics of COVID-19 patients and healthy individuals. We also assessed the effects of genetic variants on kidney susceptibility using expression quantitative trait loci (eQTLs) databases.

Results: We identified a subtype of renal tubular cells, which we named PT-3 cells, as being vulnerable to SARS-COV-2 infections in the kidneys. PT-3 cells were enriched in viral entry factors and replication and assembly machinery, but lacked antiviral restriction factors. PT-3 demonstrated higher proportion of $ACE2^{+}$/$CTSB^{+}$ double positive cells compared with other PTECs (20.54% vs 2.24%). Immunohistochemistry confirmed positive staining of PT-3 cells marker SCL36A2 (according to single cell RNA-seq datasets) on kidney sections from COVID-19 patients and healthy individuals. Urinary proteomics confirmed that the protein levels of PT-3 markers, in addition to ACE2, CTSB, and restriction factors, were significantly increased in the urine of COVID-19 patients. We further found that the proportion of PT-3 cells increased in diabetic nephropathy but decreased in kidney allografts and lupus nephropathy, suggesting that kidney susceptibility varied among these diseases. We finally identified several eQTLs that regulate the expression of host factors in kidney cells.

Conclusions: We comprehensively characterized the expression patterns and expression levels of viral host factors in human kidney cells and identified PT-3 cells, a special subtype of PTECs that facilitates the SARS-CoV-2 invasion of the kidney. The detection of PT-3 cells markers in human urine may be used to assess the risk of renal infection during COVID-19.

Funding: Government Support - Non-U.S.

SA-OR02

Selective Tropism of SARS-CoV-2 in Genome-Edited Kidney Organoids Reveals Nephropathic and Therapeutic Effects

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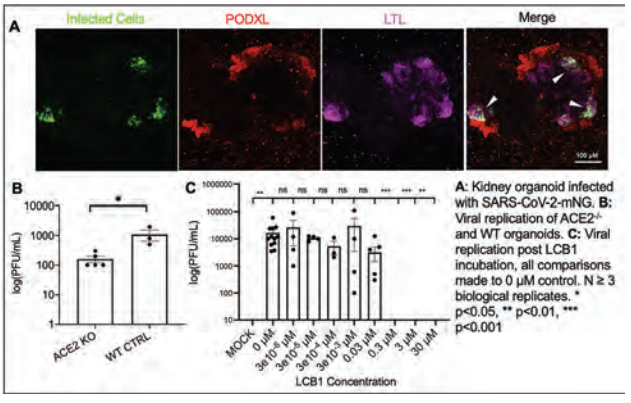
Background: Kidneys are critical target organs of SARS-CoV-2 infection and COVID-19 disease, but whether renal effects are due to direct infection via ACE2 or indirect damage to other organs is unknown. The added risk of pre-existing polycystic kidney disease and efficacy of proposed therapeutics are not yet clear and difficult to assess in patients, animals, or cells. Organoids provide a gene editable platform to assess SARS-CoV-2 kidney infection and its tropism, pathophysiology, and effects of COVID-19 therapeutics.

Methods: Kidney organoids were differentiated from control, *PKD2*$^{-/-}$, or *ACE2*$^{-/-}$ stem cells, and infected with WA1/2020 SARS-CoV-2 ± mNeonGreen transgene. Organoids were infected under BSL3 conditions with supernatant collected for plaque assays and analyzed with immunofluorescence or RNA was extracted. Remdesivir was added post infection, or *de novo* designed LCB1 Spike binder proteins were pre-incubated with SARS-CoV-2 prior to infection.

Results: SARS-CoV-2 specifically infected organoid proximal tubules, producing bulbous cells with disrupted markers. In *ACE2*$^{-/-}$ kidney organoids, viral replication was reduced by 85%. In *PKD2*$^{-/-}$ organoids, cyst-lining epithelial cells were infected at comparable levels to healthy controls. Remdesivir treatment reduced viral replication by 71.4%. Pre-incubation of LCB1 spike binder peptides prevented viral replication at ≥ 0.3 μM and significantly reduced detectable SARS-CoV-2 infection.

Conclusions: Proximal tubular kidney epithelium is susceptible to SARS-CoV-2 infection. ACE2 is the primary entry receptor for SARS-CoV-2 infection, but alternate pathways facilitate low levels of infection. PKD cysts can be infected comparably to controls. Remdesivir and LCB1 treatment can protect kidney epithelium from SARS-CoV-2 replication via distinct mechanisms. This work provides insight into susceptibility of kidneys to SARS-CoV-2 and the effectiveness of current and developing therapeutics for treating COVID-19.

Funding: Other U.S. Government Support



SA-OR03

The Spike Protein of the Causative COVID-19 Virus Induces Heme Oxygenase-1: Pathophysiologic Implications

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Background: Acute kidney injury (AKI) is both a consequence and determinant of outcomes in COVID-19. The kidney is one of the major organs infected by the causative virus SARS-CoV-2. The spike protein of SARS-CoV-2 is required for viral entry into cells and is present in the urine of patients with COVID-19 and AKI. The present study examined cellular effects that result from transfecting the spike protein of SARS-CoV-2 in HEK293 kidney cells.

Methods: HEK293-$ACE2^{+}$ cells stably overexpressing ACE2 were used. Codon optimized pcDNA encoding SARS-CoV-2 spike (7788bp) or empty vector (4033bp) plasmid was transfected using Lipofectamine LTX. For studies examining the effect of quercetin (an inducer of heme oxygenase-1, HO-1), full media containing quercetin or vehicle was added at 4-6 hours post transfection. mRNA and protein expression was assessed by quantitative real-time RT-PCR and western blot respectively. Syncytium formation was assessed by acquiring phase contrast images using Olympus CK40 microscope and the area covered by syncytia was measured using ImageJ software.

Results: HEK293-$ACE2^{+}$ cells expressed SARS-CoV-2 spike protein upon spike transfection. Such expression led to syncytia formation, the sloughing of sheets of cells, and focal denudation of the cell monolayer. Spike protein expression upregulated potentially nephrotoxic genes such as TNF-α, MCP-1, and ICAM1. Spike protein expression also upregulated potentially cytoprotective genes such as HO-1, as demonstrated by HO-1 mRNA and protein expression and relevant signaling pathways (p-Akt, p-STAT3, and p-p38) involved in inducing the HO-1 gene. Quercetin, a naturally occurring compound that induces HO-1, markedly reduced syncytia formation and spike protein expression.

Conclusions: These findings introduce a clinically relevant, spike protein-induced, in vitro model for the study of AKI in COVID-19. The major conclusions of the study are: 1) Spike protein expression in kidney cells provides a useful and timely model for the study of maladaptive and adaptive responses in these cells relevant to AKI observed in COVID-19; 2) spike protein expression in kidney cells upregulates HO-1; and 3) quercetin, an inducer of HO-1, may provide a clinically relevant/feasible protective strategy in AKI occurring in the setting of COVID-19.

Funding: NIDDK Support

SA-OR04

A Novel Soluble ACE2 Protein Protects from Lethal SARS-CoV-2 Infection

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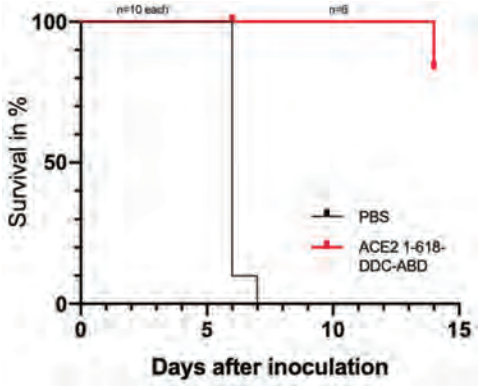
Background: Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) uses full-length angiotensin converting enzyme 2 (ACE2) as the main receptor to enter the target cells. A novel soluble ACE2 protein with increased duration of action and binding capacity to exert a decoy effect as a way to intercept SARS-CoV-2 from binding to membrane-bound ACE2 was generated. The protein was administered to a lethal mouse model of COVID-19 to examine its efficacy.

Methods: A human soluble ACE2 variant fused with a 5kD albumin binding domain (ABD) was linked via a dimerization motif hinge-like 4-cysteine dodecapeptide to improve binding capacity to the SARS-CoV-2. This novel protein (ACE2 1-618-DDC-ABD) was administered intranasally and intraperitoneally prior to viral inoculation and on the two following consecutive days. Infected animals were observed for weight, clinical score and mortality in a BSL-3 facility. Upon sacrifice, lung histopathology was evaluated, and viral loads were measured by plaque assay.

Results: Infected mice that received ACE2-1-618-DDC-ABD developed only moderate disease assessed by a clinical score, modest weight loss and lung histology. At 6 days, mortality was totally prevented in the treated group (figure), lung histopathology was markedly improved and viral lung and brain titers reduced or non-detectable. By contrast, in untreated animals, lung histology revealed extensive pulmonary alveolar hemorrhage and mononuclear infiltrates, and they all became severely ill and had to be euthanized by day 6/7 (figure).

Conclusions: This study demonstrates for the first time in vivo the preventative/therapeutic efficacy of a soluble ACE2 protein in a preclinical animal model.

Funding: Private Foundation Support



SA-OR05

Immunological Response in Dialysis and Kidney Transplant Patients with SARS-CoV-2 Infection

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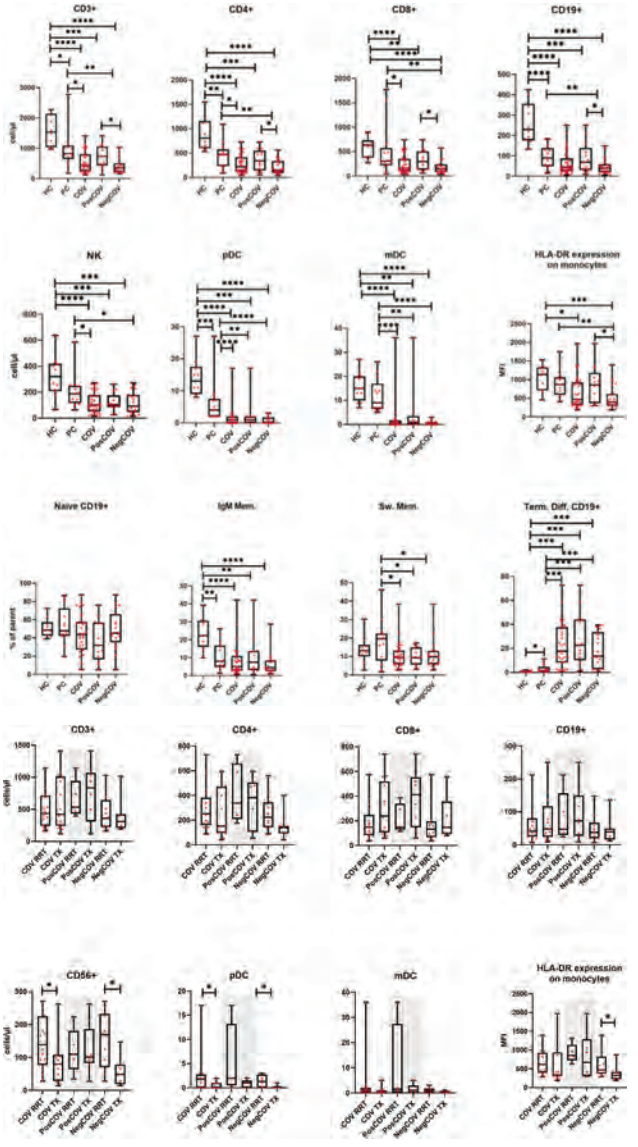
Background: Mortality for COVID-19 in dialysis(HD) and kidney transplant(TX) patients(pts) is 30%. In these pts the immunology of the disease has been poorly explored.
Methods: 32 HD or TX pts hospitalized for COVID-19 (COV), of which 13 with benign course(PosCOV) and 19 who died or developed ARDS(NegCOV), 10 controls(HC) and 12 HD/TX without COVID-19(PC), have been included. Lymphocytes subsets, dendritic cells(DC) and monocytes activation (MA) have been explored.
Results: COV showed lower counts of CD4+, CD8+, CD56+, CD19+, DC and higher counts of terminally differentiated CD19+ compared to HC and PC; CD4+, CD8+, CD19+ and MA were significantly lower in NegCOV than PosCOV. Compared to HD, TX showed lower CD56+, pDC and MA.
Conclusions: The COV group showed immunological alterations compared to HC and PC with deeper alterations of the innate immune system in TX pts with COVID-19.

Characteristics	PosCOV (13)	NegCOV (19)	p
Age (years; n - IQR)	57 (48-73)	73 (60-83)	0.035
Male/female (n)	13/0	13/6	0.035
HD/TX pt (n)	5/8	12/7	0.280
WBC (NV 4.00 – 10.80 x10^3/uL; µe - IQR)	7.045 (4.35-7.61)	6.240 (3.93-8.49)	0.668
Lymphocytes (NV 0.90 – 4.00 x10^3/uL; µe - IQR)	0.74 (0.51-1.4)	0.43 (0.36-1.02)	0.026
Neutrophils (NV 1.50 – 8.00 x10^3/uL; µe - IQR)	5.04 (2.93-6.34)	4.89 (3.06-7.75)	0.451
Monocytes (NV 0.2-1 x10^3/uL; µe - IQR)	0.57 (0.50-0.67)	0.41 (0.30-0.47)	0.003



SA-OR06

Immune Monitoring of Kidney Transplant Recipients After SARS-CoV-2 mRNA Vaccination

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Background: There is limited data on the safety and efficacy of SARS-CoV-2 mRNA vaccines in kidney transplant recipients (KTRs).
Methods: We conducted a prospective, multi-center study of 58 adult KTRs receiving mRNA-BNT162b2 or mRNA-1273 vaccines to assess vaccine safety and efficacy. Primary outcome was biopsy-proven rejection within 3 months of vaccination. Secondary outcomes included adverse events, serum creatinine, proteinuria, donor-derived cell-free DNA (ddcfDNA) levels, and antibody and cellular immunity generation against SARS-CoV-2.
Results: Median age was 62 with 41% females. Median time post-transplantation was 48 months. Only one patient (2%) developed acute cellular rejection though patient had been recently converted to belatacept. There were no severe adverse events or deaths during follow-up. Two patients (3%) developed SARS-CoV-2 infection, one of whom required hospitalization. There was no significant change in serum creatinine, proteinuria or ddcfDNA during the study. Following vaccination, 36%, 25% and 20% of KTRs developed anti-spike, anti-S1 and anti-RBD antibodies. KTRs on mycophenolate-based and steroid-maintenance regimens were less likely to develop an anti-spike antibody response. 100% of KTRs with anti-spike and anti-RBD antibodies had a neutralizing response, compared to 44% in KTRs with anti-spike but without anti-RBD antibodies (RR 2.25, 95% CI 1.08-4.67). There was a significant increase in IFN-gamma spots per 10^6 PBMCs incubated with S1 peptides following vaccination (p=0.0143).

Conclusions: SARS-CoV-2 vaccination in KTRs was safe and associated with the generation of cellular immune response and in a third of patients with anti-spike antibody response. The degree of protection gained by these responses needs to be evaluated in future studies.

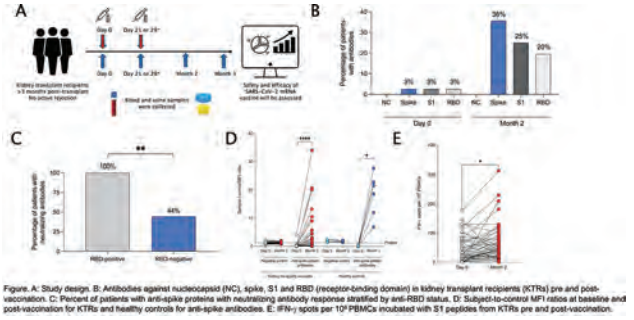

Figure. A: Study design. B: Antibodies against nucleocapsid (NC), spike, S1 and RBD (receptor-binding domain) in kidney transplant recipients (KTRs) pre and post-vaccination. C: Percent of patients with anti-spike proteins with neutralizing antibody response stratified by anti-RBD status. D: Subject-to-control MFI ratios at baseline and post-vaccination for KTRs and healthy controls for anti-spike antibodies. E: IFN-γ spots per 10^5 PBMCs incubated with S1 peptides from KTRs pre and post-vaccination.

SA-OR07

SARS-CoV-2 Vaccine Impact on COVID-19 Incidence in Maintenance Dialysis Patients

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Background: Maintenance dialysis patients are highly susceptible to SARS-CoV-2 and historically, when infected, >60% need emergency department or hospital care and mortality approaches 20% in 90 days. We evaluated the impact of vaccination against SARS-CoV-2 on incident COVID-19 cases in dialysis patients from 260 clinics in 28 states.

Methods: All adult maintenance dialysis patients without prior COVID-19 treated by Dialysis Clinic, Inc. who received one dose of vaccine were classified as "partially vaccinated" and at 14+ days after completing the manufacturer recommended series were classified as "fully vaccinated"; else were "unvaccinated". During the study period from 2/1/21 to 5/19/21, all new test-confirmed COVID-19 cases were documented. Every day at-risk for each patient was assigned to vaccination status and contributed to the denominator. Case rates per 10,000 days at-risk were compared using logistic regression.

Results: Among 13,717 eligible patients contributing 1,426,187 days at-risk, 327 new COVID-19 occurred. Only 4% were in fully vaccinated patients, with 25% in partially vaccinated and 70% in unvaccinated patients. Unvaccinated patients had 10-fold higher risk of COVID-19 than fully vaccinated patients (Table). Only 3 of 13 (23%) breakthrough cases were symptomatic, and 1 of 13 (8%) was hospitalized for COVID-19 with no deaths due to COVID-19. In contrast, 67 (29%) of unvaccinated and 34 (40%) of partially vaccinated patients were hospitalized for COVID-19, with 6 and 2 deaths, respectively.

Conclusions: Overall incidence of COVID-19 declined compared to rates prior to the study period. Regardless, there is marked risk reduction of incident COVID-19 for SARS-CoV-2 vaccinated maintenance dialysis patients, and most breakthrough infections were asymptomatic in fully vaccinated patients. These preliminary results support aggressive vaccination and a plan for maintenance of immunity to alleviate the devastating COVID-19 toll for dialysis patients.

COVID-19 Incidence from 2/1/21 to 5/19/21

Status	# Unique Patients*	Patient-Days at-Risk	# New COVID-19	new COVID-19/10,000 Pt-Days	Odds Ratio
Unvaccinated	3891	666,922	230	3.4	10.4 (6.9,18.2)
Partially Vaccinated	1112	366,775	84	2.3	6.9 (3.9,12.4)
Fully Vaccinated	8714	392,490	13	0.3	Reference

* Mutually exclusive status at the end of follow-up (may have contributed time at-risk in other statuses).

SA-OR08

Genetic Findings in COVID19-Positive Patients from a Cohort of Kidney and Liver Patients at Columbia University

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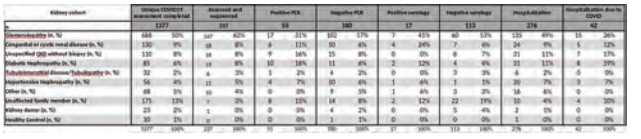
Background: Patients with preexisting chronic kidney (CKD) and liver disease and liver are more at risk from COVID-19, but reasons for variability in disease susceptibility and severity is still poorly understood. Given the high infection rate in New York City, we conducted a COVID-19 assessment survey in a cohort of CKD and liver patients previously consented into genetic studies.

Methods: Between March and August 2020, we completed 1601 unique IRB-approved COVID-19 assessment surveys. The survey covered COVID-19 symptoms, exposure risk, PCR and/or serology testing, and hospitalization. 298 of those patients were exome sequenced. We analyzed differences in COVID-19 PCR, serology and hospitalization rate and genetic analysis to identify possibly associated variants in the immune/coagulation pathways, suggested to be involved in COVID-19 susceptibility/severity by recent publicationw. We also analyzed variants based on the American College of Medical Genetics and Genomics (ACMG) guidelines for clinical annotation of genetic results

Results: Hispanic/Latino patients were more likely to have a positive COVID-19 PCR (Fisher Exact Test p: 0.01, 29.5% vs 16.7%), serology (Fisher Exact Test p: 0.02, 22.9% vs 9.7%) and hospitalization (Fisher Exact Test p: 0.01, 29.5% vs 16.7%). Patients with glomerulopathy had lower positive COVID-19 PCR tests (Fisher Exact Test p: 0.01, 14.7% vs 48.7%). Analysis of exome data identified an excess number of rare variants in genes in the immune dysregulation pathways among patients with positive COVID-19 PCR test, (fisher p: 0.01, 75% vs 18%). These results were mostly driven by rare variants in *CASP10,* which were more common among the Hispanic/Latino population.

Conclusions: We confirm that Hispanic/Latino ethnicity is a significant risk factor for positive COVID-19 PCR, serology and hospitalization. The analysis of the genetic mechanisms in immune/coagulation pathways identified an excess of rare variants in the *CASP10* gene, results that overlap with Hispanic/Latino ethnicity.



SA-OR09

APOL1 Risk Variants, AKI, and Death in Black Veterans with COVID-19

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Background: Health disparities exist in rates of acute kidney injury (AKI) and death related to COVID-19. Black patients with two copies of apolipoprotein L1 (*APOL1*) variants G1 or G2 have significantly increased rates of renal disease. It is unknown whether *APOL1* is associated with an increased risk for AKI in COVID-19 infection.

Methods: We performed a retrospective study of 990 Black patients in the VA Million Veteran Program hospitalized with COVID-19 between March 2020 and January 2021. The primary exposure was having 2 *APOL1* risk variants (APOL1 high-risk group), compared to having 1 or 0 risk variants (*APOL1* low-risk group). The primary outcome was AKI. The secondary outcomes were AKI severity stages and death. We performed a subgroup analysis in individuals with eGFR> 60 ml/min/1.73m2.

Results: 392 (39.6%) patients developed AKI, 28 (7%) required dialysis and 122 (12.3%) died. Patients categorized as *APOL1* high-risk group had a significantly higher risk of AKI (adjusted odds ratio [OR] 1.98; 95% confidence interval [CI]: 1.29-3.05; p=0.002), higher AKI severity stages (OR 2.06; 95% CI: 1.39-3.04; p<0.001) and death (OR 2.15; 95% CI: 1.23-3.67; p=0.006). The association with AKI persisted in the subgroup with normal kidney function (OR 1.92; 95% CI: 1.15-3.22; p=0.01). Figure 1. shows the proportion of patients by AKI stages according to *APOL1* risk group.

Conclusions: *APOL1* renal risk variants were associated with higher risk of AKI, AKI severity, and death in Black Veterans hospitalized with COVID-19, even amongst individuals with prior normal kidney function. We identify a specific genetic contribution to COVID-19 health disparities.

Funding: Veterans Affairs Support

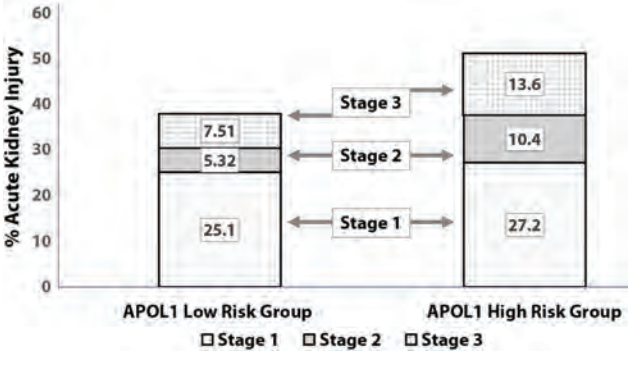

Fig. 1 Proportion of patients experiencing AKI stages severity by *APOL1* risk group

SA-OR10

Neutrophil Extracellular Traps and Endothelial Injury in COVID-19 Associated AKI

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Background: Neutrophil Extracellular Traps (NETs) release has been implicated in the pathomechanism underlying severe end-organ damage in COVID-19. While NETs are difficult to measure, cell free DNA (cfDNA) has been shown to be a surrogate measure for NETosis. The aim of this study was to determine whether circulating levels of cfDNA may be associated with development of acute kidney injury (AKI) in COVID-19.

Methods: Blood samples were collected prospectively in the emergency department from adult patients admitted to the hospital with COVID-19. cfDNA levels and serum biomarkers of AKI, thrombotic microangiopathy, and inflammation were correlated, as well as development of severe AKI defined by KDIGO SCr Stages 2+3 and need for renal replacement therapy (RRT).

Results: 51 patients were enrolled, median age 50.5 years (IQR 41-66). Age, race, coronary artery disease, heart failure, chronic kidney disease, and chronic liver disease were associated with severe AKI, while hypertension was protective. cfDNA levels were higher in those who developed severe AKI ($p<0.001$) and needed RRT ($p=0.020$) during hospitalization. cfDNA positively correlated with SCr, NGAL, cystatin C, neutrophil count, neutrophil-to-lymphocyte ratio, C3a, C5a, Scb5-9, IL-6, IL-8, IL-10, TNF-α, LDH, CRP, ferritin, fibrinogen, and negatively correlated with ADAMTS13/VWF ratio and lymphocyte count. In the multivariable logistic regression model adjusted for age, comorbidities, and SCr, one unit increase in cfDNA value was associated with a 4.6% increased odds of severe AKI (OR=1.046; p=0.040). Diagnostic performance of cfDNA is shown in Table 1.

Conclusions: Intravascular NETosis could be an important factor in development of microthrombosis and COVID-19 associated AKI. Further research is urgently needed to understand the role of NETosis in COVID-19 and evaluate therapeutic avenues.

Diagnostic Performance of cfDNA for COVID-19 AKI

	cfDNA Cut-Off (ng/mL)	Sensitivity	Specificity	AUC (95%CI)
Severe AKI	161.3	0.67	0.92	0.82 (0.67-0.97)
Need for RRT	142.0	0.75	0.77	0.76 (0.54-0.98)

SA-OR11

Identification of Molecularly Distinct Sub-Phenotypes in AKI and Association with Long-Term Clinical Outcomes

Pavan K. Bhatraju,[1] David K. Prince,[1] Sherry Mansour,[2] Talat Alp Ikizler,[3] Edward D. Siew,[3] Amit X. Garg,[4] Alan S. Go,[5] James S. Kaufman,[6] Paul L. Kimmel,[7] Steven G. Coca,[8] Chirag R. Parikh,[9] Mark M. Wurfel,[1] Jonathan Himmelfarb.[1] *[1]University of Washington, Seattle, WA; [2]Yale University, New Haven, CT; [3]Vanderbilt University, Nashville, TN; [4]Western University, London, ON, Canada; [5]University of California San Francisco, San Francisco, CA; [6]New York University, New York, NY; [7]The George Washington University Milken Institute of Public Health, Washington, DC; [8]Mount Sinai Health System, New York, NY; [9]Johns Hopkins University, Baltimore, MD.*

Background: AKI is a heterogeneous clinical syndrome with varying causes, pathophysiology and diverse clinical outcomes; however, staging AKI by serum creatinine does not fully capture underlying patient heterogeneity. Our goal was to identify AKI sub-phenotypes more tightly linked to underlying pathophysiology and long-term clinical outcomes.

Methods: We independently applied latent class analysis (LCA) and k-Means clustering to 29 clinical, plasma and urinary biomarker data measured during hospitalization to identify AKI sub-phenotypes in the ASSESS-AKI study. AKI sub-phenotype associations were examined with the composite of major adverse kidney events (MAKE), defined as incident or progressive chronic kidney disease, long-term dialysis, or all-cause death during study follow-up.

Results: Among 769 AKI patients both LCA and k-Means clustering identified two AKI sub-phenotypes. Class 1 was characterized by a higher prevalence of prior congestive heart failure and favorable blood inflammatory and urinary tubular injury biomarkers, while class 2 was characterized by higher rates of prior chronic kidney disease and less favorable biomarkers. After a median follow-up of 4.7 years, the risk for MAKE was higher with class 2 (HR 1.41; 95% CI, 1.08 to 1.84) compared with class 1 adjusting for demographics, hospital level factors and KDIGO Stage of AKI. The higher risk of MAKE among class 2 was explained by a higher risk of chronic kidney disease progression and dialysis (**Figure 1**).

Conclusions: In this analysis, we identify two molecularly distinct AKI sub-phenotypes with differing risk of long-term outcomes, independent of current criteria to risk stratify AKI. Future identification of AKI sub-phenotypes may facilitate linking therapies to underlying pathophysiology to prevent long-term sequalae after AKI.

Funding: NIDDK Support

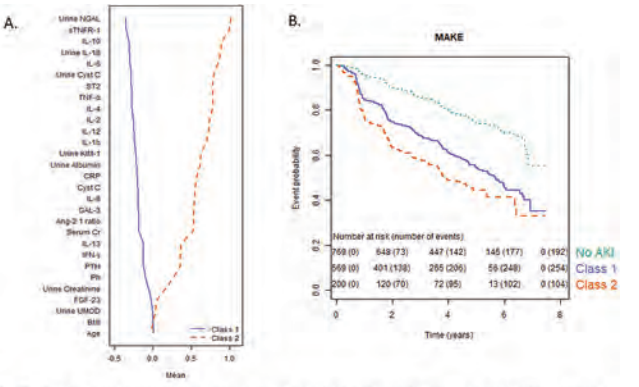

Figure 1a. 29 different continuous variables used in clustering analyses by AKI sub-phenotypes. Individual continuous variables were placed on a *z* scale with a mean of zero and standard deviation of one. Variables are presented from top to bottom in order of maximum separation between class 1 and 2.

Figure 1b. Kaplan-Meier curves for major adverse kidney events (MAKE), CKD incidence, CKD progression, dialysis and death by AKI sub-phenotypes

SA-OR12

Association of Mild-to-Moderate AKI with CKD Progression Among Individuals with CKD: The CRIC Study

Anthony N. Muiru,[1] Jesse Y. Hsu,[2] Kathleen D. Liu,[1] Paul E. Drawz,[3] Ana C. Ricardo,[4] James P. Lash,[4] Jonathan J. Taliercio,[5] Edward J. Horwitz,[6] James H. Sondheimer,[7] Jing Chen,[8] Jiang He,[8] Lawrence J. Appel,[10] Alan S. Go,[9] Chi-yuan Hsu.[1] *[1]University of California San Francisco, San Francisco, CA; [2]University of Pennsylvania, Philadelphia, PA; [3]Regents of the University of Minnesota, Minneapolis, MN; [4]University of Illinois at Chicago, Chicago, IL; [5]Cleveland Clinic, Cleveland, OH; [6]The MetroHealth System, Cleveland, OH; [7]Wayne State University School of Medicine, Detroit, MI; [8]Tulane University School of Medicine, New Orleans, LA; [9]Kaiser Permanente, Oakland, CA; [10]Johns Hopkins Medicine, Baltimore, MD.*

Background: Observational studies have suggested that even mild episodes of AKI have a large effect on accelerating CKD progression (EJ See et al 2019;95:160-172). These seem inconsistent with clinical trials in which reducing AKI rate did not translate into reducing CKD risk (AX Garg et al JAMA 2014: 311:2191-8, SG Coca et al JASN 2016; 27: 2529-42). These differences may be due to incomplete control of important confounders such as proteinuria since proteinuria is both a strong risk factor for development of AKI and CKD progression.

Methods: To better address potential residual confounding, including confounding by pre-AKI proteinuria and pre-AKI eGFR slope, we quantified the independent association between an episode of mild-to-moderate AKI (identified using inpatient SCr measurements and staged using KDIGO guidelines) on eGFR trajectory (defined using outpatient research protocol measurements) in the prospective Chronic Renal Insufficiency Cohort (CRIC).

Results: Mean age of the 3150 CRIC participants included was 65 years, 44% were female, and 43% self-identified as Black. Mean baseline eGFR was 50 mL/min/1.73m^2, median urine protein-Cr ratio was 0.1g/g, and 54% had diabetes. 433 participants experienced at least one episode of AKI (68% stage 1; 24% stage 2). In linear mixed effects models, after controlling for demographics, pre-AKI proteinuria, pre-AKI eGFR slope, and time-updated diabetes mellitus, heart failure, SBP, and receipt of ACE-I/ARBs, an episode of AKI was not significantly associated with eGFR change (difference in mean eGFR at year 1 = -0.7 mL/min/1.73 m2, 95% CI -2.7 to 1.2 mL/min/1.73 m^2 95%, p=0.46). There was no detectable change in eGFR slope from before to after AKI (difference in eGFR slope = 0.1 mL/min/1.73 m^2 per year) (p=0.82 and 95% CI -0.7 to 0.8 mL/min/1.73 m^2 per year).

Conclusions: Prior observational studies showing an association between mild-to-moderate AKI and CKD progression may be exaggerated due to residual confounding. After accounting for key potential confounders hitherto not considered in published analyses, mild-moderate AKI was not independently associated with an absolute drop in eGFR nor eGFR slope after AKI.

Funding: NIDDK Support

SA-OR13

Evidence for Kidney Involvement in an Acute Graft vs. Host Disease Model of Allogeneic Stem Cell Transplant (HSCT) in Non-Human Primates

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Background: Kidney injury is increasingly recognized as a significant cause of morbidity and mortality in recipients of HSCT. The frequency of kidney injury can be as high as 73% and among patients with kidney injury who require dialysis, mortality

approaches 100%. Acute graft-versus host disease (aGVHD) has emerged as an important risk factor for kidney injury in HSCT patients but whether the kidney itself is a target of aGVHD has not been established. In this study and utilizing a non-human primate model of HSCT we tested the hypothesis that the kidney undergoes inflammatory changes consistent with aGVHD.

Methods: For this study we used a non-human primate (NHP) model of allogeneic HSCT (allo-HCT) and aGVHD, in which a donor graft is transplanted into MHC haploidentical recipients pre-conditioned with myeloablative total body irradiation. Transplant recipients received no post-transplant immunosuppression, which enabled interrogation of the natural history of aGVHD. Apheresis was performed after G-CSF mobilization and an unmanipulated G-CSF mobilized apheresis product was transplanted into MHC haplo-identical transplant recipients in the allo-HCT cohort (N=3). As controls we used normal animals that did not undergo any intervention (N=4). NHP were euthanized one week after transplant and kidneys saved for histology and IHC (CD3, CD20, CD68, CD 56 and Granzyme B).

Results: As expected control kidneys had normal renal histology. In contrast, kidneys from allo-HCT recipients had evidence of mesangiolysis and tubulitis. By IHC we determined increased expression of $CD68^+$ monocyte lineage cells, Granzyme B^+ cytotoxic T lymphocytes and $CD\text{-}3^+$ T lymphocytes. There was no difference in the expression of $CD56^+$ NK cells while the number of $CD20^+$ B lymphocytes was lower in allo-HCT as compared to controls.

Conclusions: These studies demonstrate that aGVHD results in renal injury characterized by tubulitis and mesangiolysis and linked to increased infiltration by monocytes and T lymphoctes. These findings suggest that the kidneys are a target of aGVHD and may explain the high frequency of acute kidney injury post allo-HCT.

Funding: NIDDK Support

	CD3	CD68	CD56	CD20	Granzyme B
Control	184.4 ± 17.7	12.68 ± 3.7	50.4 ± 9.4	0.78 ± 0.13	6.35 ± 9.4
Allo-HCT	463.8 ± 22.2‡	35.17 ± 5.1 †	33.3 ± 4.9	0.37 ± 0.11 †	165.4 ± 36.4‡

† P, 0.005 vs Control, ‡ P < 0.0001 vs Control

SA-OR14

Serial Intravital Imaging of Ischemia-Reperfusion Injury Reveals the Dynamics of Tubular Injury and Repair

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Background: The kidney has a remarkable capacity to recover from acute kidney injury (AKI), but the involved dynamics of cellular damage and repair are incompletely understood. In this study, we investigated ischemia-reperfusion injury (IRI)-induced proximal tubule (PT) cell death and proliferation of the same renal cells over time using serial intravital 2-photon microscopy (2PM).

Methods: We performed 21 minutes IRI of the left kidney followed by abdominal imaging window implantation for serial imaging of the same tissue at 1 h and day 1, 2, 3, 4, 7, 14 and 21 after IRI. CycB1-GFP reporter mice identified proliferating cells by GFP-expression in S-G2-M cell cycle-stages.

Results: Necrotic tubular cell death, as detected by Propidium Iodide (PI)-staining, was primarily observed 1 h post IRI and mostly affecting PTs with 10.1±4.1 %, 12.3±3.8% and 1.9±.8% PI-positive nuclei per S1, S2 and distal tubule (DT)/collecting duct (CD) segments (Mean±SEM, n=8 each). From day 1, injured PTs shedded brushborder contents, which correlated with epithelial flattening and onset of proliferation (p=.002, r^2=.39). Tubular proliferation started day 1, peaked day 3 and was highest in S2 segments with 2.7±2%, 12.4±8.7% and 0.3±.9% (Mean±SEM, n=8 each) of GFP-positive nuclei per S1, S2 and DT/CD segments (p=.02. for S2 vs. S1 and p>.001 for S2 vs. DT/CD). While in S1 segments proliferation derived mainly from surviving cells in immediate proximity to PI-positive cells, in S2 segments also cells further distant from injured sites proliferated. We observed shedded cytosolic content from injured PT regions flowing downstream into previously PI-negative PTs, which spatially coincided with their proliferation one day after the appearance of shedded material in the lumen. By day 4, several PT segments revealed severe cast formation and epithelial vacuolization with nuclear karyolysis. 75% of the vacuolized tubule population reached full recovery before day 14 post IRI, while the remaining 25% failed to recover, resulting in nephron loss.

Conclusions: This is the first study to track IRI-induced injury and regeneration in the same renal cells over time. Our data uniquely links initial tissue damage to regenerative capacity of the renal PT in AKI and suggests distinct mechanisms for initiation of PT proliferation in S1 and S2 segments.

Funding: Private Foundation Support

SA-OR15

Genetic Validation of Hdac8 as a Therapeutic Target for AKI

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Background: We previously identified 4-phenylthiobutanoic acid (PTBA), which enhances repair in multiple models of AKI, and showed that histone deacetylase 8 (Hdac8) is a target of PTBA. Here, we show that loss of genetic deletion of Hdac8 protects against AKI in zebrafish, human kidney organoid and mouse models, and that Hdac8 mediates the efficacy of PTBA.

Methods: *hdac8*$^{sa14948/-}$ and wild type zebrafish were injected with gentamicin to induce AKI, treated +/- the PTBA prodrug, UPHD25, and AKI severity evaluated by survival, tubular proliferation, DNA damage response, and apoptosis with EdU, γH2AX, and TUNEL staining, respectively. Tamoxifen treated male UB-CRERT2; *Hdac8*$^{Y/LoxP}$ (Hdac8 KO) were evaluated over 28 days after severe ischemia reperfusion AKI (IR-AKI) by transdermal GFR (tGFR) and Sirius red staining for fibrosis. Hemin treated Hdac8 KO human kidney organoids were evaluated for injury and inflammatory markers.

Results: *hdac8*$^{-/-}$ zebrafish had enhanced survival after AKI compared to wild type controls associated with increased tubular cell proliferation, γH2AX expression, and reduced apoptosis. There was no improvement in survival in *hdac8*$^{+/-}$ mutant zebrafish with AKI, but when *hdac8*$^{+/-}$ mutants were treated with sub-therapeutic doses of UPHD25, they had improved survival. In mice, Hdac8 KO had increased tGFR at day 28 (CRE- vs. +, 495.1 (46.6) vs. 704.2 (77.1) ml/min/100gm, p<0.05), associated with reduced fibrosis in the outer medulla, and organoids showed a suppression of inflammatory markers.

Conclusions: Loss of Hdac8 reduced severity of injury and improves repair in models of AKI. Studies in *Hdac8*$^{+/-}$ mutants using sub-therapeutic doses of UPHD25 indicate that PTBA efficacy is mediated in AKI via Hdac8. Increased γH2AX expression with reduced apoptosis after AKI suggests that *hdac8*$^{-/-}$ null zebrafish preferentially uses mechanisms of DDR for repair. These data provide strong genetic evidence that Hdac8 is a valid therapeutic target for AKI; mediates PTBA effects; and suggest a potential mechanism by which Hdac8 deletion induces productive repair.

Funding: NIDDK Support

SA-OR16

Loss of Proximal Tubular Krüppel-Like Factor 15 in Kidney Injury Is Detrimental Through Suppression of Fatty Acid Oxidation

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Background: Loss of fatty acid oxidation in the proximal tubule (PT) is a critical mediator of acute kidney injury (AKI) and eventual fibrosis. The transcription factor PPARα is a key regulator of fatty acid oxidation (FAO); however, *Ppara* knockout mice do not have kidney injury at baseline, suggesting that other important regulators remain to be described. Krüppel-like factor 15 is expressed in PT, downregulated in AKI, and with PPARα, regulates FAO in cardiomyocytes. Our aim was to investigate the role of PT KLF15 in AKI and fibrosis.

Methods: PT-specific *Klf15* knockdown (*Klf15*^{PTKO}) mice were generated by breeding *Klf15*$^{fl/fl}$ and *Pepck*-Cre mice. Kidney injury was induced using the PT-specific DNA damaging agent aristolochic acid I (AAI) or by ischemia-reperfusion (IR). Blood was collected for serum biochemistry, and kidneys harvested for histological and immunofluorescence analyses. Chromatin immunoprecipitation (ChIP) studies were undertaken to detect binding of KLF15 to FAO gene promoters. Primary PT cells were harvested from *Klf15*$^{fl/fl}$ mice and *Klf15* knocked out by infection with adenovirus-Cre (control = adenovirus-GFP), followed by qRT-PCR analysis and live cell metabolic assays using a Seahorse bioanalyzer. Gene expression and eGFR data for human CKD patients in Nephroseq were utilized for correlation analyses.

Results: PT KLF15 expression was downregulated in response to injury in control mice. *Klf15*^{PTKO} mice subjected to AKI using AAI or IR had significantly worse injury than *Klf15*$^{fl/fl}$ mice, as assessed by higher serum creatinine and urea nitrogen levels, exacerbated histopathological features, more extensive loss of mature PT brush borders, and increased fibrosis in AAI-treated mice. ChIP studies showed binding of KLF15 to the promoters of genes encoding key FAO enzymes CPT1A and ACAA2. Knockdown of *Klf15* in primary PT cells resulted in decreased expression of *Ppara, Cpt1a* and *Acaa2*. Live cell metabolic assays demonstrated that loss of *Klf15* compromised PT cellular metabolism, particularly the ability to utilize palmitate in FAO. *KLF15* expression positively correlated with eGFR and *PPARA* expression in human kidney biopsies with CKD.

Conclusions: PT KLF15 is a key regulator of FAO, and loss of KLF15 in kidney injury is detrimental through compromised FAO.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR17

Single-Cell Transcriptomics Reveal Pyroptosis and Ferroptosis Inhibition Ameliorate Maladaptive AKI-to-CKD Progression and Epithelial-to-Immune Phenotype Switch

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Background: Following acute kidney injury (AKI) renal repair is possible to a certain extent. However, maladaptation to AKI leads to progression towards chronic kidney disease (CKD). Unwiring the incompletely understood processes driving both progression and repair might identify therapeutic targets to halt or reverse AKI-to-CKD progression.

Methods: Here we profiled transcriptomic changes at single-cell level over time in acutely injured kidneys of mice subjected to mild and severe bilateral ischemic reperfusion injury (IRI), modeling repair and maladaptation, respectively. Kidney function, structure, bulk and single-cell gene expression analyses were performed 1, 3 and 14d after ischemia. We used motif enrichment, trajectory, drug response pattern and cell-cell interaction analyses to define key drivers of failed and successful regeneration, finally informing *in vivo* experiments with 2 small molecules effectively ameliorating maladaptation.

Results: Long bilateral ischemia resulted in sustained renal failure (1-14d) and severe fibrosis at 14d, suggesting maladaptation, while after short ischemia early (1-3d) functional and structural impairment returned to baseline at 14d, suggesting repair. Analyzing 136,794 high-quality kidney cell transcriptomes, we uncover a maladaptive proximal tubule (PT) signature 14d after long IRI, characterized by sustained upregulation of pyroptosis and ferroptosis genes. We define the PT gene regulatory logic behind both regeneration and maladaptation, highlighting myeloid transcription factors (TFs) as novel potential drivers of AKI-to-CKD progression upstream of inflammasome effectors. Additionally, in cell-cell interaction analyses we show how PT cells acquire an immune phenotype during maladaptation. Finally, prompted by analyses of drug response transcriptional changes we show that inhibition of pyroptosis (VX765) and ferroptosis (liproxstatin) *in vivo* normalized single-cell transcriptomic kidney signatures despite severe IRI.

Conclusions: Using single-cell transcriptomics we reveal pyroptosis and ferroptosis as key druggable pathways of a detrimental PT signature associated with maladaptation to AKI and progression towards CKD, which was driven by TFs typically active in myeloid cells and characterized by a an epithelial-to-immune phenotype switch.

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

SA-OR18

VEGF-R2 Signaling in Renal Interstitium Exacerbates Post-AKI CKD Progression

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Background: A dire consequence of acute kidney injury (AKI) is progression to chronic kidney disease (CKD). AKI patients are at more than twice the increased risk of progressive CKD that leads to excessive morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available for. Peritubular capillary beds are significantly damaged during many types of AKI, which is closely associated with post-AKI CKD progression. Vascular endothelial growth factor (VEGF) is a well-defined angiogenic factor via its major receptor, VEGF receptor 2 (VegfR2). However, prior work from others demonstrated a role of VEGF as a negative regulator of pericyte function and vessel maturation. The functional implications of the VegfR2 signaling in renal interstitium remains poorly understood.

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of VegfR2 with constitutively expressed Foxd1-Cre (*VegfR2$^{RSC-/-}$*) as well as tamoxifen inducible Foxd1-Cre (*iVegfR2$^{RSC-/-}$*) to interrogate timing specific role of VegfR2 in renal interstitial cells in AKI-to-CKD. AKI/CKD models induced either by a renal ischemia/reperfusion injury (IRI) model or by low/dose repeated treatment of cisplatin were performed. Mice are monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis. Renal blood flow was evaluated with arterial spin labeling MRI (ASL-MRI).

Results: We found that *VegfR2$^{RSC-/-}$* mice have (I) reduced vascular injury and better blood flow post AKI, (II) are protected against AKI, and (III) have reduced AKI-to-CKD progression after renal IRI. Consistently, *VegfR2$^{RSC-/-}$* are protected against progression to CKD in a cisplatin AKI-to-CKD model. Mechanistically, it appears that the *VegfR2$^{RSC-/-}$* mice downregulate a maladaptive proliferation factor for pericytes, Thrombospondin-1 (TSP1). AKI triggers enhanced differentiation of a subpopulation of CD31+/ Foxd1+ cells, presumably caused by partial endothelial-mesenchymal transition (Endo-MT). Furthermore, *iVegfR2$^{RSC-/-}$* mice are significantly protected against renal IRI.

Conclusions: These data suggest that VegfR2 signaling in renal interstitial cells exacerbates renal IRI and its post-AKI CKD progression as well as cisplatin AKI.

Funding: NIDDK Support

SA-OR19

Immune Cells as Drivers of Kidney Myofibroblast Formation and Fibrosis After Acute Cardiac Dysfunction

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Background: Acute kidney injury (AKI) is a cause of chronic kidney disease (CKD). The AKI to CKD transition presents an opportunity for early intervention to prevent CKD. Myofibroblast formation is a hallmark of CKD. We have performed extensive mechanistic investigation in a translational model of AKI-CKD transition, cardiac arrest and cardiopulmonary resuscitation (CA/CPR), in which all animals develop CKD at 7 weeks. The purpose of this study was to identify potential immune drivers of myofibroblast formation.

Methods: Cardiac arrest was induced with potassium chloride in anesthesized intubated mice. Resuscitation was performed with epinephrine and chest compressions. Flow cytometry was used to profile the immune and mesenchymal landscapes during the AKI to CKD transition after CA/CPR (Fig. 1A). Kidney single nuclear RNA sequencing (snRNASeq) was performed at 1 day after CA/CPR, and CellChat was used to interrogate interactions between immune cells and myofibroblast precursors.

Results: Monocytes and natural killer cells increased in the kidney after CA/CPR (Fig. 1B). PDGFRB+ cells increased at 7 days (Fig. 1C), and immune cells colocalized with aSMA+ myofibroblasts after CA/CPR (Fig. 1D). snRNASeq revealed several distinct populations of kidney cells (Fig. 1E). High resolution subclustering combined with CellChat identified significantly upregulated interaction networks between immune cells and mesenchymal cells, including CD226 and CD96 signaling (Fig. 1E and F).

Conclusions: CA/CPR induces acute and lasting renal inflammation, which correlates with myofibroblast expansion. Lymphocytes communicate with myofibroblast precursors, revealing potential therapeutic targets.

Funding: Veterans Affairs Support

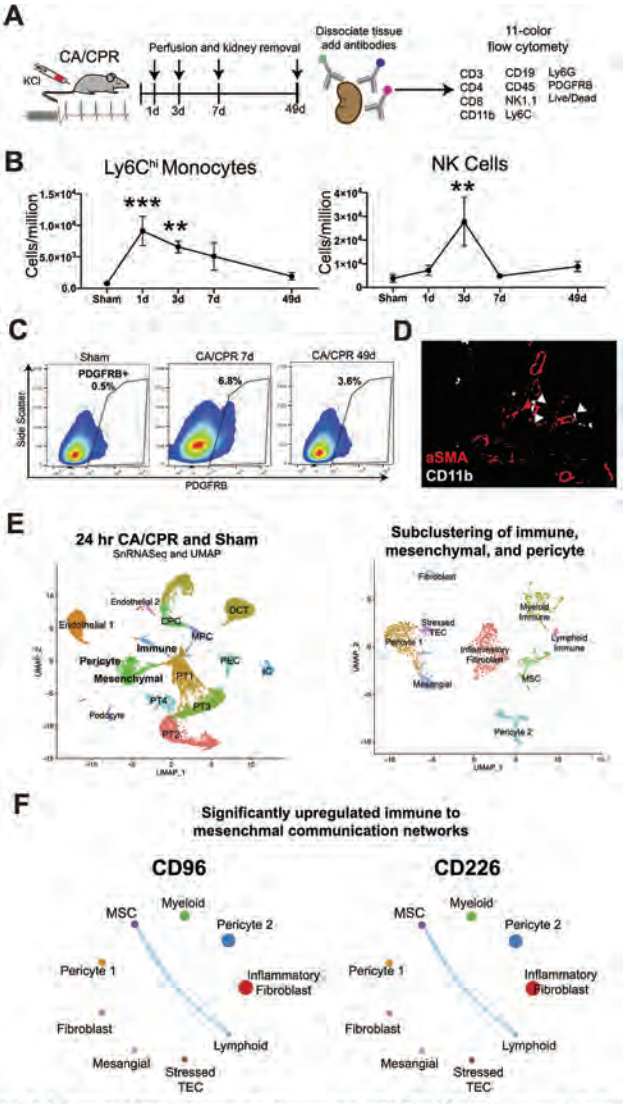

Figure 1. Assessing kidney immune and mesenchymal cells after CA/CPR. A) Workflow for flow cytometry analysis. B) Time course quantification of kidney Ly6C^{hi} monocytes and NK cells C) Quantification of PDGFRB+ (a marker for myofibroblasts and their precursors) cells in the kidney after CA/CPR. d = days after CA/CPR. D) Immunofluorescence images of alpha smooth muscle actin (aSMA), a key component of scar formation that is produced by myofibroblasts, and CD11b, a marker of myeloid cells, in the kidney after CA/CPR. Arrows denote myeloid cells in close proximity to aSMA+ cells. E) Umap clustering of cells isolated from whole kidney tissue. Clusters depict kidney cells from both vehicle and CA/CPR animals (*n*=2 kidneys and approximately 10,000 cells per group). PT = proximal tubule, IC = intercalated cells of the collecting duct, DCT = distal convoluted tubule, MPC = principal cells of the collecting duct of the medulla, CPC = principal cells of the collecting duct of the cortex, PEC = parietal epithelial cells. Right = Subclustering of immune and mesenchymal cells from panel A. TEC = tubular epithelial cell, MSC = mesenchymal stem cell. F) Circle plots depicting the immune to mesenchymal interaction networks identified. *n*=2-8/group. *P<0.05, **P<0.01, ***P<0.001 compared to sham in repeated measures one way ANOVA analysis.

SA-OR20

Differential Role of Endothelial Prolyl-Hydroxylase 1, 2, 3 in AKI

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Background: Recently, we showed that pre-ischemic inhibition of endothelial cell (EC)-HIF Prolyl Hydroxylase 2 (*Phd2*) protects against kidney ischemia-reperfusion injury (IRI). However, the role of post-ischemic inactivation of *EC-Phd2* in kidney repair remains unclear. Further, recent single-cell RNA sequencing (scRNA-seq) data suggest a role for other *EC-Phd* isoforms (*EC-Phd1* and *EC-Phd3*) in oxygen sensing. Here, we wished to address the role of post-ischemic inactivation of *EC-Phd1*, *EC-Phd2*, and *EC-Phd3* in kidney repair.

Methods: Post-ischemic inactivation of EC-*Phd1* (*EC-Phd1^{KO}*), *Phd2* (*EC-Phd2^{KO}*), and *Phd3* (*EC-Phd3^{KO}*) was achieved by the *Cdh5(PAC)CreER* inducible system. To avoid compensatory effects between *Phds*, we generated mice with concurrent deletion of EC-*Phd1, 2,* and *3* (*EC-Phd123^{KO}*) and induced recombination after IRI. Analysis was performed on day 14 post-IRI.

Results: Post-ischemic inactivation of *EC-Phd1* or *EC-Phd2* failed to protect kidneys based on mRNA expression of kidney injury molecule 1 (*Kim1*) and profibrotic genes lysyl oxidase-like 2 (*Loxl2*), transforming growth factor-beta 1 (*Tgfβ1*), and smooth muscle actin (*Acta2*) and histopathological analysis (n=7-8). Surprisingly, the inactivation of *EC-Phd3* following IRI exacerbated kidney damage and fibrosis as indicated by increased expression of *Kim1, Tgf-β*, and *Acta2* and deposition of collagen (n=6-8; p< 0.05). Likewise, post-ischemic concurrent deletion of *EC-Phd123* increased kidney damage and fibrosis assessed by histopathological analysis and increased expression of profibrotic genes and collagen deposition (n=7-8, p<0.05), respectively, compared to *Cre*-controls. These changes were associated with significant worsening of renal function assessed by blood urea nitrogen level and transdermal GFR measurements (n=7, p<0.05). scRNA-seq data of the *EC-Phd123^{KO}* post-ischemic kidneys showed significant transcriptional alterations in the EC cluster compared to *Cre*- controls with prominent changes in metabolic genes. Significant transcriptional changes were also observed in tubular, fibroblast, and inflammatory cell clusters between the two genotypes.

Conclusions: Post-ischemic concurrent inactivation of *Phd1, 2*, and *3* significantly impaired renal function, induced fibrosis which was mainly driven by *EC-Phd3* inactivation. We delineated a critical role for EC-*Phd3* in post-ischemic AKI repair.

Funding: NIDDK Support

SA-OR21

Finerenone and Kidney Outcomes in Patients with CKD and Type 2 Diabetes: Results from FIGARO-DKD

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Background: In the FIDELIO-DKD trial, finerenone reduced the risk of kidney outcomes in patients with predominantly advanced chronic kidney disease (CKD) and type 2 diabetes (T2D). FIGARO-DKD investigated the effects of finerenone in patients with less advanced CKD and T2D. The primary outcome of FIGARO-DKD was a cardiovascular composite; here we report the secondary kidney outcomes.

Methods: FIGARO-DKD (NCT02545049) was a randomized, double-blind, placebo-controlled phase III trial. Patients with T2D, urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g and estimated glomerular filtration rate (eGFR) ≥25–≤90 mL/min/1.73 m^2 or UACR ≥300–≤5000 mg/g and eGFR ≥60 mL/min/1.73 m^2, optimized renin–angiotensin system blockade, and screening serum potassium ≤4.8 mEq/L were randomized to finerenone or placebo. The key secondary kidney outcome was an eGFR 40% composite of time to kidney failure, sustained ≥40% eGFR decline from baseline, or renal death. Another similar kidney composite endpoint, exchanging a sustained ≥40% eGFR decrease with a ≥57% decrease, and change in UACR from baseline to month 4 were pre-specified outcomes in the hierarchical testing strategy.

Results: In the 7352 patients included in the analysis, 62% of patients had baseline eGFR ≥60 mL/min/1.73 m^2 and 49% had baseline UACR <300 mg/g. Over a median follow-up of 3.4 years, 350 (9.5%) patients treated with finerenone and 395 (10.8%) patients with placebo had a 40% eGFR composite endpoint event (hazard ratio [HR]=0.87, 95% confidence interval [CI] 0.76–1.01; p=0.069). There was a clinically meaningful prolongation of the time to the 57% eGFR composite endpoint with finerenone (HR=0.77, 95% CI 0.60–0.99). Greater reduction in UACR at month 4 was observed with finerenone (ratio of least-squares means 0.68, 95% CI 0.65–0.70). Overall, the incidence of adverse events were similar between treatment arms.

Conclusions: In FIGARO-DKD, patients with stage 1–4 CKD and T2D, finerenone induced a pronounced reduction in albuminuria. Kidney composite outcomes observed were directionally similar to that seen among patients with more advanced kidney disease in the FIDELIO-DKD trial.

Funding: Commercial Support - Bayer AG

SA-OR22

Finerenone in Patients with CKD and Type 2 Diabetes by SGLT-2i Treatment: The FIDELITY Analysis

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Background: The aim of the FIDELITY analysis is to evaluate the efficacy and safety of finerenone, a novel, nonsteroidal, selective mineralocorticoid receptor antagonist, across the spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELIO-DKD and FIGARO-DKD trials. Sodium-glucose co-transporter-2 inhibitors (SGLT-2is) are recommended for patients with CKD and T2D to reduce the risk of CKD progression, thus their combined use with finerenone is of interest. We report the pooled FIDELITY analysis of patients by SGLT-2i use.

Methods: This prespecified analysis combines patient-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase III, randomized, double-blind, placebo-controlled, multicenter clinical trials. Patients were randomized 1:1 to oral finerenone or placebo. Patients had T2D and either a urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g and estimated glomerular filtration rate (eGFR) ≥25–≤90 mL/min/1.73 m^2, or UACR ≥300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2, with optimized renin–angiotensin system blockade. Efficacy outcomes included a cardiovascular (CV) composite endpoint of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure, and a kidney composite endpoint of time to kidney failure, sustained ≥40% eGFR decline from baseline, or renal death.

Results: The FIDELITY analysis includes 13,026 patients. Approximately 7% of patients (n=877) received an SGLT-2i at baseline (finerenone: 6.7% [n=438]; placebo: 6.7% [n=439]). Compared with placebo, finerenone reduced the risk of the CV composite endpoint irrespective of SGLT-2i use at baseline (with SGLT-2i: hazard ratio [HR]=0.63, 95% confidence interval [CI] 0.40–<1.00; without SGLT-2i: HR=0.87, 95% CI 0.79–0.96; *p*-interaction 0.41), additional findings for efficacy outcomes, in addition to overall safety and hyperkalemia-related events by SGLT-2i treatment, will be presented.

Conclusions: FIDELIO-DKD and FIGARO-DKD comprise the largest cardiorenal outcomes program to date; therefore, combining the data for the SGLT2i subgroup in the FIDELITY analysis may provide further insights into the effects of receiving both finerenone and an SGLT-2i.

Funding: Commercial Support - Bayer AG

SA-OR23

Sodium-Glucose Cotransporter 2 Inhibitors as Adjunct Therapy for Type 1 Diabetes and the Benefit on Cardiovascular and Renal Disease Evaluated by Steno Risk Engines

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Background: Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have beneficial cardiovascular and renal effects in persons with type 2 diabetes but no studies have shown whether this can be demonstrated in type 1 diabetes (T1D). We aimed to estimate the risk of cardiovascular disease (CVD) and end-stage kidney disease (ESKD) in persons with T1D with and without treatment with SGLT2i.

Methods: The study is based on 3,660 adults with T1D treated from 2001-2016 who fulfilled the inclusion criteria of age 30-75 years and an eGFR >45 ml/min/1.73 m^2. The Steno Type 1 Risk Engine was used to calculate 5-year cumulative risks of ESKD and in the subset of 3,284 (89.7%) without previous CVD at baseline, 5- and 10-year cumulative risk of CVD were estimated. The effect of SGLT2i was simulated by changing the recorded HbA_{1c} and systolic blood pressure (SBP) values in accordance with results from the DEPICT studies. Individual absolute change in HbA_{1c} and SBP was simulated as randomly drawn numbers from a normal distribution with mean (standard deviation (SD)) of -3.6 (0.9) mmol/mmol and -1.12 (2.8) mmHg. The recorded eGFR and albuminuria were changed in accordance with results from the Tandem studies; no change in eGFR and mean (SD) %-change in albuminuria of -23.7 (12.9).

Results: The SGLT2i induced change in the risk variables translated into an overall 5-year CVD relative risk reduction of 6.1% (95%CI 5.9,6.3), with up to 11.1% (10.0,12.2) in the subgroup with albuminuria. Similar results were seen for the 10-year risk of CVD. For the estimated 5-year risk of ESKD, we found an overall relative risk reduction of 5.3% (5.1,5.4) with up to 7.6% (6.9,8.4) in the subgroup with albuminuria.

Conclusions: Using the Steno T1 CVD and renal risk engine we estimated the risk of CVD and ESKD in persons with T1D with and without treatment with SGLT2i and found a substantial CVD and ESKD risk reduction, especially in the subgroup with albuminuria. Our model provides an estimate of benefit that may balance the risks associated with use of SGLT2 inhibition in T1D.

SA-OR24

Renal Autologous Cell Therapy (REACT) for Type 2 Diabetic Kidney Disease: Preliminary Results with Renal Cortex Implantation

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Background: Diabetic Kidney Disease (DKD) is the leading cause of kidney failure in the United States. REACT in preclinical trials demonstrated stability and improved kidney function without adverse effects. We present the 12 month findings of an ongoing Phase II multicenter randomized clinical trial (RCT) evaluating autologous homologous cell therapy on DKD progression in patients with stages 3a-4 DKD.

Methods: In this open label 1:1 RCT, 83 participants, 30-80 yrs, eGFR 20-50 ml/min/1.73m^2 were randomized to either REACT or a control group of standard of care. All patients had a kidney biopsy with renal progenitor cell isolation and expansion by cGMP. The treated group received two cell implants into the kidney cortex at six-month intervals with CT guidance. The control received standard of care treatment (SoC) including maximized hypertension, diabetes and comorbidity management. The primary endpoint is change in eGFR. The current analysis compares the mean eGFR and UACR of completers in each group at 12 months.

Results: No differences in Hgb or HbA1c were present between groups at baseline or 12 months. Annualized mean eGFR increased and UACR decreased in the treatment group from time of first injection to 12 months (Table). Major bleeding complications occurred in 1% of each group following biopsy or cell injections. There were no cell-related adverse events.

Conclusions: Preliminary findings indicate implantation of progenitor REACT into the renal cortex in DKD is safe and improved annualized eGFR and UACR. Further data will follow completion of the study.

Funding: Commercial Support - ProKidney

Screening Data	Treated	Control	p value
Age (yrs)	65.6±1.5	64.5±1.4	0.61
Gender % (male)	71.4	63.4	
Caucasian %	90.5	73.2	
African American %	4.8	12.2	
Hemoglobin g/dL	12.7±0.3	12.5±0.2	0.63
HbA1c %	7.2±0.2	7.1±0.2	0.59
eGFR min/mL/1.73m2	34.2±1.3	31.48±1.3	0.67
UACR (mg/gm)	1143±29.4	1621±87.5	0.48
12-month Analysis	Treated	Control	p value
Hemoglobin	11.8±0.75	12.1±0.41	0.66
HbA1c	7.5±0.33	7.05±0.35	0.30
eGFR	38.5±3.5	28.2±2.0	0.02
UACR	455±244	834±237	0.28

All Data: Mean ± Standard Error

SA-OR25

Neuroblastoma Suppressor of Tumorigenicity 1 (NBL1) and Risk of Progression to ESKD in Diabetes

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Background: *TGF*-β-related signaling proteins have been implicated in the development of end-stage kidney disease (ESKD) in diabetes. Most of this evidence has come from cellular and animal studies focusing on individual proteins and, to date, no study has demonstrated the involvement of these proteins in the etiology of ESKD in humans.

Methods: Using aptamer-based SomaScan platform, 25 TGF-β-related circulating proteins including ligands, receptors, and inhibitors were measured in baseline plasma obtained from 4 different cohorts of 754 Caucasian and Pima Indian subjects; including 219 with Type 1 diabetes (T1D) and CKD stage 3 (CKD3) and 144 with T2D and CKD3, and 238 T1D subjects with CKD1,2 and 153 T2D Pima Indian subjects with CKD1,2. All patients were followed for 10 years to ascertain onset of ESKD.

Results: In logistic regression analysis, NBL1, FSTL3, RGMB, and TGF-β RIII were strongly associated with progression to ESKD in all cohorts (Table 1). In multivariable logistic regression analysis for 4 proteins and clinical variables, NBL1, a secreted BMP antagonist never before implicated in kidney diseases, was identified as the only protein very strongly and independently associated with progression to ESKD. Importantly, renal structural parameters, measured quantitatively in research kidney biopsies obtained from Pima Indian subjects, were strongly associated with circulating level of NBL1.

Conclusions: Our study did not find any associations with conventional TGF-β-related proteins but pointed to NBL1 as a very important factor in progression to ESKD. NBL1 is a novel strong biomarker for kidney disease progression, and regulation of this protein may become new therapeutic targets to retard progression to ESKD in diabetes.

Funding: NIDDK Support, Other NIH Support - the National Institutes of Health (NIH) (DK041526 and DK110350)

Table 1. Logistic regression for each group

	Joslin Cohorts (Caucasian)						Pima Indian Cohort	
	T1D CKD3 (n=219)		T2D CKD3 (n=144)		T1D CKD1-2 (n=238)		T2D CKD1-2 (n=153)	
	OR	Bonferroni P	OR	P	OR	P	OR	P
NBL1	3.39	9.3x10-12	3.54	7.2x10-7	2.05	1.4x10-5	2.92	5.2x10-6
FSTL3	2.41	3.5x10-8	2.31	6.6x10-5	2.24	2.6x10-6	1.45	0.041
RGMB	2.06	3.8x10-6	2.12	2.1x10-4	1.37	0.034	2.01	5.1x10-4
TGF-β R III	1.64	3.3x10-3	1.58	0.014	1.40	0.024	1.50	0.027

SA-OR26

Genome-Wide Association Study (GWAS) in the Million Veteran Program of Diabetic Kidney Disease (DKD) Highlights Biology of the Glomerular Basement Membrane (GBM) and Tubular Transporter in DKD

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Background: Diabetes is the most common cause of end-stage renal disease (ESRD) worldwide. Diabetic Kidney Disease (DKD) is defined by reduced kidney function and/or albuminuria. We here study the genetic determinants of DKD.

Methods: Our primary outcome was a composite of low estimated glomerular filtration rate (eGFR), or end-stage renal disease (ESRD). Cases had to meet criteria for diabetes for at least 5 years before the onset of DKD, while controls had to meet diabetes criteria for at least 7 years without DKD. Our secondary outcome was proteinuria/macroalbuminuria, no specific diabetes duration was required for the proteinuria cases. We conducted a large GWAS in 50,355 participants (21,273 cases) of European ancestry, and 18,144 (7,700 cases) of Non-Hispanic Blacks. Cases and controls were regressed onto additively coded genotypes imputed to a 1000 Genomes panel, with MAF>1%, adjusting for model 1: age, sex and 10 race/ethnicity-specific principal components and model 2: model 1 plus median HbA1c, BMI, and systolic blood pressure. Inverse-variance-weighted fixed-effects meta-analysis was conducted across race groups.

Results: Two loci reach genome-wide significance in the transethnic GWAS for low GFR or ESRD: rs113795872 (*CUBN*, p=9.8E-14), and rs71149134 (*UMOD*, p= 3.761 E-32). We replicated the association with the one variant in *COL4A3* reported as associated with DKD rs55703767 (p=0.02). Five loci that reach GWAS significant association with persistent gross proteinuria: *CUBN* (p=1.77 E-25), *UMOD* (4.5E-14), *CCD158* (8.17 E-10), *SHROOM3* (6.69 E-09), and *CEBPG* (1.5 E-08).

Conclusions: Our study found 5 genome-wide significant associations with different manifestations of DKD. Some of the involved genes play a role as a component of the glomerular basement membrane or renal tubular function and may represent targets for therapy.

Funding: Veterans Affairs Support

SA-OR27

Urinary Complement Proteome and 10-Year Risk of ESKD in Diabetes

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Background: Our pilot urinary inflammatory proteomics identified enrichment in the Complement system in subjects with progressive diabetic kidney disease (DKD). Thus, we aimed to comprehensively evaluate the Complement proteome reflected by: i) relationships of urinary profiles with prospective ESKD risk, and ii) kidney tissue expressions in DKD.

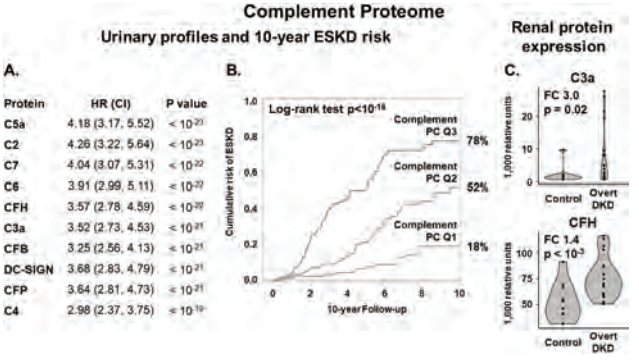
Methods: Our prospective cohort study comprised 371 Joslin Kidney Study subjects with Type 1 (T1D) or Type 2 (T2D) Diabetes and an overt DKD (mean eGFR 45 mL/min/1.73m^2, ACR 1,075 mg/g). Our main outcome was 10-year ESKD risk. We measured 82 Complement proteins in baseline urine with aptamer proteomics; 8 were validated by

quantitative immunoassays. We evaluated kidney tissue expressions of the Complement system with aptamer proteomics in 23 subjects with an overt DKD and 10 controls.

Results: 160 (43%) subjects developed ESKD in 10 years. Multiple Complement proteins were associated with ESKD risk in Bonferroni-adjusted Cox models (risk per tertile change of the top protein, C5a: HR 4.2, $p<10^{-23}$; Fig. A). Cumulative 10-year risk for subjects with low levels of the top proteins built into Principal Component-based tertiles (PC) was 18%, vs. 78% for those with high levels (Fig. B). Accuracy of biostatistical and machine learning models built on the top proteins ranged from c=0.85 to 0.87. Quantitative measurements correlated with proteomics measurements and our outcome (median CFH in ESKD progressors: 214 vs. non-progressors: 8 ng/mg; $p<10^{-14}$). Of the top 10 urinary Complement proteins, 5 had increased renal expressions in subjects with DKD compared to controls. Renal expression of C3a featured the highest fold change, and CFH had the most significant association (Fig. C).

Conclusions: This study revealed robust associations of the urinary Complement proteome with 10-year risk of ESKD in subjects with T1D and T2D, with select correspondence in kidney protein expressions. These findings strongly suggest that the Complement system is an important driver of DKD progression.

Funding: Other NIH Support - NIH R01 DK123459, Private Foundation Support



SA-OR28

Circulating Metabolites to Predict Renal Outcomes in CANVAS Type 2 Diabetes Mellitus Population

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Background: Albuminuria and eGFR are biomarkers for kidney disease progression but fail to explain all future risk. Additional biomarkers that better represent underlying disease pathophysiology may improve the prediction of progression from chronic kidney disease (CKD) to end stage renal disease (ESRD). We examined if baseline plasma metabolites predict renal outcomes in the Canagliflozin Cardiovascular Assessment Study (CANVAS) participants.

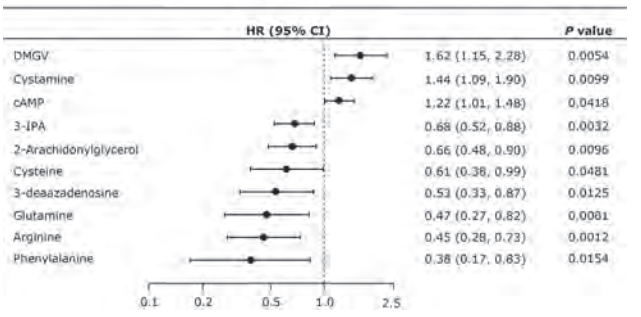
Methods: Plasma metabolites were assayed from a subset of the CANVAS study participants by HPLC (HILIC)-mass spectrometry using targeted assays. Forty-two metabolites were analyzed for association with the renal outcome (40% eGFR decline, end-stage kidney disease, or renal death) using Cox regression.

Results: We included 967 (22%) of the 4,330 CANVAS participants comprising 341 females (35%), mean age 63 ± 8 years, and BMI 33 ± 5 kg/m^2. All patients had T2DM with mean HbA1c 8.2 ± 0.9%, eGFR 75.5 ± 18.3 mL/min/1.73m^2, and median ACR (1Q, 3Q) 11.89 (6.5, 37.49). During a median follow-up of 5.6 years, 63 (6.5%) patients experienced a renal event. There were 10 metabolites significantly associated with the renal outcome (all P <0.05) when adjusted for age and gender (**Figure**) and treatment effect. In a fully adjusted model (age, gender, race, BMI, HbA1c, cholesterol, blood pressure, history of heart failure, baseline ACR and eGFR), arginine alone remained significant (P = 0.01).

Conclusions: Lower baseline plasma arginine levels are independently associated with high risk for renal events in patients with T2DM.

Funding: Commercial Support - Janssen Research & Development, LLC

Figure: Hazard ratios of metabolites associated with renal events in CANVAS study.



SA-OR29

Uremic Solutes Are Associated with Cardiovascular Death in Diabetic Kidney Disease

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Background: Cardiovascular disease (CVD) is a major cause of mortality among people with diabetic kidney disease (DKD). The pathophysiology of CVD in DKD is not explained adequately by traditional CVD risk factors. Three small molecular weight, uncharged uremic solutes, asymmetric and symmetric dimethylarginine (ADMA, SDMA) and trimethylamine-N-oxide (TMAO) have been linked to CVD in ESKD. These solutes may be markers of CV mortality in non-ESKD DKD, as well as DKD progression to ESKD.

Methods: Uremic solutes in plasma and urine were assayed by mass spectrometry from a random subcohort of 555 REGARDS Study participants with diabetes and eGFR <60 ml/min/1.73m^2 at study entry. Plasma concentrations and urine:plasma (U/P) ratios of each solute were tested for association with CV mortality (primary outcome), all-cause mortality and incident ESKD (secondary outcomes). Cox regression models estimated the hazard ratios (HR) per $\log_2$ increment, adjusted for demographic and CVD risk factors, baseline eGFR and urine albumin to creatinine ratio (UACR).

Results: Mean (SD) baseline eGFR was 44 ± 12 ml/min/1.73 m^2, median (IQR) UACR was 32 (11, 203) mg/g. CV death, overall mortality and ESKD occurred in 120, 285 and 89 participants, respectively, during mean 6.2 years of follow-up. Higher plasma ADMA, and lower U/P ratios of all three solutes were associated with increased CV mortality (Table). Higher plasma concentrations and lower U/P ratios of all three solutes were significantly associated with all-cause mortality. Only higher plasma SDMA was associated with incident ESKD.

Conclusions: Higher plasma concentration and lower U/P ratio of ADMA were independently associated with CV and all-cause mortality in DKD. The strong associations of U/P ratios with CV mortality outcomes suggest a connection between renal clearance of uremic solutes and CVD pathogenesis.

Funding: NIDDK Support

Table 1. Association of plasma biomarkers and U/P ratios (per two-fold higher) with mortality and incident ESKD outcomes.

Biomarker	Continuous (log2)
Plasma ADMA	
Adjusted HR CV mortality (95% CI)	2.10 (1.07, 4.14)
Adjusted HR all-cause mortality (95% CI)	2.79 (1.79, 4.33)
Plasma SDMA	
Adjusted HR all-cause mortality (95% CI)	2.35 (1.66, 3.33)
Adjusted HR incident ESKD (95% CI)	2.07 (1.18, 3.63)
Plasma TMAO	
Adjusted HR all-cause mortality (95% CI)	1.14 (1.01, 1.30)
U/P ADMA	
Adjusted HR CV mortality (95% CI)	1.53 (1.23, 1.90)
Adjusted HR all-cause mortality (95% CI)	1.34 (1.17, 1.53)
U/P SDMA	
Adjusted HR CV mortality (95% CI)	1.69 (1.37, 2.09)
Adjusted HR all-cause mortality (95% CI)	1.37 (1.19, 1.58)
U/P TMAO	
Adjusted HR CV mortality (95% CI)	1.38 (1.21, 1.57)
Adjusted HR all-cause mortality (95% CI)	1.26 (1.15, 1.39)

SA-OR30

Essential Branched-Chain Amino Acids and Ribonic Acid Are Associated with Cardiorenal Events in Type 1 Diabetes

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Background: Diabetic kidney disease and cardiovascular disease (CVD) remain the leading causes of morbidity and mortality in diabetes despite recent advances in treatment. Further understanding of the underlying pathophysiology is needed. We investigated associations between serum metabolites and cardiorenal events.

Methods: The study comprised of 637 individuals with type 1 diabetes and various degrees of albuminuria. Non-targeted serum metabolomics was performed using two-dimensional gas chromatography coupled to time-of-flight mass-spectrometry. Longitudinal data on combined cardiorenal events (coronary events, peripheral arterial interventions, stroke, eGFR decline ≥30%, end-stage kidney disease and all-cause mortality) were obtained from National Danish Health registries and analyzed by Cox proportional hazards models. Adjustments included sex, baseline age, HbA_{1c}, mean arterial pressure, smoking, body mass index, statin treatment, p-triglycerides, total p-cholesterol, eGFR, albuminuria, previous CVD and correction for multiple testing by false discovery rate (FDR).

Results: Of the included participants, 55% were male and baseline mean age was 55 ± 13 years. 28% had macroalbuminuria, 25% microalbuminuria and 47% normoalbuminuria. The mean eGFR was 81 ± 26 ml/min/1.73m^2. A total of 75 metabolites were included in the analyses. Over a median (IQR) of 5.2 (4.8-5.7) years, 173 cardiorenal events were recorded. In adjusted analyses, ribonic acid was associated with a higher risk of cardiorenal events. (HR 1.4, CI [1.2-1.8], p_{FDR}=0.04). The essential branched-chain amino acids leucine (HR 0.8, CI [0.7-0.9], p_{FDR}=0.04) and valine (HR 0.8, CI [0.6-0.9], p_{FDR}=0.02) were associated with a lower risk of cardiorenal events.

Conclusions: In individuals with type 1 diabetes and various degrees of albuminuria, ribonic acid was associated with an increased risk of cardiorenal events and two essential branched-chain amino acids with a decreased risk, independently of relevant confounders. These findings might indicate important pathophysiology in the development of cardiorenal disease.

SA-OR31

Voclosporin Is Effective in Achieving Complete Renal Response in Severe Lupus Nephritis

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Background: Voclosporin is a novel calcineurin inhibitor with a favorable metabolic profile and a consistent dose-concentration relationship. The Phase 3 AURORA 1 trial demonstrated that compared to mycophenolate mofetil (MMF) and low-dose steroids, adding voclosporin significantly increased complete renal response (CRR) rates in patients with lupus nephritis (LN). We report the results of a post-hoc analysis evaluating if the efficacy of voclosporin in patients with severe LN is similar to the overall population of AURORA 1.

Methods: Patients with systemic lupus erythematosus, biopsy-proven active LN (Class III, IV or V ± III/IV), and proteinuria of ≥1.5 mg/mg (≥2 mg/mg for Class V) were eligible to enroll in AURORA 1. Overall, 179 and 178 patients were randomized to the voclosporin (23.7 mg BID) and control arms, respectively. All patients received MMF (1 g BID) and low-dose oral steroids. Severe LN was defined as baseline UPCR ≥3 mg/mg with Class III or IV biopsy (± Class V) with active lesions. Renal function and serology were evaluated to ensure the population was representative of severe disease in clinical practice. CRR was defined as UPCR ≤0.5 mg/mg with stable renal function, use of low-dose steroids and no use of rescue medication.

Results: There were 76 and 72 patients in the voclosporin and control arms, respectively, with severe disease. Mean (SD) UPCR at baseline was 5.9 (2.4) mg/mg (Table 1). CRR at one year was 34.2% and 11.1% in the voclosporin and control arms, respectively (odds ratio 4.43, p=0.001; Figure 1).

Conclusions: In patients with severe LN, adding voclosporin to MMF and steroids results in statistically significantly higher CRR rates. This is clinically meaningful given that patients with severe disease are at higher risk of worse long-term outcomes and development of ESKD.

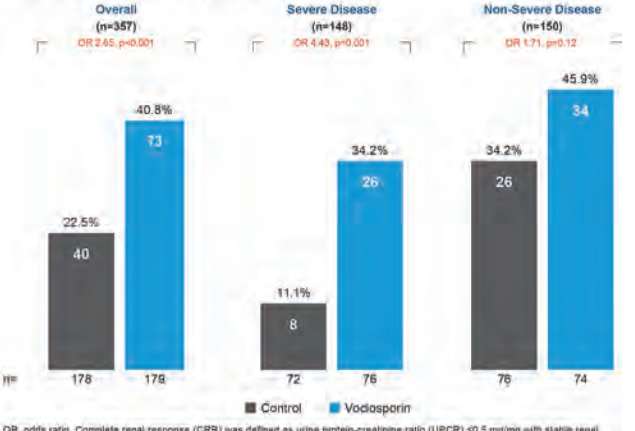
Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

Table 1. Key Clinical Characteristics at Baseline and Week 52

Parameter	Baseline		Week 52	
	Severe Disease (n=148)	Non-Severe Disease (n=150)	Severe Disease (n=148)	Non-Severe Disease (n=150)
Time since LN diagnosis, years Mean (SD)	3.2 (4.1)	4.5 (5.8)		
eGFR,[a] mL/min/1.73 m^2 Mean (SD)	87.6 (29.5)	91.6 (29.8)	89.6 (32.8)	93.2 (29.8)
Serum creatinine, mg/dL Mean (SD)	0.9 (0.3)	0.9 (0.3)	1.1 (1.0)	1.0 (0.8)
UPCR, mg/mg Mean (SD)	5.9 (2.4)	2.1 (0.4)	2.3 (2.9)	1.0 (1.4)
Complement 3 Mean (SD), mg/dL Low <90 mg/dL, n (%)	77.9 (34.0) 96 (64.9)	86.6 (35.4) 80 (53.3)	97.6 (32.8) 52 (35.1)	96.5 (32.5) 58 (38.7)
Anti-dsDNA, IU/mL Mean (SD)	110.9 (129.3)	109.9 (129.9)	48.3 (60.7)	54.7 (83.2)

[a]Patients with baseline eGFR <45 mL/min/1.73 m^2 were excluded from the study. Anti-dsDNA, anti-double stranded DNA; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SD, standard deviation; UPCR, urine protein-creatinine ratio.

Figure 1. Complete Renal Response Rates at One Year



OR, odds ratio. Complete renal response (CRR) was defined as urine protein-creatinine ratio (UPCR) ≤0.5 mg/mg with stable renal function in the presence of low-dose steroids and no use of rescue medication.

SA-OR32

Effects of Belimumab (BEL) on Renal Outcomes in Patients (pts) with Relapsed and Newly Diagnosed Active Lupus Nephritis (LN)

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Background: Despite standard therapy (ST) for LN, only 20–40% of pts achieve Complete Renal Response (CRR) at 0.5–1 year and 20–25% relapse in 3–5 years. The aim of this study was to assess effects of BEL on renal outcomes in relapsed and newly diagnosed pts with LN.

Methods: Post hoc analysis of the Phase 3, randomized, double-blind, 104-week BLISS-LN study (GSK BEL114054; NCT01639339). Pts with active LN received monthly intravenous (IV) BEL 10 mg/kg or placebo (PBO) + ST. Randomization was stratified by induction regimen: high dose corticosteroids (HDCS) + cyclophosphamide (CYC), followed by azathioprine + low-dose corticosteroids (LDCS), or HDCS + mycophenolate mofetil (MMF), followed by MMF + LDCS. We assessed Primary Efficacy Renal Response (PERR; uPCR ≤0.7; eGFR no more than 20% below pre-flare value or ≥60 ml/min/1.73m^2; no rescue therapy) and CRR (uPCR <0.5; eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73m^2; no rescue therapy) at Week 104 and time to renal-related event or death in relapsed vs newly diagnosed pts.

Results: Of 446 pts included in this analysis, 150 had relapse of LN and 296 were newly diagnosed. Positive effects of BEL vs PBO on PERR and CRR were noted in both subgroups and were numerically greater in relapsed vs newly diagnosed pts (**Table**). BEL-treated pts had a lower risk at any time of experiencing a renal-related event or death vs PBO in both subgroups (**Table**).

Conclusions: These data suggest BEL improved PERR and CRR rates more potently in relapsed pts, in which PERR and CRR were substantially less frequent compared with newly diagnosed LN.

Funding: Commercial Support - GSK

Table. Effect of BEL 10 mg/kg IV on PERR and CRR at Week 104 and time to renal-related event or death in newly diagnosed and relapsed pts with LN

	Relapsed		Newly diagnosed	
	PBO (n=75)	BEL 10 mg/kg IV (n=75)	PBO (n=148)	BEL 10 mg/kg IV (n=148)
PERR at Week 104, n (%)	17 (22.7)	27 (36.0)	55 (37.2)	69 (46.6)
OR (95% CI) vs PBO	2.31 (1.07, 5.01)		1.36 (0.85, 2.20)	
p-value	0.0331		0.2036	
CRR at Week 104, n (%)	8 (10.7)	17 (22.7)	36 (24.3)	50 (33.8)
OR (95% CI) vs PBO	3.11 (1.16, 8.31)		1.49 (0.88, 2.51)	
p-value	0.0237		0.1355	
Time to renal-related event or death*, n (%)	23 (30.7)	12 (16.0)	40 (27.0)	23 (15.5)
HR (95% CI) vs PBO	0.47 (0.23, 0.95)		0.55 (0.33, 0.93)	
p-value	0.0354		0.0242	

*Time to renal-related event or death is a composite endpoint defined as the first event occurring after Day 1 among the following: 1) death, 2) end-stage kidney disease, 3) doubling of serum creatinine, 4) renal worsening as evidenced by increased proteinuria and/or impaired renal function, or 5) renal disease-related treatment failure

OR, 95% CI and p-value are from a logistic regression model run within the subgroup level for the comparison between BEL and PBO with covariates of induction regimen (CYC vs MMF), race (Black African descent vs other), baseline uPCR, and baseline eGFR

HR, 95% CI and p-value from Cox proportional hazards model for the comparison between BEL and PBO adjusted for induction regimen (CYC vs MMF), race (Black African descent vs other), baseline uPCR, and baseline eGFR

CI, confidence interval; HR, hazard ratio; OR, odds ratio

SA-OR33

Antibodies Anti-Rituximab Do Not Affect Response to Rituximab in Idiopathic Nephrotic Syndrome

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Background: Previous studies reported how infusion of the chimeric anti-CD20 rituximab results in production of antibodies anti-rituximab, that may limit the efficacy of further infusions. Among other reasons, the reduced immunogenicity of fully humanized anti-CD20 antibodies should increase their efficacy. In a randomized clinical trial, we compared the efficacy of ofatumumab *vs.* rituximab in children and young adults with steroid dependent nephrotic syndrome. As secondary endpoints, we evaluated possible role of anti-CD20 rituximab.

Methods: We randomized 140 children treated with single infusion of rituximab or ofatumumab, with a follow up of 24 months. We measured anti-rituximab antibodies IgG at the enrolment in 64/140 (46%) patients who have previously received rituximab and at 6 months in patients in the rituximab arm. Median time of the previous rituximab was 36 (12-51) months before enrolment.

Results: As primary endpoint, ofatumumab was not superior to rituximab in maintaining remission (**Fig 1a**). Serum anti-rituximab IgG were undetectable at baseline in 64 participants who had previously received rituximab. Six months following rituximab infusion, anti-rituximab antibody levels increased in 14 (42%) of the 33/64 patients who were randomized in the rituximab arm (**Fig 1b**). Among patients with relapse in rituximab arm, the efficacy of a second infusion of rituximab, infused in accordance with the protocol, was not affected by the presence of anti-rituximab antibodies (**Fig 1c**).

Conclusions: Previous exposure to rituximab results in production of anti-rituximab antibodies, which persist for a limited time. Presence of circulating anti-rituximab antibodies does not affect response to rituximab in steroid dependent nephrotic syndrome.

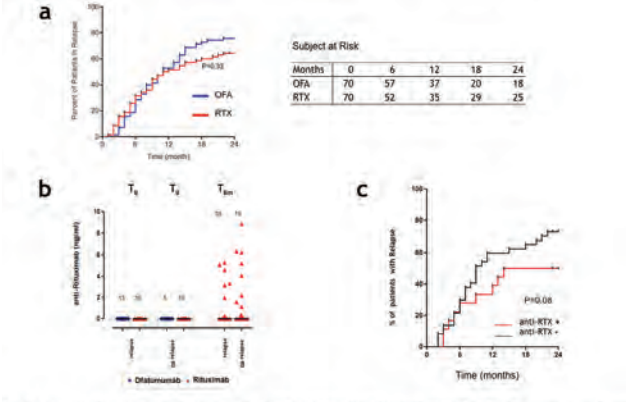

Figure 1. a) Relapse-free survival by treatment arm (Odds Ratio [OR] 1.06; 95% confidence interval [CI] 0.55 to 2.06). **b)** Circulating levels of anti-rituximab antibodies in patients receiving ofatumumab (blue) and rituximab (red) at the enrolment; the same cohort who received rituximab was tested 6 months after the infusion. **c)** Survival curve in patients in rituximab arm receiving a second infusion, with and without circulating anti-rituximab antibodies.

SA-OR34

Glomerular Exostosin as a New Subtype and Activity Marker for Membranous Lupus Nephritis

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Background: Exostosin (EXT) expression has been shown to be related to membranous lupus nephritis (MLN). This study analyzed the distribution of EXT in MLN and its correlation with the activity, histological transformation and prognosis of MLN.

Methods: The renal biopsy specimens from MLN, other types of lupus nephritis (LN), other disease-related membranous nephropathy (MN), and PLA2R-related MN were included. EXT expression was detected by immunohistochemistry and was quantitatively determined by computer image analysis. The correlations between proteinuria and EXT expression, the differences between EXT-positive and EXT-negative MLN, and the relationship between pathological changes and EXT expression were analyzed by repeated renal biopsy.

Results: Of the 153 MLN, 47.7% were EXT positive; of the other types of LN, only 6.8% were EXT positive. The EXT-positive rates for Hashimoto's thyroiditis, Sjogren and HBV related MN were 16.7%, 10.0% and 10.0%, respectively. EXT was negative in psoriasis, mercury poisoning, tumor and GVHD or the PLA2R related MN. The EXT-positive rates in groups with 24-h urinary protein of <1 g, 1.0-2.9 g, 3.0g-4.9 g and ≥5.0 g were 32.3%, 39.6%, 50.0% and 68.4%, respectively (P=0.013), and EXT expression intensity was also positively correlated with proteinuria (r=0.78, P<0.001). When the EXT-positive was compared with the EXT-negative MLN, 24h urinary protein (P<0.001) and the proportion of massive subepithelial immune deposits (P<0.001) were higher, and the serum albumin (P<0.001), and CI (P<0.05) and renal tubular atrophy score (P<0.05) were lower. There were no significant differences in renal survival between the two groups. A total of 47 MLN (18 EXT-positive and 29 EXT-negative) underwent repeat renal biopsy after treatment or recurrence. For EXT-negative MLN, EXT remained negative in repeated biopsy regardless of pathological type (class V or class V+III/IV after transformation); for EXT-positive MLN, EXT became negative or EXT expression was reduced after renal remission, and as shown in repeated biopsy after recurrence: 62.5% of MLN without histological transformation were still EXT positive, but 80% of cases whose histological class became class V with III or IV were EXT negative.

Conclusions: Our study indicated that EXT expression in MLN could be used as a marker of diagnosis and activity, and a histological subtype marker of MLN.

SA-OR35

Computationally Extracted Peritubular Capillary Shape Is Associated with Progression in Glomerular Diseases

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Background: In CKD models, the association between peritubular capillary (PTC) density and outcome has been demonstrated, but little is known about PTC pathomic features in glomerular diseases. We explored whether computer extracted features quantifying PTC shape and density can predict risk of progression (40% eGFR decline or kidney failure) in proteinuric diseases.

Methods: N=358 PAS-stained whole slide images from the NEPTUNE database were included: 133 Focal Segmental Glomerulosclerosis (FSGS), 55 IgA Nephropathy (IgAN), 109 Minimal Change Disease (MCD), and 61 Membranous Nephropathy (MN). The presence of segmental sclerosis (SS) further subclassified IgAN and MN. The kidney cortex was manually annotated, and a pre-trained deep learning model generated PTC segmentations (Fig. 1). Average PTC flatness (the PTC major and minor axis ratio) and cortical density (PTC pixels/unit cortical area) were digitally measured. Unadjusted Cox proportional hazards models were used to associate normalized PTC flatness and density with outcome across and within each disease, within cases with SS (FSGS, IgAN+SS, MN+SS) and w/o SS (MCD, IgAN w/o SS, MN w/o SS), and within gender and age.

Results: PTC flatness ≥0.469 significantly associated with a hazard ratio (95% CI) of progression of 1.99 (1.19-3.33) compared with normalized PTC flatness <0.469 (p=0.0109) (Fig. 1). PTC cortical density ≥ 0.135 associated with a hazard ratio (95% CI) of progression of 0.689 (0.398 – 1.19) compared with normalized PTC cortical density <0.135 (p=0.16). PTC flatness significantly associated with outcome in FSGS (p=0.045), in the presence of SS (p=0.022), in males (p=0.0138), and adults (p=0.016), but not in children, females, or patients w/o SS.

Conclusions: PTC flatness was significantly associated with progression in glomerular diseases, particularly in patients with SS. This association is age and gender dependent.

Funding: Private Foundation Support

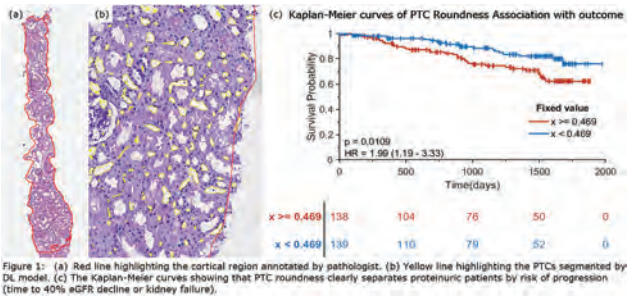

Figure 1: (a) Red line highlighting the cortical region annotated by pathologist. (b) Yellow line highlighting the PTCs segmented by DL model. (c) The Kaplan-Meier curves showing that PTC roundness clearly separates proteinuric patients by risk of progression (time to 40% eGFR decline or kidney failure).

Figure 1

SA-OR36

Abstract Withdrawn

SA-OR37

Upregulated JAK-STAT Signaling and Augmented Potassium Efflux Characterize Induced Pluripotent Stem Cell-Derived Podocytes of Black Patients with APOL1-Associated FSGS

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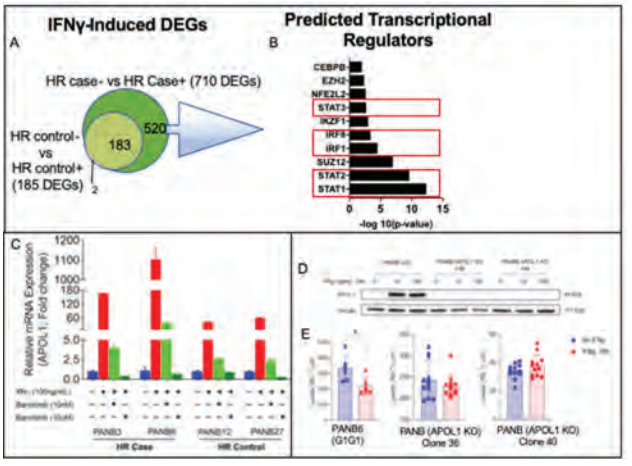
Background: High risk (HR) APOL1 genotypes account for 70% of excess risk of FSGS among Blacks. It is unknown why ~20% of carriers of HR APOL1 genotypes develop FSGS or other APOL1 nephropathies while 80% kidney disease-free. The possible role of genetic modifiers has been proposed. Also, the mechanism by which variants APOL1 cause podocyte injury is unknown. We previously reported that overexpression of variants APOL1 in HEK293 cells caused cytotoxic loss of cellular K^+. it is unknown if physiologic expression of APOL1 by IFNγ also causes K^+ loss in patient-derived podocytes.

Methods: We recruited Blacks with biopsy-proven FSGS (n=16) or with normal GFR and no proteinuria (n=20). 68.7% and 10% of FSGS cases and healthy controls carried HR APOL1 genotypes, respectively. Markers-confirmed iPSC-podocytes generated from 7 HR cases and 2 HR controls were treated or not with IFNγ followed by whole genome transcriptomics and measurement of cellular K^+. Additionally, APOL1-knockout iPSC-podocytes were generated using CRISPR-Cas9.

Results: Notably, the 520 differentially expressed genes (DEGs) unique to HR cases are transcriptionally regulated by JAK-STAT signaling (Fig. A-B). Consistent with this finding, IFNγ induces a higher expression of APOL1 in HR cases which was blocked by JAK1/2-specific inhibitor, Baricitinib (Fig C). Importantly, for the first time, we demonstrated that physiologic expression of variant APOL1 under its endogenous promoter causes significant loss of cellular K^+ in iPSC-podocyte of HR cases and was abolished by APOL1-knockout (Fig D-E).

Conclusions: JAK-STAT signaling may be an important modifier of APOL1-associated FSGS that upregulates APOL1 expression and function (K^+ efflux). Inhibition of JAK-STAT signaling and/or blockade of APOL1-mediated cation-transport may represent targeted therapeutic approach for APOL1-associated FSGS.

Funding: Other NIH Support - Common Fund (NIH Director's New Innovator Award)



IFNγ induces higher JAK-STAT signaling, APOL1 expression and Rb^+ efflux in iPSC-podocytes of HR cases. APOL1 KO blocks Rb^+ efflux.

SA-OR38

Transcriptional Reprogramming by Wilms' Tumor 1 and FoxC2 Mediates a Repair Response During Podocyte Injury

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Background: We previously demonstrated a transcriptional response to injury in podocytes and identified WT1 as one of the most upstream transcription factors binding nearly all genes known to be crucial for maintenance of the glomerular filtration barrier. We now demonstrate that FoxC2 transcription factor is a major component of the response to injury, binding many of the same genes as WT1. Here, we focus on understanding WT1 and FoxC2 transcriptional mechanism in response to injury.

Methods: We used Adriamycin (ADR)-induced podocyte injury as a model for human Focal Segmental Glomerulosclerosis in mice and performed FoxC2 ChIP-seq from isolated podocytes. WT1 is required for the podocyte response to injury. Conditional *Wt1* knockout and *FoxC2* knockdown mouse models were used to decipher the transcriptional mechanism through which WT1 and FoxC2 regulate podocyte gene expression during injury, using transcriptomic approaches.

Results: WT1 is required for the podocyte response to injury. Indeed, the transient increased expression of podocytes genes in mice after injury, was abolished in the absence of *Wt1*. We found that FoxC2 was also actively involved during this response. By ChIP-seq, we detect 4214 FoxC2 binding sites before injury, rising to 12,532 after ADR. In contrast to WT1, that maintains a moderate degree of binding during the later stages of injury, FoxC2 binding is essentially absent. Using a set of 48 podocyte genes encoding components of the glomerular filtration barrier, ChIP-seq analyses demonstrated that WT1 and FoxC2 both acquire novel binding sites during the early stages of injury. One co-bound site is at the Wt1 transcriptional start site, where binding of both WT1 and FoxC2 increases dramatically after injury. Furthermore, WT1 and FoxC2 may be co-immunoprecipitated and knockdown of *Wt1* or *FoxC2* in immortalized podocytes demonstrated their mutual dependence for binding target genes.

Conclusions: Together, these results demonstrate that WT1 and FoxC2 mediate transcriptional reprogramming during podocyte injury. This transcriptional reprogramming may be initiated by the dramatic increased binding of WT1 and FoxC2 at the *Wt1* transcriptional start site after injury. Irreversible podocyte injury leading to FSGS may result from the nearly complete loss of FoxC2 binding to target genes during later stages of injury.

Funding: NIDDK Support

SA-OR39

Cytosolic Phospholipase A2: A Drug Target in FSGS

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Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common glomerular cause of end stage kidney disease (ESKD) in children. The refractory nature of FSGS renders treatment of FSGS as one of the most difficult challenges in pediatric nephrology. A significant knowledge gap in understanding the mechanism of progression in FSGS hampers development of successful treatment strategies. We demonstrated that patients with FSGS present with a distinct urinary lipid profile characterized by increased fatty acids (FA) and lysophosphatidylcholines (LPC), metabolites of cytosolic phospholipase A2 (cPLA2). We propose that LPC and FA incites proinflammatory and proapoptotic response in podoctes and proximal tubule epithelial cells (PTECs). We hypothesize that increased cPLA2 activity induces apoptosis, fibrosis and progression in FSGS by harboring intracellular LPC and FA.

Methods: A bigenic model of FSGS was induced by mutation of Fyn and Cd2ap (Fyn–/–Cd2ap+/–) in podocytes. A second model of FSGS was generated by adriamycin injection in mice. Animals subjected to adriamycin were treated by intraperitoneal cPLA2 inhibitor (AACOCF3-4mM) versus saline for 6 weeks. Untargeted lipidomics was performed in urine and kidney lysates of FSGS mice by CSH-QTOF MS/MS. cPLA2 expression in podocytes and PTECs was investigated by RNA sequencing. Western blotting and immunofluorescence staining was utilized to examine cPLA2 expression.

Results: Lipid profiling revealed increased urinary LPC and FA and increased LPC levels in kidney lysates of FSGS mice reminiscent of human data. FSGS mice kidneys displayed increased cPLA2 activity in podocytes and PTECs. RNA seq data revealed upregulation of cPLA2 in podocytes and PTECs in FSGS mice. Treatment with AACOCF3 decreased proteinuria and ameliorated kidney dysfunction, FSGS pathology and tubulointerstitial fibrosis.

Conclusions: Our data strongly suggest that increased cPLA2 expression contributes to progression of FSGS by harboring production of proinflammatory and propapoptotic lipid metabolites. We propose that upregulated cPLA2 activity leads to podocytes and PTEC damage by perpetuating oxidative injury, apoptosis, inflammation and subsequent fibrosis in FSGS. We postulate that targeting cPLA2 pathway for drug development will improve outcomes in FSGS. Furthermore urinary lipid metabolite profile is a promising biomarker to monitor disease progression and treatment response in FSGS.

Funding: Commercial Support - Kaneka

SA-OR40

Glomerular 3D Co-Culture to Study Podocyte Disease Ex Vivo in a Personalized Manner

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Background: As a cause for glomerular disease, podocyte damage and related changes in the glomerular filtration barrier are typical findings. However, podocyte cell culture is challenging due to the inability of terminally end differentiated primary podocytes to proliferate and due to altered morphology and expression of cell-specific markers in immortalized podocytes. Besides, classical mono-cultures limit paracrine cell-cell-contact and communication by 2-dimensionality. To investigate cell-cell-interaction and to improve cell culture conditions we want to generate a 3D co-culture model of glomerular cells. Moreover, we want to study podocyte disease by personalizing the 3D co-culture model using patient-derived podocytes.

Methods: In order to generate 3D glomerular spheroids, immortalized differentiated podocytes, glomerular endothelial cells and mesangial cells were co-cultured in a hanging media droplet or via agarose microwells. Time laps experiments displayed spheroid formation and spheroids were characterized regarding extracellular matrix proteins and cell-specific marker expression by qPCR, histological sections, immunostainings and electron microscopy. Patient-specific podocytes and podocytes from healthy controls were generated from skin fibroblasts via reprogramming into human induced pluripotent stem cells (hiPSCs) and subsequent differentiation into hiPSC-podocytes.

Results: Spheroid formation could be imaged in time laps experiments and sectioning showed encapsulation of the spheroid. SEM could display the ultrastructure and produced extracellular matrix and collagen IV and laminin were quantified by immunostaining and qPCR. In the 3D model podocytes formed protrusions, shown by TEM, that were not seen in 2D. After reprogramming of fibroblasts, generated hiPSCs showed an increased expression of common pluripotency markers. Subsequently differentiated cells were positive for podocyte specific markers and developed distinct primary and secondary foot processes.

Conclusions: 3D co-culture is a model enabling paracrine cell-cell-contact and communication and providing better physiological conditions. Patient-specific hiPSC derived podocytes have the potential to personalize the 3D co-culture.

SA-OR41

Anemia, Iron Deficiency, and FGF-23 in CKiD Study

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Background: Fibroblast growth factor 23 (FGF23) is an important bone-derived hormone implicated in the pathogenesis of chronic kidney disease-mineral bone disorder (CKD-MBD), CKD progression, and CKD-associated cardiovascular morbidity. It has recently been demonstrated that anemia-related factors, specifically iron deficiency and erythropoietin, can also increase FGF23 production. The objectives were to determine whether anemia and/or iron deficiency are associated with increased FGF23 levels.

Methods: In the largest national pediatric CKD cohort (the Chronic Kidney Disease in Children (CKiD) Study), anemia, iron and FGF23 profiles were characterized in a cross-sectional analysis. Participants included children aged 1 month to 16 years old with mild to moderate CKD.

Results: In a cross-sectional analysis of 686 pediatric CKD patients (median (IQR) age 11 (8, 15) years, 62% male, 14% Hispanic), the median eGFR was 55 (41, 71) ml/min/1.73m^2, and the median age-related hemoglobin standard deviation score (SDS) was -1.1 (-2.3, 0.2). Anemic subjects had higher C-terminal FGF23 levels than non-anemic subjects (153 vs 103 RU/mL, p<0.0001). In bivariate analyses, log-transformed C-terminal FGF23 was inversely associated with hemoglobin SDS, serum iron, eGFR, and serum calcium and was positively associated with age-related phosphate SDS. In a multivariable linear regression model, log-transformed C-terminal FGF23 was inversely associated with hemoglobin SDS (see Table 1). Log-transformed intact FGF23 was not significantly associated with hemoglobin SDS or serum iron.

Conclusions: Decreased hemoglobin concentrations are independently associated with increased C-terminal FGF23 levels in pediatric CKD. Future analyses will assess relationships among longitudinal changes in hemoglobin SDS, iron parameters, and FGF23.

Funding: NIDDK Support, Other NIH Support - Additional funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Heart, Lung, and Blood Institute (U01DK66143, U01DK66174, U24DK082194, U24DK066116)

Table 1: Univariable and multivariable linear regression modeling of determinants of circulating log-transformed C-terminal FGF23

Parameter	Univariable analysis		Multivariable analysis		
	Std	P-value	Std	P-value	VIF
Age (years)	0.04	0.27	-0.18	0.001	1.33
Sex (male) (yes versus no)	0.08	0.04	-0.02	0.66	1.05
eGFR (ml/min/1.73m2)	-0.38	<0.0001	-0.33	<0.0001	1.13
Calcium (mg/dL)	-0.07	0.046	-0.07	0.22	1.33
Phosphate SDS	0.23	<0.0001	0.15	0.005	1.14
Serum Iron (µg/dL)	-0.12	0.02	-0.05	0.32	1.20
Hemoglobin SDS	-0.27	<0.0001	-0.13	0.02	1.43

SA-OR42

Elevated Load with Normal Mean in Pediatric Hypertension (HTN): What Does It Mean?

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Background: Current pediatric ambulatory blood pressure monitor (ABPM) guidelines define HTN as mean blood pressure (BP) ≥ 95th percentile for gender and age/height and load ≥ 25%. Those with a normal mean BP but elevated load are "unclassifiable." Adult ABPM criteria is based solely on mean BP using an absolute threshold. Applying pediatric versus adult ABPM criteria in adolescents has been a topic of research recently as the 2017 pediatric BP guidelines use adult norms to define clinic HTN in patients (pts) ≥ 13 years (yrs). However research on the utility of BP load in defining pediatric HTN is limited. We aimed to evaluate the significance of elevated BP load in "unclassified" pts by ABPM including association with left ventricular hypertrophy (LVH).

Methods: Retrospectively, pts 13-17 yrs with ABPM data between 9/2018 and 7/2019 were categorized by pediatric ABPM guidelines using only ABPM data. Data collected included gender, age, height, ABPM systolic and diastolic BP mean and load for 24hr, day, and night, and left ventricular mass index (LVMI). Unclassifiable pts were re-categorized to HTN or normal BP using the adult threshold for mean BP only. LVH was defined as LVMI > 51 g/m$^{2.7}$.

Results: 495 pts (335 M) had ABPM. 146 had HTN; 198 (121 M) were "unclassified." 52 pts with normal BP and 101 of unclassified pts had LVMI data. There was no significant difference in mean LVMI in pts with "unclassified" versus normal BP (41 vs 40 g/m$^{2.7}$ p=0.62) nor presence of LVH (11% vs 9.6% p =0.81). Of the 198 unclassified pts, 150 (76%) were re-categorized (re-cat) to HTN by adult criteria, and there was no difference in LVMI compared to pts re-cat to normal BP (42.6 vs 39.4 g/m$^{2.7}$ p=0.23). Pts re-cat to HTN, had significantly higher loads for night BP and 24 hr systolic BP compared to those with normal BP. However, there was no difference between the mean loads when comparing those with LVH versus no LVH.

Conclusions: For adolescents with a normal mean BP by pediatric criteria, elevated BP loads are not associated with LVH. Furthermore, applying adult criteria to define HTN would appropriately re-classify those with higher loads. Regardless, after re-classification, there is still no difference in LVMI. Applying adult ABPM standards for adolescents would simplify interpretation without sacrificing significance.

SA-OR43

Using Electronic Health Record(EHR) Data to Evaluate Kidney Function Decline in Children with CKD

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Background: This study utilized EHR data from pediatric centers to identify children with CKD and examine risk factors for kidney function decline.

Methods: We used PEDSnet, a network with EHR data from >7million children in 7 health systems, to identify children aged 1-18 yrs between 2009-2020 who met CKD

criteria: two eGFR<90 mL/min/1.73m² separated by ≥90 days without an intervening higher value. CKD progression was defined as composite outcome: eGFR<15 mL/min/1.73m², 50% eGFR decline, chronic dialysis, or kidney transplant. Subcohorts were based on CKD etiology: glomerular, non-glomerular or malignancy. We assessed impact of hypertension(HTN) (≥2visits with HTN code) and proteinuria (≥1 lab value ≥1+) within 2yrs of cohort entrance on outcomes.

Results: We identified 7395 children, median age 14.1yrs, 36% females, 23% blacks, median follow-up 4.2yrs. Median initial eGFR was 75.5 ml/min/1.73m²; 36% had proteinuria; 46 % had HTN. Children with glomerular CKD were more likely to reach outcomes (p<0.001). Children with HTN, proteinuria, or both were more likely to reach outcomes(p<0.001).

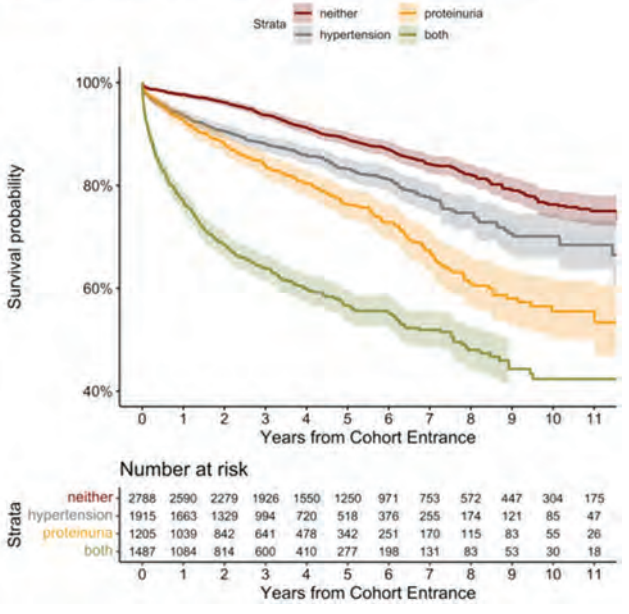
Conclusions: The EHR may be used to study large numbers of children with CKD. Risk factors for CKD progression were glomerular disease, HTN and proteinuria.

Funding: Other U.S. Government Support, Commercial Support - Institute for Advanced Clinical Trials for Children, Bayer

Endpoint reached by sub-cohort

	Non-Glomerular (N=5739)	Glomerular (N=1091)	Malignancy (N=565)	Overall (N=7395)
Any	844 (14.7%)	491 (45.0%)	154 (27.3%)	1,489 (20.1%)
eGFR halved	722 (12.7%)	424 (38.9%)	142 (25.1%)	1,293 (17.5%)
eGFR<15	504 (8.8%)	359 (32.9%)	91 (16.1%)	954 (12.9%)
Kidney transplant	192 (3.3%)	132 (12.1%)	28 (5.0%)	352 (4.8%)
Chronic dialysis	64 (1.1%)	90 (8.2%)	15 (2.7%)	169 (2.3%)

Figure: Kaplan-Meier curves for hypertension and proteinuria



SA-OR44

Risk Factors for Kidney Injury in Children with Solitary Functioning Kidney

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Background: Patients with a solitary functioning kidney (SFK) are at increased risk of kidney injury, for which several risk factors have been suggested. Large differences exist between previously reported cohorts, which hampers translation of these findings into clinical care. Our objective was to investigate the risk of and risk factors for proteinuria, high blood pressure, a decreased glomerular filtration rate (GFR), or use of antihypertensive medication in our nationwide study of children with SFK.

Methods: Children with congenital and acquired SFK were recruited in >30 hospitals throughout The Netherlands. Information on risk factors for and signs of kidney injury were collected from electronic patient files. Kaplan-Meier curves were used to estimate survival without signs of kidney injury and Cox regression was used to evaluate risk factors.

Results: Of 982 patients who provided informed consent, detailed clinical information was available from 898 (91%). After a median follow-up duration of 9.7 years, proteinuria was present in 118 patients (15%), high blood pressure in 184 (22%), and a GFR <60 ml/min/1.73m² in 23 (3.2%), while antihypertensive medication was used by 90 patients (9.8%). In total, 319 patients (36%) exhibited ≥1 sign of kidney injury and the median age at first sign of kidney injury was 4.4 year. Cumulative proportions of children with kidney injury were 20% at 5 years, 29% at 10 years, and 35% at 15 years of age. Kidney injury rates were higher in patients with a congenital cause of SFK compared to an acquired cause (odds ratio (OR) 1.6, 95% confidence interval (CI) 1.1-2.3), and in patients with unilateral renal agenesis compared to multicystic dysplastic kidney (OR 1.4, 95% CI 1.0-1.9).

Conclusions: Data from this largest SFK cohort so far indicate that one third of patients with SFK has one or more signs of kidney injury at 15 years of age. The cause of the SFK may influence the risk of kidney injury. Other risk factors will be investigated in our cohort to develop care strategies based on individual-patient risk profiles.

SA-OR45

Nephrotoxic Medications and Associated AKI in Hospitalized Neonates

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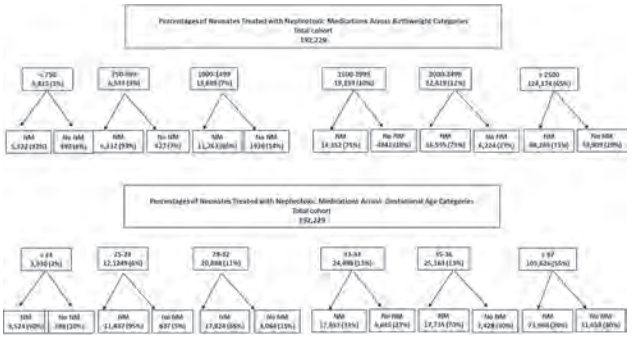
Background: Hospitalized neonates in the NICU are frequently treated with nephrotoxic medications (NM), a risk factor for acute kidney injury (AKI) which is associated with increased neonatal morbidity and mortality. Neonatal treatment with NM and subsequent AKI, especially in periviable neonates could be detrimental to nephrogenesis.

Methods: Multicenter retrospective analysis of hospital discharges (2005-2016) using the national Pediatric Hospital Information System database, including 49 pediatric hospitals across the U.S. Treatment with 37 NM in first 28 postnatal days across demographics and clinical variables, and relationship with AKI were evaluated.

Results: Of 192,229 neonates, 74% were treated with at least one NM, Figure 1. AKI prevalence was significantly higher in the NM group (aRR 3.68 [95% CI: 2.85, 4.75]), Figure 2. The aRRs of treatment were increased in <32-week, and <2000 g infants. NMs were prescribed to 90-95% of ≤ 28-week gestational age (GA) neonates. Most treatments with NM (95-98%) occurred in the first 3 postnatal days. IV aminoglycosides were the most frequent NM prescribed; 28% were treated with ≥ 4 calendar days. Most common diagnoses were infections (25%) and patent ductus arteriosus (20%).

Conclusions: The smallest and most immature preterm neonates are frequently treated with NM. the prevalence of AKI is higher in the NM treated group. The long-term implications of treatment with NM and subsequent AKI on nephrogenesis warrant attention in future studies.



Multivariable Adjusted Relative Risks of Treatment with Nephrotoxic Medication by Demographic and Clinical Risk Factors.

	Ever received nephrotoxic treatment	≥ 3 nephrotoxic medications in 24 hours	≥ 4 days of intravenous aminoglycosides
	aRR [95% CI]		
Gestational Age (weeks)			
≤24 weeks	**1.22 [1.12, 1.33]**	**5.67 [3.90, 8.25]**	0.69 [0.34, 1.41]
25-28 weeks	**1.34 [1.27, 1.42]**	**3.95 [2.76, 5.64]**	0.95 [0.62, 1.46]
29-32 weeks	**1.24 [1.19, 1.30]**	1.14 [0.81, 1.61]	**0.68 [0.54, 0.87]**
33-34 weeks	1.06 [0.99, 1.13]	0.69 [0.46, 1.02]	**0.49 [0.36, 0.66]**
35-36 weeks	0.98 [0.90, 1.05]	0.92 [0.66, 1.28]	**0.86 [0.76, 0.98]**
≥37 weeks	Reference	Reference	Reference
Birth Weight (grams)			
≤750	**1.24 [1.16, 1.33]**	**6.14 [4.29, 8.79]**	0.83 [0.45, 1.55]
750-999	**1.30 [1.24, 1.37]**	**3.83 [2.65, 5.55]**	0.98 [0.60, 1.58]
1000-1499	**1.22 [1.17, 1.27]**	**2.03 [1.39, 2.94]**	0.79 [0.61, 1.02]
1500-1999	**1.06 [1.01, 1.12]**	0.89 [0.64, 1.23]	**0.58 [0.45, 0.74]**
2000-2499	1.03 [0.98, 1.09]	0.85 [0.60, 1.20]	**0.65 [0.53, 0.80]**
≥2500	Reference	Reference	Reference
Race			
White	Reference	Reference	Reference
Black	0.99 [0.96, 1.03]	**0.73 [0.54, 0.99]**	1.08 [0.89, 1.29]
Asian	1.04 [0.99, 1.10]	0.60 [0.32, 1.13]	1.02 [0.66, 1.57]
Multiracial	1.05 [0.98, 1.13]	0.75 [0.24, 2.31]	0.68 [0.40, 1.15]
Other	0.91 [0.81, 1.03]	0.87 [0.54, 1.40]	0.90 [0.74, 1.10]
Ethnicity			
Hispanic/Latino	1.04 [0.94, 1.14]	**1.42 [1.02, 1.96]**	1.08 [0.81, 1.45]
Non-Hispanic/Latino	Reference	Reference	Reference
Sex			
Female	**0.96 [0.95, 0.97]**	0.91 [0.76, 1.09]	**0.93 [0.90, 0.97]**
Male	Reference	Reference	Reference
Discharge Year			
2005-2008	**1.17 [1.08, 1.27]**	3.13 [2.03, 4.83]	**2.82 [1.89, 4.21]**
2009-2012	**1.07 [1.00, 1.13]**	1.41 [1.09, 1.82]	**1.78 [1.41, 2.24]**
2013-2016	Reference	Reference	Reference
Major comorbidities			
Infections	**1.34 [1.28, 1.41]**	**3.33 [2.51, 4.40]**	**3.57 [2.96, 4.31]**
PDA	**1.11 [1.05, 1.16]**	**2.72 [2.09, 3.55]**	**1.43 [1.25, 1.65]**
Seizures	**1.26 [1.21, 1.31]**	**2.17 [1.62, 2.91]**	0.91 [0.78, 1.07]
Congenital heart disease	**1.06 [1.02, 1.10]**	**1.89 [1.51, 2.35]**	**1.38 [1.25, 1.53]**
AKI	**1.19 [1.15, 1.24]**	**3.22 [2.40, 4.31]**	0.90 [0.74, 1.09]

Covariates: gestational age, birth weight, race, ethnicity, sex, 5-minute Apgar scores, and discharge year. Birthweight aRRs were obtained by creating separate models replacing gestational age with birthweight to avoid collinearity.

SA-OR46

Urinary VEGF as a Prognostic Biomarker of CKD in Premature Infants with Lung Disease

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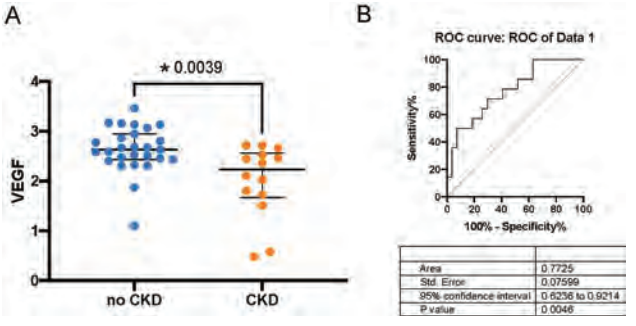
Background: Premature neonates are at risk for chronic kidney disease (CKD). Lung disease is an emerging risk factor for CKD in infants. Impaired angiogenesis may be implicated as it is required for both lung and kidney development, repair from injury, and perturbations contribute to CKD development. VEGF is a marker of angiogenesis. We hypothesize that urinary VEGF would be lower in infants with lung disease who go on to developed CKD.

Methods: Using data from the REPAIReD study (NCT01378273) an ancillary of the PENUT trial, we assessed urinary VEGF in 40 infants with severe lung disease defined by respiratory support or supplemental oxygen at 36 weeks post-menstrual age (PMA). We measured urinary VEGF at 30-34 weeks PMA. Our outcome measure was CKD at 22-26 months (estimated glomerular filtration rate <90 ml/min/1.73m^2). Urinary VEGF was determined with electro-chemiluminescent multi-analyte ELISA (Mesoscale). We compared values using Spairo-Wilk testing and ROC analysis with Youden's index.

Results: Fourteen infants (35%) developed CKD. Urinary VEGF at 30-34 weeks PMA was lower in infants that developed CKD (2.23 *vs*, 2.63 log pg/mL; p=0.004). The AUC for VEGF to predict CKD was 0.77 (95% CI 0.62-0.92, p=0.005). Using a likelihood ratio of 2.32, a threshold of 2.47 log pg/mL gives a sensitivity of 72% and specificity of 70%.(Figure 1)

Conclusions: In this small cohort of premature infants with severe lung disease, urinary VEGF levels were lower in premature infants who went on to developed CKD compared to similar neonates who did not develop CKD. Additional urinary VEGF analysis in this cohort is ongoing. Low urinary VEGF may be a marker of abnormal angiogenesis and vascular repair in the kidney. Our findings suggest that urinary VEGF may help predict CKD in premature infants with lung disease.

Funding: NIDDK Support



In infants with severe lung disease (A) those that develop CKD have lower urinary VEGF levels (p=0.004) and (B) urinary VEGF predicts CKD status with an AUC of 0.77 (p=0.005)

SA-OR47

Hyperoxia Exposure in Neonatal Period Is Associated with Decrease in HB-EGF Expression in Mice Kidneys

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Background: Acute Kidney Injury (AKI) is common in preterm infants and may cause long-lasting renal damage. Hyperoxia exposure in the postnatal period has been linked to chronic kidney disease (CKD) in adulthood in survivors or preterm birth. The mechanism of hyperoxia-driven AKI in premature infants is not clearly understood. Activation of the epidermal growth factor receptor (*EGFR*) by EGF or heparin-binding EGF-like growth factor (*HB-EGF*) promote renal tubular proliferation and renal recovery in AKI. In contrast, activation of transcribing growth factor (*TGF-a*) signaling may lead to fibrosis and CKD. We hypothesize that hyperoxia exposure in neonatal mice leads to kidney injury via alteration in the expression of EGFR and its ligands.

Methods: Pups of C57BI/6J mice were exposed to hyperoxia (FiO2 0.85) and compared to littermate controls exposed to room air from postnatal days 3-10. One kidney from each pup was fixed in formalin and embedded in paraffin for histological analysis. The other kidney was snap frozen and RT-PCR was performed from the RNA isolated from this kidney.

Results: We analyzed renal tissues from 15 newborn mice (from 3 litters) exposed to hyperoxia and 5 mice (from 1 litter) exposed to normoxia. Relative mRNA levels of *HB-EGF* were significantly decreased in renal tissues of pups exposed to hyperoxia (mean:0.006 ± 0.001) compared to those exposed to normoxia (mean:0.012 ± 0.002) ($p < 0.05$). Both *EGFR* and *TGF-a* were not elevated in pups exposed to hyperoxia. Hyperoxia-exposed pups were also noted to have elevated *a-SMA* and fibronectin compared to the controls. *TGF*-β levels were also similar between exposed and non-exposed animals (Figure 1).

Conclusions: *HB-EGF* may contribute to hyperoxia-related renal injury in preterm neonates and may be a therapeutic target in these infants.

Funding: Other NIH Support - NIH, NHLBI K08 HL151907

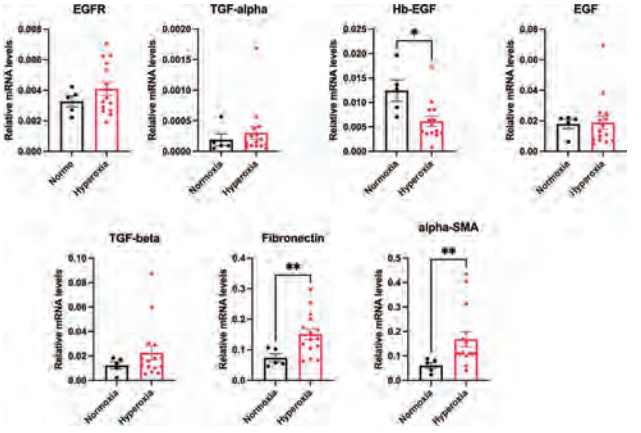

Figure 1: *p < 0.05; **p < 0.005.

SA-OR48

Identification of Molecular Mechanisms Regulating Mammalian Nephrogenesis Duration and Nephron Endowment

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Background: Nephron endowment generated during development confers lifelong renal filtration function, and is established via nephron progenitor cell (NPC) interactions with the adjacent stroma and ureteric bud (UB). Two salient, incompletely understood features of nephrogenesis are (1) the coordinated cessation of nephrogenesis in independent niches and (2) a striking 10-fold variation in nephron number between kidneys from different individuals. Preterm births are associated with premature cessation of nephrogenesis and are consequently susceptible to early-onset chronic kidney disease (CKD) and end-stage renal disease (ESRD). We leverage multiple mouse models exhibiting consistent differences in nephron number to identify mechanisms promoting prolonged nephrogenesis and/or increased nephron endowment.

Methods: NPCs from mice with elevated nephron numbers and delayed cessation (Six2$^{TGC;\ Tsc1}$, herein *Tsc1$^{+/-}$*) were evaluated via single-cell transcriptomics, translatome profiling (bulk RNA-Seq of Rpl10a-associated transcripts), metabolic indicators (*in vitro* glycolysis assays and *in vivo* hypoxia studies), and immunofluorescence. Candidate genes emerging from the RNA analyses were validated with *in vivo* genetic models for nephron number and cessation timing phenotypes.

Results: Translatome analysis revealed age and genotype-dependent patterns in signaling pathway components that were not observed in the single cell transcriptome, including differential translation of Wnt antagonists over agonists (such as Rspondin-3) in *Tsc1$^{+/-}$* NPCs. Moreover, compared to postnatal day 0 niches, Wnt agonists are less robustly translated in younger (embryonic day 14) niches, resulting in high Fgf20 levels and low R-spondin levels promoting a self-renewal environment. Further, the selective differential translation observed in the *Tsc1$^{+/-}$* model was not associated with globally elevated mTORC1 activity or changes in cellular metabolic activities.

Conclusions: We propose a model in which the tipping point for nephron progenitor exit from the niche is controlled by the gradual increase in stability of Wnt/Fzd complexes in individual cells, enhancing the response to UB-derived *Wnt9b* inputs and driving differentiation. Consistent with this, loss of one *Rspo3* allele in nephron progenitors delayed cessation and increased nephron numbers *in vivo*.

Funding: NIDDK Support

SA-OR49

Simultaneous Generation of Nephron and Renal Stroma via Progenitor Cell Replacement in Animal Fetus

Yatsumu Saito, Shuichiro Yamanaka, Kenji Matsui, Naoto Matsumoto, Tsuyoshi Takamura, Toshinari Fujimoto, Susumu Tajiri, Kei Matsumoto, Eiji Kobayashi, Takashi Yokoo. *Tokyo Jikeikai Ika Daigaku, Tokyo, Japan.*

Background: To solve the organ transplant shortage by regenerative medicine, the whole kidney, including the renal stroma—which plays important roles in homeostasis, such as structural maintenance, hemodynamics, and kidney endocrine function—must be generated. Previously, we successfully generated a rat nephron using mouse kidney as a scaffold by replacing mouse nephron progenitor cells (NPCs) with rat NPCs. Therefore,

animal fetuses can potentially generate human kidneys. Herein, we applied progenitor cell replacement to stromal progenitor cells (SPCs) and to NPCs and SPCs to verify the simultaneous generation of renal stroma and nephrons.

Methods: We harvested the metanephroi of green fluorescent protein rats to extract dissociated single cells (DSCs) by enzymatic treatment. SPCs were extracted from these DSCs by cell sorting targeting the platelet-derived growth factor receptor alpha (PDGFRa)-positive fraction. NPCs were extracted by sorting integrin alpha 8-positive fractions from the PDGFRa-negative fraction. We injected the extracted SPC fractions and both NPC and SPC fractions in the nephrogenic zone of the metanephroi of Foxd1-iDTR mice (host SPC removal model) and Six2/Foxd1-iDTR mice (host NPC and SPC removal model), respectively. The metanephroi were organ cultured for 1 week or transplanted into the retroperitoneum of NOD/Shi-*scid*/IL-2Rγ^{null} mice and collected after 2 weeks for evaluation with immunofluorescence staining.

Results: In the SPC removal model, mouse SPCs were replaced with rat SPCs in vitro, and rat stroma was extensively generated in mouse kidneys in vivo. Rat SPCs differentiated into various stromal lineage cells, e.g., mesangial cells, interstitial fibroblasts, vascular pericytes, juxtaglomerular cells, and EPO-producing cells. In the two progenitor cell removal models, cap mesenchyme-like structures were formed with aggregated rat NPCs and SPCs around the mouse ureteric bud in vitro. Rat nephrons and renal stroma were generated in the mouse kidney in vivo.

Conclusions: SPC replacement helped generate heterogeneous rat renal stromal lineage cells in the mouse kidney. Simultaneous NPC and SPC replacement enabled the generation of nephrons and renal stroma between different species.

SA-OR50

Crescents Derive from Single Podocyte Progenitors and a Drug Enhancing Their Differentiation Attenuates Rapidly Progressive Glomerulonephritis

Maria elena Melica, Giulia Antonelli, Maria Lucia Angelotti, Gianmarco Lugli, Carolina Conte, Letizia De Chiara, Fiammetta Ravaglia, Anna J. Peired, Benedetta Mazzinghi, Elena Lazzeri, Roberto Semeraro, Laura Lasagni, Paola Romagnani. *Universita degli Studi di Firenze, Firenze, Italy*.

Background: Rapidly progressive glomerulonephritis (RPGN) is characterized by crescent formation, which typically, is the consequence of diverse upstream pathomechanisms involving the specific activation of PEC, represente which represent in part renal progenitor cells (RPC). Similarities with stem cell of bone marrow prompted us to hypothesized that crescents result from clonal expansion of a single RPC, conceptually similar to monoclonal diseases originating from hematopoietic stem cells. We further hypothesized that drugs known to cure hematopoietic disease by enforcing their terminal differentiation could also attenuate crescentic glomerulonephritis.

Methods: We established a RPGN disease model in a conditional transgenic mouse based on the mT/mG and the Confetti reporter that allows lineage tracing of RPC. Mice were treated with drugs currently used in myeloproliferative disorders. Crescentic lesions were characterized by super-resolution STED microscopy. Single cell RNA sequencing of human renal progenitor cultures identify the immature progenitor subset-generating crescent in human.

Results: We observed that crescents originated from the clonal expansion of single RPC, thus suggesting a clonal stem cell disorder. Therefore, we administrated a series of drugs known to ameliorates myeloproliferative neoplasms to our mouse model. Treatment with one of the compounds induced a reduction in both proteinuria and crescent formation. 3D confocal microscopy and STED super-resolution imaging of glomeruli showed that this compound turned the uncontrolled hyperplasia of a immature PEC subset into a controlled differentiation into new podocytes restoring the injured glomerular filtration barrier. Single cell RNA of human renal progenitor cultures identified a new marker of the crescent-generating progenitor cells. Expression of this marker in biopsies of patients with RPGN associated with progression toward end stage kidney disease.

Conclusions: These results demonstrate that glomerular hyperplastic lesions derive from clonal amplification of a RPC subset and that shifting proliferation to podocyte differentiation reverses crescent formation and improves clinical outcome.

SA-OR51

A Multimodal Single Cell and Spatial Atlas of the Human Kidney in Health and Disease Delineates Cell States Associated with CKD Outcomes

Sanjay Jain,[1] Blue Lake,[2] Rajasree Menon,[5] Seth Winfree,[4] Qiwen Hu,[3] Ricardo Melo ferreira,[4] Edgar A. Otto,[5] Daria Barwinska,[4] Kian Kalhor,[2] Michael J. Ferkowicz,[4] Abhijit S. Naik,[5] Evan Murray,[6] Sean Eddy,[5] James C. Williams,[4] Karol S. Balderrama,[6] Chirag R. Parikh,[7] Eric H. Kim,[1] Peter Kharchenko,[6] Joseph Gaut,[1] Jeffrey B. Hodgin,[5] Michael T. Eadon,[4] Pierre C. Dagher,[4] Tarek M. El-Achkar,[4] Kun Zhang,[2] Matthias Kretzler.[5] KPMP, HuBMAP *[1]Washington University in St Louis, St Louis, MO; [2]University of California System, San Diego, CA; [3]Harvard Medical School, Boston, MA; [4]Indiana University School of Medicine, Indianapolis, IN; [5]University of Michigan Michigan Medicine, Ann Arbor, MI; [6]Broad Institute, Cambridge, MA; [7]Johns Hopkins University, Baltimore, MD*.

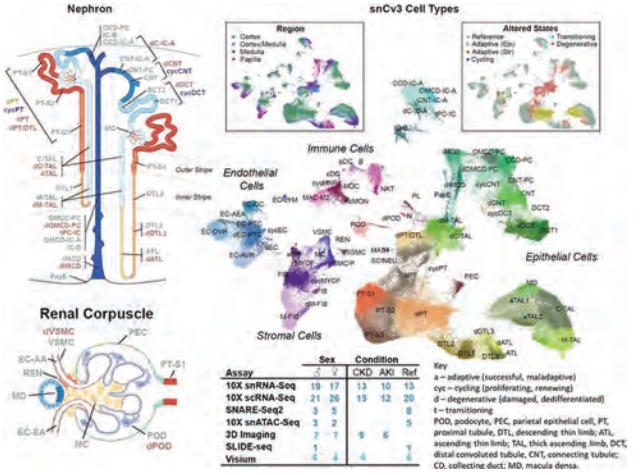
Background: The knowledge of the complexity of cell types, states and their interactions during homeostasis or disease is needed to identify the mechanisms of kidney disease.

Methods: We have applied multiple single cell or nucleus omic assays (>400,000 nuclei/cells) that capture gene regulation, expression and their spatial relationships to a broad spectrum of healthy reference (35) and disease kidney tissues (50, AKI or CKD) to establish a robust atlas of the cellular diversity representing kidney function or dysfunction.

Results: We identified 100 cell clusters including rare and novel cell populations and their spatial locations spanning the entire kidney. Among these, we define cellular states associated with kidney injury alterations that represent cycling, adaptive or maladaptive repair and degenerative states, their associated regulatory factors, and genes and pathways underlying these transitions. Molecular signatures of these states permit their classification and spatial localization within injury neighborhoods, allowing discovery of intercellular signaling relevant to acute or chronic injury. Large scale 3D imaging linked glomerular, proximal tubule and thick ascending limb injured cells to an active immune response that is uniquely associated with tubular cells. The altered state gene signatures were negatively associated with a decline in eGFR in patients with chronic kidney disease in two separate cohorts.

Conclusions: This comprehensive molecular, cellular and spatial atlas serves as a benchmark to identify nascent and altered kidney cell states, define therapeutic targets in individual patient samples and engineer healthy kidneys.

Funding: NIDDK Support, Other NIH Support - Common Fund (NHLBI)



SA-OR52

Defining the Molecular Correlate of Arteriolar Hyalinosis in CKD Progression by Integration of Single-Cell Transcriptomic Analysis and Descriptor Scoring in KPMP and NEPTUNE

Rajasree Menon,[1] Edgar A. Otto,[1] Laura Barisoni,[2] Jeffrey B. Hodgin,[1] Matthias Kretzler.[1] for the Kidney Precision Medicine Project (KPMP) *[1]University of Michigan Michigan Medicine, Ann Arbor, MI; [2]Duke University, Durham, NC*.

Background: Single cell RNA sequencing generates transcriptomic data at cellular resolution allowing the identification of cell-type specific transcript expression. We performed an integrated analysis of single cell data with descriptors from histopathology analysis of biopsy samples of CKD and AKI patients.

Methods: As part of Kidney Precision Medicine Project (KPMP), single cell analysis from 12 AKI and 15 CKD patients proceeded per KPMP guidelines (including normalization, scaling, clustering and cell-specific marker identification). Top 5000 highly variable genes expressed in the endothelial cluster identified at the low cluster granularity were analyzed using weighted co-expression network analysis. Next, the co-expressed gene sets were associated with descriptors from the histopathology analysis. A composite score was generated using the expression levels of genes for the modules that significantly correlated with the descriptors. For validation purposes, similar composite scores were also generated from tubular interstitial gene expression data of NEPTUNE cohort.

Results: The unsupervised clustering identified kidney cell clusters including glomerular, tubular and immune cell types. The weighted co-expression network analysis of endothelial genes showed a gene module significantly associated (adjusted $p < 0.02$) with arteriolar hyalinosis, one of the descriptors from the histopathology analysis; the genes in this module were enriched in the arteriolar endothelial cluster identified by high resolution clustering. KPMP CKD patients with the top composite scores had baseline eGFR < 60 (ml/min/1.73m2). In NEPTUNE, the endothelial scores significantly associated with low eGFR ($p < 0.0002$) and the composite endpoint of CKD progression (< 40% reduction eGFR or ESRD) indicating poor prognosis for the samples with high endothelial scores ($P < 0.0001$). Pathway analysis showed adipocytokine signaling as the top enriched pathway for this gene set.

Conclusions: Using integrated analysis of single cell expression data with histopathology descriptors, we identified an arteriola endothelial gene set linking arteriolar hyalinosis to CKD progression.

Funding: NIDDK Support

SA-OR53

Proteomic Characterisation of CKD Progression

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Background: Delaying or halting progression of chronic kidney disease (CKD) to established renal failure is a major goal of global health research. The mechanism of CKD progression among different CKD entities involves pro-fibrotic, pro-inflammatory and vascular pathways but current treatments are non-specific, with heterogeneity in terms of response and outcome. In depth phenotypic and proteomic data can help investigate differences between those CKD patients with rapid disease progression and those who remain stable after diagnosis.

Methods: Using eGFR slope analysis, 414 patients with a broad range of kidney disease aetiologies were divided into fast progressors (δGFR > -3 ml/min/yr; n=170) and stable patients (δGFR > 0 ml/min/yr; n=244); these composed our discovery cohort. Plasma samples were obtained, and interrogated for novel proteomic signals with SWATH-MS which enabled a digitised proteomic profile to be generated. For hypothesis testing, the t-test was used to identify differentially expressed proteins between our patient groups ($p<0.05$, after multiple testing corrections was considered statistically significant). Statistical analysis and machine learning approaches for discovery (Random Forest and Boruta Feature Selection) were performed using the computing environment R and additional software packages were obtained via the Bioconductor project.

Results: A SWATH map (on 414 patients with 943 proteins quantified) was generated and investigated in tandem with available clinical data in order to identify potential progression biomarkers. After differential expression analysis and supervised machine learning algorithms for feature selection, we identified a set of proteins that differentiate between our patient groups (AUC= 0.77). Baseline creatinine was not an accurate predictor of CKD progression (AUC=0.51). Functional enrichment analysis revealed platelet degranulation to be statistically important, suggesting a possible role for platelet function in then pathogenesis of CKD.

Conclusions: The in-depth proteomic characterisation of this large-scale CKD cohort is a step forward in generating mechanism based hypotheses that might then lend themselves to future drug targeting. Candidate proteomic biomarkers will be validated in samples from selected patients in other large CKD cohorts such as NURTuRE using a targeted mass spectrometric analysis.

SA-OR54

Capillaries Are Primary Targets in CKD and Tie2 Signaling Plays a Central Role in Disease Progression

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Background: Progressive renal diseases are associated with loss of peritubular capillaries, capillary rarefaction, but the underlying mechanisms are not well described. In both mouse models and patients, a decline in endothelial tyrosine kinase receptor (Tie2) signaling can be seen in CKD. We hypothesized that renal blood vessels through loss of Tie2 signaling upregulates Pdgfb that in turn act as a mitogen to activate pericytes and fibroblasts.

Methods: To investigate this, we utilized floxed alleles for *Tie2* and *Pdgfb* together with inducible endothelial specific Cre and lineage reporter. Additional lines (Pdgfra-H2b-GFP and Pdgfrb-GFP), were crossed into the line, resulting in reporters of myofibroblasts. Mice were subjected to an experimental model of CKD, the unilateral ureter obstruction model. Capillary density and fibrosis were evaluated at 1, 3, and 10 days after obstruction. A subset of mice was treated with an Tie2 activating antibody and evaluated the same way.

Results: Our studies show that loss of *Tie2* results in increased injury to peritubular capillaries and increased tubulointerstitial fibrosis in an experimental model of CKD. *Tie2* ecKO mice showed reduced capillary density, reduced fenestrations, and reduced vessel perfusion. Furthermore, treatment with an Tie2 activating antibody reduced both fibrosis and loss of capillaries if started at the time of injury, while endothelial specific knockout of *Pdgfb* only reduced fibrosis.

Conclusions: Our results suggest that capillaries are primary targets in CKD and that Tie2 regulation affects both capillary density and tubulointesrstitial fibrosis. Tie2 activating agents should be explored as therapies for patients with chronic kidney disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR55

Autocrine Signaling of Sphingosine 1 Phosphate in Kidney Perivascular Cells Promotes Inflammation and Fibrosis

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Background: Sphingosine 1-phosphate (S1P) is a sphingolipid that is produced inside the cell by the action of sphingosine kinase (SphK) 1 and 2. S1P is exported from cells by spinster homolog 2 (Spns2) or major facilitator superfamily 2b (Mfsd2b), and then acts on five G protein-coupled S1P receptors, S1P1 to S1P5, to affect various cellular functions. We recently showed that *Sphk2*$^{-/-}$ mice were protected from renal fibrosis when compared to wild type or *Sphk1*$^{-/-}$ mice (PMID: 27799486). We hypothesized that local S1P signaling in kidney perivascular cells affects the progression of kidney fibrosis.

Methods: Male *Foxd1Cre*$^{+}$ *Sphk2*$^{fl/fl}$, *Foxd1Cre*$^{+}$ *S1pr1*$^{fl/fl}$, *Foxd1Cre*$^{+}$ *Spns2*$^{fl/fl}$, and their littermate control mice were used. For unilateral ischemia-reperfusion injury (IRI), left kidney was clamped; right nephrectomy was performed at day 13. In the folic acid model, folic acid (250 mg/kg) was intraperitoneally injected. Mice were euthanized at day 14 to evaluate kidney fibrosis. Primary kidney perivascular cells were isolated from kidneys and used for *in vitro* studies.

Results: Both in the unilateral IRI and folic acid models, *Foxd1Cre*$^{+}$ *Sphk2*$^{fl/fl}$ and *Foxd1Cre*$^{+}$ *S1pr1*$^{fl/fl}$ mice demonstrated better kidney function (plasma creatinine/blood urea nitrogen), less kidney fibrosis (histology) with less macrophage infiltration, and suppressed expression of fibrosis-related genes (*Acta2*, *Col1a1*, *Col3a1*) in the kidneys compared with control. In *in vitro* studies, perivascular cells with *Sphk2* deficiency or *S1pr1* knockdown expressed less proinflammatory cytokines/chemokines, such as *Ccl2*, *Il6*, *Cxcl1*, after treatment with TLR2/4 agonists compared with control cells. We further identified Spns2 as the S1P transporter expressed in kidney perivascular cells. *Foxd1Cre*$^{+}$ *Spns2*$^{fl/fl}$ mice also showed protection against kidney fibrosis in the unilateral IRI model and *Spns2*-knockdown cells showed suppressed inflammatory signaling upon stimulation.

Conclusions: SphK2/S1P/Spns2/S1P1 axis enhances inflammatory signaling in perivascular cells on injury, which aggravates immune cell infiltration and subsequent fibrosis in the kidney.

Funding: NIDDK Support

SA-OR56

CD153-CD30 Signaling Is Required for Age-Dependent Tertiary Lymphoid Tissue Expansion in the Kidney

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Background: The elderly show a reduced capacity for renal regeneration after acute kidney injury (AKI). We previously showed that, after AKI, aged, but not young, kidneys exhibit tertiary lymphoid tissues (TLTs), which underlie maladaptive repair in aged injured kidneys. TLTs facilitate lymphocyte activation and differentiation *in situ* and are involved in pathophysiology in various diseases. However, the cells and signals responsible for age-dependent TLT formation in the kidneys are still undefined.

Methods: We investigated immune cells in aged injured kidneys with TLTs, 45 days after ischemic reperfusion injury, utilizing scRNAseq and bulk RNAseq, combined with flow cytometry and reporter mouse analysis. We also investigated human kidney samples harboring TLTs.

Results: We observed accumulation of CD153^{+}PD-1^{+}CD4^{+} senescence-associated T (SAT) cells and CD30^{+}T-bet^{+} age-associated B cells (ABCs), within TLTs in aged kidneys. Both SAT cells and ABCs are unique age-dependent lymphocyte populations and have been demonstrated to contribute to the pathophysiology of autoimmune diseases and obesity. By scRNAseq, SAT cells were further divided into two subpopulations, peripheral helper-like T cells and IL10-producing T cells, both of which are specialized CD4^{+} T cell subpopulations with B cell helper functions. CD153 and CD30 were specifically expressed in SAT cells and ABCs, respectively, and their expression was confined within TLTs in aged injured kidneys. In kidney injury models, CD153 or CD30 deficiency reduced ABC numbers, resulting in attenuated TLT formation with less inflammation and fibrosis and better renal function. Mechanistically, SAT cells from CD30-deficient mice exhibited decreased expression of *Il21* and *Il10*, indicating CD153-CD30 signaling was required for SAT cells to acquire B cell helper functions. CD153-expressing cells were detected within TLTs in human kidneys, and human Tph/TFH-like cells and ABCs in chronically inflammatory organs also expressed CD153 and CD30, respectively.

Conclusions: These findings identify CD153-CD30 signaling between SAT cells and ABCs as a pivotal regulator of age-dependent TLT formation and suggest that targeting CD153-CD30 signal may be a valuable strategy for the prevention and treatment of kidney diseases in the elderly.

Funding: Government Support - Non-U.S.

SA-OR57

Persistent DNA Damage as a Driver of CKD and Tubular Cell Senescence

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Background: Acute kidney injury (AKI) is a frequent cause of progression to chronic kidney disease (CKD) in humans. Emerging studies have shown that the transition to CKD results from impaired tubular repair due to accumulation of unresolved DNA damage in kidney tubular epithelial cells. Here we identify Fan1, a DNA repair enzyme, as a critical regulator of AKI to CKD progression in response to genotoxic and obstructive kidney injury in mice.

Methods: *Ggt1-Cre* mice were crossed with *FAN1*$^{loxP/loxP}$ mice to inactivate *FAN1* expression in kidney proximal tubules. Kidney injury was induced by cisplatin administration (5 weekly injections of 2 mg/kg) or unilateral ureteral obstruction (UUO). Histological analysis was performed using hematoxylin and eosin, periodic acid–Schiff, or Masson's trichrome staining. Tubular cell senescence was demonstrated by β-galactosidase staining at pH 6.0. Primary human kidney proximal tubular cells were used for modeling FAN1 loss of function in cell culture. RNA-seq analysis was performed on cisplatin-treated *FAN1*-deficient kidneys. Roscovitine was administered to block cell cycle activity and reduce cellular injury in cisplatin-treated *FAN1* kidneys.

Results: Kidney proximal tubule cell-specific *FAN1* inactivation sensitized the kidneys to tubular injury characterized by massive DNA damage response (DDR) activity. We found that persistent DDR triggers tubular cell dedifferentiation, aberrant cell cycle entry and G2 arrest which ultimately led to a failed tubular repair, tubular cell senescence and induced interstitial fibrosis in *FAN1* kidneys. Transcriptional profiling of *FAN1* kidneys identified that unresolved DNA damage blocks the cell cycle progression in late G2 through p53-dependent p21 upregulation. G2 cell cycle exit in *FAN1*-deficient cells was reinforced by nuclear cyclin D1 accumulation and DNA re-replication which gave rise to polyploid karyomegalic cells. Adminstration of roscovitine effectively blocked cell cycle activity and the formation of karyomegalic cells in cisplatin-terated *FAN1*-deficient kidneys.

Conclusions: Collectively, our data demonstrate that intact DNA damage response (DDR) is critical for proximal tubule regeneration after renal injury, and that Fan1 is a key effector of the DDR pathway in this process. Blocking of cell cycle activity immediately after tubular cell injury may be beneficial to augment tubular repair in the kidney.

Funding: NIDDK Support

SA-OR58

Kidney Tubule Polyploidization Drives CKD Progression After AKI

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Background: Acute Kidney Injury (AKI) is characterized by a rapid deterioration of kidney function. In addition, AKI survivors frequently develop chronic kidney disease (CKD). The traditional concept of kidney function recovery after AKI is based on a widespread proliferative capacity of injured tubular epithelial cells (TEC), which however is incompatible with the high prevalence of CKD after AKI. We recently demonstrated that TEC respond to AKI not only by proliferation, but also by undergoing polyplodization i.e. acquire more than one pair of chromosomes. Physiologically, polyploidy offers several advantages such as rapid adaptation to stress, compensation for cell loss and enhanced cell function. However, as polyploid cells can provide functional restoration but not structural recovery they can potentially drive CKD progression

Methods: We employed in vivo transgenic models based on the Fluorescence Ubiquitin Cell Cycle Indicator (FUCCI) technology in combination with YAP1 overexpression or inhibition. In these models, mice were subjected to glycerol-induced rhabdomyolysis to induce AKI. Polyploid cells have been then characterized by single cell-RNA sequencing analysis, cell sorting, FACS analysis, super-resolution and transmission electron microscopy.

Results: After AKI, YAP1 is activated triggering TEC polyploidization. In YAP1 overexpressing mice, a sustained activation of TEC polyploidization after AKI reduces early acute function loss but aggravates fibrosis, senescence caused by AKI, and AKI to CKD transition. Indeed, healthy YAP1 overexpressing mice present a consistent decline of kidney function over time suggesting an association between increased polyploidy and CKD development. Isolation of polyploid cells proved that these cells transcribe pro-fibrotic and senescent factors thus confirming their role in CKD progression. Importantly, as polyploid TEC become detrimental over time, blocking YAP1-driven polyploidy in a time-dependent manner avoids CKD development in comparison to control mice.

Conclusions: Collectively, these data suggest that: 1) polyploid TEC are pro-fibrotic leading in the long run to CKD progression; 2) blocking polyploidization in the right window of opportunity, can successfully ameliorate CKD progression after AKI.

SA-OR59

Inhibition of Cadherin-11 Ameliorates Kidney Injury via Restored Expression of Alpha-1 Antitrypsin

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Background: Chronic kidney disease (CKD) represents a massive unmet clinical need, as the pharmaceutical options for treatment of renal injury are extremely limited. A recent study identified cadherin-11 (CDH11) as a potential biomarker for CKD. CDH11 is present in kidney biopsies and urine samples of CKD patients, and its expression is increased in CKD mouse models, but it's unclear whether it mediates CKD and could be a target for therapy.

Methods: We used three mouse models of CKD to evaluate the role of CDH11: aristolochic acid nephropathy (AAN), unilateral ureteral obstruction (UUO), and uninephrectomy/angiotensin II administration (Unx/AngII). In each of these models, we inhibited CDH11 genetically using transgenic mice and pharmacologically with the administration of a functional blocking antibody to CDH11. We also used de-identified electronic medical records (IRB 211049) to verify the clinical relevance of the proposed mechanism whereby CDH11 knockout improves kidney injury.

Results: We found that CDH11 is exclusively expressed in injured murine proximal tubules (PTs). PTs play a critical role in CKD, as they are both a target and mediator of chronic injury. In models of CKD, both genetic and pharmacologic CDH11 inhibition improves renal function (BUN and proteinuria), diminishes cytokine production (TGF-β1 and IL-6 expression), and reduces tubular injury (KIM-1 and histological analysis). RNAseq from AAN- and Unx/AngII-injured kidneys revealed that CDH11 knockout mice had significantly increased expression of alpha-1 antitrypsin (A1AT) compared to wild type controls. Additionally, siRNA knockdown of CDH11 in immortalized PT cells in vitro results in elevated expression of A1AT, confirming this mechanistic link. The protease inhibitor A1AT has been shown by others to promote PT survival in several kidney injury models. Using Cox proportional hazards models, we discovered that patients with A1AT mutations have increased incidence of CKD on a per-allele basis, with hazard ratios as high as 5.35.

Conclusions: These results identify CDH11 inhibition as a novel means of improving outcomes in murine CKD models and suggest an underlying mechanism of increased A1AT expression and enhanced PT survival. These findings advance our understanding of CKD and outline a potential new therapeutic strategy.

Funding: NIDDK Support, Other NIH Support - NHLBI R35 (HL135790), Private Foundation Support

SA-OR60

SARA in the Kidney: Regulation of Cell Phenotype as a Potential Therapeutic Target in Renal Fibrosis

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Background: Epithelial cells play an important role in renal fibrosis. After injury, podocytes and renal tubular epithelial cells (TECs) dedifferentiate. When dedifferentiated, podocytes detach from the glomerular basement membrane, while TECs stimulate surrounding cells to transdifferentiate into myofibroblasts, thus resulting in glomerulosclerosis and tubulointerstitial fibrosis respectively. Our laboratory has identified a protein called Smad Anchor for Receptor Activation (SARA) as a key factor for maintaining cellular phenotype in the face of fibrogenesis. Here, we aim to determine if SARA overexpression in podocytes and TECs can prevent their dedifferentiation and reduce fibrosis in mouse models of glomerular and tubulointerstitial disease.

Methods: SARA overexpression was driven either by Podocin-Cre in podocytes (SARA^{podo}) and Pax8-rtTA, tet-O-Cre in TECs (SARA^{TEC}) in mice. SARA negative littermates (Ctrl^{podo} and Ctrl^{TEC} mice) were used as controls. SARA/Ctrl^{podo} mice were treated with Adriamycin to induce podocyte injury and SARA/Ctrl^{TEC} mice with aristolochic acid (AA) to induce tubulointerstitial fibrosis. Urine, blood, and kidneys were harvested for histological and molecular analysis. Markers for fibrosis and injury were measured by qPCR. Podocytes were isolated by flow cytometry from SARA/Ctr^{podo} mouse kidneys

Results: SARA^{podo} mice showed less glomerulosclerosis histologically and less proteinuria than Ctrl^{podo} mice after Adriamycin treatment. Tubular cell injury markers (KIM1, Sox9, NGAL) tended to be lower in SARA^{TEC} mice compared to Ctrl^{TEC} after AA treatment, but did not reach statistical significance. No significant difference in expression of markers of fibrosis was observed. Gene expression profiles of podocytes isolated from SARA/Ctrl^{podo} mice are being analyzed by RNA sequencing. This will provide insight into the mechanisms by which SARA maintains cellular phenotype and protects against renal fibrosis.

Conclusions: SARA overexpression protects podocytes and TECs against injury. Elucidating the mechanisms by which SARA functions will help unearth new molecular targets for therapies directed at glomerulopathies.

Funding: NIDDK Support

PO0001

Observational Evidence of NAD+ Biosynthetic Impairment and Urinary Metabolomic Alterations in COVID-Related AKI

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Background: Acute kidney injury (AKI) is a frequent extrapulmonary manifestation of COVID-19 and is associated with increased morbidity and mortality. We investigated alterations in the urine metabolome associated with AKI among patients with COVID-19, with the hypothesis that changes in nicotinamide adenine dinucleotide (NAD+) metabolism described in ischemic, toxic, and inflammatory AKI will be also associated with AKI in patients with COVID-19.

Methods: This is a case-control study among two adult populations with COVID-19: critically ill patients hospitalized in Boston, Massachusetts, and a general hospitalized patient population in Birmingham, Alabama. Cases had AKI stages 2 or 3 by Kidney Disease Improving Global Outcomes (KDIGO) criteria. Controls had no AKI by KDIGO criteria. Metabolites were measured by liquid chromatography - mass spectrometry.

Results: 14 cases and 14 controls were included from Boston, and 8 cases and 10 controls included from Birmingham. Urinary quinolinate to tryptophan ratio, an indicator which increases with impaired NAD+ biosynthesis, was higher among cases than controls at each location and pooled across locations (median [IQR]: 1.34 [0.59-2.96] in cases, 0.31 [0.13-1.63] in controls, unadjusted p = 0.0013; p=0.03 in analyses adjusted for age and sex). We identified alterations in tryptophan, nicotinamide, and other components of energy metabolism as well as decreases in purine metabolites which contributed to a

distinct urinary metabolomic signature that could reliably differentiate patients with and without AKI (supervised random forest class error: 1/14 for AKI and 1/14 for no AKI groups in Boston, 0/8 for AKI and 0/10 for no AKI groups in Birmingham).

Conclusions: Conserved urinary metabolic alterations spanning multiple biochemical pathways distinguish AKI vs. non-AKI in the context of COVID-related hospitalization at two large academic medical centers. AKI is further associated with derangements in NAD+ biosynthesis that suggest impaired energy metabolism in the kidney. Augmenting renal NAD+ by administering biosynthetic precursors may present a novel therapeutic opportunity to mitigate COVID-19 associated AKI.

Funding: NIDDK Support, Private Foundation Support

PO0002

Expression of SARS-CoV-2 Viral Protein ORF3A in Renal Tubular Epithelial Cells Induces Injury

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Background: The coronavirus SARS-CoV-2 is the culprit of the COVID-19 pandemic. Acute kidney injury occurs frequently in COVID-19 patients and several lines of evidence suggest local infection of kidney cells by the virus. However, this remains controversial and it is unclear how the viral proteins of SARS-CoV-2 directly impact the health of renal tubular cells infected by the virus.

Methods: The viral protein ORF3A of SARS-CoV-2 was overexpressed in HK-2 renal tubular cell line and the pronephric tubule epithelia of transgenic zebrafish. The NF-kB and STAT3 signaling pathways and target gene expression were analyzed using quantitative RT-PCR and Western blots. The expression of the renal injury marker KIM-1 was also assessed by Western blots, quantitative RT-PCR and *in situ* hybridization. Protein interactions were studied by co-immunoprecipitation and Western blots.

Results: ORF3A augments both NF-kB and STAT3 signaling by enhancing the phosphorylation of the transcription factors and results in the expression of downstream target genes and subsequently increases the expression of kidney injury molecule 1 (KIM-1) in HK-2 cells. Mechanistically, ORF3A elevates the expression of Tripartite Motif-Containing Protein 59 (TRIM59), a ubiquitin E3 ligase, which forms a protein complex with ORF3A and STAT3. This in turn excludes the phosphatase TCPIP from binding to STAT3 and inhibits the dephosphorylation of STAT3. The transgenic zebrafish expressing ORF3A in renal tubular epithelia develop severe edema starting 48 hours post fertilization and *in situ* hybridization shows elevated kim-1 expression in the pronephric tubules, indicating that ORF3A induces renal injury in zebrafish in vivo.

Conclusions: These results demonstrate that overexpression of ORF3A is sufficient to injure renal tubular epithelial cells and uncover a previously unrecognized molecular mechanism underlying the deregulation of STAT3 activity by ORF3A that leads to renal tubular cell injury. Altogether, the results of this study support the notion that direct infection of renal epithelial cells by SARS-CoV-2 may contribute to the renal complications in COVID-19 patients.

Funding: NIDDK Support, Clinical Revenue Support

PO0003

Deciphering the Impact of Cytokine Storm on APOL1 Expression in Primary Human Glomerular Endothelial Cells

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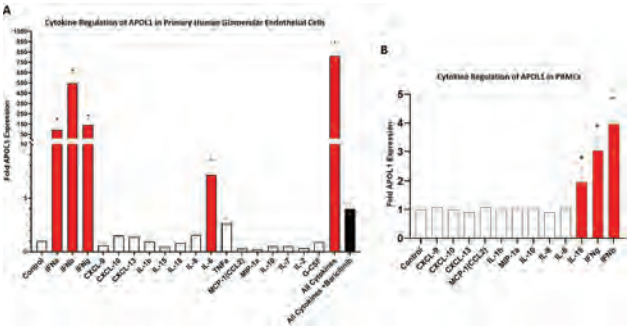
Background: High Risk (HR) Apolipoprotein L1 (APOL1) genotypes are associated with collapsing glomerulopathy in the context of interferons (IFNs), HIV, systemic lupus erythematous (SLE), and SARS-CoV2 infection. Elevated circulating inflammatory cytokines, commonly referred to as "cytokine storm" are believed to play causal role in disease pathogenesis. Although the role of IFN and TNF in APOL1 induction has been described, it is unknown if other components of "cytokine storm" implicated in COVAN and lupus glomerulopathy also induce APOL1 expression. *In vitro* and animal studies show that expression of variant APOL1 is sufficient to cause glomerulopathy in dose-dependent manner. Therefore, it is important to establish if other components of "cytokine storm" regulate APOL1 expression in human glomerular compartment.

Methods: We evaluate the direct effect of cytokines implicated in the above diseases on APOL1 expression in primary human glomerular endothelial cells, a cell type with known significance in lupus and COVAN. We also screened these select cytokines using peripheral blood monocytes (PBMCs) from patient with SLE and HR APOL1 genotype.

Results: IFNs($\beta>\gamma>\alpha$) were the strongest drivers of APOL1 expression. Importantly, we also found that IL-6 increased APOL1 expression by 7 fold compared to control ($p<0.01$) in glomerular endothelial cells. Treatment with composite of all cytokines induced the most robust APOL1 expression. However, Jak 1/2-specific inhibitor, baricitinib, markedly attenuated this effect, with reduction in APOL1 expression from 800 fold down to 4 fold. Additionally, in PBMCs of a lupus patient with HR APOL1, IL-18 also showed significant upregulation of APOL1 expression.

Conclusions: Our data suggest that other cytokines beyond interferon may be important in the pathogenesis of COVAN, HIVAN, and APOL1-associated lupus collapsing glomerulopathy and that Jak-inhibitors may be a promising novel therapeutic in these cytokine-mediated APOL1 nephropathies.

Funding: Other NIH Support - Common Fund (DP2, NIH Director New Innovator Award)



Cytokine Regulation of APOL1

PO0004

Interferon-Activated Genetic Programs and a Novel Short Isoform of the SARS-CoV-2 Receptor ACE2 in the Kidney

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Background: Severe COVID-19 causes cytokine storm, worsening patient prognosis and contributing to acute kidney injury (AKI) development. Genetic programs activated in the renal epithelium by cytokines like interferon, as well as those ablated by JAK inhibitors, like ruxolitinib, were previously not investigated in detail. Additionally, a short isoform of *ACE2, deltaACE2 (dACE2)*, of unknown function was recently identified as an interferon-stimulated gene, and it's presence, inducibility and regulation in the kidney was not explored.

Methods: We treated Human Primary Proximal Tubule (HPPT) renal epithelial cells with IFNa, IFNβ, IFNg, IL-1β and ruxolitinib and used RNA-seq to explore gene expression patterns. We performed GSEA analysis and compared this data to available AKI and renal COVID-19 datasets, as well as to other human interferon-treated tissues. We also measured mRNA expression of both *ACE2* isoforms by RT-qPCR before and after cytokine stimulation and identified changes in gene regulatory elements of the *ACE2* locus using ChIP-seq.

Results: RNA-seq analysis identified genes significantly induced by IFNα (746), IFNβ (1169), IFNγ (1280) and IL-1β (2142), mostly immunity related. We saw an overlap of 162 genes between IFNβ treatment and the post-AKI dataset and of only 35 with severe COVID-19. Comparison of kidney, lung and liver cells treated with IFNβ revealed a shared set of 153 genes and unique 685 renal genes. Using RT-qPCR we show 300- and 600-fold upregulation of *dACE2* mRNA by IFNα and IFNβ, respectively, while full length *ACE2* expression is almost unchanged. RNA-seq data revealed abundant fragment mapping to exons corresponding to *dACE2* compared to rest of the transcript. ChIP-seq analysis showed additional putative regulatory elements in *ACE2* locus, including intragenic enhancers and a *dACE2* promoter. JAK inhibitor ruxolitinib successfully ablated 79.5% (929) of genes induced by IFNβ in HPPT cells, including *dACE2*.

Conclusions: We generated and made available novel RNA-seq and ChIP-seq datasets for human renal proximal tubule cells stimulated with cytokines. We observed that type I interferons significantly upregulated only the short isoform of SARS-CoV-2 receptor *ACE2* and we linked it to JAK/STAT pathway, which may be an important factor in COVID-19 therapies using JAK inhibitors.

Funding: NIDDK Support

PO0005

Single Cell Analysis Reveals Deeper Insight of the Gateway Cell Type for SARS-CoV-2 in Kidney

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Background: Kidney injury is one of the extrapulmonary injury manifestations of COVID-19. Due to the specific expression of SARS-CoV-2 receptor angiotensinase 2 (ACE2), renal tubular epithelial cells are the main target cells of SARS-CoV-2 during kidney infection, although studies have found that the evidence of SARS-CoV-2 infection of glomerular cells. However, detailed mechanism of SARS-CoV-2 infecting kidneys still needs to be identified. Since mice don't express ACE2, humanized organoids have become important carriers for studying the mechanism of viral infection in vitro. It is still unclear whether the existing kidney organoids are suitable for studying SARS-CoV-2 virus infection.

Methods: Data source: All scRNA-seq/bulk RNA-seq were downloaded from the Gene expression Omnibus. **ScRNA-seq analysis**: The scRNA-seq was analyzed using Seurat R package. **Cell communication analysis:** Cell communication was analyzed using CellPhoneDB and Cellchat R package. **SCENIC analysis:** Gene regulatory network was analyzed using SCENIC R package. **Bulk RNA-seq analysis**: We used MuSiC R package to deconvolute bulk RNA-seq data. **GSEA analysis:** GSEA was performed using clusterProfiler package.

Results: We mined the available scRNA-seq dataset of human adult kidneys (GSE140989, GSE131882), and identified a proximal tubule subgroup, PTv cells, is susceptible to SARS-CoV-2 infection. PTv cells are highly enriched a variety of factors related to viral infections (such as ACE2, DPP4, ANPEP, CTSB, TMPRSS2 etc.). Through cell communication and gene regulatory network analysis, we inferred that PTv cells are more active than other PT cells in terms of repairment, fibrosis, development, and reabsorption. Further by analysis in the datasets of GSE139061 and GSE126805, we found that the proportion of PTv increased during acute kidney injury, suggesting that PTv could be used to predict the progression of kidney injury. Analyzing human kidney organoid scRNA-seq data (GSE109718, GSE115986, GSE108291, GSE147863, GSE119561, GSE114802, GSE136314, GSE118184), we identified that the PTv widely present in kidney organoids, indicating that kidney organoids can be used in SARS-CoV-2 related research.

Conclusions: We revealed the characteristics of the PTv, a gateway cell for SARS-CoV-2 in kidney, and provided a molecular basis for the feasibility of renal organoids to study the renal tropism of SARS-CoV-2.

PO0006

Longitudinal Proteomic Characterization of AKI in Hospitalized COVID-19 Patients

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Background: Acute kidney injury (AKI) is a known complication of COVID-19 associated with increased in-hospital mortality.

Methods: We longitudinally measured serum levels of 4,497 proteins (SomaScan) in 437 COVID-19 patients at multiple timepoints along their hospital course and identified associations with AKI. Using single cell transcriptomic data from healthy human kidney specimens, we identified cell-specific kidney intracellular markers and quantified their leakage in sera from AKI patients. We also investigated whether serum proteomics improves AKI prediction.

Results: We identified 408 upregulated and 107 downregulated proteins in COVID-AKI (144 cases, 293 controls, FDR<0.05, Fig 1A). Downregulated proteins included coagulation cascade inhibitors (protein C, heparin cofactor 2) and platelet dysregulation markers (Fig 1B), including platelet factor 4 (PF-4). Given the role of PF-4 in heparin induced thrombocytopenia (HIT), we then retrospectively analyzed 4,035 COVID-19 hospitalizations and found a significant association of HIT suspicion with COVID-AKI (aOR = 12.6, p <0.001). Intracellular AKI associated proteins were enriched for markers of the Loop of Henle, descending vasa recta endothelium, and NK cells (Fig 1C), which all have low ACE2 (Fig 1D) and TMPRSS2 expression (SARS-CoV2 receptor and activator respectively), suggesting bystander damage within the kidney, not direct viral invasion likely drives COVID-AKI. Finally, a random survival forest model incorporating protein levels had lower prediction error for incident AKI than one using only clinical variables (Fig 1E).

Conclusions: The COVID-AKI serum proteome is characterized by dysregulated platelets with clinical evidence of HIT, improves prediction of incident AKI in a machine learning model and suggests inflammation mediated renal cell death, rather than direct viral invasion via the renal ACE2 receptor.

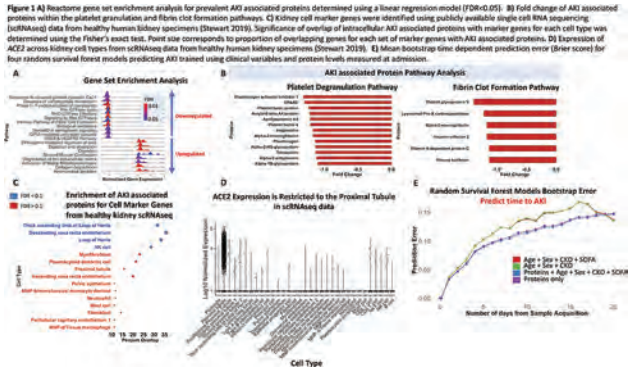

Figure 1

PO0007

TIMP-2/IGFBP7 and N-Gal Are Strongly Associated with the Development of AKI in Patients with Severe Pneumonia Caused by SARS-CoV-2

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Background: The cut-off points for the urinary kidney biomarkers (BM): TIMP2*IGFBP7 (Tissue Inhibitor of Metalloproteinase-2 *Insulin-Like Growth Factor Binding Protein-7 and Neutrophil Gelatinase associated lipocalin (NGal) in patients with AKI by SARS-CoV-2 are not defined.

Methods: Between May-August 2020 prospectively included patients with severe pneumonia caused by SARS-CoV-2 without AKI at the moment of enrollement. Fresh urine was collected at admission of critical care and was immediately frozen at -80 grades Celcius. NGal and TIMP-2*IGFBP-7 were measured in urine. We derived cutoffs based on sensitivity (S) and specificity (E) for predicting AKI using K-DIGO criteria of urinary kidney BM and some serum BM. The better cut-off of N-Gal and TIMP-2*IGFBP7 were used to construct Kaplan Meier curves to assess differences in the risk of AKI. We performed a logistic regression model for significant variables to AKI. The analysis was conducted by SPSS V25.

Results: We included 51 patients, 20 AKI and 31 matched controls. Hypertension in the AKI group was 50% vs 12.9% p=0.009. Mortality in the group with AKI was 8 (15.7%) vs 2 NO-AKI (3.9%) p=0.013. **Table 1** shows AUC of urinary and serum clinical BM for predicting AKI. TIMP2/IGFBP7 cut-off point of 0.2 ng/ml had S= 50%, E = 90%, and N-Gal 45 ng/ml had S=70.5%, E 80.6%. Survival curves for AKI were constructed after stratifying TIMP-2 IGFBP7 >0.2 vs <0.2 and N-Gal >45 vs <45 ng/ml, cut-off <0.2 of TIMP2*IGFBP7 had lower risk for AKI during (Log-rank test p = 0.002), lower risk for AKI was also observed with the cut-off <45 ng/ml for N-Gal (Log-rank test p = 0.001). Multivariate analysis indicated risk factor for AKI was higher when TIMP2*IGFBP7 >0.2 $(ng/ml)^2/1000$ (OR 10.29, 95% CI=1.26-83.60, **p=0.029**); and higher N-Gal >45 ng/ml (OR 5.57, 95% CI 1.00-30.87) **p=0.038.**

Conclusions: TIMP2*IGFBP7 and NGal in urine are excellent predictors of AKI in patients with severe pneumonia caused by SARS-CoV-2.

Funding: Government Support - Non-U.S.

Prediction of AKI using urinary and serum clinical biomarkers

Urinary (u) and Serum (s) Biomarkers	AUC	p	95% CI
TIMP-2*IGFBP7 u	0.695	0.021	0.537-0.853
N-Gal u	0.784	0.001	0.646-0.921
Creatine Phosphokinase (s)	0.694	0.021	0.548-0.840
Procalcitonine (s)	0.752	0.003	0.611-0.894
Troponine (s)	0.742	0.007	0.595-0.890

AUC= Area under the curve

PO0008

AKI in a Mouse Model of COVID-19: Therapeutic Potential of a Novel Soluble ACE2 Variant

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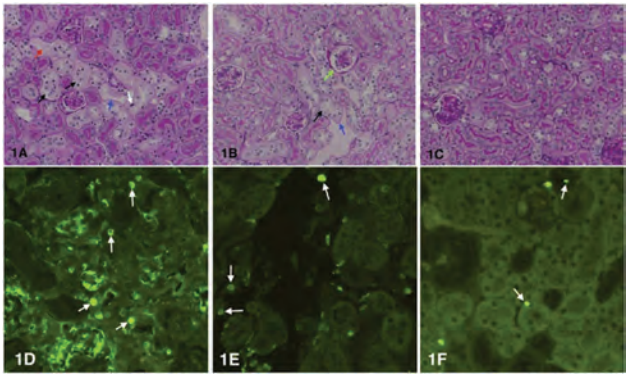
Background: We have previously shown that in the ischemia reperfusion model of AKI kidney ACE2 activity decreases and that the administration of a shorter soluble ACE2 variant markedly attenuates AKI in terms of GFR and kidney histology (Shirazi et al, ASN 2019). Here, we report the effect of a novel ACE2 variant designed to prevent/treat SARS-CoV-2 in transgenic k18-hACE2 mice infected with a lethal viral dose.

Methods: In a BSL-3 facility, transgenic k18-hACE2 mice were infected intranasally with 2×10^4 PFU SARS-CoV-2. ACE2 1-618-DDC-ABD was administered intranasally and intra-peritoneally 1 hour prior to viral challenge as well as 24 and 48 hours afterwards for a total of 3 doses. Infected control animals received PBS at the same time-points. Kidneys were removed from all animals and examined by light microscopy (LM) histologically and for apoptosis, using PAS and TUNEL staining, respectively.

Results: In mice infected with SARS-CoV-2, variable degrees of AKI were found by LM with the following features seen in the few most severe cases: proximal tubule brush border loss (black arrows, figure 1A and B), cytolysis (red arrow, figure 1A), tubular basement membrane disruption (blue arrows, figure 1A and B) and apoptosis (white arrows, figure 1A, B, D and E). In animals treated with ACE2 1-618-DDC-ABD, survival was near 100% and proximal tubular kidney injury was absent or markedly attenuated with less proximal tubule injury (figure 1C) and minimal apoptosis (figure 1F). Glomeruli appeared ischemic (figure 1B, green arrow) but otherwise normal without evidence of thrombosis.

Conclusions: Kidneys from a transgenic mouse susceptible to SARS-CoV-2 infection, like patients with COVID-19, displays variable degrees of proximal tubular injury suggesting that this model can be useful to study AKI in COVID-19. Mice that received soluble ACE2 1-618-DDC-ABD protein were essentially protected from AKI suggesting a potential preventative/therapeutic role for soluble ACE2 in this otherwise pharmacologically untreatable devastating disease.

Funding: Private Foundation Support



PO0009

Kidney Injury Molecule 1 Is a Receptor for SARS-CoV-2 in Lung and Kidney

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Background: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first reported in Wuhan in 2019 and reached pandemic proportions. SARS-CoV-2-related respiratory failure and acute kidney injury (AKI) are major complications of infection. Kidney Injury Molecule-1 (KIM-1) is a scavenger receptor expressed by kidney epithelial cells and was previously reported to be a receptor for Hepatitis virus A. We hypothesized that KIM-1 is a receptor for SARS-CoV-2 and may play an important role in COVID-19 lung and kidney injury.

Methods: Human lung and kidney autopsy samples were immunostained and analyzed. Liposomal nanoparticles displaying the SARS-CoV-2 spike protein on their surface (virosomes) were generated. Virosome uptake by A549 lung epithelial cells, mouse primary lung epithelial cells and human kidney tubuloids (3D structures of kidney epithelial cells) was evaluated in the presences or absence of anti-KIM-1 antibody or TW-37, a small molecule inhibitor of KIM-1-mediated endocytosis that we discovered. Protein-protein interaction characteristics between purified SARS-CoV-2 spike protein and purified KIM-1 were determined using microscale thermophoresis. HEK293 cells expressing human KIM-1 but not angiotensin-converting enzyme 2 (ACE2) were infected with live SARS-CoV-2 or pseudovirions expressing the SARS-CoV-2 spike protein.

Results: KIM-1 was expressed in lung and kidney epithelial cells in COVID-19 patient autopsy samples. Human and mouse lung and kidney epithelial cells expressed KIM-1 and endocytosed spike-virosomes. Both anti-KIM-1 antibodies and TW-37 inhibited uptake. Enhanced KIM-1 expression by human kidney tubuloids increased virosome uptake. KIM-1 positive cells expressed less ACE2. Using microscale thermophoresis, the EC50 for interaction between KIM-1 and SARS-CoV-2 spike protein and the receptor binding domain were 56.2±28.8 nM and 9.95±3.10 nM, respectively. KIM-1-expressing HEK293 cells without ACE2 expression had increased susceptibility to infection by live SARS-CoV-2 and pseudovirions expressing spike when compared with control cells.

Conclusions: KIM-1 is a receptor for SARS-CoV-2 in the lung and kidney and thus, KIM-1 inhibitors such as TW-37 can be potential therapeutics and/or prophylactic agents for COVID-19.

Funding: NIDDK Support, Other NIH Support - NCATS, Government Support - Non-U.S.

PO0010

Regulation of SARS CoV-2 Host Factors in the Kidney and Heart in Rats with 5/6 Nephrectomy: Effects of Salt, ARB, Dipeptidyl Peptidase 4 Inhibitor, and SGLT-2 Blocker

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Background: Host factors such as angiotensin-converting enzyme 2 (ACE2) and the transmembrane protease, serine subtype 2 (TMPRSS2) are important factors for SARS-CoV-2 infection. Clinical and pre-clinical studies demonstrated that RAAS-blocking agents can be safely used during a SARS-CoV-2 infection but it is unknown if DPP-4 inhibitors or SGLT2-inhibitors may promote COVID-19 by increasing the host viral entry enzymes ACE2 and TMPRSS2.

Methods: We investigated telmisartan, linagliptin and empagliflozin induced effects on renal and cardiac expression of ACE2, TMPRSS2 and key enzymes involved in RAAS (REN, AGTR2, AGT) under high-salt conditions in a non-diabetic experimental 5/6 nephrectomy (5/6 Nx) model. In the present study, the gene expression of *Ace2*, *Tmprss2*, *Ren*, *Agtr2* and *Agt* was assessed with qRT-PCR and the protein expression of ACE2 and TMPRSS2 with immunohistochemistry in the following experimental groups: Sham+normal diet (ND)+placebo (PBO); 5/6Nx+ND+ PBO; 5/6Nx+2% salt-diet (HSD)+PBO; 5/6Nx+HSD+telmisartan; 5/6Nx+HSD+linagliptin; 5/6Nx+HSD+empagliflozin.

Results: In the kidney the expression of *Ace2* was not altered on mRNA level under disease and treatment conditions. The renal TMPRSS2 levels (mRNA and protein) was not affected, whereas the cardiac level was significantly increased in 5/6 Nx rats. Intriguingly, the elevated TMPRSS2 protein expression in the heart was significantly normalized after treatment with telmisartan, linagliptin and empagliflozin.

Conclusions: Overall, our study indicated that there is no upregulation regarding host factors potentially promoting SARS CoV-2 virus entry into host cells when the SGLT2 inhibitor empagliflozin, telmisartan and the DPP4 blocker linagliptin are used. The results obtained in a preclinical, experimental non-diabetic kidney failure model need confirmation in ongoing interventional clinical trials.

Funding: Commercial Support - Boehringer Ingelheim Pharma GmbH & Co. KG

PO0011

ACE2 and TMPRSS2 Co-Localization in Proximal Tubules from Human Kidneys Obtained at Autopsy from COVID-19 Patients

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Background: Studies at the single cell level have revealed that the localization of TMPRSS2 is in the distal nephron whereas ACE2 is in the proximal tubule. Since TMPRSS2 is a serine protease necessary for activation of the SARS-CoV-2 S spike protein after it binds to ACE2, this spatial separation would make it difficult to explain how SARS-CoV-2 can infect the kidney. The purpose of this study was to examine the localization of these proteins by immunofluorescence in the kidneys of patients who died from COVID-19.

Methods: Human kidney slides from a Northwestern COVID-19 repository were used after IRB approval. Slides from paraffin-embedded blocks were probed with different antibodies (ACE2, TMPRSS2, ACE, NBC-1, Aquaporin 2) for immunofluorescence studies. Mouse kidneys were also examined as additional controls.

Results: In mouse kidneys, TMPRSS2 was found in the brush border of proximal tubules and co-localized strongly with ACE2. Similarly, in human kidneys from patients who died from COVID-19, with or without AKI and from non-COVID-19 subjects, ACE2 and TMPRSS2 co-localized in the proximal tubule. TMPRSS2 and ACE2 also co-localized with ACE, a marker of the apical proximal tubule and to a lesser extent with NBC-1, a marker of the basolateral proximal tubule membrane. By contrast, TMPRSS2 and ACE2 did not co-localize with Aquaporin 2, a marker of principal cells in the collecting tubule.

Conclusions: In both mouse and human kidneys, ACE2 and TMPRSS2 co-localize in the proximal tubule. In kidneys from patients with COVID-19 with or without AKI obtained at autopsy, both proteins co-localized in the proximal tubule but not in the collecting tubule. Contrary to what was suggested from single-cell mRNA analysis, the co-localization of both proteins in the proximal tubule would make it possible for the SARS-CoV-2-ACE2 complex to be activated when coronavirus reaches the kidney.

PO0012

Plasticity of Neutrophil Subsets in ANCA Vasculitis and COVID-19

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Background: A population of granulocytes appear in the PBMC layer of density separated blood and are termed Low Density Granulocytes (LDGs). These are seen in many conditions including cancer, sepsis, autoimmunity and pregnancy. We previously identified LDGs in acute and remission ANCA vasculitis (AAV) and hypothesise that these LDGs are also present in Covid-19 (C-19) and our aim is to phenotype these cells and determine whether LDGs are a disease specific cellular response to inflammation. Of particular interest is the expression of intracellular Arginase 1 (Arg-1), an enzyme linked to T cell suppression in many disease situations.

Methods: LDGs were isolated using a modified percoll preparation and analysed by both traditional and imaging flow cytometry, in patients with active and remission ANCA vasculitis, in patients with severe moderate and mild C-19 and in healthy controls. The phenotyping panel included CD14, CD15, CD16, CD10, CD33, CD62l. Intracellular Arg-1 was stained following permeabilisation with saponin.

Results: We identified extensive populations of LDGs in both AAV and Covid-19 peripheral blood. LDG levels are associated with disease severity. Arginase 1 is differentially expressed in neutrophil populations from AAV and C-19. In C-19 Arginase levels are correlated to disease severity suggesting that Arginase release may be associated with favourable outcome. Interestingly, all neutrophil fractions show lower levels of Arginase in C-19 patients whereas in AAV only LDGs have lower levels. Healthy controls have high Arginase expression.

Conclusions: Neutrophil subsets display disease specific responses in C-19 and AAV demonstrating their plasticity in inflammatory settings and warrant further investigation.

Funding: Government Support - Non-U.S.

PO0013

Plasma TNFR1 Predicts Major Adverse Kidney Events in Hospitalized Patients with COVID-19

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Background: Patients hospitalized with COVID-19 are at risk for major adverse kidney events (MAKE). Predicting which patients will experience progression of disease and poor outcomes remains elusive. We sought to develop a biomarker-based risk model for predicting MAKE in patients hospitalized with COVID-19.

Methods: We applied least absolute shrinkage and regression methodology (LASSO) to a prospectively enrolled cohort of 432 patients admitted with COVID-19 who had

blood specimens collected (median 2 days [IQR 2-4 days] from admission) from March 2020-January 2021, at three large academic medical centers. Clinical variables and 26 plasma biomarkers were used as candidate features in the prediction models for the outcome of MAKE, defined as KDIGO stage 3 AKI, dialysis-requiring AKI, or in hospital mortality. Cross-validation was used for optimal shrinkage parameter selection and model AUCs were optimism-corrected using bootstrapping.

Results: MAKE occurred in 85 (20%) patients within 60 days of admission. Application of LASSO to the 26 biomarkers selected IL-12, IL-13, IL-6, Tie2, FLT1, NGAL, MCP1, YKL40, Ang1, Ang2, and TNFR1, which yielded an AUC of 0.88 (95% CI 0.85-0.91). Plasma TNFR-1 alone had an AUC of 0.88 (0.84,0.91). When LASSO was applied on the clinical variables and TNFR1, 4 clinical variables (age, black race, obesity, WHO COVID severity score) and TNFR1 were selected with an AUC was 0.88 (95% CI 0.87-0.89). Random Forest models of biomarkers and clinical variables had similar prediction performance. A cutoff of TNFR1 at 3005 pg/ml had a sensitivity of 69%, specificity of 89%, PPV of 60% and NPV of 92% for occurrence of MAKE over 60 days.

Conclusions: In this multi-center cohort study, plasma TNFR1 by itself produced a robust prediction for MAKE in patients hospitalized with COVID-19 that did not improve when combined with multiple clinical variables and was equivalent to combined inputs of 10 other plasma biomarkers.

Funding: NIDDK Support

PO0014

AKI in COVID-19: Risk Factors for Mortality and Estimating Burden Using an ARIMA Model

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Background: Incidence of Acute Kidney Injury (AKI) among COVID-19 patients is 35%. Requirement for Renal replacement therapy (RRT) is estimated to be 15%-20%. We aimed to identify risk factors associated with mortality and need for RRT in COVID-19 patients with AKI. We also estimated burden of the pandemic on inpatient hemodialysis (HD) unit.

Methods: Inpatients above 18 years, diagnosed with COVID-19 on RT-PCR between March-June 2020 were included in the study. AKI was defined using KDIGO guidelines. Data collected included demographics, serum creatinine, time to AKI, comorbidities, albuminuria, need for RRT and intubation. All inpatient HD sessions from January 2016 to June 2020 were included to estimate burden of COVID-19. CVVHD, PIRRT and PD were excluded. Statistical analysis included logistic regression, ANOVA, z-test for proportions and Chi-square test. Interrupted time series analysis using Auto Regression Interference and Moving Average (ARIMA) was used to predict proportion of bedside HD sessions from January 2020.

Results: 1991 patients positive for COVID-19 on RT-PCR were included. 683 (34.2%) were found to have AKI. 185 patients (27.1%) required RRT. Mortality among AKI patients was 64.7%. Age (OR=1.04; CI 1.03 to 1.06), AKI after 1 week (OR=2.15; CI 1.06 to 4.35), albuminuria (OR=2.57; CI 1.11 to 5.93), need for RRT (OR=2; CI 1.26 to 3.19) and intubation (OR=4.6; CI 2.71 to 7.75) were the mortality risk factors. Albuminuria (OR=2.97; CI 1.04 to 8.46), CKD (OR=3.5; CI 1.67 to 7.34) and intubation (OR=7.8; CI 5.14 to 11.91) were the risk factors for RRT. Diabetes and hypertension did not increase mortality or the need for RRT. To estimate the burden of pandemic, 24086 HD sessions between Jan. 2016 to June 2020 were analyzed. Proportion of bedside HD was significantly higher in 2020 when compared to previous years ($p<0.01$) due to isolation protocols. ARIMA model showed a significant difference in the mean proportion of bedside HD sessions for 2020 between observed and expected values ($p<0.01$). Personnel requirement showed an extra burden of 870 nurse-hours with March-April accounting for 76%. This was due to increased number of bedside sessions requiring a 1:1 nurse-patient ratio as opposed to in unit sessions where nurse-patient ratio is 1:2.

Conclusions: Time to AKI, albuminuria and RRT are important risk factors for mortality in COVID-19 patients with AKI.

PO0015

Renal Comorbidities and New Acute Kidney Failure Drive Unfavorable Outcomes Among COVID-19-Positive Sickle Cell Trait Carriers

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Background: The sickle cell trait (SCT) in the hemoglobin beta gene (HbS; rs334) affects millions of Americans, especially African Americans (AA; minor allele frequency [MAF]=7.8%) and Hispanic Americans (HA; MAF=1%). We investigated the impact of SCT on the severity and sequelae of COVID-19 infection in the Million Veteran Program (MVP). Pre-COVID diseases and laboratory findings present in electronic health records (EHR), as well as acute events following 60 days of COVID-19 infection, and their effect on COVID-19 mortality among SCT patients were examined.

Methods: COVID-19 clinical data on genotyped MVP participants (SCT^+ = 2,729, SCT= 129,848; $COVID^+$=13,841, $COVID^-$=118,736) was extracted from EHR. Outcomes analyzed were: severe disease (or mortality) vs. not severe (or survival). Ethnic-specific firth logistic regression for SCT was performed on European (EA), African (AA), Hispanic (HA) and Asian (ASA) groups, adjusting for sex, age, age^2, and 20 genetic principal components. Ethnic-specific phenome-wide association (PheWAS and LabWAS) for SCT captured 20+ years of comorbidities and historical laboratory values and was used to contrast effects of COVID-19. Multiple testing corrections were applied.

Results: HbS is associated with increased COVID-19 mortality in AA (N=3,749; OR=1.8 [1.14-2.84], p=0.01) with a similar trend in HA. PheWAS revealed significant associations of rs334 with phecodes for pulmonary embolism, chronic renal disease, diabetic kidney disease, hypertensive renal disease, gout, sickle cell disease/trait, and hemolytic anemia (FDR $p < 0.1$). After adjusting for SCT, past renal disease was significantly associated with higher COVID-19 deaths among AA. Increased incidence of acute kidney failure (AKF) and chronic kidney disease (CKD) were seen within 60 days of infection with COVID-19. We estimated direct and indirect effects of AKF or CKD in AA SCT carriers via a mediation framework. On average 20.7% (95% CI: 3.8% - 56.0%) of the total effect of SCT on COVID-19 death was found to be mediated through AKF, and that for CKD was 12.4% (95% CI: 0% - 63%).

Conclusions: SCT is associated with an elevated risk of mortality with COVID-19 infection. Both pre-existing chronic medical conditions and new acute events after COVID-19 may contribute to adverse COVID-19 outcomes with SCT.

Funding: Veterans Affairs Support

PO0016

Comparison of Mortality in Hospitalized COVID-19 Patients with AKI vs. ESRD

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Background: Patients hospitalized with COVID-19 illness are at high risk for developing acute kidney injury (AKI) and have high mortality rates. Chronic kidney disease (CKD) and end stage renal disease (ESRD) are independent risk factors for COVID-19 disease severity and mortality. Our study compares mortality rates of hospitalized patients with COVID-19 illness who 1) develop AKI with baseline normal renal function, 2) develop AKI with baseline moderate-to-severe CKD stages 3 or 4, and 3) have ESRD.

Methods: Consecutive patients admitted with COVID-19 illness referred to Nephrology with AKI or ESRD on dialysis were included. Retrospective data collected included: Demographics, medical history including CKD stage, labs, O2 therapy, AKI diagnosis (KDIGO), and renal replacement therapy (RRT). Chi-square test was used to evaluate the unadjusted association between CKD stage and mortality. Multivariate logistic regression models were constructed to estimate associations between CKD stage and mortality adjusting for potential confounders.

Results: 166 patients were analyzed: 87 patients had AKI with baseline normal renal function (GFR > 60 ml/min (AKI-N), 41 patients had AKI on CKD Stage 3 or 4 (AKI-CKD3/4), and 38 patients had ESRD. Mechanical ventilation was used in 33[37.9%] AKI-N, 20[48.8%] AKI-CKD3/4, and 10[26.3%] ERSD patients, p = 0.069. Three [3.5%] AKI-N received iHD, and 9[10.3%] received CRRT/PIRRT. Six [14.6%] AKI-CKD3/4 received iHD and 7[17.1%] received CRRT/PIRRT. Of all AKI patients, 55.5% had Stage 3 AKI. 34[89.5%] ESRD patients received iHD and 2[5.3%] received PD. AKI-CKD3/4 were more likely to receive RRT than AKI-N, p = 0.035. Death occurred in 36[41.4%] AKI-N, 26[63.4%] AKI-CKD3/4, and 9[23.7%] ESRD patients, (p=0.001). Multivariate logistic regression modeling for mortality accounting for age, race, gender, diabetes mellitus, hypertension, obesity, and CHF revealed increased odds of mortality for AKI-CKD3/4 (OR=2.59, p=0.006) and decreased odds of mortality for ESRD patients (OR=0.5, p=0.001), compared to AKI-N.

Conclusions: COVID-19 patients with ESRD had less mortality than AKI-N, while AKI-CKD3/4 had higher mortality than both ESRD and AKI-N patients. Prospective studies to determine specific criteria for early initiation of RRT in COVID-19 AKI patients are warranted, as it may decrease mortality especially in those with baseline CKD 3/4.

PO0017

AKI Associated with COVID-19: Differences Between Previously Healthy Kidney Individuals and CKD Patients

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Background: Renal injury associated to COVID-19 has an incidence of 3-9%, which ranged from urinary abnormalities up to acute kidney injury (AKI-COVID19), which is mainly observed in critical care patients. The main risk factors for AKI-COVID19 appearance are: oncologic disease, sepsis, heart failure. However, it has not described if there are differences between AKI-COVID19 in patients with previously healthy kidney (AKI-NRF) and those with chronic kidney disease (AKI-CKD), thus we decided to explore it in patients who were assisted during the first pandemic wave (2020) in Clinica de la Costa, Barranquilla, Colombia

Methods: 572 patients with confirmed diagnosis of COVID-19 (PCR) were evaluated. Out of them 188 developed AKI and their epidemiological data, serum parameters, and functional status were recorded. Statistical analysis and comparison between AKI-NRF and AKI-CKD patients were performed

Results: From 720 individuals evaluated at the emergency room for suspicion of COVID-19, 572 of them were admitted with confirmed SARS-CoV-2 infection. Most of them were male (59%), median age 55 years, with hypertension (36%), obesity (23%), diabetes (18%), heart disease (5%), and COPD (9%). Almost all patients were robust (97%). 188 COVID-19 patients developed AKI (33%), although 149 (26%) presented a previous normal renal function (AKI-NRF), while 39 (7%) had CKD (AKI-CKD). Most of CKD patients (91%) developed AKI. There was a predominance of male gender, old age (≥ 60 years), frailty status (CFS ≥ 4), diabetes mellitus, obesity, COPD in AKI group (AKI-NRF and AKI-CKD subgroups) respect to NO AKI group (n: 380). The prevalence of hypertension and cardiac disease was significantly higher in AKI-CKD respect to AKI-NRF, and even higher respect to NO AKI. However, there was a tendency of higher mortality rate in AKI-NRF (69%) compared to AKI-CKD (56%). Even though, this trend did not reach statistical significance (p=0.09), mortality rate in AKI compared to NO AKI (16%) (p=<0.0001) did. D-dimer was slightly higher in AKI-NRF compared to AKI-CKD (p=0.06)

Conclusions: There was a trend to higher mortality rate and D-dimer levels in AKI-NRF individual compared to AKI-CKD patients

PO0018

AKI in Inpatients with COVID-19: Risk Factors and Mortality

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Background: AKI in hospitalized patients with COVID-19 is a common adverse complication. Our aim was to investigate risk factors associated with AKI and whether AKI in this setting is independently associated with in-hospital mortality at 30 days.

Methods: All adult patients admitted with a positive SARS-CoV-2 PCR between 3 /2021 to 1/2021 to nineteen hospitals who had a COVID-associated billing diagnosis and no history of ESKD or kidney transplant were included. AKI was defined according to the Kidney Disease Improving Global Outcomes guidelines. Risk factors associated with AKI were evaluated with univariable and multivariable logistic regression, and mortality was evaluated using Kaplan-Meier and Cox Proportional Hazards models.

Results: The study cohort included 9,681 patients, of which 3,666 (38%) met criteria for AKI. Compared with patients without AKI, patients with AKI were older [mean (SD) age 67 (16) vs. 60 (18) years], more likely to be male (58% vs. 47%), and more likely to be black (21% vs. 15%). Patients with AKI were also more likely to have diabetes mellitus (52% vs. 32%), hypertension (78% vs. 57%), CKD (55% vs. 17%), and coronary artery disease (20% vs. 11%). Patients with AKI were also more likely to be on ACEi/ARB on admission (51% vs. 37%), require mechanical ventilation (21% vs. 3.2%) or have higher WBC, hs-CRP, ferritin, D-dimer, and cardiac troponin). P-values were <0.001 for all of the aforementioned comparisons. Risk factors significantly associated with AKI in the multivariable model included age, sex, race, hypertension, CKD, diabetes, ACEi or ARB on admission, mechanical ventilation, WBC on admission, hs-CRP, ferritin, d dimer and troponin. Death occurred more frequently in patients with AKI (22.1%; n=811) than in those without (3%; n=178). Patient with AKI had higher mortality risk as compared to those without AKI, hazard ratio (HR) 3.08 (95% CI 2.56-3.71), that remained significant even after controlling for all variables associated with AKI, such as age, sex, race, comorbidities, inflammatory biomarkers, elevated troponin, and COVID-related treatments, HR 1.64 (95% CI 1.34-2.01).

Conclusions: Patients with COVID-19 who develop AKI have a higher mortality. We found risk factors associated with AKI in the setting of COVID, and that the increased mortality risk associated with AKI in COVID-19 is independent of these factors.

PO0019

Burdens of AKI and CKD Among COVID-19 Survivors

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Background: COVID-19 is known to be associated with increased risk of acute kidney injury (AKI) during the acute phase of the infection. However, the burden of AKI and chronic kidney diseases (CKD) after the first 30 days of COVID-19 infection is not clear.

Methods: 181,384 COVID-19 patients from the United States Veterans Health Care System who survived the first 30 days of infection were enrolled and compared with 4,397,509 non-infected controls on burden of AKI and CKD at 6 months. Adjusted comparisons were conducted across severity of infection measured based on intensity of care received, and by subgroups based on age and pre-existing health conditions.

Results: With a median follow up of 150 (interquartile range: 115, 221) days, the adjusted excess burden of AKI due to COVID-19 was 6.07 (95% confidence interval: 5.46, 6.69) and excess burden of CKD was 7.19 (5.78, 8.55) per 1000 persons at 6 months. The excess burden of AKI increased with the severity of acute infection(excess burden 1.28 (0.68, 1.86), 28.11 (25.94, 30.26) and 73.18 (67.53, 79.02) per 1000 persons at 6 months for COVID-19 patients without hospitalization, hospitalized and admitted to intensive care units, respectively). The excess burdens of CKD were 1.66 (0.19, 3.08), 36.41 (31.71, 41.11) and 82.55 (71.93, 93.78) for those not hospitalized, hospitalized and admitted to intensive care units, respectively. The burden of AKI and CKD increased with increased age (≤60, 60-70, >70 years) and increased pre-existing health conditions (Charlson comorbidity index of 0, 1-3 and >3) (Table).

Conclusions: Our results suggest that COVID-19 survivors, including those without hospitalization or pre-existing health conditions, suffered burden of AKI and CKD after the first 30 days of the infection. We provide insight into the burdens of AKI and CKD by population groups; our estimates may help guide nephrology care for COVID-19 patients.

Funding: Veterans Affairs Support

Population		AKI Adjusted excess burden per 1000 persons at 6 months (95% Confidence interval)	CKD Adjusted excess burden per 1000 persons at 6 months (95% Confidence interval)
Overall		6.07 (5.46, 6.69)	7.19 (5.78, 8.55)
Age (years)	≤ 60	1.33 (0.81, 1.86)	0.87 (0.18, 1.57)
	60-70	6.36 (5.15, 7.69)	6.53 (4.02, 9.11)
	>70	12.32 (11.12, 13.58)	19.24 (15.43, 23.14)
Charlson comorbidity index	0	2.62 (2.14, 3.14)	3.60 (2.42, 4.75)
	1-3	8.87 (7.91, 9.88)	10.57 (8.08, 13.08)
	>3	25.07 (21.82, 28.42)	20.17 (13.92, 26.75)

Outcomes were ascertained from 30 days after COVID-19 infection until end of follow-up.
Excess burden estimated as the burden difference between COVID-19 and control groups per 1000 persons at 6 months.

PO0020

Association Between BMI and Risk of AKI in Hospitalized Patients with COVID-19

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Background: Acute Kidney Injury (AKI) is a frequent complication in ICU patients with a negative impact on patient outcomes. High body mass index (BMI) is reported to be associated with a higher risk of AKI in critically ill patients. Obesity is also a risk factor for developing COVID-19 and for severe illness requiring hospital admission, mechanical ventilation and is associated with mortality

Methods: A multi-center retrospective cohort study was conducted on 2,716 electronic health records (EHR), (n=1,719 in first surge dates of 3/1/20 until 7/16/20), (n=997 in second surge dates of 10/15/20 until 2/28/21 with COVID-19. Patients without a recorded BMI value were excluded. AKI at admission was defined as the difference between first measured creatinine and nadir creatinine within the first 7 days of admission that was greater than 0.3 mg/dL[JB1]. The Chi-squared test was used to compare BMI as a categorical variable between AKI and non-AKI groups at admission. The Mann–Whitney U test was used for the same comparison when BMI was treated as a continuous variable. A p-value less than 0.05 is considered statistically significant.

Results: BMI was dichotomized to < 25kg/m^2 and >= 25 kg/m^2. The non-AKI group had a significantly higher percent of patients with BMI greater or equal to 25 kg/m^2 (80.2% vs. 73.7%, p = 0.0108). BMI was not found to be associated with either peak CRP or peak D-Dimer among AKI patients in both surges.

Conclusions: A direct relationship between BMI and AKI is well known, mostly from data that included surgical patients with multiple comorbidities and did not account for peri operative stress[JB1]. The proinflammatory state in obesity may lead to endothelial damage. In CKD and ESRD, obesity is paradoxically associated with a better prognosis. Few studies have shown an inverse relationship between BMI and AKI risk. High levels of lipoproteins in obesity is thought to lead to endothelial protection in the kidney vasculature. A 'pre-conditioning' effect of obesity attenuating against abrupt bursts of hyper-inflammation on renal vasculature has been shown. Altered adipokine and cytokine profiles produced by adipose tissue can exert protective effects by decreasing inflammation. We describe here the first study showing an inverse relationship between BMI and developing AKI at hospital admission in COVID-19.

PO0021

Association Between Inflammation Markers in Patients with SARS-Cov-2 with the Development and Severity of AKI

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Background: Acute Kidney Injure (AKI) is a common complication associated with SARS-CoV2 infection. Sepsis, direct cellular injury due to the tropism of the virus, and systemic inflammation are mechanisms involved in its development.

Methods: Prospective Cohort from March-2020 to March-2021 including 200 patients ≥18 yrs with SARS CoV2 for RT-PCR. All patients with development of AKI (KDIGO classification) during their hospitalization were registered. Age, gender, hospitalization time, oxygen use, SOFA, APACHE II, BRESCIA, PAFI, Leukocytes, creatinine (CrS) andinflammation markers (procalcitonin, ferritin, RCP, LDH, D-dimer) were registered.

Results: The incidence of AKI was 40%, 77% were male, 64% had AKI 1 and 36% were AKIN 2 y 3. The use of higher supplemental oxygen, APACHE, BRESCIA, D-Dimer and procalcitonin at day 9 and 12 were associated with AKI. In a logistic regression analysis, risk factor to AKI was septic shock (RR; 1.7-117; *p*=0.013). Other results are shown in Table

Conclusions: Inflammatory markers (d-Dimer and procalcitonin) were associated with the development and severity of AKI but only septic shock was predictive of the development of AKI

Comparison of socio-demographic in patients with SARS CoV-2 and AKI

	AKI=80	No AKI=120	p
Age (years)	61 ± 15	55 ± 14	NS
Weight, (kg)	87 ± 19	86 ± 21	NS
Hospitalization (days)	7 ± 6.13	2 ± 2.0	NS
Oxigen used (L/min)	2.4 ± 1.17*	1.8 ± 1.0*	0.001
APACHE II score	12.7 ± 5.7	8.9 ± 6.0	0.001
SOFA score	4 ± 3.0	3 ± 2.3	NS
Brescia-Covid score	2.42 ± 1.05*	1.93 ± 0.90*	0.004
d-Dimer (ng/mL)	2.92 ± 1.97*	2.15 ± 1.6*	0.007
Ferritin (ng/mL)	830 ± 609	791 ± 480	NS
RCP (mg/dL)	158 ± 112	152 ± 109	NS
Procalcitonin 9 Day 12 Day	2.85 ± 5.3* 3.5 ± 5.3*	0.9 ± 1.25* 0.50 ± 0.60*	0.035 0.012
CrS (AKI 1) (mg/dL) CrS(AKI 2-3) (mg/dL)	0.81 ± 0.40* 3.0 ± 2.0*		

PO0022

Impact of COVID-19-Associated AKI on Subsequent Development of CKD

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Background: There is paucity of data about post-hospital discharge kidney-related outcomes in individuals with COVID-19-associated acute kidney injury (CoV-AKI) during the pandemic. We hypothesized that patients who survive a hospital admission due to COVID-19 and AKI are at risk for acquiring residual chronic kidney disease (CKD) thereafter.

Methods: We conducted a retrospective observational study examining records of patients hospitalized at Ochsner Medical Center over a 3-month period (March-May 2020) with COVID-19 and diagnosis of AKI by KDIGO. We examined the rate of full recovery of AKI (serum creatinine value back to within 10% of baseline or < 1.2 mg/dL) at 9 months post-hospital discharge. Factors associated with recovery were assessed.

Results: Among 916 admissions due to COVID-19 within the study [220 (24%) to an intensive care unit], there were 226 (26%) cases of AKI, 98 of them (43%) with AKI-requiring dialysis (AKI-RRT). Patients with CoV-AKI had a median age of 67 (34-99) and 58% were men. Self-identified black race accounted for 65% of the cohort. Among those with CoV-AKI, there were 111 in-hospital deaths (49%). Of 115 patients with CoV-AKI who were discharged alive, 9-month follow-up data were retrieved in 97 (missing data in 18). Full recovery of kidney function was achieved by 76 (78%). Among those who progressed to residual CKD, 11 (11%) patients were declared to have end-stage kidney disease (ESKD) requiring dialysis. Baseline CKD stages 3-5 was associated with lower rate of full renal recovery [23/76 (30%) vs. 14/23 (61%); RR: 2.01, p=0.004)].

Conclusions: Full recovery from CoV-AKI was observed in ¾ of those who remain alive post-hospital discharge. About 1/10th of patients with CoV-AKI reached ESKD at intermediate-term follow-up. Preexisting CKD is associated with lower rate of recovery in CoV-AKI. These data do not seem to suggest that CoV-AKI is associated with greater risk for development of CKD compared to other forms of in-hospital AKI.

PO0023

Predictors of Recovery of Kidney Function Following AKI During Hospitalization for COVID-19

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Background: Studies have shown that COVID-19 hospitalization is associated with severe AKI. However, determinants of kidney function recovery for these patients are not well studied.

Methods: We conducted a retrospective analysis of patients admitted to our institution from March 2020 to April 2021 with diagnoses of COVID-19 and AKI. Recovery of kidney function was defined as a discharge creatinine less than 0.3 mg/dL above baseline. Data on patients' demographics, comorbidities, AKI stage, ICU admission, and laboratory values were collected by chart review. Univariate analysis and a multivariate logistic regression model were used to identify factors associated with kidney recovery.

Results: Of 216 patients, the average age was 66.3 years and 56.0% were men. 62% of patients had recovery of kidney function by discharge. Univariate analysis identified congestive heart failure (CHF, p = 0.063), AKI-D (p < 0.001), AKI stage (p < 0.001), ICU admission (p < 0.001), and lower albumin (p = 0.040) as correlates of non-recovery at discharge. In the multivariate logistic regression model [(AUC: 0.732, 95% CI (0.664-0.800)], CHF (p = 0.010), AKI-2 (p = 0.011), AKI-3 (p = 0.001), and ICU admission (p = 0.006) remained associated with non-recovery (Table 1). Follow-up data, at a median of 64 days post-discharge, was available for 61% of the cohort (n = 131). Of these patients, 14% had new recovery after discharge, while 18% had no improvement compared to discharge. At 60 days post-discharge, 8.4% had new CKD. At discharge, 3% of all patients were dialysis dependent. Baseline CKD (p = 0.030) and CHF (p = 0.037) were associated with non-recovery at 60 days post-discharge.

Conclusions: History of CHF, severity of AKI, and ICU admission are predictors of non-recovery of kidney function in patients with COVID-19 and AKI.

Table 1. Univariate and Multivariate Analysis of Predictors of Kidney Recovery

	Kidney Recovery (n = 134)	Lack of Kidney Recovery (n = 82)	P-value	Multivariate aOR (95% CI)	P-value
Age (years)	66.1 +/- 15.5	66.6 +/- 14.3	0.808	—	—
Sex				—	—
Female	60 (44.8%)	35 (42.7%)	0.764		
Male	74 (55.2%)	47 (57.3%)			
Race				—	—
African American	58 (43.2%)	29 (35.4%)	0.250		
White	55 (41.0%)	42 (51.2%)	0.145		
Asian	2 (1.49%)	0 (0%)			
Other	18 (13.4%)	7 (8.54%)	0.279		
American Indian	0 (0%)	1 (1.22%)			
Ethnicity				—	—
Hispanic	22 (16.5%)	9 (11.7%)	0.342		
Non-Hispanic	111 (83.4%)	68 (88.3%)			
Baseline CKD	60 (44.8%)	31 (37.8%)	0.315	—	—
CKD 3a	29 (48.3%)	12 (38.7%)	0.205		
CKD 3b	22 (36.7%)	10 (32.3%)	0.398		
CKD 4	9 (15.0%)	9 (29.0%)	0.276		
AKI-D	20 (14.9%)	30 (36.6%)	<0.001	—	—
Comorbidities					
Diabetes	59 (44.0%)	41 (50.0%)	0.393		
Hypertension	107 (79.9%)	65 (79.3%)	0.918		
Obesity	26 (19.4%)	18 (22.0%)	0.652		
Morbid Obesity	43 (32.1%)	28 (34.1%)	0.755		
Congestive heart failure	26 (19.4%)	25 (30.5%)	0.063	0.39 (0.188-0.794)	0.010
COPD	24 (17.9%)	12 (14.6%)	0.531		
Liver disease	7 (5.22%)	6 (7.32%)	0.532		
Immunosuppression	24 (17.9%)	15 (18.3%)	0.943		
AKI Stage					
Stage 1	74 (55.2%)	20 (24.4%)	<0.001	[REF]	
Stage 2	28 (20.9%)	22 (26.8%)	0.200	0.34(0.150-0.783)	0.011
Stage 3	32 (23.9%)	40 (48.8%)	<0.001	0.26(0.115-0.607)	0.002
Biomarkers					
Peak Ferritin (ng/mL)	1892 +/- 3663	2136 +/- 2710	0.634		
Peak D-dimer (ng/mL DDU)	2585 +/- 8615	1519 +/- 1775	0.351		
Minimum Fibrinogen (mg/dL)	497 +/- 181	548 +/- 179	0.193		
Minimum Albumin (g/dL)	2.78 +/- 0.630	2.60 +/- 0.65	0.040	0.652 (0.357-1.19)	0.165
Minimum Hemoglobin (g/dL)	10.2 +/- 7.50	9.26 +/- 2.72	0.279		
Peak Proteinuria					
1+	43 (37.4%)	24 (32.4%)	0.487		
2+	29 (25.2%)	20 (27.0%)	0.782		
3+	19 (16.5%)	18 (24.3%)	0.189		
4+	4 (3.48%)	0 (0%)			
Trace	12(10.4%)	8 (10.8%)	0.935		
Negative	8 (6.96%)	4 (5.41%)	0.670		
ICU admission	64 (47.8%)	61 (74.4%)	<0.001	0.32 (0.140-0.718)	0.006

PO0024

Recovery from AKI Requiring Kidney Replacement Therapy in Critically Ill Patients with COVID-19

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Background: Acute kidney injury (AKI) requiring kidney replacement therapy (KRT) occurs in as many as one in five critically ill patients with COVID-19. Expanding on previous work by this group, we examined the association of clinical factors at the time of KRT initiation with the outcome of kidney recovery at hospital discharge, accounting for the competing outcome of death.

Methods: We used data from the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID), a multicenter cohort study that enrolled adults with COVID-19 admitted to ICUs at 68 hospitals across the US from March 4 to June 22, 2020. Among those who acutely required KRT, the outcome of kidney non-recovery (continued dialysis dependence at hospital discharge) was explored with multinomial logistic regression, with kidney recovery (independence from dialysis at discharge) as the reference outcome and death as an alternate outcome. Exposures of interest included demographics, baseline medical status, and markers of illness acuity at the time of KRT initiation.

Results: Of 876 patients with AKI-KRT, 588 (67%) died, 95 (11%) survived to discharge and remained dependent on KRT, and 193 (22%) survived to discharge without KRT dependence. Patients with lower baseline eGFR had greater odds of kidney non-recovery, with OR 8.58 (95% CI: 3.03-24.28) among patients with eGFR ≤15 vs >60. Reduced urine output on the day of KRT initiation was also associated with kidney non-recovery, with OR 4.23 (95% CI: 1.61-11.15) for urine output <50 mL/day vs >500 mL/day (**Figure**).

Conclusions: Among critically ill patients with COVID-19 with AKI requiring KRT, lower baseline kidney function and reduced urine output at the time of KRT initiation are associated with kidney non-recovery.

Funding: NIDDK Support

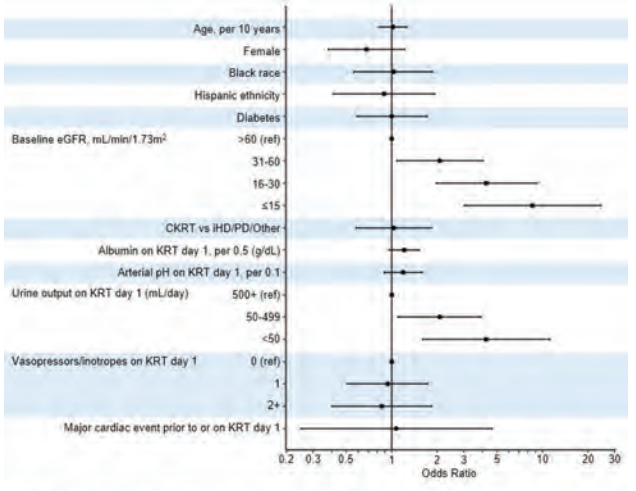

Figure. Multivariate multinomial regression, outcome of nonrecovery vs recovery
eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; CKRT, continuous kidney replacement therapy; iHD, intermittent hemodialysis; PD, peritoneal dialysis

PO0025

Critically Ill Patients with COVID-19 and AKI: Clinical Characteristics and Outcomes

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Background: Acute kidney injury (AKI) is a well-recognized complication of COVID-19. In this retrospective cohort study, we describe the clinical characteristics and outcomes of patients with severe COVID-19 in 8 intensive care units (ICUs) during the first wave of the pandemic.

Methods: Demographic, clinical, laboratory characteristics, and outcome data, including need for renal replacement therapy (RRT), mechanical ventilation, mortality, and RRT dependence at discharge and at 3 and 6 months, were extracted from the electronic medical record (EMR) between March and July 2020. Using nadir-to-peak serum creatinine, AKI and its stages were defined by the KDIGO consensus. Group comparisons were performed using ANOVA and chi square tests.

Results: After excluding 20 patients with end-stage kidney failure, 479 patients with severe COVID-19 were included. Table 1 displays the characteristics and outcomes of the cohort stratified by AKI. 409 (89.2%) patients developed AKI, with 194 (42.3%) developing stage-3 AKI. Male gender, white race, obesity, and COPD were associated with higher stages of AKI severity. 83 patients (18.1%) required RRT of which 27 (32.5%) survived, and 12 (44.4%) remained dialysis-dependent at hospital discharge. Follow up at 3-months and 6-months indicated dialysis dependence in 5 (45.5%) and 4 (36.4%) of 11 patients (1 died), respectively.

Conclusions: AKI is highly prevalent in our cohort and peak serum creatinine occurs within 3 days of intubation. Long-term dialysis dependence is of concern and merits further study. Multivariable analyses are under way to identify factors that are associated with severe AKI, need for RRT and in-hospital death.

Table 1: Characteristics and Outcomes of Critically Ill Patients with COVID-19 Stratified by AKI Status

		Stages of AKI			
Characteristics	**No AKI (n=88)**	**AKI I (n=103)**	**AKI II (n=94)**	**AKI III (n=174)**	**P value**
AKI stage					
No AKI	41 (46.6%)	7 (6.8%)	2 (2.1%)	0 (0.0%)	
AKI 1	32 (36.4%)	69 (67.0%)	4 (4.3%)	0 (0.0%)	<0.001
AKI 2	14 (15.9%)	21 (20.4%)	73 (77.7%)	2 (1.2%)	
AKI 3	1 (1.1%)	6 (5.8%)	15 (16.0%)	172 (98.9%)	
Age (years)	64.6 ± 14.8	68.4 ± 15.1	67.0 ± 17.0	67.0 ± 12.6	0.67
Sex					
Male	43 (48.9%)	64 (62.1%)	59 (62.8%)	127 (73.0%)	<0.001
Female	45 (51.1%)	39 (37.9%)	35 (37.2%)	47 (27.0%)	
Race					
White	59 (67.1%)	56 (54.9%)	47 (51.1%)	73 (43.2%)	
Black/AA	9 (10.2%)	31 (30.4%)	21 (22.8%)	54 (32.0%)	0.001
Hispanic	16 (18.2%)	9 (8.8%)	16 (17.4%)	23 (13.6%)	
Asian/American Indian	4 (4.6%)	6 (5.9%)	8 (8.7%)	19 (11.2%)	
Comorbidities					
Hypertension	53 (60.2%)	68 (66.0%)	55 (58.5%)	120 (69.0%)	0.24
Hyperlipidemia	40 (45.5%)	47 (45.6%)	41 (43.6%)	65 (37.4%)	0.14
Coronary artery disease	13 (14.8%)	14 (13.6%)	7 (7.5%)	22 (12.6%)	0.52
Heart failure	14 (15.9%)	11 (10.7%)	12 (12.8%)	24 (13.8%)	0.90
Atrial fibrillation	10 (11.4%)	15 (14.6%)	12 (12.8%)	21 (12.1%)	0.93
Diabetes mellitus	36 (40.9%)	39 (37.9%)	34 (36.2%)	72 (41.4%)	0.84
COPD	15 (17.1%)	18 (17.5%)	9 (9.6%)	14 (8.1%)	0.01
Asthma	17 (19.3%)	8 (7.8%)	8 (8.5%)	18 (10.3%)	0.17
OSA	8 (9.1%)	6 (5.8%)	1 (1.1%)	11 (6.3%)	0.37
Liver disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	0.13
CVA	5 (5.7%)	14 (13.6%)	8 (8.5%)	21 (12.1%)	0.29
DVT/PE	8 (9.1%)	6 (5.8%)	7 (7.5%)	11 (6.3%)	0.56
Dementia	12 (13.6%)	12 (11.7%)	16 (17.0%)	23 (13.2%)	0.87
CKD	6 (6.8%)	9 (8.7%)	10 (10.6%)	21 (12.1%)	0.15
Obesity	21 (23.9%)	27 (26.2%)	21 (22.6%)	41 (23.6%)	0.04
Morbid Obesity	17 (19.3%)	18 (17.5%)	22 (23.7%)	44 (25.3%)	0.04
Serum creatinine (mg/dL)					
Baseline	0.82 ± 0.22	1.05 ± 0.33	0.90 ± 0.29	1.23 ± 0.64	
Admission	0.90 ± 0.43	1.24 ± 0.44	1.44 ± 0.65	2.04 ± 1.67	<0.001
Nadir	0.68 ± 0.43	0.87 ± 0.40	0.79 ± 0.38	1.33 ± 1.13	
Peak	0.98 ± 0.42	1.50 ± 0.54	1.95 ± 0.89	5.30 ± 2.33	
Discharge	0.81 ± 0.43	1.10 ± 0.56	1.33 ± 0.87	3.60 ± 2.31	
Blood (by urine dipstick)					
Negative	54 (55.7%)	58 (45.8%)	36 (43.9%)	44 (28.8%)	
1+	15 (24.6%)	16 (19.3%)	17 (20.7%)	37 (24.2%)	0.001
2+	10 (16.4%)	17 (20.5%)	17 (20.7%)	46 (30.1%)	
3+	2 (3.3%)	12 (14.5%)	12 (14.6%)	26 (17.0%)	
Protein (by urine dipstick)					
Negative	24 (39.3%)	25 (30.5%)	30 (36.6%)	19 (12.3%)	
Trace	2 (3.3%)	4 (4.9%)	2 (2.4%)	2 (1.3%)	<0.001
1+	20 (32.8%)	17 (20.7%)	24 (29.3%)	52 (33.8%)	
2+	14 (23.0%)	34 (41.5%)	26 (31.7%)	73 (46.8%)	
3+	1 (1.6%)	2 (2.4%)	0 (0.0%)	10 (6.4%)	
Selected admission laboratory data					
Procalcitonin (ng/mL)	0.56 ± 1.50	2.83 ± 13.91	1.83 ± 6.50	1.32 ± 3.21	<0.001
CRP (mg/dL)	14.0 ± 10.3	14.2 ± 10.9	15.7 ± 12.2	18.4 ± 11.8	0.006
LDH (U/L)	403.8 ± 164.2	477.4 ± 281.6	457.1 ± 253.8	526.6 ± 245.9	<0.001
Ferritin (ng/L)	1288.7 ± 2773.1	1514.5 ± 3002.6	1627.2 ± 3485.4	1581.1 ± 3239.8	0.004
D-dimer (ng/mL)	14.72 ± 3.37	15.06 ± 3.04	15.86 ± 5.63	15.69 ± 5.84	0.17
PT (seconds)	1.18 ± 0.35	1.21 ± 0.32	1.30 ± 0.68	1.28 ± 0.68	0.40
INR	34.8 ± 7.4	40.2 ± 16.5	40.6 ± 21.9	42.8 ± 22.9	0.01
PTT (seconds)	621.0 ± 197.2	657.9 ± 202.0	648.3 ± 236.9	736.7 ± 224.0	<0.001
Fibrinogen (mg/dL)	621.0 ± 197.2	657.9 ± 202.0	648.3 ± 236.9	736.7 ± 224.0	<0.001
Total bilirubin (mg/dL)	0.51 ± 0.29	0.52 ± 0.35	0.61 ± 0.56	0.67 ± 0.77	0.049
AST (IU/L)	52.0 ± 62.4	62.3 ± 67.3	63.3 ± 64.9	83.9 ± 146.8	<0.001
ALT (IU/L)	39.8 ± 50.0	47.1 ± 64.8	41.4 ± 38.7	57.5 ± 150.4	0.01
Requirement for intubation	38 (43.2%)	58 (56.3%)	69 (73.4%)	156 (89.7%)	<.0001
Mechanical ventilation (days)	7.7 ± 7.5	9.0 ± 8.4	11.0 ± 10.8	12.5 ± 9.7	<.0001
APACHE IVa score	60.4 ± 23.6	69.2 ± 25.7	73.7 ± 28.9	84.6 ± 27.1	<.0001
Requirement for RRT					
HD	0 (0.0%)	0 (0.0%)	0 (0.0%)	66 (37.9%)	<.0001
CVVHD	0 (0.0%)	0 (0.0%)	0 (0.0%)	22 (12.6%)	
Hospital LOS (days)	12.1 ± 9.6	12.8 ± 8.4	16.4 ± 11.4	17.7 ± 13.1	<.0001
In-hospital death	22 (25.0%)	42 (40.8%)	43 (45.7%)	124 (71.3%)	<.0001
HD dependence at discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (7.0%)	0.000

PO0026

Increased Markers of Disease Severity in COVID-19 Patients with Hospital-Acquired vs. Community-Acquired AKI

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Background: The etiology of AKI in COVID-19 correlates strongly with age, comorbidities, and laboratory markers of disease severity. Outpatients with COVID-19 have different exposures that may cause AKI than hospitalized patients; thus, the etiology of AKI occurring before hospitalization [community-acquired AKI (CA)] may differ from those with hospital-acquired AKI (HA).

Methods: Excluding ESKD and hospital transfers, all COVID-19 PCR-confirmed cases admitted to 4 hospitals from 3/01/20 to 5/31/20 had data collected electronically through 7/31/20 including readmissions. Baseline C-EPI eGFR was determined by chart review for the period of 6 months prior to 5 months post-admission. AKI and recovery from AKI were scored using KDIGO staging. CA was defined as AKI with the highest level of creatinine (Cr) on admission, rising Cr on admission, or RRT started within 48 hours of admission without a subsequent AKI event after recovery. All AKI occurring > 48 hours was considered HA. To test which laboratory values correlated with CA or HA, we used a model adjusted for demographics, BMI, Elixhauser comorbidity index (ECI), and CKD stage.

Results: The table shows patients with HA and CA had similar demographics with only the ECI differing significantly. CA had less severe AKI, improved recovery to baseline, and lower mortality than HA. The lower mortality in CA was directly related to the lower stage of AKI. Within a given stage of AKI, mortality was not different between CA and HA. Recovery of renal function was significantly better in CA stage 1 vs. HA (8% vs. 26%, $p = 0.001$) but was not different for stage 2 or 3. In an adjusted model, higher

maximum dimers, ALT, AST, Bili, BNP, lactic acid, CRP, ferritin, LDH, neutrophils, troponin and lower minimum lymphocyte count were significantly associated with HA compared with CA. In contrast, on admission, only higher BNP, higher CRP, lower CPK and higher total CO_2 were associated with HA versus CA.

Conclusions: Compared to patients with CA, patients with HA had higher stages of AKI that correlated with higher mortality. They also had worsened recovery from stage 1 AKI and increased markers of COVID severity (except for CPK) in-hospital and on admission. We propose that factors other than COVID-19 disease severity led to CA, with volume and rhabdomyolysis as possible contributors.

PO0027

Hospital-Acquired AKI in COVID-19 Has a Similar Prognosis with or Without Prior Community-Acquired AKI

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Background: Recent meta-analyses suggest that Hospital Acquired AKI (HA) has a worse prognosis than Community Acquired AKI (CA). The effect of prior CA on HA in COVID-19 is largely unknown. COVID-19 case series that use lowest hospital creatinine (Cr) rather than outpatient baseline Cr may underestimate CA incidence.

Methods: Excluding ESKD and hospital transfers, COVID-19 PCR confirmed cases admitted to 4 hospitals between 3/01/20 & 5/31/20 had data collected through 7/31/20 including readmissions. Baseline Cr was adjudicated by manual review from 6 months prior until 5 months post admission. AKI and renal recovery were scored using KDIGO staging. CA is AKI with the highest Cr on admission, rising Cr from admission, or RRT in 48 hrs of admission. HA is AKIs occurring after >48 hrs. HA with CA (HA+CA) is AKI occurring in CA patients after renal recovery for > 48 hrs.

Results: AKI was present in 402 of 706 patients with COVID-19. HA+CA occurred in 63. Patients with HA+CA were older, had more comorbidities, lower eGFR, and lower admission albumin than patients with HA. Laboratory markers of COVID severity were similar in patients with HA or HA+CA and much worse than CA. Outcomes, including stage of AKI, renal recovery, ICU parameters, and mortality were similar in HA and HA+CA and much better in CA.

Conclusions: In COVID-19, HA + CA occurs in older patients with more comorbidities than HA but shares similar adverse disease markers and poor outcomes. We hypothesize that among older patients who recover from CA, those with severe disease markers are at risk for HA+CA.

Funding: Clinical Revenue Support

Outcomes of Patients with No AKI compared with different types of AKI

	No AKI N= 304[1]	CA N= 215[1]	HA+CA N=63[1]	HA N=124[1]
Age	56 (44, 68)	66 (54, 79)[A]	70 (61, 78)[A]	65 (54, 75)[A,C]
Female	51 %	48 %	54 %	48 %
African American	60 %	61 %	68 %	59 %
Caucasian or White	22 %	26 %	25 %	27 %
Elixhauser comorbidites	5 (0, 8)	8 (4, 17)[A]	15 (8, 24)[A,B]	11 (4, 18)[A,C]
Baseline e-GFR	93 (79,105)	81 (57, 96)[A]	72 (53, 88)[A]	87 (62, 103)[A,C]
AKI Stage 1		67 %	30 %[B]	34 %[B]
AKI Stage 2		14 %	27 %	20 %
AKI Stage 3		19 %	43 %[B]	46 %[B]
Renal Recovery		78 %	51 %[B]	54 %[B]
Mortality	3.6 %	16 %[A]	32 %[A,B]	38 %[A,B]
ICU Admission	10 %	44 %[A]	76 %[A,B]	77 %[A,B]
Intubation	0.3 %	4.7 %[A]	14 %[A,B]	26 %[A,B]
RRT	0 %	5.6 %	16 %[B]	24 %[B]
Min lymphocyte	1.16 (0.78, 1.65)	0.92 (0.66, 1.27)[A]	0.60 (0.39, 0.93)[A,B]	0.69 (0.50, 0.97)[A,B]
Albumin on Admit	3.90 (3.70, 4.10)	3.75 (3.40, 4.10)[A]	3.60 (3.32, 3.98)[A,B]	3.80 (3.50, 4.00)[A,C]
Max ALT	28 (18, 54)	34 (18, 78)	60 (25, 124)[A,B]	73 (33, 147)[A,B]
Max BNP	33 (19, 102)	86 (41, 210)	216 (77, 889)[B]	184 (51, 574)[B]
Max CRP	88 (42, 143)	151 (89, 234)[A]	247 (153, 329)[A,B]	266 (162, 373)[A,B]

[1]Median (IQR); n (%)

[A] p-value[2] <0.05 compared to No AKI

[B] p-value[2] <0.05 compared to CA AKI

[C] p-value[2] <0.05 compared to HA+CA

PO0028

Temporal Patterns in Incidence of AKI Associated with COVID-19 Using the National COVID Cohort Collaborative (N3C) Database

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Background: Acute kidney injury (AKI) is a common complication of patients hospitalized with coronavirus disease 2019 (COVID-19), however, the epidemiological studies are limited by single or few centers and short duration. How the incidence of COVID-19-associated AKI has changed over the last 18 months since start of the pandemic is not known.

Methods: We used the N3C enclave to collect data from 42 centers from all geographical regions of the United States of patients hospitalized with COVID-19 from December 2019 to May 2021. Unique patient visit occurrence ID data across various hospitalizations for each center was harmonized to uniformly collect information on serum creatinine (SCr), acute dialysis, end-stage kidney disease (ESKD) and transplantation. From a total of 127,223 patients hospitalized with COVID-19, 3,662 patients with pre-existing ESKD and 20,090 with < 2 measures of SCr were excluded. AKI and AKI stages were defined by KDIGO criteria. Baseline SCr was defined from the outpatient values before hospitalization when available or lowest inpatient value if not available. We analyzed how the incidence of in-hospital AKI changed over time (every 4-month period). Mann-Kendall Test was used to test for monotonic trends of the AKI incidence.

Results: Of the 103,471 patients hospitalized with COVID-19, 31,634 (30.6%) were diagnosed with AKI (mean age 63.3 years, 43.7% female, 32.4% non-white, and 19.5% Hispanic). 14,129 (13.7%) patients were diagnosed with AKI-1, 7,996 (7.7%) had AKI-2 and 9,509 (9.2%) patients had AKI-3 (6,285 [6.1%] without dialysis and 3,224 [3.1%] with dialysis). The incidence of 'all AKI' decreased from 38.8% in Dec 2019-March 2020 to 26.2% in March-May 2021 (p-value for trend = 0.086) and the incidence of AKI-3 declined from 15.5% to 6.5% (p = 0.086).

Conclusions: This is the largest and most nationally representative cohort of patients hospitalized with COVID-19 with the highest number of cases of AKI and of AKI-3 reported thus far. The incidence of COVID-19-associated AKI has shown a non-statistically significant decline during the past 18 months of the pandemic.

PO0029

AKI Prediction and Recovery in Hospitalized Patients with COVID-19

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Background: AKI is a complication in patients hospitalized with COVID-19 and is associated with poor outcomes. We aimed to develop predictive models for AKI development and recovery in patients hospitalized with COVID-19.

Methods: Patients with a positive SARS-CoV2 PCR admitted to 19 Texas hospitals from 3/13/2020-1/1/2021 were included. AKI presence and stages were determined using KDIGO guidelines. Individuals with AKI present on admission (POA) were excluded for predictive models. Patients were followed for 90 days to evaluate for renal recovery (serum creatinine ≤1.1 times baseline). Nested models for AKI were built using logistic regression: Model 1 included age, sex, race, smoking status, presence of hypertension (HTN), diabetes (DM), chronic kidney disease (CKD), coronary artery disease (CAD), and chronic heart failure (CHF), and use of ACEI/ARB; Model 2, added admission WBC, hs-CRP, and hemoglobin; Model 3, added ferritin and D-Dimer to Model 2 to assess for accuracy improvements. 10-fold stratified cross validation was done to evaluate model performance.

Results: Of 8392 patients, 2702 (32%) had AKI, of which 2281 (84%) recovered by 90 days: 92% of stage 1, 75% of stage 2, and 40% of stage 3 AKI, p for trend <0.001. After excluding AKI present on admission, 776 of 5671 developed AKI during the hospitalization. Percentages of AKI stages 1, 2 and 3 were 67%, 8%, and 25%. Overall, 152 (20%) of 776 required RRT. Patients with AKI were older, more likely to be male, black, and have hypertension, diabetes, coronary artery disease, congestive heart failure, and CKD. The interval improvement of each AKI predictive model was statistically significant, with last model AUC of 78.1 (95% CI 76.3%-79.9%) and all p<0.001. The final model had improvement in all metrics when compared to Models 1 and 2, with a sensitivity of 69%, specificity 76%, positive predictive value 32%, negative predictive value 94%, positive likelihood ratio 3.02, and negative likelihood ratio 0.40.

Conclusions: AKI is common among patients hospitalized with COVID-19, but a large proportion recover renal function by 90 days. Recovery rate is lower based on stepwise higher stages of AKI. Addition of inflammatory biomarkers to demographics and medical comorbidities can improve prediction of AKI in this patient population.

PO0030

Clinical Characteristics and Outcomes of COVID-19 Patients with AKI at Community-Based Hospital

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Background: The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and later called Covid-19 has resulted in significant morbidity worldwide. The virus can cause various complications and affect many organ systems. Preliminary reports have shown that Acute Kidney Injury (AKI) is common in patients with Covid-19, however, outcomes of kidney injury in hospitalized patients, especially at the community-based hospitals are not well described. The aim of this study was to describe the incidence, severity, and outcomes of Covid-19 patients with AKI at the community-based hospital.

Methods: This was a single-center, retrospective observational cohort study. All patients (age ≥18) with positive by polymerase chain reaction testing for Covid-19 who required hospitalization were included in the study. Patients with End-Stage Kidney Disease and kidney transplants were excluded. We compared outcomes of patients with and without AKI. We used univariable and multivariable Cox regression model to evaluate the relationship between AKI and in-hospital mortality.

Results: 220 patients were included in the study. 89 (40%) patients developed AKI, of whom 6 (7%) required Kidney replacement therapy (KRT) and 131 (60%) did not develop AKI. In-hospital mortality of patients with AKI was markedly higher than patients without AKI. Among the patients with AKI, 39 (43.8%) experienced in-hospital death while in patients without AKI, 23 (17.5%) died (P<0.001). Unadjusted HR was 2.01 (CI 1.23-3.14; P<0.001). The risk of in-hospital death remained significantly high following adjustment for baseline demographics and comorbidities with adjusted HR 1.8 (CI 1.50-2.74, P=0.015). The median hospital length of stay of patients who were discharged alive differed based upon AKI status. Patients with AKI-KRT had the longest median length of stay (15.5 days IQR 8.5-23.7), followed by patients with AKI non-KRT (7 days, IRQ 5-14) and patients without AKI (6 days, IQR 4-10).

Conclusions: AKI is a common condition among patients hospitalized with Covid-19 and is associated with an increased risk of in-hospital mortality. It is important to consider this complication in the management of Covid-19 patients.

PO0031

Risk Factors for AKI and Mortality in COVID-19 in Western Mexico

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Background: Acute kidney injury (AKI) in COVID-19 is associated with disease severity. The aim of this study was to identify risk factors associated with the development of AKI and its clinical impact, such as need for RRT and mortality.

Methods: Retrospective cohort study of hospitalized adult patients COVID-19, with normal kidney function, from April to December 2020 in Western Mexico.

Results: 882 patients (60.8% men) with a mean age of 58.9y were included. 342 (38.8%) had a prior diagnosis DM, 412 (46.7%) HTN, 161 (18.3%) obesity, 59 (6.7%) heart diseases, 25 (2.8%) neurological disease, 47 (5.3%) lung disease. 216 (24.5%) smoking history. 270 patients (30.6%) developed AKI, 95 (10.77%) KDIGO stage 1, 44 (4.98%) stage 2, and 84 (9.52%) stage 3. 59 patients required RRT (6.23%), and 111 patients (12.6%) mechanical ventilation. Overall mortality was 30.6% (270 patients). Risk factors for mortality were: DM, HTN, neurological disease, age > 65 y, need for MV, and MAP < 65 mmHg, hyperNa, increased D-dimer or decreased HCO3 at admission. Risk factors for AKI were: DM, HTN, heart disease, age > 65 y, need for MV, and MAP < 65 mmHg, hyperNa, increased D-dimer or decreased HCO3 at admission. Image shows risk factors, ORs with CI.

Conclusions: A high incidence of AKI in the Mexican population compared to reports from other countries, with a significantly high risk for death.

PO0032

Follow-Up Study of Survivors of Stage 2 or 3 In-Hospital AKI with or Without COVID-19

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Background: Acute kidney injury (AKI) is a hallmark of hospitalized patients with Coronavirus Disease 2019 (COVID-19) and associated with in-hospital mortality. Recent data suggests glomerular filtration rate (GFR) continues to decline after discharge in COVID-19 AKI survivors, but there are very few reports describing the long-term post-discharge outcomes.

Methods: This is an ongoing prospective study of 161 survivors of KDIGO stage 2 or 3 AKI who were admitted at Stony Brook Medicine (SBM) for COVID-19 between March-June 2020. 'CKD' was defined as patient's final outpatient serum creatinine (SCr) value remaining >10% or 50% above baseline (defined as the lowest SCr during hospitalization) and final GFR < 60 ml/min/1.73m^2. CKD was divided into 'incident' and 'progressive' based on baseline CKD status. We also investigated the readmission rate with and without AKI and post-discharge mortality. A comparison cohort of 66 AKI survivors concurrently admitted to SBM who tested negative for COVID-19 were also analyzed for all outcomes.

Results: COVID-19 AKI survivors were more likely to be non-White, Hispanic, have a lower prevalence of baseline CKD and greater severity of illness (mechanical ventilation, acute respiratory distress syndrome, vasopressor use and greater length of hospital stay) during hospitalization compared to COVID-19 negative survivors ($p \leq 0.01$). COVID-19 negative AKI survivors were more likely to have re-hospitalization ($p = 0.03$), although no difference was noted in re-hospitalization with AKI among the 2 groups. 29 out of 161 (18%) of COVID-19 positive AKI survivors died after their discharge from COVID hospitalization as compared to only 1 out of 66 patients (1.5%) of the COVID-19 negative AKI survivors ($p<0.001$). 42 (26.1%) of COVID-19 positive and 17 (25.8%) of the COVID-19 negative patients had a SCr and eGFR measure > 90 days after discharge. COVID-19 positive AKI survivors (11.9-19.0%) had no difference in the rate of incident or progressive CKD compared with COVID-19 negative AKI survivors (17.6%).

Conclusions: COVID-19 positive survivors of Stage 2 or 3 in-hospital AKI were more likely to have greater severity of illness during hospitalization and greater post-discharge mortality compared to COVID-19 negative AKI survivors. We did not find a difference in the rates of incident or progressive CKD at 10 months follow-up.

PO0033

Comparing COVID Acute Respiratory Distress Syndrome Patients on Extracorporeal Mechanical Oxygenation (ECMO) to Non-COVID Patients: Incidence and Effects of AKI

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Background: AKI has historically plagued those with ARDS and during the pandemic especially so with large resultant mortality rates. During the past year those centers so equipped offered ECMO to treat severe COVID pneumonia. We compared the

non COVID ARDS requiring ECMO with patients with COVID pneumonia requiring ECMO. The aim of the study was to understand the difference in the renal outcomes and its effects of mortality and thereby help in prognostication.

Methods: This is a single center retrospective study where patients with COVID pneumonia needing ECMO in between March 2020 to April 2021 were compared with non COVID ARDS patients needing ECMO between April 2013 to April 2021. The 2 groups were compared and risk ratio calculated for the incidence of AKI, the need for Renal replacement therapy (RRT) and the mortality associated with it.

Results: After excluding the patients who did not meet the criteria, 26 COVID patients treated with ECMO were compared with 22 patients with non COVID ARDS treated with ECMO. The median age of COVID group was higher (48 years vs 36 years) and the median number of days needing ECMO for the COVID group was higher (13 days vs 31 days). Incidence of AKI and the AKI needing RRT were similar in the 2 groups. The overall mortality in patients with COVID pneumonia was higher. Patients with COVID who developed AKI had 1.32 times the risk of mortality, which increased to 1.62 when RRT was needed.

Conclusions: This is a first study comparing the renal outcomes of COVID ARDS requiring ECMO and non COVID ARDS requiring ECMO. Even though the median age and the median number of the days on ECMO were higher for the COVID group, surprisingly the incidence of AKI and those needing RRT were similar. But there was a significantly higher mortality when patients on ECMO developed AKI and even higher for those on RRT. This could be attributed to the cytokine storm seen with causing a multiorgan dysfunction which can manifest in the form of AKI. Presence of AKI needs to be identified early and can be used for the prognostication in COVID pneumonia.

Incidence of AKI	21/26 (80.7%)	16/22(72%)	1.12
AKI needing RRT	15/21 (71%)	11/16 (68%)	1.04
Overall Mortality	16/26 (61%)	9/22 (40%)	1.5
Mortality with AKI	12/21 (57.1%)	7/16 (43%)	1.32
Mortality on RRT	11/15 (73%)	5/11 (45%)	1.62
Median Age	48 yrs	36 yrs	
Median No. of days on ECMO	31 days	13 days	

PO0034

Rapid Deterioration or a Long Road to Recovery for COVID-19 Patients with AKI

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Background: Global reports on the rates, risk factors and outcomes of acute kidney injury (AKI) with COVID-19 exhibit high variability. We evaluated all patients admitted with AKI to our centre where COVID-19 status was determined by PCR, and assessed risk factors for poor outcomes including death.

Methods: Retrospective study of all patients admitted with AKI between 13/03/2020 and 13/05/2020. All variables including COVID-19 status, demographics, co-morbidities and laboratory parameters were collected from electronic patient records. We used competing risk-regression models to assess association with mortality by subdistribution hazards ratio (SHR).

Results: Of 576 patients admitted with AKI, 257 (43.6%) were positive for COVID-19. Demographics and clinical characteristics of our cohort included: mean age 66.7 years, 58% male, 40.5% Caucasian, 56.3% hypertension, 33.1% diabetes. Overall 52.5% patients had AKI stage 1, 18.6% AKI stage 2, and 28.8% AKI stage 3. Patients with AKI stage 3 were 3.4 (95% CI 2.27-5.02) times more likely to be diagnosed with COVID-19 than those with AKI stage 1. Other factors associated with an increased likelihood of COVID-19 diagnosis adjusted for AKI stage were young age (p=0.004), non-Caucasian ethnicity (p=0.001), low lymphocyte count (p=0.002) and raised CRP, ferritin and D-dimer (p=0.001). Case fatality percentage of this cohort was 32.5% (10%, 19% and 35% mortality in COVID-19 negative patients with AKI stages 1, 2 and 3 respectively, compared with 33%, 52% and 71% in the COVID-19 positive counterparts). Patients with COVID-19 were 3.6 (95% CI 2.2-4.3) times more likely to die than those negative for COVID-19 (p<0.001). Furthermore, death in patients with COVID-19 and AKI stage 3 occurred rapidly, with 50% of patients dying within 10 days, 70% within 15 days and 95% within 21 days of admission. Those in the same group who survived had prolonged recovery, with 50% remaining inpatients in hospital for over 31 days.

Conclusions: In patients with AKI, those who were positive for COVID-19 was associated with severe AKI, younger age, non-Caucasian ethnicity, raised inflammatory markers, and suffered from high case fatality. Severity of AKI in conjunction with COVID-19 was associated with high and rapid death rates, or prolonged hospital admission with increased morbidity.

PO0035

Association of Endotoxemia with AKI in Critically Ill Patients with SARS-CoV-2 Infection

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Background: AKI is frequently complicated by sepsis. Endotoxin (lipopolysaccharide), a component of the outer wall of gram-negative bacteria, has been investigated and acknowledged as one of the triggers of lethal shock during sepsis and drivers of cytokine storm. In studies, septic shock was present in 6.4% patients with severe COVID-19, but blood cultures and respiratory cultures were negative in 76%. Initial cohort study of COVID-19 patients from China showed 4.5% developed AKI, subsequent reports showed higher prevalence. While these data suggest that patients with COVID-19 are at risk for septic shock and AKI, mechanisms mediating these processes in the setting of severe coronavirus 2 (SARS-CoV-2) infection remain unclear.

Methods: We conducted a single-center, cross-sectional study in critically ill patients with COVID-19 to test the prevalence of endotoxemia and whether endotoxemia is associated with the development of AKI. Patients were recruited using criteria: Age ≥ 18yr, MODS ≥ 9, sepsis and intensive care unit admission, excluded if pregnant, requiring chronic dialysis or chronic immunosuppressive medications. Blood endotoxin activity (EA) measured in patients who met the criteria using the FDA-approved Endotoxin Activity Assay (EAA). EAA is a chemiluminescent bio-assay based on the oxidative burst reaction of activated neutrophils to complement coated LPS-IgM immune complexes. Patients divided into low (0.0 – 0.39 EA units), intermediate (0.40 – 0.59 EA units), high (≥ 0.60 EA units), and non-responder (NR) (patients whose neutrophils do not have the ability to respond to preformed immune complexes in the EAA) group based on measurements from the EAA.

Results: In this study, endotoxemia observed in 24/32 (75%) of our critically ill patients with COVID-19, despite only 2 patients having positive blood cultures for gram-negative organisms. The incidence of AKI was higher in the high EA group (7/14, 50%) as compared to intermediate EA group (1/10, 10%), p=0.01. The need for renal replacement therapy (RRT) was higher in the elevated EA group (4/14, 29%), with none of the patients in the intermediate group requiring RRT, p=0.008.

Conclusions: This study demonstrates the high prevalence of endotoxemia in critically ill patients with COVID-19, regardless of presence of bacteremia. We also observed that high EA was associated with AKI and the need for RRT.

PO0036

AKI in Extracorporeal Support

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Background: Acute kidney injury (AKI) is common in critically ill patients receiving extracorporeal membrane oxygenation (ECMO). Use of continuous renal replacement therapy (CRRT) with ECMO may help optimize fluid balance and correct electrolyte abnormalities but may also worsen outcomes. The relationship between AKI, CRRT, and survival in ECMO patients remains poorly defined. The aim of this study was to evaluate AKI outcomes in the setting of ECMO support. We assessed factors that may influence AKI severity, as well as the safety of combined CRRT with ECMO

Methods: We performed a retrospective analysis of patients that received ECMO from 2018-2021 at a tertiary hospital, using a prospectively maintained database. All patients requiring CRRT received continuous veno-venous hemodiafiltration (CVVHDF). Data collected includes demographics, ECMO and CRRT parameters, anticoagulation, baseline kidney disease, baseline serum creatinine (sCr), ECMO and CRRT duration, hospital length of stay (LOS), complications (patient and device-related), and outcomes.

Results: To date, 16 ECMO patients with AKI have been analyzed. Mean age was 46.6 +/- 15.6 years. Eleven (68%) were male, and 50% were African American. ECMO indication included respiratory failure due to COVID-19 (43%), followed by respiratory failure from sepsis (19%). Initial ECMO modality was VV- in 75% and VA- in 25%. Mean baseline sCr and sCr at CRRT initiation were 1.3+/-1 mg/dL and 3.93+/-1.1 mg/dL, respectively. Mean ECMO duration was 30+/-37 days, and mean CRRT duration was 26+/–21 days. Elevated plasma hemoglobin (mean peak 103 mg/dL) levels occurred in 14 (88%) patients. Of 10 (63%) patient surviving to discharge, 3 (30%) were dialysis dependent. sCr at CRRT start did not influence CRRT duration: for sCr<4 mg/dL, mean CRRT duration was 37 days, and for sCr>4 mg/dL, mean CRRT duration was 20 days (p=0.21). Mean creatinine at discharge was 1.78+/-1.1 mg/dL.

Conclusions: Our results suggest that CRRT can be safely combined with ECMO to achieve satisfactory patient outcomes. Dialysis independence seems attainable in most patients; however, additional patient enrollment is underway to support this concept with a greater degree of confidence.

PO0037

RAAS Inhibition and Risk of AKI in COVID-19

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Background: Direct viral invasion of the kidney via ACE2 has been hypothesized as a mechanism of AKI in COVID-19 (COVID). The impact of RAASi on the risk of AKI in COVID is not known. We hypothesized that active use of RAASi preceding admission would be associated with a greater proportional risk of AKI in COVID than influenza (flu).

Methods: In this retrospective cohort, we compared the AKI incidence by RAASi status in 11,898 hospitalized Veterans with COVID or flu between Oct 1, 2019 and Sept 30, 2020. To control for confounding, propensity score weighting balanced baseline conditions, labs, and co-therapies in 4 exposure groups: RAASi users with COVID, non-users with COVID, RAASi users with flu, and non-users with flu. Weighted logistic regression estimated the main effects of RAASi and COVID, and their interaction.

Results: In flu, 7% of RAASi users had a stage 2-3 AKI vs 5% of non-users, a 2% increase (p=0.03). In COVID, 16% of RAASi users had a stage 2-3 AKI vs 12% of non-users, a 4% increase. While the absolute increase in AKI incidence for RAASi users vs non-users was greater in COVID patients vs flu, the difference was not statistically significant (p=0.66) and the RAASi association was proportionally smaller in COVID (see interaction in Table). Similar absolute differences were observed in stage 1-3 AKI (Table), and the interaction was also not statistically significant (p=0.66).

Conclusions: COVID was associated with a greater incidence of AKI than flu. RAASi was associated with an increased incidence of Stage 2-3 AKI in patients with COVID or flu. The proportional effect of RAASi was similar in COVID and flu patients. These findings do not support a disproportionate risk of AKI among RAASi users with COVID.

Funding: Veterans Affairs Support

AKI Incidence Rates and Odds Ratios in COVID and Flu by RAASi Status

	Stage 1-3 AKI	Stage 2-3 AKI
IR: No RAASi | Flu	25%	5%
IR: RAASi | Flu	28%	7%
IR: No RAASi | COVID	31%	12%
IR: RAASi | COVID	35%	16%
OR: COVID vs Flu | No RAASi	1.33 (1.12-1.58)	2.72 (1.89-3.92)
OR: RAASi vs No RAASi | Flu	1.16 (0.95-1.42)	1.60 (1.04-2.46)
OR: COVID by RAASi Interaction	1.06 (0.83 - 1.35)	0.90 (0.56-1.45)

IR: Incidence Rate, OR: Odds Ratio.

Rates and Stage 1-3 ORs are based on the entire weighted cohort. Stage 2-3 ORs are in the subset of Stage 2-3 and no AKI patients.

PO0038

Dexamethasone Reduces AKI in Critical COVID-19 Patients

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Background: More than 50% of severe COVID-19 patients develop acute kidney injury (AKI) and a high percentage of them will require renal replacement therapy (RRT). The aims of this study were to identify AKI prevalence and associated factors in patients with COVID-19 and invasive mechanical ventilation (IMV).

Methods: Prospective cohort analysis of all COVID-19 patients with IMV, admitted to our Institute in Mexico City (Mar 2020 - Jan 2021). AKI was defined according to KDIGO guidelines. Patients with CKD stages 4 or 5 were excluded. Demographic, clinical, laboratory, and treatment variables were registered. AKI development was analyzed by uni- and multivariate logistic regression, mortality by survival analysis.

Results: Of 552 COVID-19 patients, AKI was detected in 196 (35.5%). Among AKI; 80 (40.8%) were Stage 2, and 116 (59.2%) Stage 3. The incidence of each AKI stage was lower in patients treated with dexamethasone (DEXA, Fig. 1A) and decreased the requirement of RRT (30 vs 16, p=0.05). For the multivariate analysis, AKI was grouped into no AKI/Stage1 and Stage 2/3 AKI; DEXA treatment was associated with less AKI incidence (OR 0.34, 95%CI 0.23-0.51) and lower mortality in the adjusted Cox-regression analysis (Fig. 1B).

Conclusions: AKI is associated with increased mortality in COVID-19 patients with IMV. The use of DEXA is associated with lower AKI severity and lower mortality.

Table 1: Characteristics and in-hospital outcomes for AKI vs no AKI.

	All (N=552)	No-AKI (N=356)	AKI (N=196)	P value
Age (yr), median (IQR)	53 (44-63)	53 (41-62)	54 (46-64)	0.03
Male, n (%)	397 (72)	167 (69)	230 (74)	0.56
Comorbidities, n (%) Diabetes mellitus Hypertension	151 (27.4) 152 (27.6)	93 (26) 90 (25.4)	58 (29.6) 62 (31.6)	0.38 0.11
BMI (kg/m2), median (IQR)	30.1 (27.3-34.1)	29.7 (27.1-33.2)	30.9 (27.5-35.4)	0.45
PCR (mg/dL) Ferritin (mg/dL) PaO2/FiO2 ratio	19.2 (12.3-28.5) 794 (458-1300) 107 (82-147)	18.9 (10.8-25.7) 763 (459-1281) 105 (83-144.8)	21.1 (13.9-30) 790 (459-1344) 105.5 (76-144.8)	0.48 0.57 0.52
Dexamethasone, n (%)	267 (48.4)	201 (56.5)	66 (35.5)	<0.01
SOFA ICU, median (IQR)	4 (4-6)	4 (4-6)	5 (4-7)	<0.01
Mortality, n (%)	215 (39)	107 (49.8)	108 (55)	<0.01

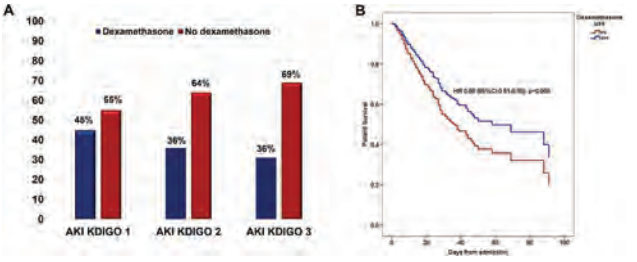

Figure 1: A. AKI development according to DEXA use. B. Mortality according DEXA use.

PO0039

Volume Balance and AKI in Critically Ill Patients with SARS-CoV-2

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Background: Evidence from the management of critically ill patients suggests restrictive volume management strategies and avoidance of volume overload improve ICU outcomes. Restrictive practices have been applied to the management of patients with SARS-CoV-2 (COVID-19), but data describing volume management and its associated outcomes in those with and without acute kidney injury (AKI) in this setting are lacking.

Methods: We conducted a single-center retrospective cohort study of ICU patients with COVID-19. 7-day cumulative volume balance from ICU admission in excess of -5% (negative balance) or +5% (positive balance) of ICU admission weight as well as AKI based on KDIGO guidelines were identified. Associations between volume balance, AKI and clinical outcomes (dialysis, mechanical ventilation, and inpatient mortality) were explored.

Results: 194 of 374 ICU admissions (51.9%) had AKI with 60 of 374 (194) (16.0%, 30.9% of those with AKI) requiring dialysis. 110 of 374 (29.4%) developed negative balance and 40 of 374 (10.7%) developed positive balance. Inpatient mortality was higher in those with AKI and negative balance (28%) and positive balance (35%) compared to those with neutral balance (16%) (p=0.039). Of the subjects with negative balance (Table), despite no difference in their net volume balance, inpatient mortality was significantly higher in those with AKI compared to those without AKI (p=0.048). Using the Kaplan-Meier estimator, patients with no AKI had no difference in inpatient survival when compared on the basis of volume balance (p=0.69). However, in those with AKI, inpatient survival was significantly lower for positive and negative volume balance compared to neutral balance (p=0.01).

Conclusions: Negative and positive volume balance are associated with higher inpatient mortality particularly in patients with AKI. Future research must investigate the impact of negative balance on morbidity and mortality in patients with and without AKI.

Outcomes of ICU Patients with Negative Balance by AKI Status

	AKI (N=68)	No AKI (N=42)	p-value
Cumulative 7-Day Fluid Balance (L), Median (IQR)	-6.1 (-7.7, -4.0)	-6.1 (-7.8, -5.3)	0.30
AKI-D	25 (37%)		
Mechanical Ventilation	29 (43%)	11 (26%)	0.081
Days of Mechanical Ventilation, Mean (SD)	5.4 (3.4)	6.3 (4.1)	0.50
Mortality	19 (28%)	5 (12%)	0.048

PO0040

Urinary Findings Reveal Dominant Tubular Injury in Hospitalized Patients with COVID-19

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Background: Renal manifestations during infection with SARS-CoV-2 are prevalent and include proteinuria and hematuria as well as acute kidney injury (AKI). Possible mechanisms of renal involvement with COVID-19 are acute tubular injury (ATI) due to cytokine storm, direct virus-induced tubulopathy or glomerular injury related to podocytopathy. However, a kidney biopsy or urine studies including direct urine microscopy have rarely been performed. Our aim was to examine the urinalysis, level of

protein excretion and microscopy findings in urine collected from hospitalized COVID-19 patients in order to better elucidate the nature of COVID-19 related kidney involvement.

Methods: We collected fresh urine samples from 92 patients admitted to the COVID-19 ward at Samson Assuta University Hospital in Israel. Urine samples were collected randomly, regardless of renal function or prior medical history. Urinalysis and urine chemistry were performed in addition to direct urine microscopy analyzed by an experienced nephrologist.

Results: Urine samples were collected from 55 men and 37 women, most of whom (64%) had severe COVID-19 at the time urine samples were obtained. AKI at different levels of severity was diagnosed in 37 patients (40%). Proteinuria and hematuria were present in 43% and 38% of urinalysis samples, respectively, suggesting glomerular involvement. Urine protein to creatinine and albumin to creatinine ratios were measured in 76 patients (83%). Median urinary albumin to protein ratio (UATPR) was very low –0.16, indicating a tubular origin of the proteinuria. Direct urine microscopy was performed on 58 samples, of which granular casts were detected in 43% (25 samples) and in 5 of them granular casts were spotted without evidence of AKI. Additionally, uric acid crystals and amorphous urate were found in 19 (33%) of microscopy samples. Median urine pH was 5.5 which likely contributed to precipitation of uric acid. Notably, urine sediment clues of either nephrotic or nephritic syndrome were absent in all examinees.

Conclusions: Urinary sediment findings and a very low UATPR support ATI as the main mechanism for kidney injury in COVID-19 patients. Acidic urine and uric acid crystals may have resulted from viral related ACE2 down regulation, enhanced angiotensin II and aldosterone mediated urinary acidification. Further studies are needed to shed light on COVID-19 related kidney involvement.

PO0041

Urinary Epidermal Growth Factor as a Protector in COVID-19 Patients with AKI

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Background: Acute Kidney Injury (AKI) in hospitalized patients with infection by SARS-Cov-2 (COV-AKI) is a multifactorial syndrome with immune and inflammatory responses. Knowing the cytokine profile will help to understand the pathogenesis.

Methods: Single center, prospective study at the National Institute of Respiratory Diseases (INER), Mexico. Between May-August 2020 we included patients with severe pneumonia by Sars-Cov-2. We collected urine for citokines quantification with a Human Cytokine Magnetic 30-plex panel by Luminex, TIMP-2 and IGFBP7 by ELISA and N-Gal by Architect®. Clinical and laboratory data were gathered from medical file. We evaluated for AKI defined by the 23rd ADQI consensus with [TIMP2]x[IGFBP7] >0.3. We used $\chi 2$ and Mann Whitney-U test to compare groups. We calculated the area under the curve (AUC) for EGF, determined the best accuracy cut-off point and correlated EGF with NGAL, [TIMP2]x[IGFBP7] and GFR with a Spearman-rho. We did a univariate and multivariate logistic regression.

Results: We included 51 patients with 53 years-old median age and 58.8% men. Hypertension and D-dimer were higher in the AKI group. In the urinary citokines there were differences for RANTES as risk factor and EGF as protective factor. The analysis was consistent considering all the values and taking out the outliers. The AUC for EGF was 0.788 (p=0.01, 95% CI: 0.59-0.97), with the best accuracy cutoff of 4600 pg/mL. EGF showed correlation with NGAL ρ-0.62 (**p<0.01**), [TIMP2]x[IGFBP7] ρ-0.71 (**p<0.01**) and CKD-EPI GFR ρ+0.74 (**p<0.01**). EGF shows protective effects with statistically differences in the univariate and multivariate logistic regression *(Table 1)*.

Conclusions: Patients without AKI had more expression of uEGF; this cytokine could be involved in the renal protection against the development of COV-AKI. EGF has an inverse correlation with NGAL and [TIMP2]x[IGFBP7] and a positive correlation with the GFR.

Funding: Government Support - Non-U.S.

Univariate and multivariate analysis for AKI

Variables	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Age >60y	3.07 (0.82-11.48)	0.09	1.92 (0.28-13.07)	0.50
Male	2.30 (0.73-7.19)	0.15	3.85 (0.73-20.16)	0.11
Hypertension	7.87 (1.54-40.27)	0.01	7.27 (0.94-55.82)	0.056
NGAL >40	6.02 (1.71-21.09)	0.005	4.09 (0.82-20.34)	0.08
D-Dimer	3.52 (0.82-15-16)	0.09	3.71 (0.49-27.99)	0.20
EGF >4600	0.18 (0.04-0.80)	0.02	0.08 (0.008-0.87)	0.03
EGF >4600 w/o outliers	0.05 (0.008-0.40)	0.004	0.095 (0.01-0.81)	0.03

CI: Confidence Interval; OR: Odds Ratio; w/o: without

PO0042

The Assessment of Bronchoalveolar Lavage (BAL) Fluid Composition in Critically Ill Patients with and Without COVID-19 and AKI

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Background: Recent reports identified enrichment of T cells and monocytes in the BAL fluid of patients with COVID-19 pneumonia, in contrast to neutrophilia in patients with non-COVID-19 pneumonia, which suggests a distinct immunopathology. We evaluated whether AKI, an independent risk factor for adverse outcomes, modifies BAL cell composition in critically ill patients.

Methods: We retrospectively analyzed BAL specimens from 710 critically ill patients undergoing evaluation for pneumonia at an academic medical center from 3/2018-11/2020. Kruskal-Wallis tests compared distributions of BAL fluid % cell counts by COVID-19 and AKI status. Multivariable linear regression models tested the associations of COVID-19 status with the BAL fluid % cell counts. We tested for effect modification by AKI status. AKI was defined by the KDIGO criteria.

Results: Mean age was 60±15 years and median baseline serum creatinine was 0.8 [0.6–1.1] mg/dl. COVID-19 was positive in 34.5% and AKI occurred in 42.8% of patients. Figure 1A shows differences in BAL fluid cell composition by COVID-19 and AKI status. Highest % of neutrophils were in COVID-19(-) AKI(-) patients and lowest in COVID-19(+) AKI(-) patients. Macrophages, monocytes, and lymphocytes were highest in COVID-19(+) AKI(-) patients and lowest in COVID-19(-) AKI(-) patients. COVID-19(+) patients had a significantly lower % of neutrophils and a higher % of monocytes and lymphocytes after multivariable adjustment (Figure 1B). Patients who were AKI(+) had decreased % of neutrophils when COVID-19(-), while the opposite effect was noted for COVID-19(+) (P for interaction=0.007).

Conclusions: AKI may differentially modify the cell BAL fluid cell composition among patients with suspected pneumonia based on their COVID-19 status.

Funding: Private Foundation Support

Figure 1A

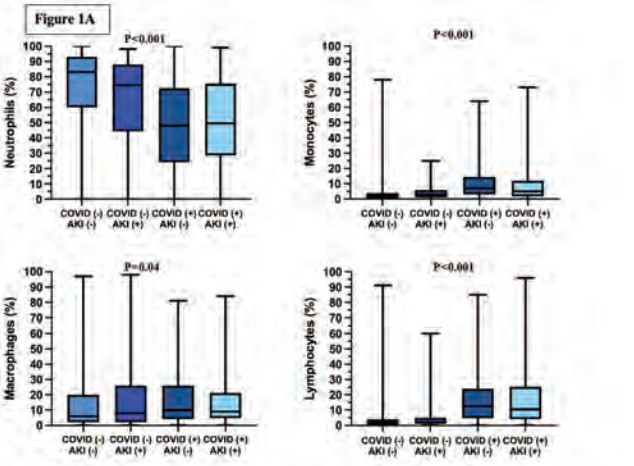

Figure 1B

BAL cell fluid composition	Beta Coefficient	95% Confidence Interval
Neutrophils	-19.4%	-24.2 – -14.8
Monocytes	5.5%	4.2 – 6.7
Lymphocytes	12.9%	10.9 – 15

Beta coefficient is for COVID-19(+) compared to COVID-19(-) after adjustment for age, sex, race, diabetes, congestive heart failure, malignancy, baseline kidney function, and AKI status

PO0043

Clinical Outcome and Antibody Response in COVID-19-Positive Pediatric Kidney and Liver Transplant Recipients

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Background: The COVID-19 pandemic has profoundly impacted transplantation activity worldwide. Nevertheless, data on the clinical and laboratory features of SARS-CoV-2 infection in pediatric recipients of solid organ transplant (SOT) recipients are scarce.

Methods: We describe clinical and laboratory manifestations, including serologic response, and short-term outcomes of 25 pediatric recipients of SOT who tested positive for SARS-CoV-2 during the first nine months of the epidemic in Israel.

Results: The mean age was 15.2±4 years; 14 (56%) were kidney and 11 (44%) liver transplant recipients. Twenty-three (92%) of the patients were symptomatic. The most common symptoms were fever (44%), headache (44%), cough (40%), and fatigue (36%). Most (84%) had a mild disease. Two patients (8%), both kidney transplant recipients with additional comorbidities, had severe respiratory disease and required adjustments in their immunosuppression therapy. None were admitted to the pediatric intensive care unit or died, and all the patients fully recovered after a median of 27 [interquartile range 21-41] days. Significantly longer virus shedding time was found among kidney and pancreas transplanted recipients than among liver transplant recipients (35.1±9.8 vs.19.6±4.7 days, p=0.0005). Following a median of 7 (5-10.5) weeks after COVID-19 diagnosis, 3 (22%) reported residual symptoms, mainly fatigue; 22/23 (96%) had positive antibody responses.

Conclusions: Our study demonstrated that while the majority of pediatric recipients of SOT developed a mild disease with a positive serologic response, a relatively high percentage (8%) developed a severe disease. This emphasizes the need for close monitoring of this particular population, especially those with comorbidities.

PO0044

COVID-19 Seropositivity in New York ESKD Patients

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Background: Patients on hemodialysis (HD) with COVID-19 infections have increased emergency room visits, hospitalization, and mortality. We evaluated COVID-19 seroprevalence in a dialysis organization in NYC.

Methods: We collected data on patients undergoing maintenance HD in four different units in Manhattan, New York. Data was collected regarding demographics, cause of kidney failure, time on dialysis, and insurance. Covid antibody was tested using the elecsys Anti-SARS-CoV-2 immunoassay. We performed univariate analysis using Chi square test and multivariate linear logistic regression models to identify variables associated with COVID-19 seropositivity.

Results: Seropositivity was detected in 108 (20.2%) out of the 535 patients tested. In univariate analysis, age, HD unit, race, institutionalized status, time on dialysis, and type of insurance were associated with seropositivity. In multivariate analysis race, age, time on dialysis were not associated with COVID seropositivity Patients uninsured, or those covered by medicaid, had a significantly higher likelihood of testing positive for COVID antibodies than patients covered by private insurance (OR, 8.02, P=0.05). In reference to the Chinatown unit, patients receiving treatment at the 34th Street unit (OR, 4.90, p=0.002) and the Lower Manhattan unit (OR, 3.42, p=.02) were more likely to test positive., Institutionalized patients were almost eleven times more likely to test positive for the antibodies than those not institutionalized (OR, 10.97, p<0.001). Race was not significantly associated with antibody positivity.

Conclusions: Our study showed increased prevalence of COVID-19 antibodies in Institutionalized and uninsured/Medicaid patients but no association with race suggesting socioeconomic status, is more important than race in determining the risk of COVID-19 infection in patients on maintenance dialysis.

PO0045

Prevalence and Dynamics of SARS-CoV-2 Nucleocapsid IgG in Kidney Transplant Recipients

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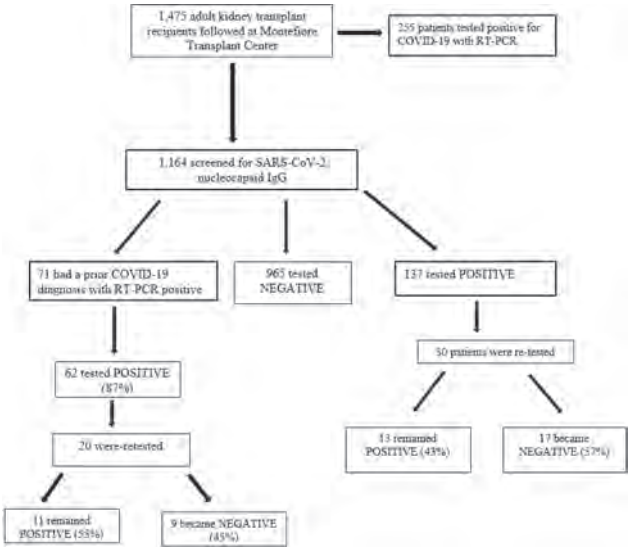
Background: We aimed to investigate the prevalence and dynamics of SARS-CoV-2 IgG in kidney transplant recipients in the Bronx, New York, one of the epicenters of the pandemic

Methods: Between March 16 and May 5, 2021, 255 patients tested positive by SARS-CoV-2 RT-PCR. From May 3 to May 5, 2021, 1,164 patients were screened for SARS-CoV-2 IgG antibodies and 199 (17.1%) were tested positive (Figure).

Results: 62 of the 199 patients were previously diagnosed COVID-19 by RT-PCR, while the remaining 137 did not have significant symptoms and had not been previously tested by RT-PCR. Overall prevalence of COVID-19 diagnosis by RT-PCR and/or SARS-CoV-2 IgG in 1,348 patients tested were 29.1%. Seventy-one RT-PCR+ patients were screened for SARS-CoV-2 IgG antibody and 62 (87%) were positive at a median 106 days (81-168) A total of 50 patients of 199 who were previously tested positive for SARS-CoV-2 IgG (30 diagnosed with IgG and 20 with RT-PCR) were retested at a median time of 112 days (IQR: 81-121). Twenty-six patients (52%) became seronegative at a median time of 105 days (IQR: 84-141) from their first positive IgG. Nine of 20 (45%) patients who were diagnosed by RT-PCR became seronegative at a median time of 108 days (IQR: 81-168) from their first positive IgG while 17 of 30 (57%) patients who were initially diagnosed by a positive IgG, became seronegative at a median time of 121 days (IQR: 90-145) from the date of diagnosis.

Conclusions: In summary, 35% of kidney transplant recipients were asymptomatic or mildly symptomatic and developed SARS-CoV-2 IgG without requiring testing by RT-PCR. However, half of the patients who initially developed antibodies lose them over time raising the questions of lasting immunity against SARS-CoV-2 and how effective are those antibodies in preventing future infection.



PO0046

Kidney Outcomes in Long COVID-19

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Background: Early epidemiologic evidence has suggested that the coronavirus disease 2019 (COVID-19) increases the risk for subsequent disease even after its acute phase. We aimed to describe post-acute kidney disease sequalae of COVID-19.

Methods: In a cohort of 1726683 US Veterans identified from March 01, 2020 to March 15, 2021, we examined the risk of AKI, progression of kidney disease, ESKD, and MAKE following the acute phase of the infection (30 days) in those with COVID-19 (89216) compared to those without (1637467), using weighted survival regressions. Linear mixed models characterized intra-individual eGFR trajectory.

Results: In a cohort of US Veterans with a median follow up of 172 days (IQR: 133-281), those with COVID-19 were at a higher risk of AKI (aHR=1.94 (95%CI: 1.86-2.04)), eGFR decline ≥30% (1.29 (1.25-1.34)), eGFR decline ≥40% (1.44 (1.37-1.51)), eGFR decline ≥50% (1.62 (1.51-1.74)), ESKD (2.96 (2.49-3.51)), and MAKE (1.66 (1.58-1.74)). Compared to non-hospitalized Veterans without COVID-19, excess burden 6 months after infection was higher by severity of COVID-19 infection, including AKI (3.17, 45.21, and 74.19 per 1000 persons in those non-hospitalized, hospitalized, and admitted to ICU, respectively), eGFR decline ≥ 30% (3.01, 44.71, 72.23), and MAKE (2.01, 31.92, 79.13). COVID-19 was associated with an excess rate of decline in eGFR following the acute phase of the infection (-2.30, -7.68, -9.70 mL/min/1.73m^2/year in those non-hospitalized, hospitalized, and admitted to ICU).

Conclusions: COVID-19 is associated with increased risk of adverse kidney outcomes after the first 30 days of the infection; excess burden was higher in those with a more severe infection.

Funding: Veterans Affairs Support

PO0047

COVID-19-Associated Kidney Injury: A Single-Center Community Experience of 684 Consecutive Patients

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Background: Acute kidney injury associated with COVID-19 is poorly understood; majority of the published literature currently available in the United States comes from major academic institutions. This study aims to describe the epidemology and general outcomes of hospitalized patients with COVID-19 at a large tertiary community hospital.

Methods: This is retrospective descriptive study of the incidence of acute kidney injury for hospitalized patients with COVID-19 between March 1st - May 31st at a single-center community teaching hospital in Cook County, Illinois. Patients diagnosed previously with End Stage Renal Disease (ESRD) and kidney transplant recipients were excluded, as were incidental positives and multiple COVID-19 hospitalizations. Acute kidney injury (AKI) was defined by KDIGO criteria. Baseline creatinine (SCr) was defined as the median SCr from the previous 365 days until 7 days prior to admission. If no baseline SCr was available, admission SCr was used as the baseline. Results are descriptive.

Results: Of the 684 patients admitted the hospital with COVID-19 infections, 231 (33.8%) developed an AKI. Stage 1 129 (55.8%), Stage 2 36 (15.6%), Stage 3 66 (28.6%). Urine microscopy showed proteinuria 104 (45.1%), hematuria 129 (55.8%), leukocyturia 129 (55.8%); Median FE Na 0.3 [0.1 - 0.7] and FE Urea 21.1 [15.0 - 29.5].

Renal biopsy performed on four patients demonstrated acute tubular necrosis. Fifty-two (22.5%) patients received KRT; most commonly with CKRT in 26 (50%) or combination of CKRT and HD in 17 (32.7%). Median hospital day for initial dialysis was 5.0 [2.0 - 10.0]; mechanical ventilation 0.0 [1.0- 4.0], ECMO 1.0 [0 - 4]. LOC was significantly longer for AKI patients (overall 8.7 [4.8 - 17.3], No AKI 7.7 [4.0 - 12.7], AKI 15.0 [7.1 - 27.2] days p <0.01). Most common co morbidities were Type 2 diabetes and hypertension. D-dimer, LDH, CRP, procalcitonin and IL-6 were significantly higher. Upon discharge, 138 (59.7%) were discharged without KRT, whereas 12 (5.2%) patients required KRT. Nine (3.9%) went hospice, and 72 (31.2%) died. One patient was still admitted to the hospital.

Conclusions: Acute kidney injury is a poor prognostic indicator for patients with COVID-19. The mortality rates and outcomes of patients with AKI in this setting are comparable to previously published studies.

PO0048

Kidney Recovery Post Coronavirus Infection in Hospitalized Kidney Transplant Recipients: A Single-Center Observational Study

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Background: Kidney transplant recipients (KTR) are at an increased risk of severe disease and death caused by coronavirus-19 infection. There is a paucity of information on the evolution of graft function among hospitalized KTRs who overcome the infection.

Methods: The study included adult KTRs at a single transplant institute who were diagnosed with Coronovirus-19 virus and needed hospitalization between March 15, 2020 and January 15, 2021. We analyzed patient demographics, comorbid risk factors, and inpatient clinical course for patients that were able to recover from the infection. Kidney function was analyzed pre-infection, during initial hospitalization and up to 12 months post infection.

Results: We identified 48 kidney transplant recipients who were diagnosed with Coronavirus-19 infection during the study period. Eighteen KTRs among these needed hospitalization for symptoms of fever and respiratory distress. Four patients died of Coronavirus-19 infection related complications and were excluded from the study. The 14 remaining patients in the study were predominantly black (78%), with a median time since transplant of 4 years. 64% of the patients developed AKI, with an average peak serum creatinine of 2.64 mg/dl and GFR of 34. The mean serum creatinine and GFR of the group were 2mg/dl and 44 at baseline (prior to infection). This represented an increase in their serum creatinine and GFR of 34% and 29% respectively. The median follow-up post infection was 7.5 months. Serum creatinine and GFR were 1.83 mg/dl and 48 at 3 months, and 2.2 mg/dl and 40 at 6 months post infection. New onset proteinuria was noted in 5 out of the 14 patients (36%), with complete resolution of same in all at 3 months follow up. 75% patients with AKI had complete recovery at 3 month follow-up. The mean baseline GFR of patients who had incomplete recovery was 32. There was only 1 graft loss and this was in a patient who had chronic rejection and had a baseline Cr of 3.8 mg/dl at time of coronavirus-19 infection.

Conclusions: AKI is common among KTRs that are hospitalized with Covid-19 infection. Most of these recover, although we noted that patients with baseline lower kidney function (GFR < 32) and existing proteinuria had a lower recovery rate.

PO0049

Risk Factors for RRT and Mortality in Patients with COVID-19-Related AKI in São Paulo, Brazil

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Background: In COVID-19, as in SARS, the degree of kidney injury can have major implications for the clinical outcomes. Early reports indicate that, among patients with COVID-19, AKI is common and is associated with worse outcomes. However, COVID-19-related AKI among ICU patients in Brazil has not been well described.

Methods: This was a retrospective observational study of the electronic health records of patients with COVID-19-related AKI admitted to the *Hospital das Clínicas* in the city of São Paulo, Brazil, between March and August of 2020. We applied only KDIGO criteria 2 and 3. We used logistic regression to analyze risk factors for the composite outcome of mortality or RRT.

Results: Among the 694 patients with COVID-19-related AKI, the mean age was 63 years and mortality was 66.4%; 41% needed vasoactive drugs, 66% needed mechanical ventilation, and 72% needed dialysis. Univariate analysis showed the following risk factors for mortality and RRT at admission: male sex; diabetes; CKD; vasoactive drug use; mechanical ventilation; acidemia; elevated lactate, magnesium, potassium, creatinine, C-reactive protein, creatine phosphokinase, total bilirrubin; proteinuria; hematuria; and increased fractional excretion of potassium (n=98) and sodium (n=110). The factors that remained significant in the multivariate analysis were male sex, vasoactive drug use, serum magnesium >2.5 mg/dL and oliguria (24-h urine output <500 mL).

Conclusions: In ICU patients with COVID-19-related AKI, in Brazil and elsewhere, in-hospital mortality is high. The exact mechanism by which hypermagnesemia increases mortality in such patients merits further study. Supported by FAPESP.

Funding: Government Support - Non-U.S.

Risk factors for mortality or RRT in patients with COVID-19-related AKI in Brazil

	Univariate analysis	P	Multivariate analysis	P
	OR (95% CI)		OR (95% CI)	
Age, per year increase	1.01 (1-1.02)	0.13	1 (0.99-1.02)	0.66
Male sex	1.74 (1.15-2.62)	0.008	1.86 (1.2-2.9)	<0.01
Serum creatinine at ICU admission, per unit increase	1.12 (1.01-1.25)	0.004	1.03 (0.94-1.14)	0.61
Vasopressor use at admission	2.96 (1.71-5.43)	<0.001	4.07 (2.35-7.46)	<0.001
Serum magnesium > 2.5 mg/dL	3.54 (2.08-6.2)	<0.001	2.09 (1.1-4.36)	0.03
Oliguria	0.99 (0.99-0.99)	0.005	3.31 (1.83-6.44)	<0.001

PO0050

Mortality in an Emergency-Only Hemodialysis Population from COVID-19 in a Large Safety Net

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Background: The COVID-19 pandemic has shown to disproportionately impact certain populations highlighting health, economic and social disparities. An especially vulnerable group is the emergency-only hemodialysis (EoHD) patient population at Grady Health System, 91% of whom are Hispanic with a median age of 52. This population initially included 102 EoHD patients followed from 4/2020 to 5/2021. A COVID screening protocol was developed to assess disease prevalence, and patients who tested positive were isolated and treated accordingly. The aim of this study is to estimate the mortality rate in this at-risk population.

Methods: From 4/2020 to 5/2021, COVID PCR tests were administered either as scheduled screenings or diagnostically if a patient presented with symptoms; patients testing positive were isolated per health department and hospital policy recommendations. In total 494 PCR tests were performed, and 444 were screening; each patient received an average of 4.8 tests. Hospital admissions, complications, and mortality data were collected and analyzed using statistical software.

Results: A total of 102 patients comprised the EoHD cohort at the onset of the study in 4/2020. Of this population, 58 (58%) patients tested positive for COVID and 19 (33%) of these COVID cases required hospitalization. The majority of positive cases (n = 32, 55%) were in asymptomatic patients and detected with screening tests while the remaining were diagnostic results. Eleven (11%) patient deaths occurred during the study, and two (2%) were attributed to COVID related complications. The remaining causes of death included hemorrhagic shock (1), cardiac arrest (1), heart failure (2), and unspecified, non-COVID related illnesses (5). The prevalence of COVID infection in patients who had diabetes and/or hypertension was non-significant (p-value = 0.2).

Conclusions: Amongst the EoHD population, the risk of COVID-19 is disproportionately high compared to the general population possibly due to chronic exposure to healthcare settings and socioeconomic disadvantages. One would expect the mortality from COVID to be higher in this cohort as compared to the general population due to ESRD and associated comorbid conditions. However, our results show that COVID attributable deaths in the EoHD population was 2%, which is comparable to the 1.8% mortality rate observed in the general U.S. population.

PO0051

Excess COVID and Non-COVID Mortality Among Patients with ESKD in 2020

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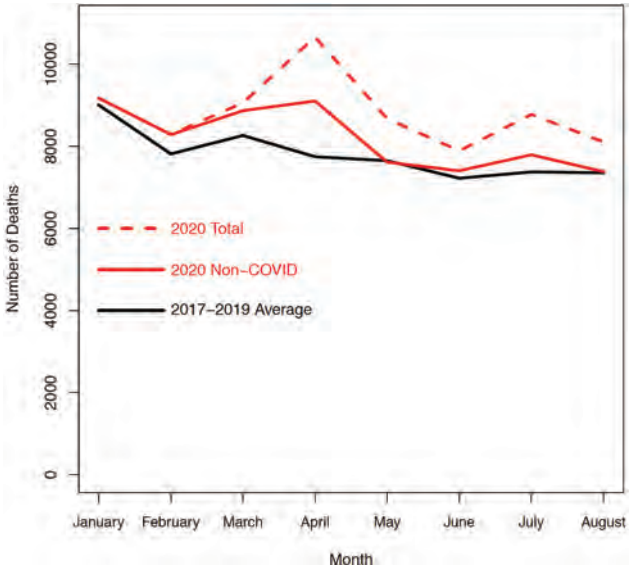
Background: Patients with ESKD are at high risk of mortality from COVID-19. The extent to which increased mortality in the ESKD population in 2020 was related to COVID-19 vs other causes in the setting of disruption of healthcare delivery is not clear.

Methods: We used the Death Notification Form (CMS-2746) to examine excess all-cause and COVID-related mortality in Jan through Aug of 2020 among the whole ESKD population and by race/ethnicity adjusting for age and comorbidity. We further examined causes of non-COVID-related mortality in 2020 compared with 2017-2019.

Results: All-cause mortality increased by 13.1% during Jan-Aug 2020 compared with mortality during the same period in 2017-2019. Peak overall and excess mortality occurred during Apr (Figure), when 14.7% of all deaths were attributed to COVID-19. COVID-related deaths declined to a nadir of 6.2% of all deaths in June and then increased again in Jul and Aug. Excess mortality was approximately twice as high among Black and Hispanic patients as among whites. Between Feb and Apr, there was substantial excess non-COVID mortality in addition to COVID mortality, whereas most excess mortality during May to Aug was related to COVID-19. There were 4310 excess deaths during Feb-Apr 2020. 1576 (37%) were due to COVID-19, and 517 (12%) were attributed to pneumonia. Thus, approximately half of the excess mortality was not due to COVID-19, including 1635 excess deaths due to cardiac arrest, cause unknown.

Conclusions: Patients with ESKD experienced substantial excess mortality in 2020 relative to prior years that affected Black and Hispanic patients disproportionately. Approximately half of the excess mortality was likely caused by COVID-19. There was also excess mortality in the early phase of the pandemic that was not attributed to COVID-19.

Funding: NIDDK Support



Number of overall and COVID-related deaths in 2020 vs 2017-2019

PO0052

Associations of Dialysis Modality and Setting with Incidence of COVID-19 Diagnosis and Hospitalization

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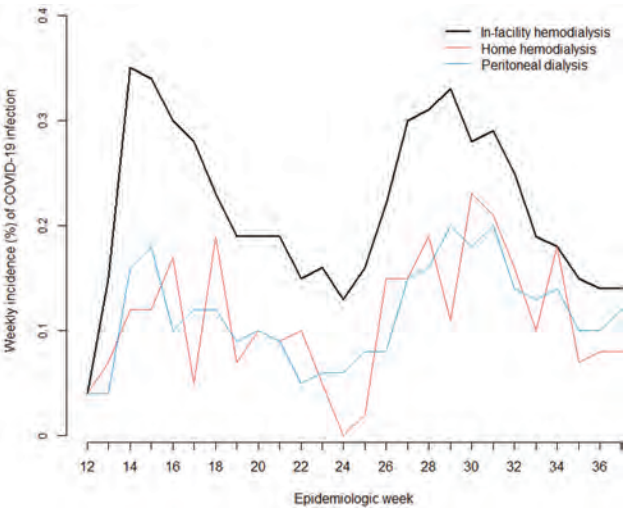
Background: The novel coronavirus 2019 (COVID-19) pandemic has resulted in substantial morbidity and mortality among patients undergoing maintenance dialysis. Patients performing home hemodialysis (HHD) or peritoneal dialysis (PD) may be able to minimize exposure to the community, thus lowering risk of COVID-19 infection. We assessed whether HHD and PD were associated with lower risks of COVID-19 infection and hospitalization, compared to in-facility hemodialysis (IHD).

Methods: We analyzed Medicare Parts A and B claims accrued during 2020. For each epidemiologic week from week 12 (beginning March 15) to week 37 (September 6), we identified patients with a Medicare-covered outpatient dialysis treatment during the preceding 7 days. We stratified patients into cohorts of IHD, HHD, and PD; we limited the IHD cohort to patients without residency in a skilled nursing facility during the 28 days preceding the epidemiologic week. During each week, we estimated the incidence of COVID-19 infection and COVID-19 hospitalization, per Medicare claims with ICD-10-CM diagnosis code U07.1. Using logistic regression with adjustment for demography, comorbidity, and state, we estimated odds ratios of outcomes during weeks 12-22, 23-33, and 34-37.

Results: Incidence of COVID-19 infection (figure) and COVID-19 hospitalization peaked twice: during weeks 14-16 and weeks 29-30. During weeks 12-22, adjusted odds ratios (AORs) of COVID-19 infection for HHD versus IHD and PD versus IHD were 0.55 (95% CI, 0.43-0.71) and 0.52 (0.46-0.58), respectively. During weeks 23-33, corresponding AORs were 0.63 (0.50-0.78) and 0.63 (0.57-0.69).

Conclusions: Both home dialysis modalities were associated with similarly lower risks of COVID-19 infection and hospitalization. Nephrologists and dialysis provider should consider counseling patients about potentially lower risk of infectious respiratory disease with home dialysis.

Funding: NIDDK Support



PO0053

Understanding Dialysis Patient COVID-19-Related Mortality

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Background: Reported COVID mortality in dialysis patients is high and ranges from 15-25%. We reviewed data from a prospective 14-month study of seriously ill (SI) dialysis patients pre-COVID (May 2019-January 2020) and during COVID (February 2020-June 2020) to better understand COVID-related mortality in SI and not SI patients.

Methods: We recruited 10 dialysis centers (6 in NYC, 3 in Denver, CO, and 1 in Dallas, TX) with 1,507 patients. Dialysis staff screened patients monthly with the surprise question (SQ)—*Would I be surprised if this patient died in the next 6 months?*—and recorded outcomes. Those with a "No" response were identified as SI. A SQ "No" response is known to identify older patients with multiple comorbidities and an increased risk of early mortality. In this rolling population, we calculated the monthly mortality risk prior to and during COVID and determined the relative risk of death (RR) for SI compared to not SI during both periods. We also compared the increased mortality risk during COVID between patients dialyzed in NYC vs. Denver and Dallas and used logistic regression to determine whether COVID-19-related mortality differed by geographic region.

Results: Over 14 months, dialysis centers screened a monthly average of 1,342/1,507 (89.1%) patients and identified 274 (18.2%) as SI, with more consistent screening pre-COVID than during COVID (98.6% vs. 71.2%). Pre-COVID, the monthly mortality rate for SI patients was 2.8% and for not SI patients 0.4%, (RR 7.02, 95% CI, 4.76-10.44). During COVID, the monthly mortality rate for SI patients increased to 4.8% and for not SI to 1.5% (RR 3.19, 95% CI, 2.28-4.44). The absolute increase in monthly mortality risk from pre-COVID to COVID was greater for SI than for not SI patients, 2.0% vs 1.1%. The excess monthly mortality was higher in NYC (2.3% for SI and 1.2% for not SI) than in Denver and Dallas (1.3% for SI and 0.7% for not SI), but the difference was not significant (p = .12).

Conclusions: A "No" response to the SQ identified SI dialysis patients whose 5-month mortality during COVID increased to 23.9% (annualized rate 57.4%). For not SI, the 5-month mortality rate during COVID increased to 7.5% (annualized rate 18%). These findings underscore the importance of advance care planning not only for SI patients but also for all dialysis patients, who are particularly vulnerable to concurrent infections such as COVID-19.

Funding: Private Foundation Support

PO0054

Temporal Trends in Mortality and Hospitalization Related to SARS-CoV-2 in Dialysis Patients in Québec (Canada)

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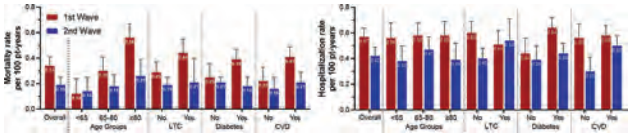
Background: In Canada, Quebec province was the most severely hit region during the first year of the SARS-CoV-2 pandemic. We aimed to compare characteristics and outcomes of dialysis patients during the first and second SARS-CoV-2 transmission surges in this province.

Methods: The QRN-COVID-HD study included adult dialysis patients from 13 units in Quebec, with SARS-CoV-2 PCR tests performed between Mar-Sept 2020 (1st wave) and Oct 2020-Feb 2021 (2nd wave). Crude and stratified rates of mortality, hospitalization and intensive care unit (ICU) admission within 90-day of SARS-CoV-2 positivity were calculated with mixed effect Poisson regressions. Adjusted predictors of 90-day outcomes were evaluated using mixed effect logistic regressions and negative binomial regressions (as appropriate).

Results: Over this 12-month period, 431 patients were infected with SARS-CoV-2 (211 1st wave; 220 2nd wave). Most characteristics (including age) were similar in the two waves although 2nd wave patients were less frequently living in long-term care facilities and had more diabetic nephropathy. Overall, 214 (50%) patients were hospitalized at least once and 214 (26%) died within 90-day of SARS-CoV-2 positivity, with 78% of hospitalizations and 84% of deaths directly attributed to SARS-CoV-2. Mortality and hospitalization rates were lower for 2nd compared to 1st wave patients. **Figure** In contrast, ICU admissions were similar in both waves (0.14, 95% CI 0.10-0.19 [1st] vs. 0.13, 95% CI 0.09-0.18 [2nd] per 100 pt-yrs). When adjusted for case-mixed differences, the 2nd wave remained associated with lower risk of mortality (OR 0.55, 95% CI 0.32-0.95), hospitalization (OR 0.45, 95%CI 0.28-0.71) and days in hospital (IRR 0.49, 95% CI 0.46-0.53), but similar risk of ICU (OR 0.73; 95% CI 0.39-1.37).

Conclusions: Dialysis patients with SARS-CoV-2 infections had more favorable clinical outcomes during the 2nd wave, which is consistent with observations in the general population and may be related to improved clinical care.

Funding: Government Support - Non-U.S.



PO0055

COVID-19 Outcomes in Hospitalized Patients with CKD

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Background: Current research revolving around Coronavirus Disease 2019 (COVID-19) has identified that patients with co-morbid illnesses are at risk for worse outcomes.

Methods: This is a retrospective study comprising an observational dataset of 149 hospitals that included hospitalized patients (n=9366) aged 18 and above with a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Polymerase Chain Reaction (PCR) positive result between January 1st, 2020 and May 29th, 2020. Main outcomes and measures included hospital length of stay, Intensive Care Unit (ICU) admission, ventilator dependency, development of Acute Kidney Injury (AKI) and in-hospital death. Baseline patient characteristics were recorded, including demographic variables and comorbidities.

Results: A total of 9,366 patients were included in the analysis, of which 4765 (50.8%) were males, with mean age of 55.4 years (SD=18.6). Patients with CKD (n=1092, 11.7%) had a significantly higher length of hospital stay (Mean of 10.5 vs 4.9 days), ICU admission rates (23.3% vs 13.0%), ventilator dependency (24.5% vs 9.3%), AKI (6.2% vs 1.9%) and in-hospital death (20.5% vs 5.9%). In a multivariable logistic regression model, in-hospital death was independently related to presence of CKD.

Conclusions: This study confirms the independent association between a personal history of CKD and poor outcomes among hospitalized patients with COVID19, including in-hospital death.

Table 1. Outcome analysis according to CKD status for hospitalized patients with COVID19 in an observational database (n=9366).

Outcome	CKD present (n=1092/9366)		CKD absent (n=8274/9366)		P-Value
	Number	Percent (%)	Number	Percent (%)	
In-hospital death	224/1092	20.5	487/8274	5.9	<0.0001
In-hospital death or discharge to hospice	308/1092	28.2	709/8274	8.6	<0.0001
Intensive care unit (ICU) admission	254/1092	23.3	1072/8274	13.0	<0.0001
Ventilator dependency	268/1092	24.5	765/8274	9.3	<0.0001
Development of Acute Kidney Injury (AKI)	68/1092	6.2	160/8274	1.9	<0.0001
Length of hospital stay	Mean 10.5 days (SD=14.3)		Mean 4.9 days (SD=7.0)		<0.0001
Length of ICU stay	Mean 14.8 days (SD=1.3)		Mean 14.1 days (SD=14.3)		0.54

PO0056

COVID-19 Among Hospitalized Patients with Kidney Disease: Experience at a Midwestern Medical Center

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Background: Manifestations of novel coronavirus disease-2019 (COVID-19) range from minimal symptoms to organ failure and death. Preliminary studies suggest that acute kidney injury (AKI) is a common complication of COVID-19 and may predict adverse outcomes. Patients with chronic kidney diseases may be vulnerable to increased risk of serious COVID-19-related complications.

Methods: In this (ongoing) retrospective cohort study, we examined the characteristics, presentations, treatments, and outcomes of COVID-19 among hospitalized patients with AKI, dialysis-dependent end-stage kidney disease (ESKD-D) or kidney transplantation (KTx) at an urban, Midwestern tertiary center (3/19/2021–3/25/2021).

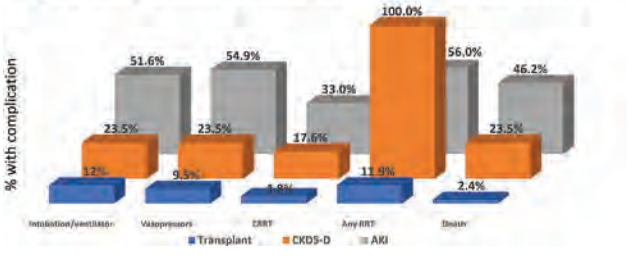
Results: Among 184 patients, 91 had AKI (49%), 51 CKD5-D (28%), and 42 patients were KTx recipients (23%). Monthly cases ranged from 6 in March to 35 patients in December 2020. Among the cohort, 61% were Black (including 50% AKI, 82% ESKD-D, and 57% KTx). Overall, 35% required mechanical ventilation, with highest use in the AKI group (51%). 48% of AKI patients required renal replacement therapy (RRT) and 9% treated with ECMO. Mechanical ventilation was lower among KTx recipients (12%) and 9% required RRT. The most common medical treatment was dexamethasone (48%). Mortality was 46% in the AKI and 23% in CKD5-D groups, but 2% among KTx recipients.

Conclusions: We observed high mortality associated with COVID-19 among hospitalized patients with kidney disease, especially in those with AKI. Public health and therapeutic studies should focus on mitigating COVID-19 disease transmission and optimizing outcomes in this vulnerable population.

Table. Characteristics, Treatments and Key Outcomes of Study Cohort

	Overall (n=184)	AKI (N=91)	Dialysis (N=51)	Transplant (N=42)
	%	%	%	%
Respiratory support				
Nasal cannula or simple face mask	26.1	19.8	45.1	16.7
High-flow nasal cannula	8.7	13.2	3.9	4.8
Non-invasive (CPAP or BIPAP)	6.5	11.0	2.0	2.4
Intubation/Ventilator	34.8	51.6	23.5	11.9
ECMO	4.3	8.8	0.0	0.0
No supplemental oxygen support	33.2	22.0	29.4	61.9
Circulatory Support				
Vasopressors	35.9	54.9	23.5	9.5
Inotropes	12.5	24.2	2.0	0.0
Mechanical circulatory support	2.2	4.4	0.0	0.0
None	58.2	42.9	74.5	71.4
Treatment for COVID Infection				
Hydroxychloroquine	6.5	4.4	11.8	4.8
Azithromycin	22.3	28.6	17.6	14.3
Convalescent serum or plasma	6.0	9.9	0.0	4.8
Remdesivir	14.7	20.9	3.9	14.3
Dexamethasone	47.8	57.1	41.2	35.7
Tocilizumab	1.6	2.2	0.0	2.4
RRT requirement				
Intermittent HD	34.2	23.1	88.3	7.1
CRRT	22.3	33.0	17.6	4.8
PD	1.1	0.0	3.9	0.0
No RRT requirement	50.0	52.7	0	90.5
Mortality	29.9	46.2	23.5	2.4
Contributing causes, among deaths				
ARDS	15.8	31.9	0.0	0.0
Hypoxia/AHRF	9.2	13.2	9.8	0.0
Sepsis	4.9	7.7	3.9	0.0
Other	8.7	13.2	5.9	2.4

Figure. Clinical Outcomes of Hospitalized Kidney Patients with COVID-19



Cohort Characteristics and Key Outcomes

PO0057

Decision-Making During Uncertain Times: A Qualitative Study of Kidney Patients, Care Partners, and Nephrologists During the COVID-19 Pandemic

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Background: Older adults faced treatment decisions for kidney failure during the COVID-pandemic, despite high risk of hospitalization, intensive care, and death. Given heightened uncertainty, clinicians needed to adapt communication about risks, benefits, and treatment decisions during the COVID-19 pandemic. Understanding how to support decision-making during uncertain times can guide clinicians in future public health crises.

Methods: Qualitative study using semi-structured interviews (August-December 2020) with CKD stage 4-5 patients, age 70+, carepartners, and clinicians in Boston, Portland, Maine, San Diego, and Chicago. Thematic analyses were conducted.

Results: Among 76 participants (39 patients, 17 carepartners, 20 clinicians) 13 patients (33%) identified as Black, and 7 (18%) were receiving dialysis. Four themes characterized treatment decision-making during the COVID-19 pandemic: Difficulty communicatng risk: balancing hope with caution; Clinicians' increased support for home dialysis; Patient confidence in chosen modality; and Coping with uncertainty and isolation in CKD. Clinicians struggled to balance discussion of COVID-19 risks while preserving hope. Black patients reported fewer conversations about COVID-19 risks than White patients and had more unaddressed questions. Clinicians reported being more open to home dialysis than pre-COVID-19. While some patients expressed interested in conservative management, few clinicians offered conservative management as an option. All patients who had initiated treatment prior to COVID-19, irrespective of modality, believed that their treatment was safest and optimal during the pandemic. With few clinical converations incorporating COVID-19-specific risks, patients and carepartners struggled to cope, finding both in-person and telehealth visits safe but isolating.

Conclusions: Although clinicians struggled communicating about COVID-19 leaving patients with unadressed concerns, patients across modalities felt safe and confident in their treatment. Clinicians developed an openness to home dialysis, though few offered conservative management despite patient preferences. Research should examine optimal approaches to enhance communication and shared-decision making to prepare for future systemic challenges.

Funding: Private Foundation Support

PO0058

Risk Factors for In-Hospital Mortality Among Patients Hospitalized with COVID-19 and ESKD

Jackson Heilbronn, Amir Abdi Pour, Giv Heidari-Bateni, Lida Gharibvand, Kwame B. Agyeman, Sahib D. Grewal, Mohammad Sharif, Sergio Infante, Mita Zahra E. Co, Sayna Norouzi. Loma Linda Medical Center *Loma Linda University, Loma Linda, CA.*

Background: End Stage Kidney Disease (ESRD) has been shown to be a risk factor for poor outcomes in the setting of COVID-19 infection. Our study aims to identify risk factors for mortality in ESRD patients hospitalized with COVID-19.

Methods: We conducted a retrospective analysis from March 1st, 2020 to January 31st, 2021 at Loma Linda University Medical Center. Inclusion criteria included patients admitted with diagnosis of COVID-19 and history of ESRD prior to admission. Risk factors for hospital mortality were identified with univariate and multivariate logistic regression methods.

Results: A total of 92 patients (age 59.9±13.7) were included in the analysis of which 21(18.6%) were deceased. Univariate analysis (Figure 1) demonstrated that age odds ratio (OR) with 95% confidence interval (CI) for mortality 1.05 (95% CI: 1.01-1.09, P= 0.03), Positive D-dimer OR = 6.3 (95% CI: 1.29-27.9, P= 0.02), ejection fraction less than 50% OR=1.08 (95% CI: 2.62-28.77, P= <.0001), and ferritin >300 ng/ml OR=1.02 (95% CI: 1.01-1.03, P= 0.04) were associated with increased risk of hospital mortality. Adjusted multivariate analysis demonstrated that only ejection fraction less than 50% was associated with increased risk of mortality (OR 9.9, 95% CI: 2.2-45.1, P <.01)

Conclusions: Age, elevated D-dimer, elevated ferritin and heart failure with reduced ejection fraction were identified as risk factors for hospital mortality of ESRD patients with COVID-19 infection.

Figure 1. Unadjusted Univariate Analysis

Variables	OR (95% CI)	P-Value
Age	1.05 (1.01, 1.09)	0.03
Sex	1.00 (0.37, 2.68)	1
African American	1.07 (0.08, 13.90)	0.96
Hispanic	2.96 (0.60, 14.54)	0.18
Others	1.50 (0.18, 12.46)	0.71
D-Dimer	6.33 (1.29, 27.91)	0.02
Ejection Fraction	1.08 (2.62, 28.77)	<.0001
Ferritin	1.02 (1.01, 1.03)	0.04
Length of Stay in hospital	1.06 (0.99, 1.14)	0.06

*Race groups were compared to White.

PO0059

Risk Factors for In-Hospital Mortality Among Patients Hospitalized with COVID-19 and AKI

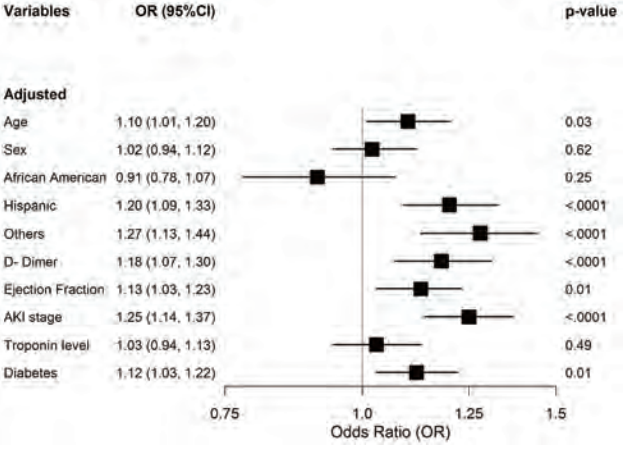
Sahib D. Grewal, Amir Abdi Pour, Giv Heidari-Bateni, Lida Gharibvand, Jackson Heilbronn, Mohammad Sharif, Mita Zahra E. Co, Kwame B. Agyeman, Sergio Infante, Sayna Norouzi. Loma Linda Medical Center *Loma Linda University, Loma Linda, CA.*

Background: Coronavirus disease- 2019 (COVID-19) has the highest mortality in patients with advanced age and those with pre-existing chronic medical conditions. Limited data, however, is available with regard to COVID-19 mortality in acute kidney injury (AKI). We aimed to identify risk factors associated with mortality in patients hospitalized for COVID-19 with AKI.

Methods: This is a retrospective cohort study conducted at Loma Linda University Medical Center (LLUMC) from March 1st, 2020 to January 31st, 2021. Inclusion criteria included patients admitted to LLUMC with diagnosis of COVID-19 and AKI during the admission based on the Risk Injury Failure Loss ESRD (RIFLE) criteria. Univariable and multivariable logistic regression models were utilized to explore risk factors associated with in-hospital mortality.

Results: A total of 320 patients (age 66.5 ± 14.4) were included in the analysis, of which 88 (28%) were deceased. Multivariable regression analysis (Figure 1) demonstrated that age greater than 70 had adjusted odds ratio (OR) with 95% confidence interval (CI) for mortality 1.10 (95% CI: 1.01, 1.20, p=0.03). An Ejection Fraction of less than 50% had OR=1.13 (95% CI: 1.03, 1.23, p=0.01), AKI-injury stage had OR=1.25 (95% CI: 1.14, 1.37, p=<0.001), positive D-dimer levels had OR=1.18 (95% CI: 1.07, 1.30, p=<0.001) and diabetes had OR=1.12 (95% CI 1.03, 1.22, p=0.01), all significant risk factors for mortality. In addition, Hispanics had a higher risk of mortality with OR=1.20 (95% CI 1.09, 1.33, p=<0.001) when compared to Caucasians.

Conclusions: Diabetes, age greater than 70, Hispanic background, Heart failure with reduced ejection fraction, AKI-injury stage, and positive D-dimer level are identified as risk factors associated with higher mortality amongst patient admitted with COVID-19 and AKI.



PO0060

Outcomes of COVID-19 Infection in Dialysis vs. Kidney Transplant Patients: A Nationwide Cohort Study from Qatar

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Background: COVID-19 infection carries a high burden and poor outcomes in patients who are immunosuppressed like kidney transplant or on dialysis. Our study aim is to compare outcomes between dialysis and kidney transplant patients infected with COVID-19 in the State of Qatar.

Methods: Retrospective cohort study reviewing medical, laboratory and radiographic data of all dialysis and kidney transplant recipients' patients in our national registry (between February and August 2020). Data collected from a national-based electronic medical record.

Results: 76 patients on dialysis patients had COVID19 vs 43 kidney transplants (p=ns). Kidney transplant patients with COVID19 tended to be younger than dialysis patients (52 vs. 58 years old, p=0.007), has less hypertension and more history of deep venous thrombosis. Clinical presentation did not differ between both groups with more asymptomatic in dialysis patients compared to kidney transplant patients (14.5% versus 2.3%, p=0.03). More patients died from COVID19 in the dialysis patients vs. kidney transplant patients (11 (14.5%) vs. only 1 (2.3%), p=0.034). Inflammatory markers were significantly higher in dialysis patients (IL6 peak and Ferritin) compared to kidney transplant patients.

Conclusions: Our national study showed similar incidence and severity of COVID19 in dialysis compared to kidney transplant in Qatar. Mortality and inflammatory markers were higher in dialysis patients.

	Dialysis N:76	Transplant N:43	p value
Age	58.7±14	52.0±10.4	0.007
Sex: Male / Female	56 (73.6) / 20 (26.3)	34 (79.0) / 9 (20.9)	0.158
Ethnic group: Middle east / South Asia / East Asia / Others	34 (44.7) / 26 (34.2) / 9 (11.8) / 7 (9.2)	27 (62.7) / 16 (37.2) / 0 / 0	0.058 / 0.742
Comorbidities: DM / Hypertension / IHD / CHF / Asthma / H/O DVT / Atrial Fibrillation	48 (65.7) / 75 (98.7) / 19 (25) / 2 (2.6) / 7 (9.2) / 4 (5.3) / 8 (10.5)	22 (51.1) / 39 (90.6) / 5 (11.6) / 1 (2.3) / 3 (6.9) / 5 (11.6) / 2 (4.6)	0.663 / 0.03 / 0.524 / 0.823 / 0.515 / 0.010 / 0.212
Vaccination: Flu vaccine	52 (68.4%)	30 (69.7)	0.246
SARS-Co2 symptoms at diagnosis: Fever / Cough / GIT symptoms / Sore throat / SOB / Body pain / Asymptomatic	44 (57.9) / 43 (56.6) / 7 (9.2) / 8 (10.5) / 19 (25) / 4 (5.3) / 11 (14.5)	18 (41.8) / 21 (48.8) / 6 (13.9) / 4 (17.2) / 6 (13.9) / 8 (18.6) / 1 (2.3)	0.812 / 0.259 / 0.548 / 0.630 / 0.303 / 0.02 / 0.03
Hypoxia	18 (23.7)	9 (20.9)	0.730
Chest x ray finding: Normal / Unilateral / Bilateral / Not done	21 (27.6) / 10 (13.2) / 45 (59.2) / 0	14 (32.5) / 7 (16.2) / 16 (37.2) / 6 (13.9)	0.270 / 0.421 / 0.110
Hospital stay (days)	18.1±13.5	22.7±33.2	0.411
ICU stay (days)	18.1±13.5	22.7±33.2	0.411
Outcome: Alive / Dead	65 (85.5) / 11 (14.5)	42 (97.6) / 1 (2.3)	0.034 / 0.034
ARDS	14 (18.4)	5 (11.6)	0.351
ICU admission	19 (25)	9 (20.9)	0.615
Mechanical Ventilation	13 (17.1)	5 (11.6)	0.423
Ferritin base	1225.7±1478.2	393.2±526.4	0.001
IL-6 peak	717.3±2059.3	13.4±51.0	0.029

PO0061

One-Year Experience of COVID-19 Disease of 700 Chronic Dialysis Patients from Ecuadorian Highlands

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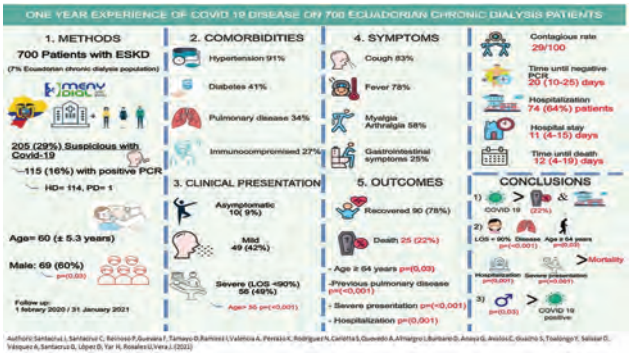
Background: In December 2019, first Covid-19 disease cases were reported. The pandemic spread with 114.217.365 cases and 2.533014 deaths worldwide in March 2021, with 286.155 cases and 15.811 deaths in Ecuador. The aim of this work was to share COVID-19 disease impact on 700 chronic dialysis patients from Ecuadorian highlands, which represents almost 7% of Ecuadorian dialysis population, after one year of pandemic.

Methods: Observational-prospective-multicenter study on 700 Latin-American chronic dialysis patients of five different cities from Ecuadorian highlands. Patients were followed since February first, 2020 until 31 January 2021. Patients with COVID-19 symptoms were identified and diagnosis was made exclusively with positive nasopharyngeal swabs PCR testing. Oxygen saturation below 90% at presentation (LOS) classified disease presentation as severe, moderate if symptoms without LOS and asymptomatic if no symptoms. Hospital-stay, time until negative PCR, mortality and laboratory findings were collected.

Results: A total of 205 patients (29%) presented COVID-19 symptoms; 115 tested positive (16%), 60% were men (p=0.03), 25 subjects died (22%). Mortality was related with age above 64 years old, saturation < 90%, severe disease (p=0.03), previous pulmonary pathology and hospitalization (p=0.01). Hospitalization was needed in 74 patients (64%) with hospital stay 11 days (4-15), days until death during hospitalization of 12 days (4-19) and time until negative PCR 20 days (10-25). Symptomatic time was 16 days (11-26).

Conclusions: COVID-19 disease was more frequent in men and has added up to 22% of extra mortality to chronic dialysis population. Patients older than 64 years old, previous pulmonary pathology, LOS at presentation are at higher risk of mortality. Health care burden due to COVID-19 is high in dialysis population suggesting that vaccination programs must include dialysis patients and staff involved in their care to diminish mortality, infections and health care burden.



PO0062

Mortality in COVID-19 Patients with CKD with and Without Kidney Replacement Therapy in Western Mexico

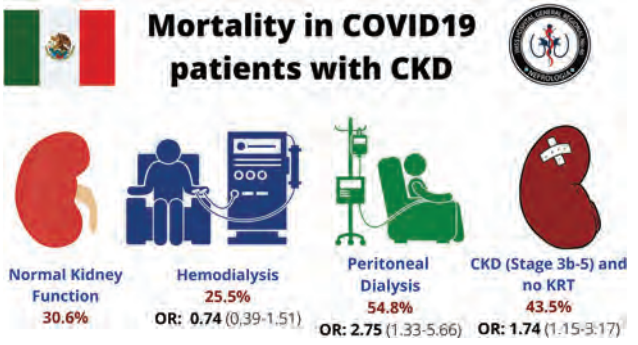
Alejandro Garcia Rivera, Ríos C. Katia yuritzi, Arantxa K. Aguilar, Marcos A. Elias Lopez, Jesús A. Rico sánchez, Luz Yareli Villegas Gutierrez, Mario Valdez Avendaño, Fabiola V. Rios Rios, Mauro G. Montemayor Villacobos, Mónica L. Morales Guillén, Rubén Lara Monterrubio, Roxana Villanueva Macedo, José J. Gutiérrez Hernandez, Ramon A. Soto Rodriguez, Hugo B. Espinoza, Omar H. Sanchez Vazquez, Jorge fernando Topete reyes, Renato Parra Michel, Carolina R. Alvarez. *Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Especialidad en Nefrologia, Hospital General Regional No 46 del IMSS, Guadalajara, Mexico.*

Background: COVID-19 is a new disease of pandemic proportions. Currently, there are no reports on clinical outcomes in patients with CKD with and without KRT in the Mexican population. Our aim was to describe the clinical outcomes in patients with CKD.

Methods: Retrospective cohort study of hospitalized adult patients COVID-19 confirmed with RT-PCR, from April to December 2020 in a second-level hospital in Western Mexico. Information was obtained from medical records.

Results: 1012 patients were included, of which 130 patients (12.8%) had CKD (65.3% men), with a mean age of 53.8 years, 43.8% with Diabetes Mellitus and 82.3% with Hypertension. 84 patients (64.6%) were on KRT, within which 47 patients were on hemodialysis, 31 on peritoneal dialysis and 6 with a kidney transplant. 46 patients had no KRT, in stages ranging from KDIGO 3b to 5. 78.4%. 14 patients (10.7%) required mechanical ventilation. In our study, mortality among patients with normal kidney function was 30.6%. Regarding patients with CKD, patients on hemodialysis had a mortality of 25.5% (OR 0.74, 95% CI 0.39-1.5), patients on peritoneal dialysis had a mortality of 54.8% (OR 2.75, 95% CI 1.33-5.66), patients with CKD and no KRT had a mortality of 43.5% (OR 1.74, 95% CI 1.15-3.17).

Conclusions: In our population, an increased mortality was found in patients with CKD with and without KRT, highlighting the mortality of patients on PD.



	CKD with no KRT (n=46)	Hemodialysis (n=47)	Peritoneal Dialysis (n=31)	Kidney Transplant (n=6)	p Value
Age (years)	53.9	54.2	54.3	56.5	
Male (%)	76.08%	59.57%	61.29%	66.66%	
Diabetes (%)	58.6%	34.04%	45.16%	0%	
Hypertension (%)	80.43%	63.08%	96.77%	33.33%	
Hemoglobin (g/dL)	12.16 (± 3.09)	9.60 (± 2.76)	9,03 (± 0.40)	10.83 (± 3.09)	<0.001*
Lymphocytes (K/uL)	1,92 (± 6.35)	0.91 (± 0.63)	0.91 (± 0.61)	0.64 (± 0.33)	0.552
Platelets (K/uL)	222.0 (± 143.5)	185.1 (± 114.1)	190.84 (± 149.2)	336.1 (± 219.2)	0.070
Urea (mg/dL)	112.8 (± 92.3)	129.9 (± 85.9)	145.4 (± 75.6)	107.2 (± 77.7)	0.397
Albumin (g/dL)	3.05 (± 0.79)	3.38 (± 0.74)	2.25 (± 0.78)	3,60 (± 0.21)	0.002*
K (mEq/L)	5.20 (± 0.98)	5.12 (± 1.05)	4.81 (± 1.26)	5.17 (± 0.92)	0.364
Na (mEq/L)	134.1 (± 5.9)	135.7 (± 4.3)	135.3 (± 6.1)	135.66 (± 3.01)	0.108
D Dimer (U/L)	1309 (± 1677)	984 (± 864)	851 ± (872)	831 (± 1363)	0.486
HCO3 (mEq/L)	15.2 (± 6.35)	15.3 (± 6.77)	15.3 (± 6.17)	18.1 (± 6.59)	0.167
Mortality (%)	43.5%	25.5%	54.8%	33.3%	0.032*

PO0063

African Americans Have Lower COVID-19 Mortality Risk Than Caucasians in CKD

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Background: In the general population, African Americans have increased mortality risk with COVID-19. However, this has not been well-studied in CKD population.

Methods: We analyzed a national Veteran cohort using data from the VA COVID-19 Shared Data Resource for COVID-positive patients (N=196,269) from 3/1/2020 - 3/9/2021. Diagnosis of COVID-19 was defined as a confirmed positive laboratory test result. Index date was defined as the date of first positive COVID-19 test or the first negative test for patients who never tested positive for COVID-19. Baseline eGFR was defined as at least one outpatient serum creatinine measurement obtained within two years before the index date or the average of the two closest serum creatinine measurements obtained within two years before the index date. We identified 58,743 patients with valid eGFR measurements. Of this cohort, 51,002 were African American or Caucasian. Mortality data were available for 50,830 patients. We used Cox regression models to compare COVID-19 mortality in African Americans versus Caucasians based on pre-COVID eGFR stratification.

Results: Of the COVID-positive patients with available eGFR and mortality data, baseline mean age was 60 ± 17 years, 24% African American, 76% Caucasian, and 21% with eGFR <60. There were 627 deaths among African Americans and 2,480 deaths among Caucasians. Average follow-up duration was 0.5 ± 0.3 years in African Americans and 0.4 ± 0.2 years in Caucasians. While there was no difference in mortality risk between African American and Caucasian Veterans without CKD, African Americans had lower mortality risk when compared to Caucasians in the CKD subgroup (Table 1).

Conclusions: In the CKD subgroup, African Americans have lower COVID-19 mortality than Caucasians. The reasons for this observation are unclear.

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

Table 1. Risk of Mortality in African Americans versus Caucasians in COVID-19 by eGFR Groups

	Incidence Rate		HR* (95% CI)
	African American	Caucasian	
All eGFR groups	0.11	0.17	0.99 (0.90, 1.08)
eGFR ≥60	0.06	0.10	1.01 (0.88, 1.16)
eGFR 45 to <60	0.17	0.37	0.81 (0.68, 0.98)
eGFR <45	0.42	0.78	0.87 (0.74, 1.03)

*Model adjusted for demographics and comorbidities

PO0064

COVID-19 Among a Population of Predominantly American Indian and Hispanic American Kidney Transplant Recipients

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Background: COVID-19 leads to higher mortality among organ transplant recipients when compared to the general population.

Methods: In this study, 52 renal transplant recipients with COVID-19 were followed through 60 days from the date of initial diagnosis. We analyzed basic demographics, therapeutics used, and clinical outcomes among patients who survived and those who did not.

Results: Of the entire cohort, 53.8% were Hispanic Whites, 38.5% American Indian, and 5.8% were non-Hispanic Whites. 48% required hospital admission and 17% died, with 15% of deaths attributed to complications secondary to COVID-19. All those who died were either American Indian or Hispanic. Comorbidities among the non-survivors included hypertension (100%), chronic kidney disease (67%), diabetes (78%), and either being overweight or obese (100%). 89% had acute kidney injury and 56% required renal replacement therapy. Gender, blood type, and panel reactive antibody prior to transplant did not correlate with disease severity. There was no improvement in mortality during the fall/winter surge compared to the spring/summer surge, though therapies improved during the pandemic. None of the patients who received monoclonal antibody progressed to severe disease or died.

Conclusions: In conclusion, mortality with SARS-CoV-2 infection remains high among kidney transplant recipients, especially from ethnic minority groups. However, therapy with monoclonal antibody was associated with a reduced progression to severe disease and better outcomes. Therefore, it should be considered as a therapy in this high-risk group of patients if they satisfy the eligibility criteria listed by the Food and Drug Administration. Finally, further studies are needed to corroborate the findings from our study.

	Alive (n=43)	Dead (n=9)	Overall (n=52)
Age			
Mean (SD)	53.8 (16.7)	60.7 (11)	55.0 (16.0)
Race			
American Indian	14 (32.6%)	6 (66.7%)	20 (38.5%)
Black	0 (0%)	0 (0%)	0 (0%)
White	28 (65.1%)	3 (33.3%)	31 (59.6%)
Asian	1 (2.3%)	0 (0%)	1 (1.9%)
Native Hawaaiian/Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)
Ethnicity			
Hispanic	25 (58.1%)	3 (33.3%)	28 (53.8%)
Not Hispanic	18 (41.9)	6 (66.7%)	24 (46.1%)
Hypertension			
Absent	6 (14%)	0 (0%)	6 (11.5%)
Present	37 (86%)	9 (100%)	46 (88.5%)
Diabetes			
Absent	21 (48.8%)	2 (22.2%)	23 (44.2%)
Present	22 (51.2%)	7 (77.8%)	29 (55.8%)
CKD			
Absent	24 (55.8%)	4 (44.4%)	28 (53.8%)
Present	19 (44.2%)	5 (55.6%)	24 (46.2%)
AKI	13 (30.2%)	8 (88.9%)	21 (40.4%)
Absent	30 (69.8%)	1 (11.1%)	31 (59.6%)
Present	13 (30.2%)	8 (88.9%)	21 (40.4%)
Bamlanivimab			
Not Given	33 (76.7%)	9 (100%)	42 (80.8%)
Given	10 (23.3%)	0 (0%)	10 (19.2%)

PO0065

Prospective Study of COVID-19 in Patients Receiving Dialysis in Alberta Kidney Care South

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Background: People with kidney failure who are on facility-based hemodialysis (FBHD) are at high risk for COVID-19 infection due to inherent alterations in their immune system as well as the requirement to travel to a health care facility multiple times per week. In Alberta Kidney Care South, AKCS, public health measures and standardized screening of all patients entering clinics and HD units was initiated in March 2020 with COVID-19 testing of all patients who presented with a temperature, COVID related symptoms or a history of exposure to COVID-19.

Methods: All COVID-19 test results performed for AKCS patients are tracked in the electronic kidney database. We performed a 14-month prospective observational study (March 2020 to May 2021) to determine the incidence of confirmed COVID-19 infections, the prevalence of symptoms amongst COVID + patients and outcomes of hospitalization and death for FBHD, home hemodialysis (HHD) and peritoneal dialysis (PD) patients within the Alberta Kidney Care South program.

Results: We report on our preliminary results up to December 31, 2020. From a population of 1 329 patients, (931 FBHD, 102 HHD and 296 PD) 46(3.5%) patients were COVID positive. COVID-19 prevalence was 3.5% in FBHD (33/931), 4.4% in PD (13/296) and no HHD patients. The mean age of the cohort was 61 ± 16.5 years with 14(30%) female and comorbidities of hypertension 43(93%), diabetes 35(76%), coronary artery disease 16(35%) and heart failure 10(22%). COVID-19 testing was done for the following reasons: contact with a known COVID-19 person in 4(8.7%), resident of a long-term care facility in 3(6.5%) and for symptoms in 31(67%). The most common symptoms were fever (defined as T> 37.3C) with 20(43%), cough 10(22%) and sore throat 6(13%). Overall, 14 patients (30%) were admitted to hospital, 4 of whom went to the ICU and 5(11%) died. There were no differences in hospitalization between FBHD and PD (30% vs 31% respectively p = 0.971), ICU admissions (12% vs 0%, p=0.189) or death (12% vs 8 %, p=0.664).

Conclusions: The prevalence of COVID-19 amongst FBHD and PD patients was similar to the general population but with higher rates of hospitalization, ICU admissions and death. People on HHD appear to have very low rates of COVID-19 as compared to either PD or FBHD.

PO0066

Patients on Chronic Maintenance Hemodialysis with and Without COVID-19 Infection: Comparison of Baseline Characteristics and Mortality

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Background: The COVID-19 pandemic has impacted nearly all aspects of the care of patients, particularly those with chronic conditions. There is a need for higher quality of evidence to better identify populations at risk, in various clinical situations. We analyzed the difference in demographic characteristics in patients with end stage kidney disease (ESKD) who were started on hemodialysis (HD) in 2020 and contracted COVID-19, with those who remained free of the infection in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federate medical records network, to identify 7405 unique adult patients ≥ 18 years from 37 healthcare organizations (HCOs), mostly in the United States, for whom maintenance HD was initiated for ESKD between 1/1/2020 and 12/31/2020 (study period). From this group, we then identified patients who had a confirmed diagnosis of COVID-19 infection during the study period. We calculated the odds ratio (OR) and 95% confidence interval (CI) of mortality in the first three months of initiation of HD for the COVID group.

Results: 903 patients (from 33 HCOs) had a confirmed diagnosis of COVID-19 infection. Patients in the COVID-positive group were less likely to be white (p=0.019), and more likely to: —be of Hispanic/Latino ethnicity (p<0.0001), —have had a previously failed kidney transplant (p<0.0001) —have diabetes mellitus (DM) (<0.0001), and —have a BMI above 31 (p=0.003). A total of 628 patients died during the study period. After propensity matching, COVID exposure was associated with higher odds of mortality (OR: 2.32; CI: 11.66, 3.24). The survival probability at the end of 3 months was 84.4% for the COVID group, compared with 92.5% for the no-COVID group (p<0.0001).

Conclusions: During the study period, among the patients who were started on HD for ESKD, those who contracted COVID-19 infection were more likely to be Hispanic/Latino, less likely to be white, more likely to have a previously failed kidney transplant, more likely to have DM, and to have a BMI above 31. The COVID-positive group also had a higher mortality and a lesser 3-month survival probability compared to the control group.

PO0067

Kidney Transplant Patients with and Without COVID-19 Infection: Comparison of Baseline Characteristics and Outcomes

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Background: The COVID-19 pandemic has been associated with enormous impact on morbidity and mortality, particularly among individuals with chronic conditions and among patients on chronic immunosuppressive therapy. There is a need for higher quality of evidence to better identify populations at risk, in various clinical situations. We analyzed the difference in kidney transplant (KT) rejection, kidney transplant failure and mortality in patients who received a KT in 2020 and contracted COVID-19 with those who remained free of the infection, in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federate medical records network, to identify 3773 unique adult patients ≥ 18 years, who had received a kidney transplant (KT) between 1/1/2020 and 12/31/2020 at 34 healthcare organizations (HCOs), mainly in the United States. From this group, we then identified patients who had a confirmed diagnosis of COVID-19 infection after KT. We calculated the odds ratio (OR) and 95% confidence interval (CI) of mortality, KT rejection, and KT failure in the two groups during the first 3 months after KT (study period).

Results: A total of 590 patients from 27 HCOs had a confirmed diagnosis of COVID-19 infection. Patients in the COVID group were more likely to be of Hispanic/Latino ethnicity (P < 0.0001). A total of 78 patients died during the study period. After propensity matching, COVID-19 exposure was associated with a higher odds of 3-month mortality (OR: 3.22; CI: 1.56, 6.62). The survival probability at the end of 3 months was 94.4% for the COVID group compared with 98.6% for the no COVID group (p<0.0001). Exposure to COVID-19 was also associated with a higher odds of KT failure (OR: 1.50; CI: 1.01, 2.20) during the study period. There was no statistically significant difference between the two groups regarding KT rejection during the study period.

Conclusions: During the study period, among the patients who received kidney transplant in 2020, those who contracted COVID-19 infection were more likely to be Hispanic/Latino, had higher mortality, were more likely to have KT failure and have less survival probability. There was no statistically significant difference between the two groups regarding KT rejection.

PO0068

Characteristics and Outcomes of Patients with COVID-19 Infection Requiring Extracorporeal Membrane Oxygenator with and Without Continuous Renal Replacement Therapy: A Single-Center Study

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Background: Up to 1-in-3 cases of severe COVID-19 infection can cause respiratory failure sometimes necessitating extracorporeal membrane oxygenation (ECMO) support. Acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is a common complication, yet risk factors & outcomes in these patients are not well studied.

Methods: A retrospective single-center study included 40 patients who received ECMO support for severe COVID-19 infection from Jan 20 to April 21. We extracted demographic, clinical, & laboratory variables on all patients. Primary outcome was hospital mortality; other recorded outcomes were total length of stay, ventilator, ECMO, & CRRT days, dialysis dependence at discharge. Group comparisons with & without CRRT were made by 2-sample Wilcoxon test for continuous variables & Fisher's exact test for categorical variables. Association of CRRT use & primary outcome was assessed by multivariable logistic regression (odds ratio (OR), 95% confidence interval (CI)).

Results: Overall cohort was 62.5% male, 32.5% black, with a median age of 51 years & BMI of 39.4. Thirty percent were diabetic & 42.5% were hypertensive. Of the 40 ECMO patients, 36 were on veno-venous, 2 on arterio-venous, & 2 utilized both veno- and arterio-venous circuits. 19/40 (47.5%) of ECMO patients required CRRT for AKI (3/19 patients CRRT was connected through the ECMO circuit). The median CRRT days were 20. Compared to those without CRRT, ECMO with CRRT patients needed a median of 19 ventilation days vs 15, 19 ECMO days vs 11, & 28 hospital days vs 32. Overall mortality was 50% (68.4% ECMO+CRRT vs 33.3% in others; p-value 0.0562). Logistic regression indicated that CRRT use in ECMO was associated with increased adjusted odds of death (6.37 OR, 1.12-36.19 95% CI). Of those who did not experience hospital mortality in the ECMO+CRRT group, 83% were dialysis-dependent at discharge.

Conclusions: Overall, extracorporeal support offers a meaningful bridge until organ recovery in severe COVID-19 infection. Despite necessitating ECMO, 50% of patients were able to be liberated from ECMO & survived. However once renal failure ensued, all patients required CRRT, which in turn predicted poor outcomes.

PO0069

Hypertension After Multisystem Inflammatory Syndrome in Children (MIS-C)

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Background: MIS-C is an inflammatory condition in children associated with previous SARS-CoV-2 infection that has significant morbidity. Yet, long-term consequences of MIS-C remain unknown. The objective was to determine the prevalence of hypertension (HTN) and pre-HTN during the inpatient stay and post-hospitalization period in children diagnosed with MIS-C.

Methods: A retrospective study of children ≤18 years of age admitted to a tertiary center with MIS-C between 3/1/2020-2/28/2021 was performed. Children with a minimum of three documented outpatient blood pressures (BPs) were included. All available BPs were averaged and indexed (SBPi/DBPi) to the 95%ile for age, sex and height for the inpatient stay and post-hospitalization period. HTN was defined as mean SBPi or DBPi >1 during the inpatient stay and post-hospitalization period, or taking blood pressure medications for the diagnosis of HTN. Pre-HTN was defined as mean systolic or diastolic BP >90%ile for age, sex and height. Data were analyzed using paired tests and logistic regression.

Results: Among 66 children with MIS-C (mean age 9.4±4.6 years, 59.1% male, 21.2% Black, BMI z-score 0.48±2), 1.5% were hypertensive while hospitalized compared to 18.2% with post-hospitalization HTN (p<0.001). 4.5% were prehypertensive while hospitalized compared to 21.2% of MIS-C children post-hospitalization (p=0.003). Mean SBPi (0.91±0.13 vs. 0.86±0.06, p=0.03) and DBPi (0.87±0.13 vs. 0.77±0.09, p<0.0001) were significantly greater post-hospitalization compared to during hospitalization. In a multivariate model, Black race (OR 10.9 CI 1.6-75.2, p=0.02) and greater BMI z-score (OR 2.9 CI 1.2-7, p=0.02) were significantly associated with post-hospitalization HTN. Acute kidney injury (21.2%), inpatient steroids (86.4%), outpatient steroids (3%), vasoactive support (36.4%) and other clinical/demographic variables were not associated with post-hospitalization HTN (all p>0.05). After hospitalization, no MIS-C patients were started on antihypertensives for the management of HTN. No left ventricular hypertrophy was noted on echocardiography at six months post-hospitalization in those with HTN.

Conclusions: MIS-C appears to be associated with the development of post-hospitalization pediatric HTN and pre-HTN. Follow-up of children who have recovered from MIS-C requires careful BP monitoring and consideration of antihypertensive medication.

PO0070

The Role of Hypertension in Incidence and Morbidity of COVID-19: A One-Year Review in US Veterans

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Background: The discovery that ACE2 was a co-receptor of COVID-19 as well as early clinical findings induced interest in the role of hypertension (HTN) and its treatment with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) with regard to COVID-19 incidence and morbidity. We examined the effect of demographic and common risk factors of HTN and treatment with ACEI, ARBs, calcium channel blockers (CCB) and beta blockers (BB) in patients with COVID-19.

Methods: The VA COVID resource data combines hospital data, administrative and clinical record search results. The prevalence of HTN was defined by its presence in the last 2 years prior to COVID-19 testing. New event (incidence) was determined as occurrence within 60 days thereafter. ACEI and ARB, and CCB and BB were combined, basic demographic and risk factors were categorized for comparisons. Data sets were propensity matched, statistical analysis (SAS enterprise guide 7.1) used frequency distributions (chi square). The data was limited to the first year of collection.

Results: Of 1,305,466 veterans, we found positive tests (18.1%), HTN (56.9%), ACE or ARB (33.7%), and CCB or BB (15.4%). HTN and treatment had no effect on COVID-19 incidence (OR HTN 1.08, ACE/ARB 1.01, CCB/BB 0.94). White, male patients aged over 60 years predominated. Age, race, and smoking had no effect on incidence, but DM2 (OR 1.2) and higher BMI (OR 1.4) did. We then examined demographics and risk factors in the COVID-19 positive HTN population. Male gender (5.4), age > 60 years (7.5), race non-white (1.6), BMI >30 (2), smoker (2.8), and DM2 (11.8). In turn, these factors at most affected outcomes (OR) such as all-cause mortality (7.9), admissions (2.1), ICU admissions (2.5), and ventilator use (2.7) with the exception of BMI which was associated with improved outcomes (0.6). ACEI or ARB had no effect (< 1.1) while CCB or BB had a small effect (1.26) on outcome.

Conclusions: In conclusion, HTN and anti-hypertensive treatment had no effect on COVID-19 incidence. HTN is associated with age, race, smoking and a diagnosis of DM2. Treatment with ACEI or ARB has no effect on morbidity while CCB or BB had a small effect that deserves further evaluation.

Funding: Veterans Affairs Support

PO0071

Initial Blood Pressure (BP) and COVID-19 (C19) Mortality

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Background: For C19 to infect epithelia, serine proteases cleave the spike protein to enhance its binding to ACE2 and entry into the epithelia. Since viral replication highjacks components of the renin-angiotensin system, investigators speculate that hypertension (HTN) is a risk factor for severe infection; however, it is uncertain whether high BP at presentation is a risk factor for mortality in C19 infection. Thus, we tested whether BP at presentation portends mortality in C19 positive (+) vs. negative (-) hospitalized patients.

Methods: Clinical/laboratory data from C19(+) and (-) hospitalized patients at Stony Brook Hospital (SBH) from March 2020 to July 2020 were included. The initial systolic BP (SBP) categorized patients into normotensive (SBP 90-139 mm Hg), stage 1 HTN (SBP 140-159 mm Hg) and stage 2 HTN (>160 mm Hg). Subjects with a mean arterial BP (MABP) <65 (hypotensive) were excluded and the remaining cohort was re-categorized into tertiles (T) of MABP (65-85 [T1], 86-97 [T2] and ≥98 [T3]).

Results: 4436 patients were admitted to SBH and 1591 diagnosed with and 2845 without C19. Mortality of C19(+) was 4.5-fold greater than C19(-) patients. Though the diagnosis of HTN was more prevalent among C19(+) (629/1591; 39.53%) vs. (-) (1014/2845; 35.64%; $p<0.05$) patients, the average presenting SBP and MABP was significantly lower in the C19(+) cohort ($p<0.05$). After excluding hypotensive patients, the mortality of stage 1 (33/271; 12.18%) and/or stage 2 (24/150; 16.00%) SBP cohorts did not differ from the normotensives (133/1112; 11.95%) in C19(+) patients. A similar finding was noted in the C19(-) patients. T2 tertile of MABP had the lowest mortality among C19(+) patients (56/562; 9.96%) and the T1 and T3 tertile of MABP had greater mortality at 15.31% (81/529) and 12.75% (58/455), respectively, than T2 ($p<0.05$). No difference in mortality was noted across the MABP tertiles of C19(-) cohort. Two multivariate (MV) regressions models evaluating mortality were studied each comparing T1 vs T2 or T2 vs. T3. In T1 vs T2 age, gender, albumin and T1 MABP significantly contributed to mortality while in T2 vs T3 age, gender, and first respiratory rate predicted mortality.

Conclusions: Univariate analysis of MABP suggests mortality is greater in T1 and T3 cohorts compared to T2; however, MV analysis implies that a low MABP (T1), but not high MABP (T3) is a significant predictor of mortality in C19 infection.

Funding: Veterans Affairs Support

PO0072

SIADH with COVID-19-Induced Hemophagocytic Lymphohistiocytosis: A Case Report

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Introduction: The effects of COVID-19 on the body are still being unraveled as we learn more about this disease. Here we report a case of hyponatremia secondary to Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) from COVID-19 induced hemophagocytic lymphohistiocytosis (HLH).

Case Description: A 47-year-old female with hypertension was admitted with COVID-19 infection. She had persistent fever, elevated inflammatory markers (ferritin: 6094 ng/ml, C-reactive protein: 217.1 mg/l, LDH 614 unit/L), and liver tests (ALP:275 unit/L, AST 106 unit/L, ALT 196 unit/L) and was thus diagnosed with COVID-19-associated HLH. Patient was treated with dexamethasone with resolution of fever but still had elevated CRP, ferritin, and LDH. She was discharged on a dexamethasone taper but returned just over a week later with malaise, brain-fog, and poor oral intake. Patient was then found to have severe hyponatremia with a serum sodium (Na) of 119 mmol/L and the following lab data: urine osmolality: 503 mOsm/kg, urine Na: 46, serum osmolality: 262 mOsm/Kg. Moreover, she had no edema on exam, nor did she display any signs of orthostatic hypotension. This was consistent with SIADH. Her medication list didn't include any medications that can cause SIADH. No hormonal disturbances were detected. She was given high dose steroids again and Intravenous Immunoglobulin for persistent fever and lack of clinical improvement. Meanwhile, despite treatment with urea and fluid restriction, her Na stayed in the low 120's. The decision was then made to start Interleukin-1 (IL-1) antagonist therapy. 1 day after the Interleukin-1 antagonist therapy was started, sodium started rising again by around 2 meq/day till it normalized.

Discussion: HLH has a wide range of causes including viruses but all can lead to a hyperinflammatory state. SARS-CoV-2 is known to cause a cytokine storm. Cases of COVID-19 associated HLH have been reported. The proposed mechanism of SIADH is related to the surge of interleukins associated with inflammation due to HLH induced COVID-19. Particularly, IL-6 is increased with both HLH and COVID-19. IL-6 can cause the release of ADH by stimulating the hypothalamic-pituitary-adrenal axis. Thus, hyponatremia can be found in patients with COVID-19. One way of addressing that is through Interleukin receptor antagonism. More data is needed to prove the efficacy of that therapy.

PO0073

Prevalence and Outcomes Associated with Hyperuricemia in Hospitalized Patients with COVID-19

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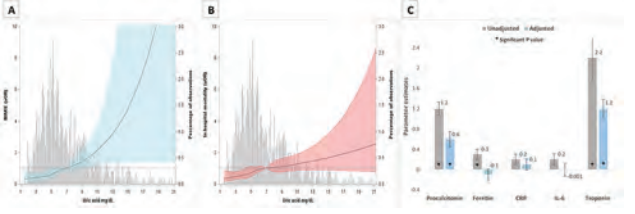
Background: COVID-19 can increase catabolism and result in hyperuricemia. Uric acid (UA) potentially causes kidney damage by alteration of renal autoregulation, inhibition of endothelial cell proliferation, cell apoptosis, activation of the pro-inflammatory cascade, and crystal deposition. Hyperuricemia in patients with COVID-19 may contribute to acute kidney injury and poor outcomes.

Methods: We included 834 patients with COVID-19 who were >18 years old and hospitalized for >24 hours in the Mount Sinai Health System and had at least one measurement of serum UA. We examined the association between the first serum UA level and major adverse kidney events (MAKE, defined by a composite of all-cause in-hospital mortality or RRT or 100% increase in serum creatinine from baseline), as well as markers of inflammation and cardiac injury.

Results: Among the 834 patients, the median age was 66 years, 42% were women, and the median first UA was 5.9 mg/dL (IQR 4.5-8.8). Overall, 52% experienced MAKE, and 32% died during hospitalization. After adjusting for demographics, comorbidities, and laboratory values, a doubling in serum UA was associated with increased MAKE (OR 2.5 per doubling, 95% CI 1.7-3.5) and in-hospital mortality (OR 1.7 per doubling, 95% CI 1.3-2.3) (**Figure A & B**). Serum UA levels were independently associated with a higher level of procalcitonin (β, 0.6; SE 0.2) and troponin (β, 1.2; SE 0.2) but was not associated with the serum ferritin, CRP, or IL-6 (**Figure C**).

Conclusions: In patients admitted to the hospital for COVID-19, higher UA levels were independently associated with MAKE and mortality in a dose-dependent manner. In addition, hyperuricemia was associated with higher procalcitonin and troponin levels.

Funding: Commercial Support - XORTX Therapeutics Inc.



A) & B) Association between serum UA and outcomes, MAKE (A) and in-hospital mortality (B) using restricted cubic spline models and mean serum UA (6.9 mg/dL) as a reference **C)** Association between serum UA and $\log_2$ transformed markers of inflammation and cardiac injury

PO0074

Association of Sodium Abnormalities with Outcomes in Hospitalized Patients with and Without COVID-19

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Background: Several reports of serum sodium (Na) abnormalities have been reported in patients hospitalized with COVID-19. However, the association of Na abnormalities with hospital outcomes have not been well-described in patients with COVID-19 (C19 +v. especially in comparison to those who tested negative (C19 -).

Methods: This is a retrospective analysis of the first surge of COVID-19 (C-19) in patients who presented to our ED from December 2019 -June 2020, with a systemic viral illness. There were 5,289 patients from the Covid19 data set, 1,703 COVID+ patients and 3,586 Covid- patients. Based on a nasal swab PCR patients were divided into two groups: C19 + and C19 –. Na levels at the time of hospitalization were used to divide patients into three groups: hyponatremia(hypoN) (<135), normonatremia (normoN)(135-145) and hypernatremia(hyperN)(>145). In C-19 patients, hypoN and hyperN were compared to normoN using multivariable (MV) models adjusting for comorbidities to calculate odds/risk (O/R) ratios for outcomes.

Results: C19 + patients, had significant increased incidence of HypoN (26.7% vs 16.2%;); and HyperN (4.2% vs 1.3%) compared to C19 -ve (Figure 1). Non MV analysis, among C19 + patients, found both HypoN and HyperN were significantly associated with mortality compared to normoN. HypoN (compared to normoN) was also associated with higher admission rate to the ICU, acute respiratory distress syndrome (ARDS), and intubation.(Figure 2a; 2b)

Conclusions: Among patients admitted with acute viral illness, Na abnormalities on admission were more prevalent in patients with COVID-19 + compared to those who tested negative. COVID-19 + patients with abnormal admission Na concentrations had increased mortality when compared to Cov - patients. Covid + patients had increased morbidity measured by admission to the ICU, need for intubation, and ARDS. Abnormalities in sodium metabolism predicts a poorer result in Covid-19 care.

Funding: Private Foundation Support

Figure 1

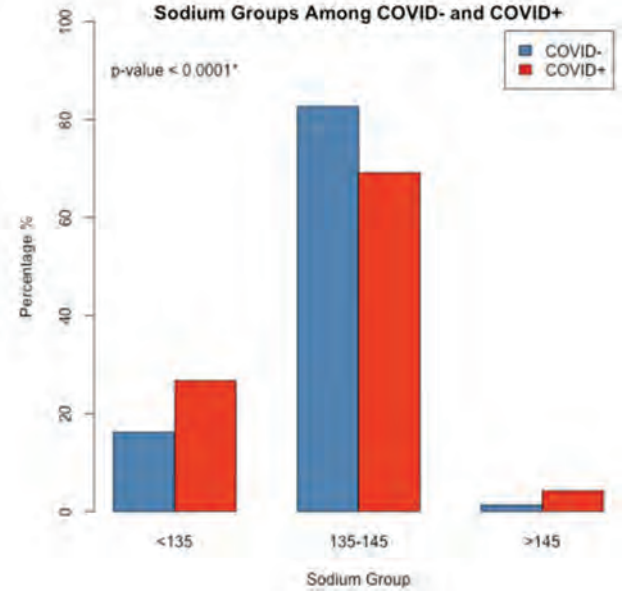
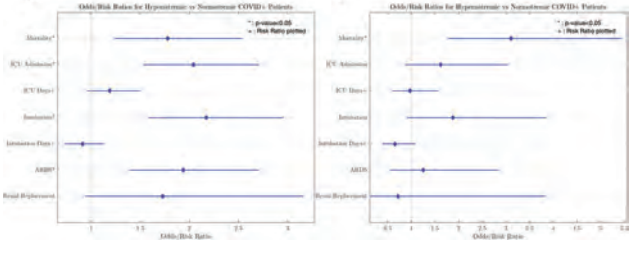


Figure 2



PO0075

Association of Obesity with 3-Month COVID-19-Related Mortality in ESKD Patients

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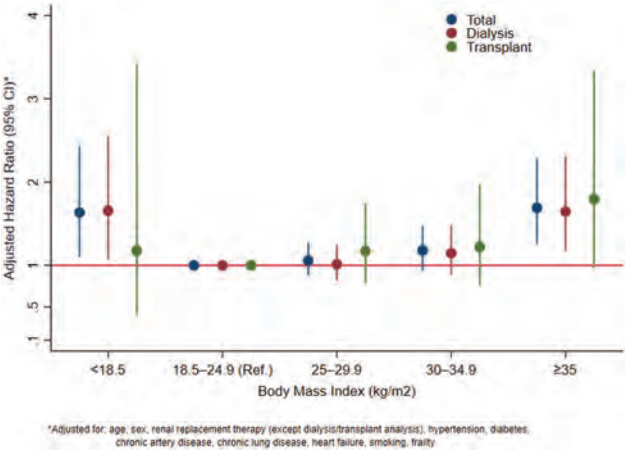
Background: In the general population obesity is associated with increased risk of mortality. However, in ESKD patients obesity is associated with lower risk of mortality, particularly in dialysis patients (i.e. the obesity paradox). In COVID-19 patients, obesity exhibits a similar association with mortality as observed in the non-COVID-19 general population. Given the obesity paradox, we questioned the association of obesity with mortality in ESKD patients with COVID-19.

Methods: Data from the European Renal Association COVID-19 Database (ERACODA) were analysed. Association of BMI (kg/m^2), divided into: <18.5 (lean), 18.5-24.9 (normal weight), 25-29.9 (overweight), 30-34.9 (obese I) and ≥35 (obese II), with 3-month mortality was investigated using Cox proportional-hazards regression. Results were investigated for the total population and, dialysis patients and kidney transplant recipients separately.

Results: In 3160 ESKD patients (mean age: 65 years, male: 61%), 99 patients were lean, 1151 normal weight (reference group), 1160 overweight, 525 obese I and 225 obese II. During follow-up of 3 months, 28%, 20%, 21%, 23% and 27% of patients died in the lean, normal weight, overweight, obese I and obese II category, respectively. In fully adjusted model, the HRs for 3-month mortality were 1.65 (95% CI:1.10, 2.47), 1.07 (95% CI:0.89, 1.28), 1.17 (95% CI:0.93, 1.46) and 1.71 (95%CI:1.27, 2.30) in lean, overweight, obese I and obese II vs normal weight patients (Figure). Results were similar among dialysis patients and transplant recipients (p-interaction=0.99).

Conclusions: In ESKD patients with COVID-19, dialysis patients or kidney transplant recipients, obesity is associated with an increased risk of mortality at 3 months. This is contrary to obesity paradox generally observed in dialysis patients. There is need to investigate why in dialysis patients with COVID-19 the survival benefit of obesity is lost.

Funding: Commercial Support - Baxter, Sandoz, Private Foundation Support



PO0076

Prevalence and Association of Dysnatremia with Outcomes in Hospitalized COVID-19 Patients

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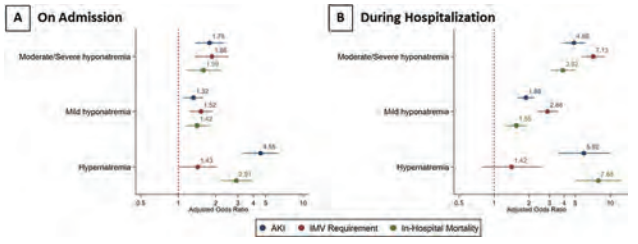
Background: Studies have reported both hypo and hypernatremia in patients hospitalized with COVID-19. We sought to examine the prevalence and association of dysnatremia with clinical outcomes among hospitalized COVID-19 patients at the Mount Sinai Health System.

Methods: We included 5,712 patients with COVID-19 who were ≥18 years old and hospitalized for ≥24 hours in the Mount Sinai Health System. Patients with ESKD, who received dialysis within the first 24 hours were excluded. We evaluated the association between serum sodium on admission (first level within 24 hours from admission) and the lowest serum sodium during hospitalization with AKI, IMV requirement, and in-hospital mortality using multivariable logistic regression models.

Results: The median age of patients was 67 (55-78) years, 57% were male, and median serum creatinine was 1.0 (IQR, 0.7-1.4) mg/dL. On hospital admission, 6% had moderate/severe hyponatremia (<130 mEq/L), 18% had mild hyponatremia (130-134 mEq/L), and 8% had hypernatremia (>145 mEq/L). After adjustment for demographics, comorbidities, and admission lab values, the adjusted OR for moderate/severe hyponatremia, mild hyponatremia, and hypernatremia on admission, compared to normal serum sodium, for in-hospital mortality were 1.59 (1.16-2.19), 1.42 (1.14-1.76) and 2.91 (2.16-3.93), respectively (**Figure 1A**). Dysnatremias during hospitalization were also associated with all three outcomes, except IMV requirement was not significantly associated with hypernatremia. (**Figure 1B**).

Conclusions: Both hypo- and hypernatremia on hospital admission and during hospitalization for COVID-19 were independently associated with AKI, IMV requirement, and in-hospital mortality. It is highly likely that dysnatremias are a marker for severity of illness and not causal for the adverse outcomes in COVID-19.



Forrest plots of the adjusted OR for AKI, IMV requirement, and in-hospital death among patients in 3 sodium categories on admission (A) and during hospitalization (B)

PO0077

The Role of CKD on Incidence and Morbidity of COVID-19: A One-Year Review in US Veterans

Mariana Garcia-Touza,[1] Elizabeth Cristiano,[1,2] Peter S. Wiegmann,[1] Vikas Singh,[1] Ram Sharma,[1] Mukut Sharma,[1] Virginia J. Savin,[1] Thomas Wiegmann.[1] *[1]Kansas City VA Hospital, Kansas City, MO; [2]University of Kansas Medical Center, Kansas City, KS.*

Background: The Coronavirus disease 2019 (COVID-19) pandemic has greatly impacted the global community. With approximately 15% of the United States (US) population having chronic kidney disease (CKD), it is important to understand how COVID-19 interacts with CKD.

Methods: We used the VA COVID-19 resource data to examine the role of CKD on incidence and morbidity of COVID-19. The database combines standard hospital data, administrative and clinical record search results. CKD is defined in this system as having occurred at any time in the 2 years prior to the COVID-19 test, while new results (incidence) refer to 60 day period after positive test. Patients with chronic kidney failure (CKF2yrs) were excluded. We examined the effect of basic demographics and common risk factors on all-cause mortality, ICU admissions, ventilator use, and dialysis. Statistical analysis (SAS enterprise guide 7.1) used frequency distributions (chi square). The data was limited to the first year of collection.

Results: The population consisted of 1,305,466 veterans. Of these, 235,857 tested positive (18.1%) and 140,143 (11.4%) had CKD. White, male patients aged over 60 years predominated (60.7%, 81.2%, 53.3%). These demographics had no significant effect on COVID-19 incidence. Hypertension (HTN), diabetes mellitus type 2 (DM2), and smoking were taken as risk factors. These were found to have little effect (OR 0.86 – 1.22) while BMI had more weight (1.41). In the positive population CKD was recorded in 28,420 (12%). In these patients, significant differences were associated with CKD, such as higher death rate (OR 4.05), ICU admission and ventilator use when compared to the total population (OR 1.24, 2.88 vs 1.25, 3.13). Need for acute dialysis was disproportionately greater(OR 36.75).

Conclusions: CKD had no effect on incidence of COVID-19. Once present it was associated with higher rates of ICU admission, ventilator use, need for dialysis and all-cause mortality. This calls for increased vigilance in our patients with CKD to prevent COVID-19 infection.

Funding: Veterans Affairs Support

PO0078

Association of the COVID-19 Pandemic with ESKD Incidence

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Background: How the COVID-19 pandemic altered ESKD incidence, dialysis initiation, and preemptive kidney transplantation is unknown.

Methods: Using Centers for Medicare & Medicaid Services data, we investigated the incidence of ESKD, dialysis initiation, and preemptive kidney transplantation by week during the first half of 2020. Using Poisson regression, we compared findings in 2020 to a forecast of 2020, had 2017-2019 historical trends continued, overall and by strata of age and race.

Results: Mean weekly counts of patients with new ESKD are shown in the **Figure**. Incidence of ESKD dropped dramatically in 2020 compared with the expected incidence, particularly during epidemiologic weeks 15-18 (April; incidence rate ratio [IRR] 0.75, 95% CI 0.73-0.78), before approaching pre-pandemic levels in weeks 23-26 (June; IRR 0.93, 0.90-0.95). Across age groups, the decrease was most pronounced during weeks 15-18 among individuals aged ≥75 years (IRR 0.69, 0.66-0.73, compared with individuals aged 45-64 years, IRR 0.80, 0.77-0.84). In terms of race, the decrease was least notable among non-Hispanic Blacks (IRR 0.85, 0.81-0.89) and was most pronounced in non-Hispanic Whites (IRR 0.72, 0.69-0.74) and Hispanics (IRR 0.73, 0.69-0.78). Dialysis initiation reached a nadir during weeks 15-18 (IRR 0.76, 0.74-0.78), and preemptive kidney transplantation decreased even more strikingly during this period (IRR 0.56, 0.46-0.67).

Conclusions: During the first wave of the COVID-19 pandemic in 2020, the number of patients starting treatment for ESKD fell to a level not observed since 2011. Changes in ESKD incidence and utilization of treatment modalities may reflect differential access to care.

Funding: NIDDK Support

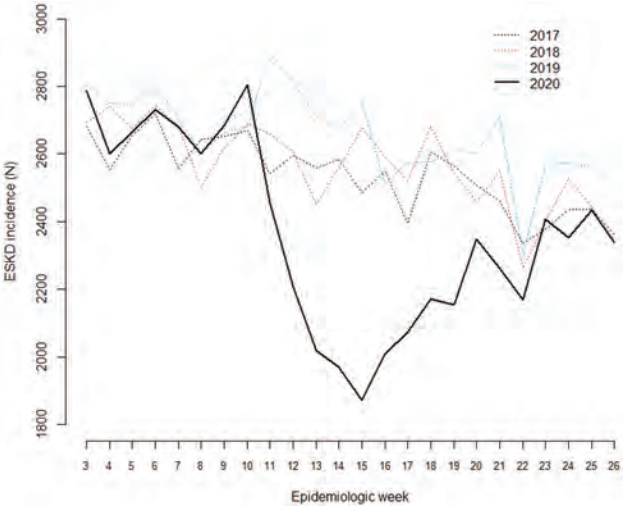

Figure. ESKD incidence, by week.

PO0079

Interim Analysis of the COSA Registry: COVID-19 Patients Treated with the Seraph® 100 Microbind® Affinity Filter

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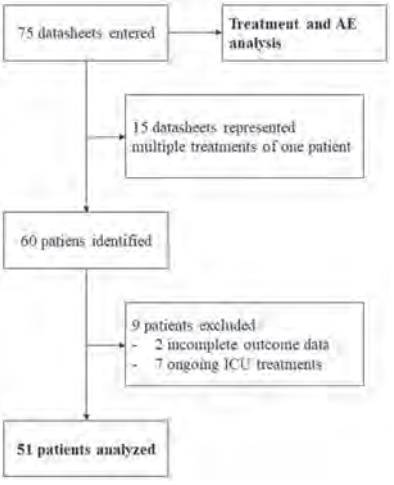
Background: The Seraph®100 Microbind Affinity Blood Filter® is a hemofiltration device that is licensed for pathogen reduction in the blood that received an emergency authorization for the treatment of COVID-19 by the FDA. The aim of this registry was to evaluate safety and efficacy of Seraph 100 treatment for COVID-19 patients.

Methods: This is an online registry in which main patient charcteristics, treatment characteristics and outcome parameters of COVID-19 patients, treated with the Seraph100 can be documented without reimbursement.

Results: Seventy-five treatment sessions in 60 patients from 12 hospitals were documented in the registry (Fig 1). Overall mortality was 42.3%. Adverse events of the Seraph® 100 treatment were reported in 8 (10.6 %) of the 75 treatments. Eight (10.6 %) of all the procedures ended prematurely due to circuit failure. Non-survivor had a higher rate of bacterial superinfection, higher level of inflammatory laboratory markers (procalcitonin and ferritin) and higher d-dimer levels(Fig 2). While predicted mortality according to SOFA score in ICU patients was >80 %, the observed mortality was 47.6 %. In non-ICU patients, 4C score predicted a mortality of 31.4-34.9 % while the observed mortality was 22.2 %.

Conclusions: Seraph 100 treatment was well tolerated and circuit failure rate was significantly lower than reported for KRT in COVID-19 patients. Compared to the calculated mortality, the observed mortality in the registry was lower.



n	51	22	29	
Invasivity (%)	42.3%			
Age (years)	63.00 [54.00 - 69.50]	64.00 [57.75 - 71.75]	57.00 [52.00 - 68.00]	0.156
Gender, Male (n)	40 (78.4)	17 (77.3)	23 (79.3)	1
White	40 (83.3)	17 (81.0)	23 (85.2)	0.707
Weight (kg)	90 [79 - 111]	90 [80.25 - 103.50]	90 [79 - 116]	0.974
Height (cm)	175.00 [170.00 - 180.00]	173.00 [170.00 - 181.00]	175.00 [173.00 - 179.00]	0.695
SOFA Score	11.50 [9.00 - 14.00]	13.00 [9.00 - 15.00]	11.00 [8.00 - 13.00]	0.129
APACHE II	12.00 [9.25 - 13.75]	12.00 [11.00 - 14.00]	10.50 [8.00 - 12.00]	0.038
Invasive ventilation (n)	34 (66.7)	16 (72.7)	18 (62.1)	0.617
PaO2/FiO2	149.62 [110.57 - 176.88]	151.25 [121.67 - 177.50]	148.00 [82.80 - 171.13]	0.391
Bacterial superinfection	19 (43.2)	14 (66.7)	5 (21.7)	0.007
CRP (mg/L)	129.00 [87.00 - 244.00]	127.00 [65.00 - 319.00]	132.50 [107.25 - 217.75]	0.928
PCT (ug/L)	1.00 [0.45 - 4.85]	3.55 [0.85 - 7.55]	0.60 [0.30 - 1.50]	0.012
Fibrinogen (mg/L)	1258.50 [825.50 - 2212.75]	2425.50 [1478.25 - 7021.50]	987.00 [675.00 - 1818.00]	0.014
Urea (mg/L)	2.82 [1.03 - 11.56]	4.60 [1.89 - 18.67]	1.58 [0.74 - 5.50]	0.039
Creatinine (mg/L)	10.38 [6.57 - 14.19]	11.58 [8.57 - 16.00]	9.13 [5.89 - 13.55]	0.118
Kidney Replacement Therapy (n)	19 (38.8)	8 (40.0)	11 (37.9)	1
ECMO treatment (n)	5 (9.8)	4 (18.2)	1 (3.4)	0.202

PO0080

COVID-19 and CKD: An Overview of Reviews to Inform the World Health Organization Scientific Brief

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Background: The World Health organization (WHO) declared COVID-19 as a global pandemic in March of 2020. Many studies have assessed the association between different comorbidities and COVID-19 outcomes. In this overview of reviews, we aim to summarize the association between CKD and different COVID-19 outcomes.

Methods: We performed a systematic search through Embase, PubMed, Epistemonikos, and Cochrane as well as preprint databases from January 1, 2020 to January 5, 2021. After searching systematic reviews, we updated the search by identifying primary studies published after August 2020, which was the date of last search in the reviews. We focused on systematic reviews and large primary studies. We followed the GRADE methodology to assess the certainty in effect estimates. Data was pooled based on random effects model.

Results: We included a total of 69 systematic reviews and 66 primary studies in our overview. We did not identify any systematic reviews that directly reports on CKD and the risk of contracting COVID-19. There was no convincing difference on the risk of acquiring COVID-19 infection in patients with and without CKD in primary studies (OR = 1.00, 95% CI 0.76-1.33). CKD is associated with higher risk of COVID-19 related mortality pooled hazard ratio (HR) 1.48 (95% CI 1.33-1.65) and pooled odds ratio (OR) 1.77 (95% CI 1.54-2.02)(moderate certainty), hospitalization pooled risk ratio (RR) 1.63 (95% CI 1.03-2.58) (moderate certainty) and disease severity pooled RR 1.56 (95% CI 1.3-1.86) (moderate certainty). Notably, the risk of COVID-19 attributed hospitalization and mortality were higher in patients with more advanced CKD stage.

Conclusions: Evidence consistently demonstrated an increased risk of mortality, hospitalization and disease severity in patients with CKD and COVID-19 infection. The results highlight the importance of recognizing patients with CKD as a high-risk group and of prioritizing these patients for COVID-19 prevention strategies including vaccination.

PO0081

Virtual Pediatric Systems: AKI in Pediatric COVID-19 Among North American Intensive Care Units

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Background: There is a dearth of large-scale studies assessing the extent of Acute Kidney Injury (AKI) in pediatric COVID-19 patients. We aim to identify the epidemiology and associated risk factors of AKI in the pediatric COVID population through the Virtual Pediatric Systems (VPS) database.

Methods: We performed a retrospective analysis on 2,597 COVID-19 pediatric patients (≤ 24 years) in the VPS COVID-19 database including both males and females with a positive status of SARS-CoV-2 infection, ICU admission, and AKI diagnosis for the AKI group using ICD-10 codes. Variables included in the analyses covered demographics, diagnosis, lab order/results, treatment modalities, length of stay, and mortality. Categorical variables were summarized as percentages while continuous variables as medians. We utilized univariate analysis and multivariate linear regression to assess the differences between the patient group with AKI and those without.

Results: An AKI incidence of 10.7% (297/2597) was found within the pediatric cohort. The AKI group had a significantly higher median hospital length of stay (9.1 days vs. 5.1), PIM2 and PIM3 probability of death (1.2 vs. 0.96 and 0.99 vs. 0.78, respectively), and proportion of mortality (7.5% vs. 1.6%) in comparison to the non-AKI group. Similarly, the AKI group experienced higher rates of interventions in comparison to the non-AKI group such as vascular access (67.0% vs. 29.8%), airway/respiratory support (55.9% vs. 43.8%), renal support (5.4% vs. 0.4%), and cardio-respiratory support (2.9% vs. 0.8%).

Conclusions: AKI is a severe complication of COVID-19 in children and adolescents. Our study suggests a 4.7-fold increase in mortality in the COVID-19 AKI group. Pediatric COVID-19 patients should be monitored for AKI development and necessitate analyses on manifestations of COVID-19 to improve health outcomes.

PO0082

Changes in Timing and Preparedness for Dialysis Initiation in the Era of COVID-19

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Background: How the COVID-19 pandemic altered aspects of dialysis initiation, such as eGFR at initiation, selection of peritoneal dialysis (PD), and, in patients initiating hemodialysis (HD), use of a central venous catheter (CVC), is not fully understood.

Methods: We analyzed the most recently updated quarterly USRDS data available. Using Poisson and logistic regression, we studied weekly changes in eGFR at dialysis initiation, use of PD (versus HD), and use of incident CVCs, overall and by strata of race, during the first half of 2020 compared to a forecast of 2020, had 2017-2019 historical trends continued.

Results: Mean eGFR at dialysis initiation decreased by 0.33 mL/min/1.73 m^2 in weeks 19-22, compared with historical trends; non-Hispanic Black patients exhibited the largest decrease, at 0.61 mL/min/1.73 m^2. The odds of initiating dialysis with eGFR <10 ml/min/1.73m^2 were highest during weeks 19-22 (May; OR 1.14, 1.05-1.17), corresponding to an absolute increase of 2.9%. Although initiation of both HD and PD fell, PD fell less, such that the odds of initiating PD (versus HD) were 24% higher (OR 1.24, 1.14-1.34) in weeks 11-14. Odds of initiating HD with a CVC increased by 30% (OR 1.30, 1.20-1.41) in weeks 15-18, representing an absolute increase of 3.3%.

Conclusions: In the first half of 2020, eGFR at dialysis initiation fell, most prominently in non-Hispanic Blacks. During the initial wave of the pandemic, odds of utilizing PD, compared with HD, increased by nearly 25%, and odds of using a CVC at HD initiation increased by 30%.

Funding: NIDDK Support

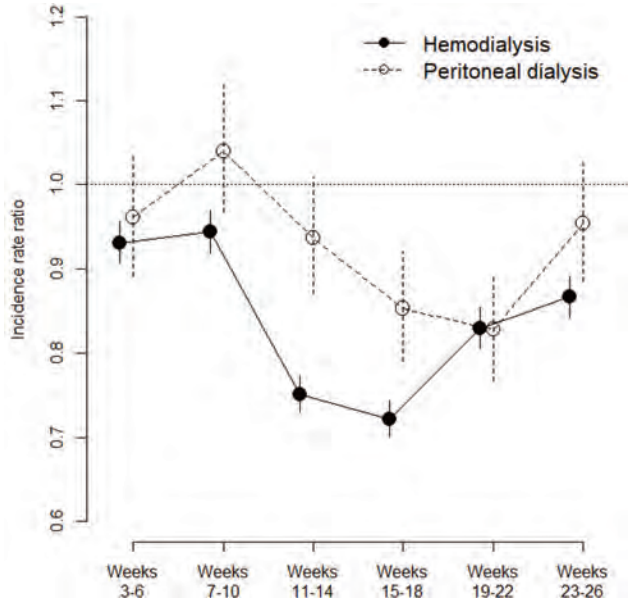

Figure. Incidence rate ratio, over time, for HD and PD relative to projected historic trends

PO0083

An ISN-DOPPS Survey of the Global Impact of the COVID-19 Pandemic on In-Centre Haemodialysis Services

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Background: Haemodialysis units (HDUs) have had to rapidly adapt practices and policies to safely continue life-sustaining HD services during the COVID-19 pandemic. We aimed to describe the impact of COVID-19 in different parts of the world.

Methods: The Dialysis Outcomes and Practice Patterns Study (DOPPS) and International Society of Nephrology (ISN) collaborated to web-survey individual HDUs. Responses were obtained in three ways: (1) a survey of DOPPS sites in China (May/ June 2020), (2) a random sample (20 units if > 40 units/ country; all units if < 40) stratified by region and HDU census (November 2020 – March 2021), and (3) an open invitation via ISN's membership list and social media (March 2021). Responses were compared between the ten ISN regions.

Results: There were returns from 412 HDUs (46% public sector, 79% urban; 70% adult, 2% paediatric, 28% adult & paediatric) from 78 countries (9% low-, 24% lower-middle-, 28% upper-middle-, 39% high-income).

Conclusions: The COVID-19 pandemic has had a significant impact on dialysis services and staffing worldwide. Differences in uptake of policies and practices across regions have likely been because of variable access to resources to enable implementation of diagnostic testing algorithms and adequate supply of PPE to implement infection prevention and control recommendations. Guidance should be consistent, adaptable to (nearly) all situations and locations, and evidence based. Going forward, the operationalisation of vaccine programs should be incorporated into guidelines. Disruptions to dialysis services should be minimised, and resource provision (including vaccines) prioritised by policymakers and governments in future waves of COVID-19 and pandemics if we are to protect HD patients, staff, and services.

Dialysis facility COVID-19 related resources, practices, and outcomes, as reported unit manager at each participating site

PO0084

The New Era of COVID-19: The Rise of Telehealth, Trends to Home Dialysis, and the "New Normal"

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Background: The objective of this study was to evaluate the impact of the COVID-19 pandemic to help conceptualize how patient care delivery, pharmaceutical representative interactions, conferences, and dialysis care may evolve.

Methods: Data was conducted between March 20, 2020 - March 31, 2021, providing coverage on the quickly evolving COVID-19 outbreak via online surveys. 50 nephrologists, neurologists, dermatologists, rheumatologists and gastroenterologists participated in each wave (total 250+) for 16 waves of research.

Results: Practice operation dynamics have changed due to the COVID-19 pandemic. Prior to 2020, 10% of practices were offering telemedicine, now nearly all (90%) offer virtual services. This migration has not come without challenges: 36% of physicians would prefer not to do telemedicine due to issues with patient access (60%), technology (53%) and their own reluctance to conduct new patient visits virtually (44%). The pandemic has created a high burnout among nephrologists compared to other specialties and nearly 20% would reevaluate their career choice if they could go back. Along with patient care, sales representative interactions have declined due to closed-door policies, with 51% of physicians reporting substantially lower or no engagements (virtual or in-person) compared to pre-COVID. Physicians are looking forward to resuming traditional in-person conferences, with 61% of vaccinated physicians planning to attend in-person if the option is available. COVID-19 has also significantly impacted HD patient care, with 66% of nephrologists reporting an outbreak among HD patients and/or staff. However, despite the obvious advantages of home care during the pandemic, only 34% of nephrologists indicated they were more likely to start a patient on a home modality due to the pandemic in March 2021 – versus 30% in March 2020. Despite their hesitancy, 80% of physicians agree the use of telemedicine will continue after the COVID-19 crisis has passed and estimate that ~20% of weekly visits will be virtual.

Conclusions: The pandemic has changed the delivery of patient care, evolving towards a more virtual model where possible – potentially creating physician burn out and interfering with the physician-patient relationship. The focus is now on the "new normal" post-COVID and the ongoing changes that will have on physicians.

PO0085

Analysis of the COVID-19 Pandemic in Home and In-Center Dialysis Populations

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Background: While dialysis patients have a high risk of complications from COVID-19, in-center hemodialysis (ICHD) patients show lower SARS-CoV-2 reproduction rates when compared to the general population (Cherif, JASN 2021), possibly related to lifestyle and interventions to prevent SARS-CoV-2 spread. Here we expand the research to study the prevalence of COVID-19 in both home (PD/HHD) and ICHD patients.

Methods: We analyzed COVID-19 cases in PD/HHD and ICHD patients from the U.S. Fresenius Kidney Care (FKC) network, from March 1 to November 27, 2020. Patients were tested for SARS-CoV-2 (confirmed by RT-PCR) when showing signs compatible with COVID-19 or exposed to an infected person. We perform statistical analysis for inter-/intra-modalities, with continuous and categorical variables being expressed as the mean (standard deviation) and absolute (relative, %), respectively.

Results: We studied 263,223 patients (age 62.8±14.5 years, 57.7% males) receiving dialysis in the FKC network (87.3% ICHD; 12.7% PD/HHD). In the FKC network, 21,175 (8.05%) were infected with SARS-CoV-2. COVID-19 infection was more prevalent among ICHD (8.56%) vs. PD/HHD (4.49%) patients. Black had a significantly higher risk than other races for both ICHD (9.10%, $p < 0.0001$) and PD/HHD (5.13%, $p = 0.0038$), without a difference between modalities ($p = 0.1827$). While white ICHD patients did not have a different risk compared to others (8.52%, $p = 0.4105$), they had

a smaller risk when dialyzed at home PD/HHD (3.82%, $p < 0.0001$), and the difference between ICHD and PD/HHD was significant ($p < 0.0001$). Similar results are shown for other patients (**Tab.1**).

Conclusions: COVID-19 infection was more common among ICHD patients. To what extent this is related to lifestyle, travel to dialysis facilities or other aspects warrants further analyses.

Funding: NIDDK Support

Table 1: Demographics of hemodialysis patients with confirmed COVID-19 on November 27, 2020. The patients received ICHD and PD/HHD in the U.S. Fresenius Kidney Care network.

Patient characteristics						
	In-center Hemodialysis		Home Dialysis		All Patients (%)	p-value[a]
	Covid Positive (%)	Covid Negative (%)	Covid Positive (%)	Covid Negative (%)		
Population	19,672 (100)	210,037 (100)	1503 (100)	32,011(100)	263,223 (100)	–
Age, years, n (%)						
<18	5 (0)	66 (0)	20 (1.3)	107 (0.3)	198 (0.1)	0.0022
18-44	2092 (10.6)	22,331 (10.6)	320 (21.3)	5709 (17.8)	30,452 (11.6)	0.0015
45-54	3154 (16)	30,305 (14.4)	343 (22.8)	5913 (18.5)	39,715 (15.1)	0.0325
55-64	4967 (25.2)	50,555 (24.1)	355 (23.6)	7752 (24.2)	63,629 (24.2)	0.135
65-74	5369 (27.3)	57,510 (27.4)	299 (19.9)	7709 (24.1)	70,887 (26.9)	0.0004
75+	4085 (20.8)	49,270 (23.5)	166 (11)	4821 (15.1)	58,342 (22.2)	0.0198
Male, n (%)	10,872 (55.3)	121,478 (57.8)	872 (58)	18,636 (58.2)	151,858 (57.7)	0.0826
Race, n (%)						
White	10,526 (53.5)	113,034 (53.8)	801 (53.3)	20,169 (63)	144,530 (54.9)	<0.0001
Black	6313 (32.1)	63,086 (30)	361 (24)	6680 (20.9)	76,440 (29)	0.1827
Unknown	2021 (10.3)	23,973 (11.4)	271 (18)	3476 (10.9)	29,741 (11.3)	<0.0001
Other	812 (4.1)	9944 (4.7)	70 (4.7)	1686 (5.3)	12,512 (4.8)	0.9141
Ethnicity, n (%)						
Non-Hispanic	13,576 (69)	155,554 (74.1)	961 (63.9)	25,028 (78.2)	195,119 (74.1)	<0.0001
Hispanic	3919 (19.9)	28,749 (13.4)	261 (17.4)	3258 (10.2)	36,187 (13.8)	0.0441
Unknown	2177 (11.1)	26,234 (12.5)	281 (18.7)	3725 (11.6)	32,417 (12.3)	<0.0001
Comorbid Conditions, n (%)						
Diabetes	9237 (47)	85,923 (40.9)	581 (38.7)	11,073 (34.6)	106,814 (40.6)	0.2101
IHD	4146 (21.1)	43,898 (20.9)	243 (16)	5063 (15.8)	53,348 (20.3)	0.9387
PAD/PVD	1776 (9)	18,630 (8.9)	90 (6)	2190 (6.8)	22,686 (8.6)	0.1558
CHF	4709 (23.9)	47,556 (22.6)	268 (17.8)	5160 (16.1)	57,693 (21.9)	0.4919
CVD	1476 (7.5)	13,085 (6.2)	73 (4.9)	1483 (4.6)	16,117 (6.1)	0.2344
COPD	1941 (9.9)	21,634 (10.3)	119 (7.9)	2404 (7.5)	26,098 (9.9)	0.2982
Hypertension	14,171 (72)	147,057 (70)	1097 (73)	22,458 (70.2)	184,783 (70.2)	0.5067

[a]Based on logistic regression for testing the hypothesis that odds ratios of ICHD and PD/HHD modalities are equal.

Abbreviations: IHD: ischemic heart disease, PAD: peripheral arterial disease, PVD: peripheral vascular disease, CHF: congestive heart failure, CVD: cerebrovascular disease, COPD: chronic obstructive pulmonary disease.

PO0086

Perception of COVID-19 Risk Among In-Center Hemodialysis Patients

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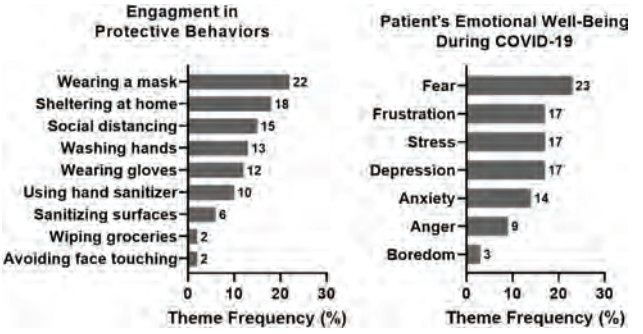
Background: Dialysis patients are at high risk for severe complications related to COVID-19. The present study examined perception of risk of COVID-19 and its impact on behavior modification and emotional well-being among in-center hemodialysis (ICHD) patients during the recent COVID-19 pandemic.

Methods: In-depth, semi-structured telephone interviews were conducted between May and July 2020 with adult ICHD patients dialyzing at a large dialysis organization (LDO). Responses were analyzed using inductive thematic analysis. The reliability of categories was examined by an independent coder.

Results: A total of 41 LDO patients were interviewed. The median age was 63 years and 54% were female. Satisfactory inter-rater reliability was achieved for all identified themes (kappa = 0.70 - 0.99). We found that the COVID-19 pandemic caused a high level of worry among ICHD study subjects; 78% of those interviewed felt that they are at high risk of COVID-19. Consequently, subjects reported a high level of compliance with appropriate protective behaviors during the pandemic, such as wearing a mask, sheltering at home, social distancing, and frequent handwashing. The perception of the actual likelihood of contracting the virus during a hemodialysis session was relatively low ($M = 3.38$ on a 0 to 10 risk scale). The pandemic had no impact on self-reported adherence to dialysis treatment schedules, medications, or diet. However, subjects reported dominating emotions of frustration, fear, stress, depression, and anxiety.

Conclusions: The study subjects were aware of the risk of COVID-19 and seemingly increased compliance with protective behaviors as a consequence. It appears that the pandemic had a strong negative impact on the study subjects' emotional well-being and that additional support in this area might be beneficial.



PO0087

Feasibility of Infection Control Measures in Hemodialysis Units to Prevent Outbreaks of COVID-19: A Descriptive Study from Quebec

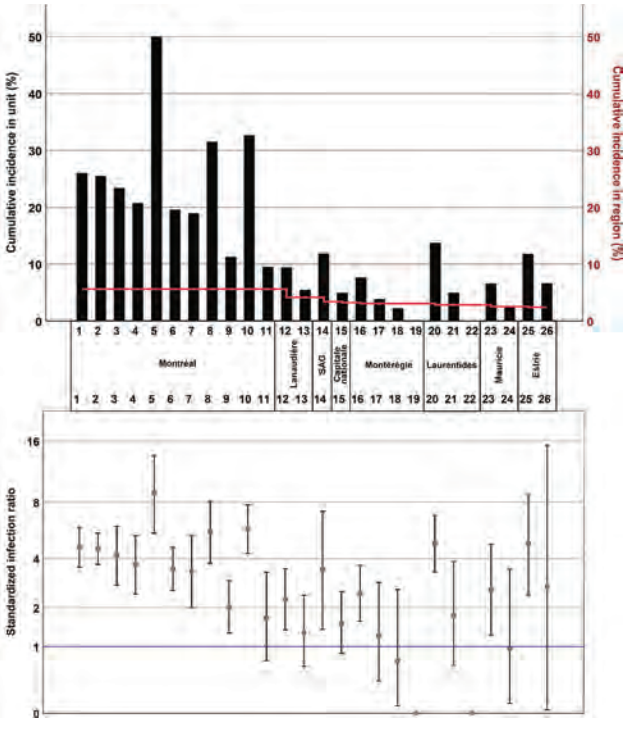
William Beaubien-Souligny,[1] Annie-Claire Nadeau-Fredette,[2] Marie-Noël Nguyen,[1] Norka Rios,[3] Marie-Line Caron,[1] Alexander Tom,[3] Rita Suri.[3,4] Quebec Renal Network *[1]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [3]Research Institute of the McGill University Health Centre, Montreal, QC, Canada; [4]McGill University, Montreal, QC, Canada.*

Background: In-center hemodialysis (HD) units pose the perfect conditions for COVID-19 transmission yet limited space and resources are obstacles to infection prevention and control (IPAC) measures. We aimed to describe IPAC measures implemented and document the infection rates within HD units during the first year of the pandemic.

Methods: We invited leaders of Quebec's HD units to collect information on IPAC measures from March 1st to June 30th 2020 and HD unit characteristics. Participating units were contacted again in March 2021 to collect information about the total number of cases. The cumulative infection rate of each unit was compared to the regional cumulative infection rate using a standardized infection ratio (SIR).

Results: Data was obtained from 38 units, representing 90% of Quebec's HD patients. 30% of units were perceived as crowded, and this was associated with objective distance measures between stations, which was much more likely to be <2m in units considered crowded (83.3% vs 19.2% $p<0.001$). IPAC measures regarding general prevention, screening procedures, physical distancing, and PPE use were implemented in 50% of units by 3 weeks and the remainder by 6 weeks. Data on cumulative infection rate was obtained in 26 units providing care to 3942 patients. The cumulative infection rate was disproportionally elevated in HD units compared to regional rates (Median SIR:2.68 IQR:1.58; 4.45)(Figure 1). No difference was noted in the SIR related to specific IPAC measures or to the physical characteristics of the units.

Conclusions: Hemodialysis units throughout Quebec were able to rapidly implement modified IPAC measures. Despite this, infection rates were disproportionally elevated.



PO0088

Safety and Efficacy of the Anti-COVID-19 Vaccination Practiced During the Hemodialysis Session

Gianmarco Lugli,[1,2] Giuseppe L. Spatoliatore,[2] Andrea Batazzi,[1,2] Silvia Pilo,[1,2] Alberto Rosati.[2] *[1]Universita degli Studi di Firenze, Firenze, Italy; [2]Ospedale San Giovanni di Dio, Firenze, Italy.*

Background: CKD patients represent a population at high risk of mortality from Covid-19. For 3 years, our hospital has been running a complete intradyalitic vaccination project (HBV, Hemophylus, Pneumococcus, Influenza) for hemodialysis patients during dialysis treatment. This study aims to evaluate the safety and the serological response of intradialysis anti-Covid19 vaccination.

Methods: 217 hemodialysis patients from 5 centers were vaccinated with Moderna (Fig. 1). Patients with a previous infection received only one dose. 10 patients (4.6%) refused the treatment. The administration took place one hour after the start of the dialysis session, and therefore with the session still in progress. 44 vaccinated patients, with no history of previous Covid19 infection, out of a total 80 dialysis patients, were selected on voluntary basis, in our HD-center, to measure and titrate the anti-RBD S1 antibodies of the virus spike antigen 14 days after the second dose.

Results: Of the 217 patients, 64.3% were male, with a mean age of 70 ± 14 years. 19 patients (8.7%) had mild adverse reactions at site of vaccine-inoculation. Neither serious adverse events nor intradialytic complications were recorded. Table 1 shows the characteristics of the 44 patients whose antibody titration was performed. Seroconversion was achieved in 41 patients (93.18%), anti-RBD S1 titer was 936,6 ± 661,7 UI/mL.

Conclusions: Our preliminary data form our study shows that intradialytic vaccination for Covid-19 is safe and effective and solves logistic problems in prophylaxis's management. This approach should be preferred in hemodialysis patients. We are planning to extend anti-RBD S1 antibodies monitoring of the Sars-Cov2 virus in all HD Centers involved in the study and to include Peritoneal Dialysis' patients.

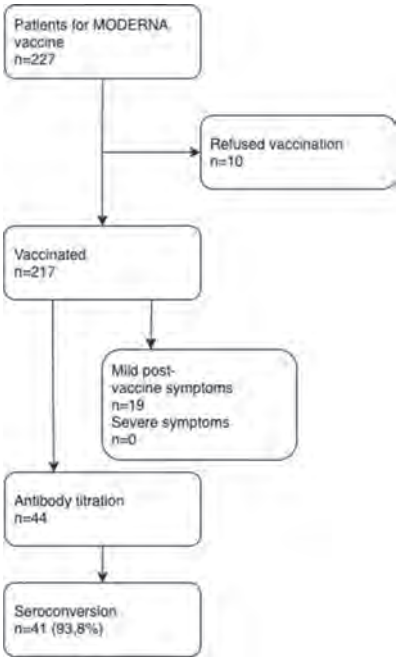


Figure 1

PO0089

Assessing the Impact of a Renal Care Management Program on Disease Progression Prior to and During the COVID-19 Pandemic

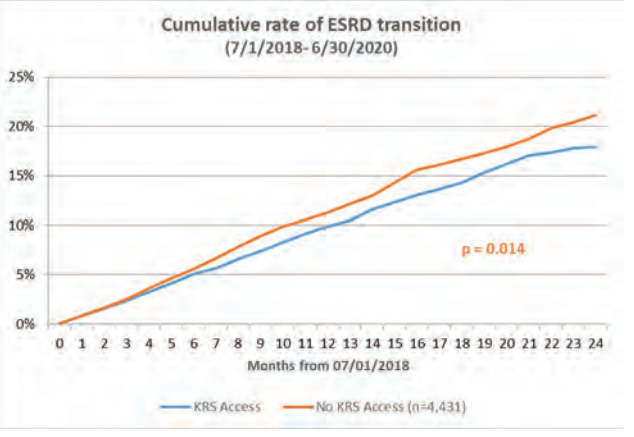
Ashley Crossman, Kevin Plosser, Rahul Dhawan, Wade M. Bannister. Optum Kidney Resource Services Team *Optum Inc, Eden Prairie, MN.*

Background: The transition to dialysis among chronic kidney disease (CKD) patients marks a significant change in health accompanied by increases in morbidity and health care costs. Delaying this transition means extending the patient's quality of life and cost savings. The effects of renal care management on the transition to dialysis and whether having access to the program impacts the risk of transitioning to dialysis as well as the timeline of transitioning to dialysis is necessary to study given the increased role of case management programs with the advent of the COVID-19 pandemic. Understanding the role of disease management programs provide direction for management programs across the globe

Methods: The design is a retrospective, cohort study of patients in the US drawn from a national claims database who were identified as having CKD 4 or 5 on July 1, 2018. The data was analyzed to determine whether program access affected the rate of transition to dialysis and the likelihood of transitioning to dialysis from 2018 to 2020.

Results: We followed the cohort of 7,992 participants (3,561 with access to Kidney Resource Services and 4,431 without access to Kidney Resource Services) during a two year period from 2018 to 2020. Those with access to Kidney Resource Services transitioned to dialysis later than those without access to the program. Further, after controlling for patient risk and characteristics, patients with access to the program had a 22 percent reduced risk of initiating dialysis compared to those without access.

Conclusions: Patients with stage 4 or 5 CKD who have access to renal care management have a reduced risk of transitioning to dialysis as well as a later transition to dialysis compared to CKD patients without access to renal care management. Further research is needed given the increased need for education during and post the COVID-19 pandemic to address social and clinical determinants of health.



PO0090

Stigma Syndemics and ESKD in Disenfranchised Urban Communities Fighting COVID-19

Insa M. Schmidt,[1] Lauren D. Stern,[1] Margaret Farr,[2] Nicole H. Nguyen,[2] Sushrut S. Waikar,[1] Merav Shohet.[2] *[1]Boston Medical Center, Boston, MA; [2]Boston University, Boston, MA.*

Background: Although COVID-19 is impacting all communities, the distribution of its harms is not equal. Poor, urban people of color with compromised health are particularly hard-hit. This study explores how patients with end-stage kidney disease (ESKD), living in underprivileged urban communities, manage their illness and treatment experiences and disease-associated stigmas in the face of COVID-19.

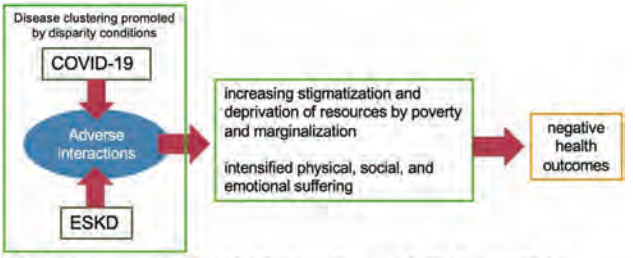
Methods: We used purposive sampling to enroll patients with ESKD at a safety net hospital in Boston, MA. 12 remote ethnographic interviews were conducted from December 2020 to June 2021. Interviews were recorded and transcribed, and data were analyzed using grounded theory and dimensional narrative analysis. We identified dominant themes reflecting the biosocial harms caused by ESKD as well as patients' sense of isolation and stigmatization before and during the COVID-19 pandemic.

Results: The mean age of patients was 56±14 years, 50% were female, and 90% self-identified as Black. Almost all patients reported adverse effects from dialysis treatment which leaves them depleted and precludes them from working. Facing the biosocial implications of dialysis, patients also experienced severe economic hardship which has been intensified by the COVID-19 pandemic. While many patients framed COVID-19 as "just one more thing" and denied increased stigmatization by others due to their potentially increased susceptibility to infection, male patients more frequently reported experiencing racial stigmatization and narrated it as contributing to and exacerbating their chronic illness and suffering.

Conclusions: Biosocial and environmental factors as well as institutional racism and stigmatization play significant roles in amplifying the burden of ESKD in patients of color who are now syndemically impacted by COVID-19 (Figure 1). A better understanding of

how these factors interplay will help to inform policy makers in alleviating tensions and structural conditions that impinge on patients' well-being and health outcomes.

Funding: Private Foundation Support



Model of stigma syndemics. Modified from Singer et al. (The Lancet, 2017).

PO0091

COVID-19 Vaccine Hesitancy and Uptake Amongst a Multiethnic Hemodialysis Population

Andrea Cove-smith, Sujanita Thyagarajan, Kieran Mccafferty, Suzanne H. Forbes, Heidy Hendra, Natasha P. O'Sullivan. *Barts Health NHS Trust, London, United Kingdom.*

Background: Broad adoption of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is key to fighting the spread of Covid-19. Hemodialysis patients are at increased risk of exposure to SARS-CoV2 and associated with high morbidity and mortality if they contract Covid-19, therefore attaining high vaccination rates in dialysis patients is of utmost importance. The aim of this study was to establish the prevalence of vaccine hesitance across the multi-ethnic population of dialysis patients in North East London, and to assess whether vaccine uptake could be improved by offering vaccination in a familiar setting by trusted healthcare professionals.

Methods: Prior to the initiation of the hemodialysis vaccine programme, a survey was conducted of 837 in-centre haemodialysis patients to identify those willing to accept the vaccine. The vaccine was then offered to all haemodialysis patients during their dialysis attendance, by their dialysis team of nurses and nephrologists.

Results: Of 674 responses, 476 (71%) patients reported willingness to accept the vaccine. However only 41% of the 232 patients of Black ethnicity stated that they would accept the vaccine with 59% undecided or declined, compared to acceptance of 77% and 82% of the Asian and White patients respectively ($p<0.0001$). The actual acceptance rate was significantly higher in all ethnic groups than that predicted by the survey (82.2% uptake in total), with 71.5%, 86.0% and 89.3% in Black, Asian and White cohorts respectively ($p<0.0001$). In total, 59.1% of patients who responded 'no' in the initial survey, accepted the vaccine when offered on the unit.

Conclusions: Though vaccine hesitancy remains a concern, even in this particularly vulnerable patient group, our data show that uptake can be improved by offering Covid-19 vaccination in a familiar environment by a trusted healthcare team.

PO0092

Navigating Vaccine Hesitancy in a Hemodialysis Clinic

Kathleen Murphy,[1] Jean Lee,[2] Lauren Zanikos,[1] Lori L. Widenr,[1] Leonor V. Pareja,[1] Louise Enderle,[1] Christina Petyo,[1] Evetta C. Frazier,[1] Marie Clerge,[1] Othello Kwaidah,[2] Ziauddin Ahmed,[2] Crystal A. Gadegbeku,[2] Avrum Gillespie.[2] *[1]Dialysis Clinic Inc, Philadelphia, PA; [2]Lewis Katz School of Medicine at Temple University, Philadelphia, PA.*

Background: Pre-vaccination, SARS-CoV2 infected 20% of our hemodialysis clinic with a 48% mortality. Vaccine access and hesitancy are significant barriers to vaccination among minority groups. Over 90% of our patients self-report as Black or African American, thus we created a multidisciplinary vaccine navigation program to optimize COVID-19 vaccination.

Methods: We surveyed the patients' vaccination attitudes before the vaccine was available. All care team members: patient care technicians, nurses, social worker, dieticians, and nephrologists were educated to provide the patients with the efficacy and safety of the vaccine. Our affiliate hospital had an mRNA vaccine clinic.

Results: Over 60% responded to the survey, 18% said they would decline vaccination and 39% were unsure. Figure 1 shows the growth of the percentage of patients receiving one and two doses of the vaccine. The first patient received a dose on 1/9/2021. On 1/28/21, the hospital vaccine clinic invited dialysis patients who used the hospital's services. On 2/4/21, we provided the hospital a complete list of patients. On 2/11/21, a vaccine hotline was implemented and a renal dietician became the dialysis clinic's vaccine navigator scheduling and tracking patients' vaccine appointments, avoiding conflicts with their dialysis times and coordinating transportation. Nurses documented vaccinations. A spreadsheet was emailed weekly to team members to track vaccinations and to remind patients of vaccine appointments. All of the staff discussed vaccination with patients who were hesitant or declining the vaccine. By 5/4/21, 89% of the patients had received at least one dose, 79% had received two doses.

Conclusions: Although many patients had vaccine hesitancy, the growth curves show the rapid adoption of the vaccine. The main barrier to the vaccine was access. Multidisciplinary care in the hemodialysis clinic can facilitate access to care and may be a model for navigating kidney transplantation.

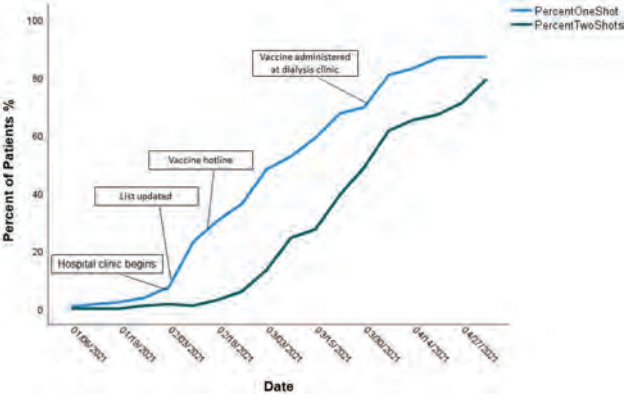


Figure 1

PO0093

Disparities in CKD Risks: Data from the CURE-CKD COVID-19 Sub-Registry

Susanne B. Nicholas,[1] Robert W. Follett,[1] Theona T. Tacorda,[1] Xiaoyan Wang,[1] Dennis Ruenger,[1] Panayiotis Petousis,[1] Bing Zhu,[1] Tyler A. Davis,[1] Davina J. Zamanzadeh,[1] Kenn B. Daratha,[2] Cami R. Jones,[2] Keith C. Norris,[1] Katherine R. Tuttle,[2] Alex Bui.[1] CURE-CKD *[1]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [2]Providence St Joseph Health, Spokane, WA.*

Background: The SARS-CoV-2 pandemic accelerated health disparities in chronic kidney disease (CKD). Here, we describe risk factors and access to care surrogates (area deprivation index-ADI) for clinical outcomes among SARS-CoV-2-tested patients in the CURE-CKD Registry.

Methods: We formed a COVID-19 Sub-Registry within CURE-CKD (1/1-6/30/2021; N=171,988) of patients with CKD, diabetes (DM)/pre-DM, or hypertension (HTN) with SARS-CoV-2 testing at UCLA Health (UCLA; N=17,884) and Providence St. Joseph Health (PSJH; N=154,104). Statistical analyses and fitted multivariable logistic regression models were adjusted for age and sex. The UCLA cohort included analyses for acute kidney injury (AKI), ADI (for poor housing, education, income), Charlson Comorbidity Index (CCI), and severe COVID-19 disease.

Results: Odds ratios (OR) of COVID-19 positivity for the combined UCLA + PSJH population, as well as OR of having severe COVID-19 disease in the UCLA cohort are presented (**Table**). OR[95%CI] for AKI were higher for ages ≥80 years (1.77[1.14-2.46]), ADI by state (1.12[1.06-1.18]), CKD (12.20[8.46-17.58]) and pre-existing DM (3.65[2.62-5.08]), $p<0.001$. In the UCLA CURE-CKD population, AKI was associated with severe COVID-19 ($r=0.26$) and ICU admissions ($r=0.29$). Mortality was associated with severe COVID-19 disease ($r=0.5$).

Conclusions: Non-White and/or LatinX race/ethnicity, ADI, CKD, DM, and older age were associated with higher risks of COVID-19 positivity, disease severity, and mortality in CURE-CKD. Efforts on viral screening, timely COVID-19 diagnosis, and optimal care delivery for patients with or at-risk for CKD are needed.

Funding: Private Foundation Support

Table: Results from the CURE-CKD COVID-19 Sub-Registry

		Odds Ratio (95% CI)	p-value
UCLA + PSJH Populations: Risk factors for COVID-19 Positivity			
Sex	Female vs. Male	0.85 (0.82-0.89)	<0.0001
Age (years)	>=80 vs. <60	1.42 (1.33-1.52)	<0.0001
	>=80 vs. 60-79	1.40 (1.31-1.50)	<0.0001
Race/ ethnicity	Latin vs. Non-LatinX	3.95 (3.69-4.22)	<0.0001
	Black vs. White	1.99 (1.84-2.16)	<0.0001
	Asian vs. White	2.03 (1.88-2.18)	<0.0001
	Hawaiian/Pacific Islander vs. White	2.33 (1.97-2.76)	<0.0001
Pre-existing	DM	1.08 (1.03-1.13)	0.003
	HTN	0.84 (0.80-0.88)	<0.0001
UCLA Health population: Risk factors for severe COVID-19			
Pre-existing conditions	CKD	3.71 (2.06-6.66)	<0.0001
	Myocardial infarction	3.55 (2.01-6.24)	<0.0001
	Pre-DM	0.33 (0.15-0.74)	0.007

PO0094

Beliefs About and Impact of the COVID-19 Pandemic on a Population of Inner City Kidney Transplant Recipients (KTRs)

Sae Morita, Galina Udod, Michael A. Goldberg, Stefan Hamaway, Perry A. Kerner, Ryan Harrington, Mariana Markell. *SUNY Downstate Health Sciences University, Brooklyn, NY.*

Background: The COVID-19 pandemic was especially stressful for indigent people with multiple health conditions. We examined beliefs and behaviors at the height of the pandemic in a population of inner-city KTRs.

Methods: 40 KTRs followed at our Center were surveyed by telephone including questions about behaviors, knowlege and attitudes regarding COVID-19 using yes/no or Likert scale answers as well as the Stress and Social Suppory and Health Beliefs Questionnaires.

Results: Mean age was 57±1.8yrs, with 22 males and 18 females, 27 (77%) Black, (4) White 11% and 8 (23%) other. Time since transplant 7.75±1.07yrs. 35% (9/26) felt difficulties were piling up so high that they could not overcome them.13% (4/31) reported it was more difficult to pay for medications and were more likely to skip doses to make them last longer (r=0.473, p=0.008). 75% (23) were afraid of COVID-19. 51% (17/33) were afraid of catching it from a family member, 54% (18) from a friend, 84% (26) limited any in person interactions, 44% (19) avoided leaving home for any reason and 45% (15) avoided going to any public spaces. Pts who reported being more afraid of COVID-19 were more likely to report poor health (r=-0.39, p=0.032), to report being afraid to leave their home (r=0.48, p=0.006), were more likely to have contacted their provider more than 4-6 times in the past two months (p=0.034), to state that their health was poor (r=-0.39, p=0.032), and to say that their condition keeps them from working (r=0.52, p=0.027). They also believed that eating Chinese food could increase COVID-19 risk (r=0.37, p=0.039).

Conclusions: In our population of inner-City KTRs: 1. Two thirds were afraid of COVID-19, including catching itfrom a friend or family member, and limited leaving their home. 3. They were also more likely to report poor health. contact their healthcare provider multiple times, as well as state their condition made it impossible to work and believe that one could catch COVID-19 from Chinese food. 4. Over 10% were financially stressed and skipped doses of medication to make them last longer and a third felt it difficult to cope overall. 5. Follow up will be necessary as the pandemic subsides to examine if there was a detrimental effect on graft survival due to multiple stressors that could affect adherence in this population.

PO0095

Barriers and Facilitators to Emotional Well-Being and Healthcare Engagement in COVID-19: A Qualitative Study Among Patients with Kidney Disease and Their Caregivers

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Background: Patients with chronic kidney disease (CKD) have disproportionately faced poor health outcomes during the coronavirus disease-19 (COVID-19) pandemic. Barriers and facilitators to patients' and caregivers' emotional well-being and healthcare engagement have not been deeply described, leaving a gap in interventions during future crisis settings.

Methods: We conducted a qualitative study among patients with CKD (stages 4-5), kidney failure, kidney transplantation, and their caregivers. Interviews were guided by Leventhal's Model of Self-Regulation that emphasized individual interpretations and emotional responses to health threats as determining factors of health behaviors. Interviews were audio-taped, transcribed, and analyzed thematically.

Results: Twenty-eight patients (median age 63, self-reported race: White 57%, Black 18%, Asian 1%, others 14%) and 14 caregivers were interviewed over six months. Barriers and facilitators related to patients' emotional well-being included 1) negative emotional responses (feelings of increased vulnerability, anxiety, social isolation, and depression); 2) coping behaviors (adaptive coping via self-preservation and emotion regulation; maladaptive coping via alcohol and unhealthy eating); 3) and the need for caregiver support for daily tasks. Barriers and facilitators to healthcare engagement included: 1) continued trust in the medical community (*" I put my faith in [my doctor's] knowledge"*); and 2) technology (telehealth was a facilitator to access for some but inadequate for multidisciplinary care *"[my] transplant evaluation was stopped…we could not go to the cardiologist")*. Caregivers reported higher burden compared to before the pandemic.

Conclusions: Patients and caregivers widely reported negative emotional reactions to enforced pandemic-related social isolation. Coping efforts were partially successful. Telehealth provided adequate access to kidney health services for some but was insufficient for those requiring multidisciplinary care. Lessons learned from the COVID-19 pandemic suggest that patients with kidney disease may benefit from psychosocial and multi-modal structural support to offset social isolation, reduce caregiver burden, and bolster access to multidisciplinary care during future crisis settings.

PO0096

Three-Month Clinical, Functional, and Mental Outcomes in Kidney Transplant Recipients Surviving COVID-19

Raphael Duivenvoorden,[1] Priya Vart,[2] Marlies Noordzij,[2] Augusto Cesar Soares dos Santos Jr,[3] Alex B. Zulkarnaev,[4] Casper F. Franssen,[2] Dirk R. Kuypers,[5] Erol Demir,[6] Hormat Rahimzadeh,[14] Julia Kerschbaum,[7] Kitty J. Jager,[12] Kultigin Turkmen,[11] Marc H. Hemmelder,[10] Marcel Schouten,[9] María L. Rodríguez-Ferrero,[13] Marta Crespo,[8] Ron T. Gansevoort,[2] Luuk Hilbrands.[1] *[1]Radboudumc, Nijmegen, Netherlands; [2]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [3]Hospital das Clinicas at Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [4]Moskovskij oblastnoj naucno-issledovatel'skij kliniceskij institut imeni M F Vladimirskogo, Moskva, Russian Federation; [5]Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [6]Istanbul Universitesi Istanbul Tip Fakultesi, Istanbul, Turkey; [7]Medizinische Universitat Innsbruck Universitatsklinik fur Innere Medizin IV Nephrologie und Hypertensiologie, Innsbruck, Austria; [8]Hospital del Mar, Barcelona, Spain; [9]Tergooi, Hilversum, Netherlands; [10]Universiteit Maastricht, Maastricht, Netherlands; [11]Necmettin Erbakan Universitesi Meram Tip Fakultesi, Meram, Turkey; [12]Amsterdam Universitair Medische Centra, Duivendrecht, Netherlands; [13]Hospital General Universitario Gregorio Maranon, Madrid, Spain; [14]Sina Hospital, Tehran, Tehran, Islamic Republic of Iran.*

Background: Kidney transplant patients are at high risk for COVID-19 related mortality. However, limited data are available on longer term clinical, functional and mental outcomes in patients that survive COVID-19.

Methods: Data from adult kidney transplant patients that presented with COVID-19 between February 1st, 2020 and January 31st, 2021 were retrieved from the ERACODA database. Data from patients with complete data for vital status, hospitalization and/or ICU admission was used for this analysis.

Results: 912 patients were included with a mean age of 56.7 (±13.7) years. 26.4% were not hospitalized, 57.5% hospitalized, and 16.1% hospitalized and ICU admitted. Three-months survival was 82.3% overall and 98.8%, 84.2% and 49.0% resp. in each group. Three-months acute rejection, need for dialysis / CVVH at any time point, and graft failure occurred in the overall group in 1.0%, 2.6% and 1.8% resp., and in 2.1%, 10.6% and 10.6% of ICU admitted patients resp. Of the surviving patients 83.3% had reached their prior functional status within 3 months. Of patients that had not yet reached their prior functional status, it was expected that 79.6% still would do so within the coming year. 94.4% had reached their prior mental status. Of patients that had not yet reached their prior mental status, it was expected that 80% of patients would do so within the coming year.

Conclusions: In patients alive at three-months follow-up, graft loss was rare, and most patients had reached their pre-COVID-19 functional and mental status.

Table 1

Outcomes	Total	Not hospitalized	Hospitalized, no ICU	Hospitalized, ICU	p-value
Acute rejection, n (%)	5 (1.0)	2 (1.4)	2 (0.7)	1 (2.1)	0.57
Required dialysis / CVVH, n (%)	13 (2.6)	3 (2.1)	5 (1.7)	5 (10.6)	<0.001
Graft Loss, n (%)	9 (1.8)	1 (0.7)	3 (1.0)	5 (10.6)	<0.001
Reached pre-COVID-19 functional status, n (%)	375 (83.3)	123 (87.9)	235 (87.0)	17 (42.5)	<0.001
Reached pre-COVID-19 mental status, n (%)	425 (94.4)	134 (95.7)	260 (96.3)	31 (77.5)	<0.001

Clinical, functional, and mental outcomes in kidney transplant recipients three months after being diagnosed with COVID-19. Data of 487 patients were available for analysis of graft function related outcomes. Data of 450 patients were available for functional and mental status outcomes.

PO0097

Clinical, Functional, and Mental Outcomes in Hemodialysis Patients 3 Months After COVID-19 Diagnosis

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Background: There is overwhelming evidence that hemodialysis (HD) patients are at high risk of death in the first month after developing COVID-19. However, less is known about their long-term mortality risk and functional and mental outcome. We aimed to assess these outcomes in a large cohort of HD patients 3 months after COVID-19 diagnosis.

Methods: From ERACODA, we included adult HD patients who presented with COVID-19 from February 1, 2020-January 31, 2021 and with complete data on vital status and hospitalization. Recovery of functional and mental status was estimated by the treating nephrologist. Logistic regression was used to calculate odds ratios (OR) with 95% confidence interval (95%CI) for the likelihood of reaching the pre-COVID-19 status.

Results: A total of 2,249 HD patients (mean age 67.5 ± 14.4 years) were included, of whom 1,087 (44%) were not hospitalized, 1,165 (48%) were hospitalized but not admitted to an ICU, and 197 (8%) were hospitalized and ICU-admitted. In these 3 groups, the survival probability at day 28 was 90%, 75% and 47%, and at 3 months 90%, 73% and 40%, respectively. For 854 patients who survived 3 months after COVID-19 diagnosis, data on functional and mental status was available. 743 (87%) reached their pre-COVID-19 functional status within 3 months. 111 patients had not yet reached this, but it was expected that 58% of them would do so within 1 year. Higher age (adjusted OR: 0.97; 95%CI: 0.96-0.99), higher frailty score (0.81; 0.70-0.93) and ICU admission (0.11; 0.05-0.26) were associated with a lower likelihood of reaching pre-COVID-19 functional status. Pre-COVID-19 mental status was reached by 803 (94%) patients. Higher frailty score (0.76; 0.65-0.89) and ICU admission (0.27; 0.11-0.67) were associated with lower likelihood of reaching prior mental status. For 56% of the 51 patients who had not yet reached their prior status, it was expected that they would do so within the coming year.

Conclusions: Three months after a COVID-19 diagnosis, most HD patients who were not admitted to the ICU were still alive. Furthermore, a vast majority had already reached their pre-COVID-19 functional and mental status at that time point.

Funding: Commercial Support - The ERACODA project receives unrestricted grants from Baxter and Sandoz., Private Foundation Support

PO0098

Anxiety in Patients with CKD During the COVID-19 Pandemic: Predictors and Consequences Among Chronic Renal Insufficiency Cohort (CRIC) Study Participants

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Background: Chronic kidney disease (CKD) is associated with anxiety and depression. Though the Coronavirus 2019 (COVID-19) pandemic has increased stressors on patients with CKD, assessments of anxiety, its predictors and consequences, including on virus mitigation behaviors are lacking.

Methods: From June to October 2020, we administered a survey about anxiety related to the COVID-19 pandemic to 1888 participants in CRIC. We examined associations of anxiety with demographics, clinical indices, health literacy, health-related behaviors and COVID-19 mitigation behaviors.

Results: Four anxiety-related constructs were assessed: one composite overall global anxiety construct and three sub-constructs: general anxiety, worry, mood/feelings. Construct scores had moderate to strong correlations with each other (0.48–0.89) and high internal consistency (Cronbach's alpha ≥0.81). In adjusted analyses, younger age, female gender, Hispanic ethnicity, cardiovascular disease, household income <$100,000, unemployment, and marginal or inadequate health literacy predicted higher anxiety. During the pandemic, higher global anxiety scores were associated with higher odds of eating less healthy foods, reduced physical activity, and weight gain as well as reporting always wearing a mask in public in the past week.

Conclusions: Several factors predict higher anxiety related to the COVID-19 pandemic. Although anxiety is typically thought to be an undesired outcome, in addition to being associated with less healthy behaviors, anxiety was associated with higher self-reported mask wearing. Our study indicates a need for interventions to support healthy behaviors and virus mitigation strategies, without provoking or worsening anxiety in patients with CKD.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences

Multivariable-adjusted logistic regression examining associations between overall anxiety composite score and self-reported behaviors.

	Odds Ratio	p value
In past week, always wear a mask in public	1.27	<0.001
In past week, always remain ≥6 feet apart from others not in household while in public	1.06	0.26
Since pandemic began, travel out of state/country	0.94	0.43
Eating less healthy during pandemic vs eating the same or healthier during the pandemic	1.27	<0.001
Less physically active during pandemic vs having the same or higher level of physical activity	1.33	<0.001
Weight gain during the pandemic vs maintaining or losing weight	1.21	<0.001

PO0099

Hand Sanitizer Overdose in the Era of COVID-19

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Introduction: Isopropyl alcohol is a common ingredient in hand sanitizers. Ingestion should be suspected if patient presents with high osmolar gap & pseudo renal failure without metabolic acidosis.

Case Description: 44 y/o female with h/o of HTN & hypothyroidism, brought to the ED for altered mental status. 2 bottles of hand sanitizers were found empty next to her. She was drowsy, unable to provide any further history. Vitals T- 36.7 C, HR 91, BP 124/84, RR 14, SaO2 97 on RA. Physical exam was unremarkable. Initial labs on admission: Serum creatinine 2.47, i-stat creatinine at 0.7, bicarb 24, AG 8, serum osmolality 341, osmolar gap of 57. Ethanol level was negative. Table1 outlines the patient's labs. Given normal bicarb, normal AG with very high osmolar gap, isopropyl alcohol ingestion was suspected. IV fomepizole was started, as some hand sanitizers contain methanol. Fomepizole was continued until osmolar gap closed. No dialysis was required. Methanol level was undetectable. Acetone level high 176. Isopropranol level high 49. Patient's mental status improved with supportive measures.

Discussion: Isopropanol ingestion presents with normal bicarb, normal AG with very high OG. Treatment is usually supportive. Clinicians should be aware of falsely elevated serum cr if measured via colorimetric method due to acetone's interference. Our case presents a new challenge added to numerous challenges physicians are facing in the COVID Era.

Labs

TEST	RESULT	Reference range
Sodium,mmol/l	136	136-145
Potassium,mmol/l	5.5	3.5-5.1
Chloride,mmol/l	104	98-107
Bicarbonate,mmol/l	24	22-32
Blood urea Nitrogen,mg/dl	9	7-18
Creatinine,mg/dl	2.47	0.52-1.23
i-stat creatinine,mg/dl	0.7	0.52-1.23
Glucose,mg/dl	132	65-99
Albumin,g/dl	4.0	3.0-4.5
Lactate,mmol/l	0.6	0.4-2
Serum Osmolality,mosm/kg	341	282-302
Serum Acetaminophen mcg/ml	<2	–
Serum Salicylate,mg/dl	<1.7	10-30
Serum Ethanol,mg/dl	<3	0
B-hydroxybutyrate	0.4	0-0.29
Serum Acetone,mg/dl	176	–
Serum Isopropyl Alcohol,mg/dl	>49	0
Serum Methanol	undetectable	–
Serum Ethylene Glycol,mg/l	<10	–

PO0100

Federated Learning for AKI Prediction in COVID-19 Patients

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Background: Predictive models are trained on single-center data and are non-generalizable, and multi-center data pooling raises privacy concerns. Federated learning (FL) trains models by updating parameters from a central aggregator without sharing raw data. We used FL to predict acute kidney injury (AKI) in COVID-19 patients within 3 (AKI_3) and 7 (AKI_7) days of admission as a use case.

Methods: We selected 4035 COVID-19 patients admitted to 5 hospitals in New York City, after excluding patients with kidney failure, to train logistic regression and logistic regression with L1 regularization (LASSO) models through 3 approaches: local data, pooled data from all sites, and a FL method.

Results: Federated models outperformed local models as measured by area under the receiver operating characteristic curve (Figure 1, Table 1). SHAP plots indicate differences in feature importance between LASSO models in AKI_3 prediction (Figure 2).

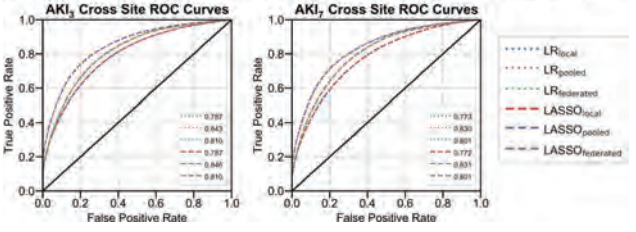
Conclusions: FL has utility for developing accurate predictive models without compromising patient data.

Funding: NIDDK Support

Table 1.

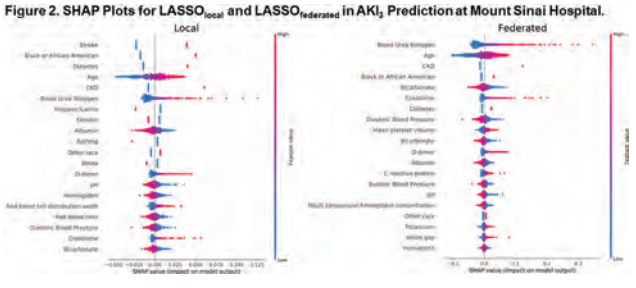
	Classifier	Model	Mount Sinai Brooklyn (AKI3: 36.6%, AKI7: 44.2%, N = 658)	Mount Sinai Hospital (AKI3: 29.6%; AKI7: 35.2%, N = 1445)	Mount Sinai Morningside (AKI3: 34.0%, AKI7: 40.4%, N = 810)	Mount Sinai Queens (AKI3: 33.0%, AKI7: 39.8%, N = 648)	Mount Sinai West (AKI3: 23.4%, AKI7: 26.6%, N = 474)	Cross Site Average
AKI within 3 Days (AKI3)	Logistic Regression (LR)	Local	0.797 (0.792 – 0.803)	0.794 (0.791 – 0.798)	0.782 (0.777 – 0.787)	0.766 (0.760 – 0.771)	0.798 (0.790 – 0.805)	0.787 (0.785 – 0.790)
		Pooled	0.831 (0.826 – 0.835)	0.840 (0.837 – 0.843)	0.818 (0.814 – 0.822)	0.850 (0.846 – 0.854)	0.874 (0.869 – 0.878)	0.843 (0.840 – 0.845)
		Federated	0.777 (0.772 – 0.783)	0.802 (0.798 – 0.805)	0.794 (0.790 – 0.799)	0.822 (0.818 – 0.827)	0.852 (0.847 – 0.857)	0.810 (0.807 – 0.812)
	Logistic Regression with L1 Regularization (LASSO)	Local	0.800 (0.794 – 0.805)	0.789 (0.785 – 0.793)	0.783 (0.778 – 0.788)	0.761 (0.755 – 0.767)	0.801 (0.794 – 0.808)	0.787 (0.784 – 0.790)
		Pooled	0.835 (0.830 – 0.839)	0.840 (0.837 – 0.844)	0.825 (0.821 – 0.829)	0.855 (0.851 – 0.859)	0.872 (0.867 – 0.877)	0.846 (0.843 – 0.848)
		Federated	0.778 (0.773 – 0.783)	0.802 (0.799 – 0.806)	0.795 (0.791 – 0.800)	0.822 (0.818 – 0.827)	0.852 (0.847 – 0.857)	0.810 (0.807 – 0.813)
AKI within 7 Days (AKI7)	Logistic Regression (LR)	Local	0.790 (0.785 – 0.794)	0.782 (0.779 – 0.785)	0.771 (0.767 – 0.774)	0.743 (0.739 – 0.748)	0.781 (0.776 – 0.785)	0.773 (0.771 – 0.775)
		Pooled	0.831 (0.827 – 0.834)	0.830 (0.828 – 0.832)	0.810 (0.807 – 0.813)	0.821 (0.817 – 0.824)	0.857 (0.854 – 0.861)	0.830 (0.828 – 0.831)
		Federated	0.783 (0.779 – 0.787)	0.796 (0.793 – 0.798)	0.791 (0.787 – 0.794)	0.792 (0.788 – 0.796)	0.843 (0.840 – 0.847)	0.801 (0.799 – 0.803)
	Logistic Regression with L1 Regularization (LASSO)	Local	0.792 (0.787 – 0.796)	0.774 (0.771 – 0.777)	0.771 (0.767 – 0.774)	0.739 (0.735 – 0.744)	0.786 (0.781 – 0.791)	0.772 (0.770 – 0.775)
		Pooled	0.833 (0.829 – 0.836)	0.827 (0.825 – 0.829)	0.814 (0.811 – 0.817)	0.822 (0.818 – 0.825)	0.858 (0.854 – 0.862)	0.831 (0.829 – 0.832)
		Federated	0.783 (0.779 – 0.787)	0.796 (0.793 – 0.798)	0.791 (0.788 – 0.794)	0.792 (0.788 – 0.796)	0.844 (0.841 – 0.847)	0.801 (0.799 – 0.803)

Figure 1. Model Performance in AKI_3 and AKI_7 Predictions.



Average model performance across hospitals by area under the receiver-operating characteristic curve.

Figure 2. SHAP Plots for $LASSO_{local}$ and $LASSO_{federated}$ in AKI_3 Prediction at Mount Sinai Hospital.



SHAP plots of LASSO local and federated models in predicting AKI within 3 days of admission at Mount Sinai Hospital.

PO0101

ANCA-Associated Glomerulonephritis and Vasculitis Following COVID-19 Vaccination in a Patient with Giant Cell Arteritis

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Introduction: A 66-year-old man with history of hypertension, chronic obstructive pulmonary disorder, latent tuberculosis, and biopsy-proven giant cell arteritis (GCA) was admitted for fevers and intermittent headaches three weeks after receiving dose 2 of the Moderna COVID-19 vaccine.

Case Description: On admission, the patient was afebrile with normal vitals and unremarkable physical examination. He noted his GCA had been in remission off treatment for two years. Labs noted new-onset microscopic hematuria and proteinuria (1.5 g/24 hr) as well as serum creatinine (SCr) of 2.2 mg/dL from 1.4 ten days prior. His sedimentation rate and C-reactive protein were also markedly elevated (119 mm/hr and 105 mg/L). Given rapidly progressive glomerulonephritis, IV Solumedrol was given for 3 days (after infection was ruled out). A kidney biopsy showed pauci-immune, necrotizing, crescentic glomerulonephritis and small vessel vasculitis (Figure 1A & 1B). Serologies returned with positive p-ANCA and high-titer myeloperioxidase antibody, confirming the diagnosis of Microscopic polyangiitis (MPA). He was transitioned to oral Prednisone and given the first of two doses of IV Rituximab. One week post-biopsy his SCr was 1.8 mg/dL.

Discussion: Renal involvement by MPA in patients with GCA is rare but has been reported. This case is unique in its temporal relation to COVID-19 vaccination. There have been reports of crescentic IgA nephropathy as well as minimal change disease following COVID-19 vaccination but we are unaware of cases of de novo or recurrent vasculitis. While causality is difficult to prove, clinicians should closely monitor patients post-vaccination.

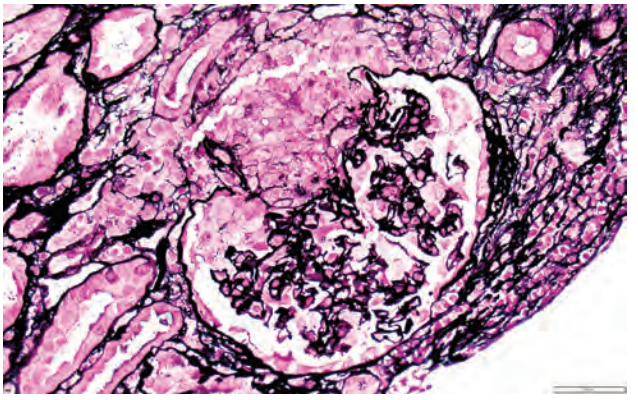

Figure 1A

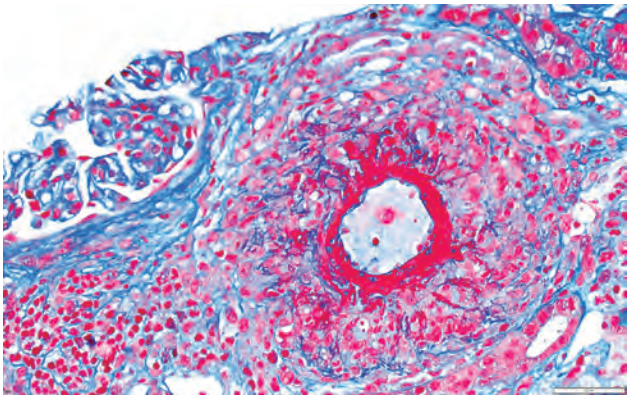

Figure 1B

PO0102

COVID-19 Pandemic Highlights Global Inequities in Chronic Hemodialysis Care: A DOPPS/ISN Survey

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Background: Patients receiving chronic hemodialysis (HD) are highly vulnerable in all settings. It is unknown whether the COVID-19 pandemic has disproportionately affected the care of chronic HD patients in low (LIC) and low-middle income (LMIC) settings. This survey aimed to identify global challenges and inequities in HD care delivery during the COVID-19 pandemic.

Methods: The Dialysis Outcomes and Practice Patterns Study (DOPPS) and the International Society of Nephrology (ISN) conducted a global online survey of HD units (HDU). Sample HDUs included DOPPS sites in China, a random sample stratified by region and HDU population, and an open invitation via ISN's membership list. The survey assessed availability of COVID-19 diagnostics and personal protective equipment, the impact of COVID-19 on HD delivery and patient outcomes from COVID-19. Responses were stratified by country income according to World Bank classification.

Results: Responses were received from 412 HDUs across 78 countries (Table 1).

Conclusions: Striking global inequities were identified in access to COVID-19 diagnostics, infection prevention, and access to routine HD care during the pandemic. Higher apparent mortality in patients on chronic HD in LICs and LMICs is likely multifactorial, reflecting poorer access to the diagnosis and care of COVID-19, as well as greater disruptions to HD delivery. Urgent action is required to address these inequities, which disproportionately affect low-income settings, exacerbate pre-existing vulnerabilities and lead to worse outcomes.

		World Bank Country Income Classification			
	All	LIC	LMIC	UMIC	HIC
	n=412	n= 15 (4%)	n=111 (27%)	n=145 (35%)	n=141 (34%)
No or low availability of diagnostic PCR for COVID-19	13.2%	61.5%	21.5%	9.4%	4.6%
Availability of same-day diagnostic PCR test for COVID 19	34.4%	21.4%	13.2%	25.5%	59.5%
Severe shortage in respirator (N95) masks	13.9%	42.9%	23.8%	4.2%	10.1%
Use of face mask beyond manufacturer's shelf life	31.1%	50%	39.6%	29.1%	24.8%
Increase in patients with missed hemodialysis treatment	32.0%	64.3%	66.3%	30.4%	5.5%
Proportion of clinics reporting >30% mortality among hemodialysis patients who contracted COVID-19	26.2%	40.0%	33.3%	25.3%	19.8%

UMIC - upper middle income country; HIC - high income country; PCR - Polymerase Chain Reaction

Distribution of responses regarding resources, practices, and outcomes during the COVID-19 pandemic, by World Bank country income classification

PO0103

A Novel Approach to Identify Nonclinical Factors That Impact Outcomes in Dialysis Patients

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Background: Nonclinical factors heavily impact quality of life and outcomes in severely ill patients. In oncology, self-reported levels of distress are routinely assessed to identify patients with higher risk of adverse outcomes and possible interventions. While similar dynamics may be at play in dialysis, this type of screening is not part of the current standard of care. In order to potentially enhance a patient-centered and holistic approach to care, we tested the use of the distress thermometer (DT) among patients dialyzing at a large dialysis organization.

Methods: Between September 2019 and January 2021, social workers administered a dialysis-adapted version of the DT. Associations between DT scores and outcomes were assessed in logistic regression models adjusted for age, race, sex, and dialysis vintage. Models in in-center hemodialysis (ICHD) patients were also adjusted for vascular access type. Additionally, outcomes were compared between patients who selected specific items off the problems lists and those who did not select that specific problem.

Results: This analysis included data from 32,174 patients (N = 25,447 ICHD and N = 6727 peritoneal dialysis [PD]). The refusal rate was 11.4% and 4.7% among ICHD and PD patients, respectively (10.0% overall). The mean ± SD DT score was 3.22 ± 2.85 for all patients, 3.29 ± 2.87 for ICHD patients, and 2.96 ± 2.75 for PD patients. High DT scores (≥7) were associated with hospitalization among both ICHD (odds ratio [95% CI] = 1.22 [1.07-1.39]) and PD (1.51 [1.11-2.05]) patients and with greater risk of PD discontinuation (1.77 [1.38-2.25]). Problems attributed to transportation and housing were associated with greater risk of missing an in-center treatment (1.36 [1.23-1.50] and 1.37 [1.23-1.52], respectively). Physical problems were associated with increased risk for hospitalization among ICHD patients (1.08 [1.06-1.10]) and PD patients (1.07 [1.02-1.11]), and missed treatments among ICHD patients (1.03 [1.01-1.04]).

Conclusions: We found that a novel screening tool may be useful in identifying dialysis patients at high risk for adverse clinical outcomes. Moreover, specific responses on this tool may help identify specific problems that are driving this risk. Practices aimed at addressing such problems could have the potential to impact quality of life and clinical outcomes.

PO0104

Cutaneous Manifestations of COVID-19 Vaccine in ESRD Patients

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Introduction: COVID-19 vaccines including Pfizer (BNT16262) & Moderna (mRNA-1273) have been authorized for emergency use by FDA since late 2020. Although there are reported cases of cutaneous manifestation post mRNA based COVID vaccines, but literature is lacking for the same in patients with ESRD. Here we report two cases of generalized cutaneous manifestations in patients with ESRD.

Case Description: A 76-year-old female with DM, HTN, SLE (in remission) & CKD 5 was admitted with bilateral leg edema & generalized skin reaction 2 weeks post receiving 1st dose of Moderna vaccine. Skin manifestations included generalized macular & blistering lesions, painful ruptured vesicles & skin weeping. Skin biopsy revealed epidermal necrosis, neutrophilic spongiosis & negative DIF. The 2nd case was a 34-year-old male with DM, HTN & ESRD on PD who was admitted with inadequate PD due to membrane failure. Also complaint of itchy, painless maculopapular rash, which was initially localized following 1st dose of Moderna vaccine but became progressive & diffuse post 2nd dose. Biopsy was nonspecific with focal epidermal squamous atypia, overall negative DIF except C3 granular staining in basement membrane. Immunological tests failed to detect ab against infectious origin. Both cases denied oral or genital ulcers, new onset diarrhea, new medication, new sexual contact or recent travel. CBC were normal & other lab tests were negative for active immunological, autoimmune or other dermatologic disease. Both cases were considered to be related to cutaneous complication of COVID vaccine in patients with ESRD. The 1st case made significant improvement post start of hemodialysis (HD), oral & topical steroid. The 2nd case gradually improved post transition to HD & use of topical steroid.

Discussion: The majority of studies looked at skin reaction to COVID19 vaccine were in non-renal disease population & reported minor, self-limited manifestations, our case report highlights a more severe & generalized skin manifestation in ESRD. Associated factors may be related to difference in vaccine response in renal patients, alteration of immunogenic reaction in uremic environment or progression due to delayed healing & concomitant presence of edema in setting of inadequate dialysis. Clinical trials for Moderna vaccine didn't include participants with renal disease & hence insufficient to determine the pharmacology & side effect profile in this population.

PO0105

Glomerular Disease in Temporal Association to SARS-CoV-2 RNA Vaccination: A Series of 16 Cases

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Background: Vaccination is considered safe in patients with chronic kidney disease. However, given the ability to activate the immune system, immunizations carry a risk of inducing inflammatory disease flares. The mass vaccination for SARS-CoV-2 provides a unique opportunity to investigate potential vaccine-associated glomerular diseases.

Methods: Kidney biopsies from patients who presented with acute kidney injury (AKI) and/or nephritic/nephrotic syndrome within three weeks of SARS-CoV-2 vaccination were included in the study (n=16). Kidney biopsies were reviewed at a single center and clinical information was provided from nephrologists for clinicopathologic correlation.

Results: Sixteen patients with a new onset of kidney disease or flare within 3 weeks of SARS-CoV-2 vaccination were identified and all had glomerular disease on biopsy. Eleven patients had two vaccine doses prior to symptom onset. The patient cohort included 6 males and 10 females, with a mean age of 58 years. Biopsy diagnoses included IgA nephropathy (n=7), minimal change disease (n=4), ANCA-associated glomerulonephritis (n=3), membranous glomerulopathy (n=1), and diffuse lupus nephritis (n=1). Thirteen patients had co-morbid medical conditions, including hypertension (n=10), diabetes mellitus (n=4), autoimmune disease (n=5), and chronic kidney disease (n=4). The most common clinical presentation was AKI with concurrent nephritic or nephrotic syndrome (n=9), followed by nephritic syndrome with preserved kidney function (n=5), nephrotic syndrome with preserved kidney function (n=1), and isolated hematuria (n=1). Three patients with AKI required dialysis. A majority of patients had an elevated serum creatinine (mean 3.4 mg/dL), 14 had proteinuria (nephrotic range in 4), 11 had hematuria, and 10 had hypoalbuminemia (mean 2.9 g/dL). Six patients had antinuclear antibodies and 4 had a positive ANCA serology at the time of biopsy. Clinical follow-up is ongoing.

Conclusions: IgA nephropathy, minimal change disease, ANCA-associated glomerulonephritis, membranous glomerulopathy, and lupus nephritis were identified with temporal association with SARS-CoV-2 vaccination. In the setting of mass vaccination, causality is unclear, but a new onset of glomerular disease should be monitored as a potential adverse event.

PO0106

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition (PGNMID) Associated with COVID-19

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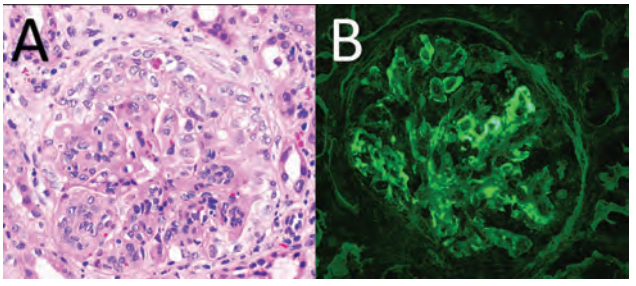
Introduction: Renal disease in COVID-19 is often due to acute tubular injury but can include multiple glomerular lesions such as collapsing glomerulopathy. This is the first reported case of COVID-19-associated PGNMID.

Case Description: A 71-year-old woman with normal baseline creatinine (Cr) was admitted with COVID-19 and discharged on oxygen and dexamethasone (Dex). She improved but returned a month later with edema and nausea. She was found to have nephrotic syndrome, hematuria, and AKI (peak Cr 8.5 mg/dL) requiring HD. Kidney biopsy revealed PGNMID with clonal IgG3-kappa. SPEP, serum free light chains (sFLC), 24h urine UPEP, bone marrow biopsy with flow cytometry, fat pad biopsy, and PET-CT

were negative for monoclonal immunoglobulin (Ig) or cell line, amyloid, or malignancy. Though symptoms had long since resolved, she was still PCR-positive for SARS-CoV-2 on nasal swab. Upon discharge she was given cyclophosphamide (Cy). Her renal function improved (Cr 2.5) and she came off HD 2 weeks later. Her outpatient oncologist opted not to continue therapy. However, 2 months later she was readmitted with nausea, dyspnea, and anasarca with recurrent AKI (Cr 6.7) and nephrotic syndrome. HD was restarted. Repeat kidney biopsy [Figure] was noted to be a "carbon copy" of the first. SPEP, spot UPEP, and sFLC were again negative. She was started on Cy, bortezomib, and Dex with similar partial response (Cr <2.5).

Discussion: PGNMID is a rare type of monoclonal gammopathy of renal significance (MGRS) that often has no detectable extrarenal monoclonal Ig or cell line. MGRS and PGNMID, though usually not postinfectious, have been reported with other viruses (e.g., viral hepatitis, parvovirus-B19). However, though causality is unclear, this is the first case of MGRS reported in association with COVID-19.



Biopsy #2 yielded 32 glomeruli, 4 globally sclerotic, 4 with crescents, and rest with highly active proliferative GN (panel A, H&E 400x), with 20% interstitial fibrosis. IF showed granular deposition restricted to IgG3-kappa (panel B, IgG3 stain 400x).

PO0107

Minimal Change Disease with Severe AKI Following the Oxford-Astra-Zeneca SARS-CoV-2 Vaccine

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Introduction: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has been associated with an increased mortality worldwide over the last year. Novel vaccines against SARS-CoV-2 offers new perspectives to control the virus. Major side effects of these vaccines, especially those affecting the kidney, appear to be uncommon. Although minimal change disease (MCD) has been reported three times following the Pfizer-BioNTech SARS-CoV-2 vaccine, no cases are described to our knowledge after the Oxford-AstraZeneca vaccine SARS-CoV-2 vaccine.

Case Description: A 71-year-old man known for dyslipidemia and a serum creatinine of 0.7 mg/dl presented with nephrotic syndrome and acute kidney injury 13 days after receiving the first injection of the Oxford-AstraZeneca SARS-CoV-2 vaccine. On admission, urine analysis revealed 2321 mg of protein per mmol of creatinine and significant hematuria as well as granular casts. His serum albumin and creatinine were 2.8 g/dl and 10.6 mg/dl, respectively. Polymerase chain reaction for SARS-CoV-2 was negative. A workup to exclude auto-immune disease, active infection and neoplasm was negative. A kidney biopsy was performed 4 days after admission and 17 days after vaccination. It showed minimal change disease with acute tubular injury. Steroid therapy was initiated. Hemodialysis was stopped 38 days after the start of therapy. At dialysis cessation, serum creatinine was 1.4 mg/dl with a marked decreasing in spot microalbuminuria.

Discussion: We suspect that this case of MCD might be related to the Oxford-AstraZeneca SARS-CoV-2 vaccine injection. To the best of our knowledge, this would be the first published case of MCD related to this vaccine. However, MCD has been described after other vaccines, including 3 cases after the Pfizer-BioNTech SARS-CoV-2 vaccine. The fact that MCD is now described with different types of SARS-CoV-2 vaccines argues on a potential mechanism not implying a direct effect of the vaccine itself, but a T cell process ignited by the vaccine that leads to podocyte injury. Since vaccination is the most promising way out of the current SARS-CoV-2 pandemic, millions of doses of vaccines will be administered around the world in a near future. Thus, nephrologists should be aware of this rare but reversible potential complication of COVID-19 vaccination.

PO0108

Focal Segmental Glomerulosclerosis (FSGS) Recurrence After mRNA COVID-19 Vaccine in a Young Adult with Kidney Transplant

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Introduction: Patient is a 21 year old Hispanic male with history of FSGS 8 years status post deceased donor kidney transplant. Other than one prior FSGS recurrence early post-transplant, which responded to plasmapheresis (PP) and rituximab, he maintained normal allograft function with stable, low level proteinuria on losartan 12.5 mg daily.

Case Description: Routine labs 1 day prior to COVID 19 mRNA vaccine series were stable with serum creatinine (sCr) 0.8 mg/dL, urine protein creatinine ratio (UPCR) 0.42 mg/mg (65 mg/dL of protein), and serum albumin 4.8 g/dL. Thirty-one days after the second COVID 19 vaccine, routine labs were significant for nephrotic range proteinuria with UPCR >6.21 mg/mg (>2500 mg/dL of protein), hypoalbuminemia (1.7 g/dL), and peak sCr of 1.3 mg/dL. Of note, he remained asymptomatic until 2 days prior to labs when noted to have periorbital and lower extremity edema associated with decreased urine output. Allograft biopsy revealed foot process effacement without definitive evidence of segmental sclerosis. Infectious workup including viral studies for SARS-CoV-2 were negative. He received methylprednisolone 1g IV for 3 days, thrice-weekly PP, rituximab 375 mg/m2 weekly x2, and an oral prednisone taper. During week 4 of PP concurrent with prednisone taper, the patient appeared clinically well with noted improvement in labs: UPCR 0.55 mg/mg, sCr 0.57 mg/dL, and serum albumin 3.5 g/dL. He is currently undergoing wean of PP and steroids.

Discussion: While there are isolated reports of new onset or recurrence of proteinuric kidney disease after an mRNA COVID-19 vaccine, to our knowledge, this is the first report of FSGS recurrence in a kidney transplant recipient. Although causality is not proven, the temporal relationship strongly suggests an association between the vaccine and the recurrence. Compared with prior reports, our patient presented somewhat later, ~1 month after dose #2 as compared to within 2 weeks after dose #1. Although the risk-benefit ratio of COVID vaccination for kidney transplant recipients remains favorable and vaccination is encouraged by national clinical guidelines, close monitoring after COVID vaccine for kidney transplant patients at risk for disease recurrence is warranted.

PO0109

IgA Nephropathy Post COVID-19 Vaccination

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Introduction: Inclusion of patients with kidney disease in COVID vaccine trials remains low. It is important to report association of disease exacerbation so that patients may undergo post vaccination monitoring. We hereby present a case of worsening IgA nephropathy temporarily associated with COVID vaccination

Case Description: 63-year-old Hispanic female with past medical history of hypertension, psoriatic arthritis presented to the hospital with gross hematuria for 6 weeks starting 3 days after 2nd dose of Pfizer COVID vaccine. Her PCP had sent her to ER 5 days after onset of hematuria as had noted a creatinine (Cr) of 1.6 with 3+ protein and >20 RBCs on urinalysis suspicious for nephritic syndrome. On review she had serum Cr of 0.5 about 4 months ago with no proteinuria or hematuria before. In the ER she was given antibiotics for urinary tract infection and outpatient referral for nephrology. She could not make the outpatient appointment and with continued gross hematuria for a month, she presented to the ER again where she was noted to have Cr of 10 mg/dl and urine protein:cr ratio of 7.3gm/gm. Renal imaging including CT urogram was normal. Renal biopsy showed IgA nephropathy, M1S0E0T1C1 with a fibrocellular crescent and acute tubular necrosis likely secondary to lyzed red cells in setting of multiple RBC casts in the tubules. She was put on 250 mg Solumedrol for 3 doses followed by 1 mg/kg of Prednisone with eventual downtrend in Cr to 4.5 in 15 days.

Discussion: There have been 2 cases reported in literature with known IgA nephropathy who developed gross hematuria post COVID 19 vaccination. SARS- COV 2 vaccines use nucleoside modified purified mRNA which does elicit higher neutralizing antibody titre and strong cluster of differentiation response leading to production of several proinflammatory cytokines. Thus, there is a concern that vaccines might exacerbate immune mediated glomerular diseases. IgA1 is involved in the pathogenesis of IgA nephropathy and patients with IgA nephropathy have higher than normal IgA1 response to other vaccines like influenza. Also while studying the antibody response to COVID 19 illness patients with IgA nephropathy are known to express higher IgA response compared to IgG and IgM along with reports of concurrent worsening of the glomerulonephritis. Nephrologists should closely follow patients with IgA nephropathy to establish the frequency of disease activation post vaccination.

PO0110

IgA Nephropathy After Receiving the Pfizer COVID-19 Vaccine: A Case Report

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Introduction: Here, we present a case of IgA nephropathy in a 22-year-old Caucasian woman with no comorbidities and prior COVID positive infection, after receiving the Pfizer vaccine for COVID-19. She initially presented to her primary care physician for an episode of gross hematuria two days after receiving the first Pfizer COVID -19 vaccine.

Case Description: She was asymptomatic for urinary tract infection, neither was she menstruating. Her renal functions were normal with a creatinine of 0.93 mg/dL. Urinalysis showed hematuria with > 50 red blood cells (RBC) per high-power field (HPF) and 2+ protein on the dipstick. She again experienced gross hematuria with > 50 RBC/HPF on urinalysis and proteinuria of 2.23g after receiving the 2nd Pfizer vaccine, at which time she was referred to the Nephrology department for further evaluation. We examined urine sediment which was significant for dysmorphic RBCs and rare granular casts. A renal biopsy showed that the majority of 14 glomeruli had global sclerosis on light microscopy, a diffuse increase of mesangium, and interstitial fibrosis with tubular atrophy. Immunofluorescence microscopy was positive for Immunoglobulin A (IgA), Lambda light chains, and anti-complement C3 antibodies. Electron microscopy revealed mesangial expansion and cellularity and peri-mesangial electron-dense deposits. These and other findings fit with the Oxford Classification of M1, S1, E0, T0, C0. Following

the biopsy, we prescribed Lisinopril 5 mg daily for control of proteinuria. We did not prescribe glucocorticoids due to the mild nature of the disease and lack of underlying inflammation. The patient continues to do well without symptoms. Her most recent labs show preserved renal function and spot proteinuria reduced to 1.3 g.

Discussion: The current case raises questions about the potential association of IgA Nephropathy with the COVID vaccine. One of several possible mechanisms includes an aberrant mucosal immune response to the initial SARS-COV-2 infection that she contracted in December 2020. This could have then predisposed her to IgA nephropathy after the administration of the vaccine. The virus' spike protein or other factors may trigger an aberrant mucosal immune IgA response which can then lead to the onset and progression of IgA nephropathy. Further case series are needed to establish a more definitive association of the COVID-19 vaccine with IgA nephropathy.

PO0111

IgA Nephropathy Flare Following COVID-19 Vaccination

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Introduction: IgA nephropathy is the most common cause of primary glomerulonephritis in people of Asian origin. It is characterized by mesangial deposition of IgA which activates Lectin and Alternative pathways that cause glomerular damage which results in hematuria and proteinuria. Untreated disease can progress to chronic kidney disease, and even end-stage kidney disease.

Case Description: We describe a case of a 28-year-old male of Chinese descent who has a biopsy-proven diagnosis of IgA nephropathy (Oxford classification M1 E0 S1 T0 C1). Patient was maintained on Losartan 100 mg daily with proteinuria under 500mg per day. He presented to the nephrology clinic for an urgent visit after he experienced gross hematuria in his urine following the second dose of his COVID-19 vaccination (Moderna). His first shot of the same vaccination was 28 days ago. After receiving his second dose, patient experienced high-grade fever (Tmax of 39F) and chills. Next morning, he again experienced high-grade fevers and on the same night, he experienced gross hematuria. On his visit to the clinic, patient was feeling back to normal. His vital signs were within normal limits. Physical examination did not reveal any crackles in his lungs or lower extremity edema. Workup revealed elevated hemoglobin in his urine with 10-20 RBCs per high power field with no WBCs. Spot urine analysis revealed urine protein-creatinine ratio of 828mg/g. A 24-hour urine collection was performed which revealed urine protein excretion to be 925 mg/24hr. All these findings were consistent with a flare of his well-established IgA nephropathy. Since patient's urine protein excretion was less than 1g/day, a decision was made to not start the patient on steroids and instead closely monitor the patient on his usual dose of Losartan 100 mg daily. Patient had not had any further complaints. He is to regularly follow up at our nephrology clinic.

Discussion: IgA nephropathy is seen in individuals with recent mucosal infection or after administration of mucosal vaccination as these phenomena result in elevated IgA secretion that can then deposit in the mesangium. Our case is unique in the sense that a non-mucosal mRNA vaccination caused IgA flare. This could indicate a possible mucosal response to COVID-19 vaccination which can be a possible mechanism as to how the vaccine protects against COVID-19. Further investigations are necessary to examine the link between the two.

PO0112

IgA Vasculitis with Renal Manifestations in a College-Aged Individual After COVID-19 Infection

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Introduction: IgA Vasculitis is one of the most common causes of primary glomerulonephritis, however there are very few cases reported in association with COVID-19. Approximately 20-50% of patients present with renal manifestations, such as IgA Nephropathy (IgAN). Here we present a case of rapidly progressing crescentic IgAN presenting after COVID-19 infection.

Case Description: A 19-year-old male presented to the emergency department with elevated creatinine after being seen in the rheumatology clinic. A timeline of the patient's symptoms is presented in Figure 1. The renal biopsy showed a rapidly progressing IgAN with 15% crescents, hence he was placed on Mycophenolate mofetil and prednisone. He was also placed on Lisinopril and low-salt diet for better control of blood pressure and fish oil for dyslipidemia. Despite aggressive immunosuppression and risk factor modification, his renal function has not improved and he continues to have nephrotic range proteinuria.

Discussion: COVID-19 is a coronavirus that enters the host cell via the ACE-2 receptor. In the kidney, ACE-2 is expressed in mesangial cells, podocytes, the parietal epithelium of Bowman's capsule, and the collecting ducts. Research suggests that the inflammatory environment from COVID-19 can activate or exacerbate immune mediated diseases in predisposed individuals. The mucosal immune response against COVID-19 might have contributed to the progression of IgAN in this patient. We plan on checking the SARS-CoV-2 anti-RBD IgA titer to see if there is a correlation between anti-RBD IgA levels and progression of kidney function. Also, the persistence of IgA antibody or memory B cells post-COVID 19 infections may have prognostic implications in advancing IgAN or even end-stage kidney disease. Although our patient has not been vaccinated, there have also been cases of patients with IgAN developing gross hematuria after receiving the mRNA COVID-19 vaccine. This suggests that the vaccine components may induce further activation of disease. This previously healthy patient is believed to have a severe and persistent case of IgAN in part due to his COVID-19 infection.

PO0113

A Biopsy-Confirmed Case of IgA Nephropathy Flare-Up with Gross Hematuria and AKI Following SARS-CoV-2 Vaccination Successfully Treated with Steroid Therapy

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Introduction: The flare of immune-mediated disease (IMDs) following SARS-CoV-2 vaccination is a rare adverse event following immunization (AEFI). A few cases of suspected IgA nephropathy (IgAN) flare-up, causing gross hematuria without an increase in Cr, have been reported, and they all resolved without treatment. Here we report a biopsy-confirmed case of IgAN flare-up with AKI following mRNA-1273 vaccination, which was successfully treated with steroid therapy.

Case Description: A 54-year-old female with history of IgAN after strep throat infection that was diagnosed with renal biopsy in 2006. Other significant co-morbidity includes obesity (BMI 31.6), hypertension, and GERD. No prior documented infection with COVID-19. She was on enalapril 20mg daily, hydrochlorothiazide 12.5mg daily, and propranolol 120mg daily. Her baseline creatinine level was 1.2. Urinalysis was positive for 2+ protein, 3+ blood, and RBC 15 /HPF. The total urine protein to Cr ratio was 1.03. Two days after receiving the second Moderna mRNA-1273 vaccine, she developed gross hematuria, which resolved in 2 days. Follow-up Cr increased to 3.04 one week after receiving the second dose of vaccine. The urinalysis showed 1+ protein, 3+ blood, RBC 50/ HPF. The total urine protein to Cr ratio was 0.67. The renal ultrasound was unremarkable. Repeat kidney biopsy showed IgA mesangial deposition, focal segmental and focal global glomerulosclerosis, mild interstitial fibrosis and tubular atrophy, and mild arteriolar hyalinosis. The patient was started on prednisone 60mg daily. Shortly after she was started on prednisone, Cr level started getting better. In 3 weeks Cr level was down to 1.7.

Discussion: This is the first reported case of biopsy-proven IgAN flare-up after SARS-CoV-2 vaccination that caused AKI. Corticosteroid is an effective treatment, promptly improving Cr. IgAN exacerbation after SARs-Cov-2 vaccination should be closely monitored for frequency and consequence to further elucidate AEFI of the novel vaccine.

PO0114

New Diagnosis of Glomerulonephritis and Relapse of Prior Glomerulonephritis Post mRNA COVID-19 Vaccination

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Introduction: Messenger RNA COVID-19 vaccine is more effective than traditional vaccines due to superior immune activation. However, the impact of mRNA COVID-19 vaccine on glomerulonephritis (GN) is limited. We report 4 cases of patients who developed new or had relapse of GN post vaccination.

Case Description: Case 1: A 43-year-old male with prior COVID-19 infection and baseline serum creatinine (SCr) of 1.2 mg/dl received Moderna vaccine 9 months after recovering from COVID-19 infection. Two weeks after the 1st dose, SCr increased to 2.5 mg/dl. He received 2nd dose 2 weeks later and SCr 3 days after was 2.7 mg/dl. Urinalysis (UA) showed 21-30 RBC/hpf and 24 hr urine protein (UP) was 14.4 g/d. A kidney biopsy revealed IgAN with moderate interstitial nephritis. He was treated with prednisone and ramipril. Case 2: A 66-year-old male with atrial fibrillation with baseline SCr 1.1 mg/dl received 1st dose of Moderna vaccine and two weeks later SCr was 1.5 mg/dl. Eight weeks after the 2nd dose, SCr was 2.4 mg/dl. UA showed 51-100 RBC/hpf and 24 hr UP 1.2 g/d. A kidney biopsy revealed IgAN with acute tubular injury and RBC casts. He was treated conservatively. Case 3: A 29-year-old female with minimal change disease who had been in remission for 2 years, received 2 doses of Pfizer vaccine. Three weeks after the 2nd dose, she developed leg edema with albumin 2.2 g/dl, 24 hr UP 10 g/d, and SCr 0.6 mg/dl. A repeat kidney biopsy showed focal segmental glomerulosclerosis, tip variant. She was treated with prednisone and tacrolimus. Case 4: A 39-year-old male with PLA2R+ membranous nephropathy who was in remission and off immunosuppressive therapy for 1.5 years received 2 doses of Pfizer vaccine. Two weeks after the 2nd dose, he developed leg edema with SCr 1.1 mg/dl, albumin 2.0 g/dl, and 24 hr UP 8.7 g/d. Tacrolimus was re-initiated.

Discussion: New cases and relapse of GN can present shortly after mRNA COVID-19 vaccination. Messenger RNA COVID-19 vaccine may be associated with reactivation of known glomerulonephritis or unmask presence of previously undiagnosed GN such as IgAN possibly due to potent immune activation. However, mechanism remains unknown and additional studies are needed.

PO0115

Impact of the COVID-19 Pandemic on Kidney Diseases Requiring Renal Biopsy: A Single-Center Observational Study

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Background: The coronavirus disease-2019 (COVID-19) pandemic impacted healthcare services for kidney disease patients. Lockdown and social distancing were mandated worldwide, resulting in closure of medical services. The diagnosis of various kidney diseases may have been delayed during the COVID-19 pandemic because non-urgent tests and visits were postponed due to closure of medical services during the lockdown.

Methods: We here report the impact of the COVID-19 pandemic on a total number of 209 native kidney diseases requiring renal biopsy for diagnosis in a retrospective observational study from a tertiary hospital in Germany.

Results: The lockdown period in March and April 2020 primarily affected patients admitted to the normal medical ward with a compensatory increased rate of renal biopsies in the postlockdown phase. In addition, there was a shift towards more patients admitted with hemoglobinuria during the COVID-19 pandemic. This phenomenon of an increased number of patients with hemoglobinuria during the COVID-19 pandemic was specifically observed in a subgroup with hypertensive nephropathy requiring renal biopsy, not attributed to the COVID-19 lockdown period itself.

Conclusions: To our knowledge, this is the first report of identifying a subpopulation susceptible to closure of medical services during the COVID-19 pandemic and diagnostic delay of specific kidney diseases. Therefore, the COVID-19 pandemic should be regarded as a risk factor especially in patients with diseases other than COVID-19 primarily admitted to the normal medical ward.

PO0116

Tip Lesion Variant of Focal and Segmental Glomerulosclerosis (FSGS): A Case Report in a Patient with COVID-19

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Introduction: Acute kidney injury (AKI) is a common complication of SARS-CoV-2 infection. Published cases report acute tubular injury as the most common pathologic finding in these patients. Glomerular disease has been reported in a minority of patients, with collapsing focal segmental glomerulosclerosis being the most common. Nonetheless, the existing evidence is sparse and inconclusive. The authors present a case of a patient diagnosed with a tip lesion variant of focal and segmental glomerulosclerosis (FSGS) and concomitant SARS-CoV-2 infection.

Case Description: A 43-year-old African woman, with no known past medical history, presented to the emergency department with a 6-day history of fatigue, headache, cough, hypoageusia, myalgia, dyspnea, nausea and vomiting. Laboratory tests confirmed SARS-CoV-2 infection. Despite fluid therapy, there was an elevation of serum creatinine from 1.1 to 1.6mg/dl and the urinalysis was positive for protein (4) and blood (2). The urinary sediment revealed 3 red blood cells per high-power field. The urinary protein/creatinine ratio was approximately 13 g, subsequently confirmed with a 24-hour urine collection (13445 mg/24hours). All immunological tests were negative with the exception of hepatitis B serology (positive for HBV past infection). Renal ultrasonography showed a right kidney of 106 mm and a left kidney measuring 99 mm with important reduction of corticomedullary differentiation. After cure criteria for COVID-19, the proteinuria was 1022 mg/24h. The kidney biopsy revealed a tip lesion variant of focal and segmental glomerulosclerosis (FSGS). Low dose angiotensin converting enzyme inhibitors were started but no corticotherapy due to spontaneous regression of proteinuria. The patient returned home 20 days after hospitalisation. After 1 month, serum creatinine levels and 24-hour urine protein decreased to 1.1 mg/dl and 1060 mg, respectively.

Discussion: To our knowledge, this is the first case report of a patient with tip lesion variant of focal and segmental glomerulosclerosis (FSGS) possibly associated with COVID-19 disease. More data from kidney biopsies will further elucidate about pathologic processes associated with kidney injury and glomerular involvement in SARS-CoV2 infection.

PO0117

Cause or Not: IgA-Dominant Infectious-Related Glomerulonephritis in a Patient Infected with COVID-19

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Introduction: IgA dominant infectious related glomerulonephritis (IGAD-IRGN) is an uncommon variant of IRGN. It has been mostly associated with S.aureus infections. In the COVID Era, thre has been one case of IGAD-IRGN related to COVID. This is a case of IGA-IRGN in a patient infected with COVID-19.

Case Description: 51 y/o male with no previous medical history who presented with a 3 day history of generalized swelling. Patient had no known medical problems and was not taking any medications. He reported drinking 3 beers daily. Denied any recent illness or sick contacts. At ED, the patient was found with anasarca and uncontrolled blood pressure. Initial blood tests showed normal renal function with hypoalbuminemia (2.9g/dL). U/A showed active sediments and nephrotic range proteinuria of about 4 g/day. Proteinuria workup was done, including serologic workup. Labs were remarkable for elevated ESR (105), low C4 (12), normal C3 (95) and elevated RF (44). ANA, HIV, HCV, light chain ratio, cryoglobulins and ANCA were negative. UPIEP showed faint IgG kappa. CXR showed hazy interstitial opacities with a perihilar distribution. Pre-biopsy COVID molecular testing came back positive. He was diuresed aggressively and received losartan for BP control. A kidney biopsy was performed and revealed MPGN pattern with IF strongly positive for IgA in addition to weaker staining for C3, and IgG. EM showed subendothelial humps with few mesangial and subepithelial deposits. The diagnosis of IgA-dominant immune complex-mediated glomerulonephritis consistent with IRGN was made.

Discussion: IGA-IRGN is a rare variant of IRGN that has been mostly associated with S. aureus infections. In this case, the recent COVID-19 infection in this patient could reasonably explain the finding of IGAD-IRGN on kidney biopsy. IGAD-COVID-related GN has been reported only once in the literature. Up until recently, most cases of COVID related kidney injury have been associated to ATN and collapsing FSGS. A immunohistochemistry test for COVID in kidney tissue was sent, which is pending at the time of this submission. If confirmed positive, this could be the second confirmed case COVID related IGAD-IRGN. It is important for nephrologists to include IGAD-IRGN in the differential diagnosis in a COVID patient with nephrotic syndrome. Renal Biopsy is of utmost importance for diagnosis.

PO0118

De Novo Henoch Schönlein Purpura (HSP) Post Kidney-Pancreas Transplant Triggered by COVID-19 Infection

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Introduction: Histologic recurrence of immunoglobulin A (IgA) nephropathy after transplant is common, however, de novo development of HSP is rare post-kidney transplant. We describe a case of HSP with cutaneous and renal allograft findings, triggered by COVID-19 (SARS-CoV-2) infection.

Case Description: A 53-year-old African American (AA) male with history of ESRD secondary to diabetic nephropathy, underwent simultaneous pancreas-kidney transplant. Three months later, he presented with rash on the upper and lower extremities, hand and wrist pain, acute kidney injury and new onset nephrotic syndrome with 6.6g proteinuria and microscopic isomorphic hematuria. He had detectable SARS-CoV-2 RNA in the nasopharyngeal specimen and mild multifocal pneumonia treated with steroids and Remdesivir. Serologic work-up for nephrotic syndrome was negative. A skin biopsy demonstrated leukocytoclastic vasculitis. Renal allograft biopsy showed membrane proliferative and sclerosing glomerulonephritis with dominant IgA staining by immunofluorescence, consistent with IgA nephropathy. He received pulse dose steroids with improvement in kidney graft function and reduction of his proteinuria to 0.6 g four months after steroid treatment.

Discussion: We postulated that our patient developed de novo HSP and nephrotic syndrome as a result of COVID- 19 infection. Podocytopathy and nephrotic syndrome linked to viral infection have been well described, particularly in AA patients with high-risk APOL1 genotype. Key cytokines known to be elevated in COVID19 infection can drive autoimmune responses, such as interferon and IL-6. Cytokine release, uncontrolled activation of both innate and adaptive immune cells, along with genetic variants likely predispose patients to the development of glomerular disease mediated by various immune mechanisms. Published biopsy series consistently demonstrate acute tubular injury as the most common renal manifestation of COVID-19, however, new onset autoimmune diseases such as IgAN may also be triggered by COVID infection. HSP can be a rare complication of COVID-19, and also rarely occurs post-transplant. Glomerular disease and systemic autoimmunity should be recognized as a complication of COVID-19, regardless of the presence or absence of pulmonary findings.

PO0119

COVID-19 Infection in Kidney Transplant Recipients: A Single-Center Case Series of 10 Cases from Dominican Republic

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Introduction: The coronavirus disease 2019 (COVID-19) has caused tremendous impact globally due to the significant morbidity and mortality caused by this virus. It is currently known that the probability of becoming seriously ill from this disease is higher in older adults, in people with pre-existing comorbidities, and those with a suppressed immune state. Therefore, transplant patients are not the exception. Considering the importance of this topic and the scarce information on the outcome of this type of patient, especially in Latin America, this series of cases is focused on our experience with 10 kidney transplant patients hospitalized for COVID-19.

Case Description: The age range of the patients was 41 to 68 years, where 8 of these were men. The most common admission symptoms were fever (80%), dyspnea (70%), myalgia/arthralgia (50%), and headache (50%). The most prevalent laboratory findings were lymphocytopenia and increased inflammatory markers such as D-dimer, LDH, procalcitonin, erythrocyte sedimentation, and ferritin. General management included supportive treatment, statins, and antithrombotic therapy, while the specific treatment options were hydroxychloroquine, antivirals, corticosteroids, intravenous ig, tofacitinib, and convalescent plasma. All the patients improved and were discharged. Two of them went to the ICU and only one required mechanical ventilation. The majority of the patients (70%) remained with their baseline immunosuppression without dose reduction or suspension.

Discussion: kidney transplant recipients are more susceptible to infections, along with increased disease severity. At the same time their immunosuppressed state may reduce the inflammatory response following this type of infection. Decisions were based on stopping or attenuating the viral load and the systemic inflammation caused by this virus, but at the same time protecting against acute allograft rejection and the coinfection with other pathogens. Our findings suggest that the use of statins and antithrombotic prophylaxis in all hospitalized transplant patients may be beneficial to reduce the risk of mortality in patients with COVID-19 infection. Also, the maintenance of immunosuppressive therapy was not associated with worse outcomes.

PO0120

ANCA Vasculitis Presenting as Hemoptysis Post COVID-19 Infection

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Introduction: COVID-19 infection has been suggested to be a trigger for a de-novo autoimmune response. This case represents one of a few reported cases of ANCA-vasculitis developing after a COVID infection.

Case Description: A 41-year-old female with a history of chronic sinusitis (not vasculitis related), obesity, right pulmonary sequestration, and mild COVID-19 infection 1-month prior manifesting as only mild cough with loss of taste and smell, was admitted with a 2-week history of progressive cough productive of blood-tinged sputum and lower extremity neuropathy. CTA of her chest showed air space opacities in right lower lobe concerning for bacterial superinfection in a host with altered pulmonary architecture. She was treated for presumed community acquired pneumonia. A week later, she presented with worsening hemoptysis and respiratory failure requiring intubation, which escalated quickly to needing extracorporeal membrane oxygenation (ECMO). Extensive bilateral airspace infiltrates due to diffuse alveolar hemorrhage and a PR3-ANCA level of 175 U/ml were strongly suggestive of a new diagnosis of ANCA-vasculitis (granulomatosis with polyangiitis). Her renal function remained normal, and urine sediment had no findings to indicate an ongoing concurrent nephritic process. She was given high dose pulse intravenous steroids, recombinant factor VII, 7 sessions of daily plasma exchange, intravenous tranexamic acid, and 1 dose of Cytoxan 500 mg/m2. She briefly had clinical improvement and required decreased ECMO support, but unfortunately, she later developed worsening pulmonary hemorrhage and hypotension, which was attributed to acute respiratory distress syndrome and thrombocytopenia, as opposed to immune mediated capillaritis. After 2 weeks of treatment, she was terminally decannulated.

Discussion: This is a rare case of ANCA-vasculitis likely triggered by COVID-19 infection. The presence of peripheral neuropathy indicates that she probably had extrapulmonary manifestations of vasculitis, although she had no evidence of renal involvement. This case report demonstrates that a high index of suspicion is needed for a new diagnosis of ANCA-vasculitis in patients with a prior history of COVID-19 infection to allow for prompt diagnosis and appropriate management.

PO0121

Deep Learning for Subphenotype Identification in COVID-19-Associated AKI

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Background: Acute kidney injury (AKI) is common in COVID-19 and associated with increased adverse outcomes. COVID-associated AKI (COVID-AKI) pathophysiology is heterogenous, and deep learning may discover subphenotypes.

Methods: We used data from 5 New York City hospitals from adults admitted between March '20-March '21 with COVID and AKI, excluding patients with kidney failure. An autoencoder compressed 58 features containing comorbidities, the first laboratory values and vital signs within 48 hours of admission for unsupervised *K*-means clustering. Outcomes were mortality, dialysis, mechanical ventilation, and ICU admission.

Results: We identified 1634 patients with COVID-AKI and discovered 3 subphenotypes. Subphenotype one had 576 patients (35%); two had 635 patients (39%), and three had 423 patients (26%) (Table 1). Subphenotype three had the lowest median blood pressures, highest median BMI, and highest rates of all outcomes. (Figure 1)

Conclusions: There are distinct subphenotypes in COVID-AKI indicating the heterogeneity of this condition.

Funding: NIDDK Support

Table 1. Demographics of COVID-Associated AKI Subphenotypes.

	Overall	Subphenotype 1	Subphenotype 2	Subphenotype 3	P-value
N (%)	1634	576 (35.3%)	635 (34.1%)	423 (25.6%)	
Age, median (IQR)	73.0 [63.0,83.0]	74.0 [63.0,84.0]	75.0 [65.0,83.0]	69.0 [59.5,78.0]	<0.001
Female, n (%)	936 (57.3)	324 (56.2)	318 (50.1)	294 (69.5)	<0.001
Race, n (%)					
Asian	63 (3.9)	11 (1.9)	31 (4.9)	21 (5.0)	0.001
African American	489 (29.9)	190 (33.0)	187 (29.4)	112 (26.5)	
White	427 (26.1)	158 (27.4)	153 (24.1)	116 (27.4)	
Unknown	655 (40.1)	217 (37.7)	264 (41.6)	174 (41.1)	
Ethnicity, n (%)					
Hispanic/Latino	379 (23.2)	100 (17.4)	183 (28.8)	96 (22.7)	<0.001
Non-Hispanic/Latino	995 (60.9)	351 (60.9)	390 (61.4)	254 (60.0)	
Unknown	260 (15.9)	125 (21.7)	62 (9.8)	73 (17.3)	
Clinical Outcomes, n (%)					
ICU Admission	651 (39.8)	174 (30.2)	236 (37.2)	241 (57.0)	<0.001
Dialysis	147 (9.0)	49 (8.5)	57 (9.0)	41 (9.7)	0.811
Mechanical Ventilation	220 (13.5)	74 (12.8)	72 (11.3)	74 (17.5)	0.014
Mortality	886 (54.2)	298 (51.7)	335 (52.8)	253 (59.8)	0.026

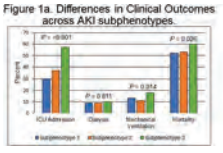

Figure 1a: Proportions of ICU admission, dialysis or mechanical ventilation usage, and mortality across subphenotypes. Figure 1b: Top 4 features with the largest log-transformed differences between subphenotypes 1 and 3.

PO0122

An ISN-DOPPS Survey of the Global Impact of COVID-19 Pandemic on Home Peritoneal Dialysis Services

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Background: Home dialysis may be able to minimize SARS-CoV2 exposure risks. The pandemic may have introduced unique challenges related to supply disruption and care delivery changes. We sought to assess the global burden of COVID-19 on peritoneal dialysis units (PD) and understand PD unit practice changes during this time.

Methods: The Peritoneal Dialysis/Dialysis Outcomes and Practice Patterns Study (PDOPPS/DOPPS) and International Society of Nephrology (ISN) administered a web-based survey (1) to dialysis units selected based on a random sample stratified by region (November 2020 – March 2021), and (2) to an open invitation via ISN's membership list and social media (March 2021). Responses were compared across 10 ISN regions.

Results: Returned surveys included 167 PD facilities across 52 countries. Changes in several care domains including clinic communication and frequency, labwork frequency, method of communication, masking policies, changes in handling of PD effluent among infected individuals, PD supply disruption, access to methods of PD catheter insertion and frequency of new patient training are highlighted (table).

Conclusions: Variability exists in routine PD care, and the availability and use of PPE, disruption in PD supplies among the different regions reflecting the availability of the resources and infrastructure differences. LMIC tended to be more severely impacted—this gap needs to be addressed in anticipation of future pandemics for treatment continuity. Although remote technology use among PD patients to communicate with their physicians has increased during the pandemic, optimal communication frequency, methods and schedule of routine bloodwork needs to be better elucidated.

Table: Change in PD facility practices from before the COVID-19 pandemic by ISN region, as reported by medical directors at each participating site

		ISN Region								
Survey question	All	Africa	Eastern & Central Europe	Western Europe	Middle East	Nth & Russia	South Asia	Oceania & South East Asia	North & East Asia	North America & Caribbean	Latin America
Survey responses, N facilities (n countries)	187 (32)	12 (4)	39 (9)	16 (8)	6 (3)	10 (4)	10 (3)	17 (2)	58 (4)	8 (3)	41 (12)
COVID-19, 1+ confirmed/suspected case	58%	91%	51%	69%	100%	80%	33%	6%	58%	38%	73%
Routine in-person visit frequency, decrease	45%	50%	69%	60%	60%	58%	13%	12%	22%	50%	0%
Communication frequency with patients, decrease	7%	0%	0%	13%	0%	40%	0%	0%	7%	25%	3%
Communication tools to use during pandemic											
Phone	98%	100%	100%	93%	100%	100%	100%	94%	99%	88%	100%
Text	73%	90%	84%	100%	100%	70%	50%	38%	89%	71%	58%
Email	50%	40%	68%	53%	50%	44%	67%	6%	43%	14%	72%
Other (remote monitoring, video chat, health portal)	68%	80%	58%	73%	100%	38%	89%	69%	71%	0%	78%
Increase in communication tools (non-phone) to patients during pandemic	98%	9%	21%	53%	50%	50%	11%	25%	43%	75%	37%
Lab frequency, increase	28%	20%	63%	47%	25%	44%	13%	31%	25%	38%	15%
Laparoscopic surgical procedures, reduced[a]	27%	88%	26%	21%	50%	17%	0%	9%	37%	50%	14%
Non-surgical gen. procedures, reduced[a]	20%	29%	25%	27%	0%	50%	0%	27%	25%	25%	0%
Number of new patients being trained for PD											
Training stopped	6%	0%	16%	13%	0%	0%	0%	0%	7%	38%	5%
Decreased	27%	60%	11%	40%	75%	40%	22%	13%	58%	38%	13%
Stayed the same	54%	40%	53%	47%	0%	50%	44%	81%	46%	25%	68%
Increased	12%	0%	21%	0%	25%	10%	33%	6%	11%	0%	13%
Use of masks for PD connections											
Masking required before task did not change	86%	90%	95%	93%	80%	89%	88%	100%	82%	88%	85%
Mask not required before and did not change	8%	20%	5%	7%	0%	0%	13%	0%	15%	0%	10%
Some change in policy	4%	20%	5%	0%	20%	11%	0%	0%	4%	13%	5%
Facility had to implement a mask reuse program for PD connections	15%	22%	11%	13%	20%	10%	13%	13%	11%	0%	14%
Modifications in procedures for handling of effluent in COVID-19 positive patients	29%	33%	34%	33%	40%	22%	14%	0%	38%	50%	24%

a. Restricted to facilities with some pre-pandemic laparoscopic use
b. Restricted to facilities with some pre-pandemic non-surgical percutaneous (skin,) procedure use
c. Includes masking during all exchanges or masking only if patient is symptomatic

Hence, work-up to exclude nephritic syndrome was requested. Reports were remarkable for positive p-ANCA and presence of MPO antibodies. Workup for GBM antibodies came back negative. Patient was started on intravenous steroids. Renal biopsy showed evidence of ANCA mediated pauci immune GN with crescents. Further on, she was transitioned to oral steroids and Rituxan where improvement of renal function was observed.

Discussion: While ANCA associated GN in SARS-CoV-2 is rare, the incidence of COVID19 cases is on the rise. The incidence of other potential complications are yet to be identified. Thus, it is important to understand and study the disease's pathophysiology to extrapolate possible complications. This will assist in the early detection of disease and help improve patient's prognosis. Also, will prevent development of chronic repercussions in patient's renal function.

PO0123

Comparison of Rates of AKI Between Two COVID-19 Surges in Hospitalized Patients in the Bronx

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Background: The incidence of AKI in COVID 19 is very variable across the world. In New York City it was as high as 36% in a large series in early 2020. However, the incidence of AKI during the second surge between Oct of 2020 to early 2021 is unknown. In this study, we compared these two COVID-19 periods for the incidence of AKI amongst hospitalized patients.

Methods: This was a multi-center, retrospective cohort study of patients hospitalized with COVID-19 between March 1st and July 16th 2020 (n=1,719), and between October 15th 2020 and February 28th 2021(n=997) in two NYC public hospitals, (total n= 2,716). Patients < 18 years, with End Stage Kidney Disease or a kidney transplant were excluded. Chi-squared test and Fisher's exact test were used to compare the clinical characteristics of the patients. A p-value less than 0.05 was considered statistically significant.

Results: The baseline clinical characteristics and demographics of the two surges were similar. The incidence of AKI as defined by KDIGO criteria, during admission decreased from 28.7% in the first surge to 18.6% in the second surge ($p<0.0001$). This trend was seen both at encounter level too as shown below. For laboratory characteristics, more patients with hypernatremia and with peak CRP > 50 (Ref range: <50) presented in the first surge than the second surge ($p<0.0001$). No differences in the peak potassium and peak D-Dimer, or ICU admission rates were seen between two surges. However, significantly more AKI patients in the first surge were on mechanical ventilation as compared to the second surge ($p=0.0196$).

Conclusions: To our knowledge this is the first comparison reported between rates of AKI in hospitalized patients with COVID-19 during two different surge periods. The difference may be related to less severe disease during the second surge, though ICU admission rate was the same. Better care established by the time of the second surge and improved therapeutics such as early use of anti-viral agents, corticosteroids, and anticoagulation may have contributed to better outcomes. Improvement in care of COVID-19 in the second surge may have contributed to a decline in the incidence of AKI. Future studies are needed to see if this trend towards lower AKI incidence continues.

PO0124

COVID-19-Induced P-ANCA-Associated Nephritic Syndrome in a Woman Without Respiratory Involvement

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Introduction: Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected our population worldwide leading to a global pandemic. The most common manifestation was infection to the lungs leading to respiratory failure. As the infection continued to spread, other complications started to emerge. Studies have identified involvement of other organs such as heart and kidneys. It has been observed that patients with severe infection are debuting with renal failure. The most common lesion is acute tubular necrosis (ATN) but other causes such as endotheliitis, nephrotic syndrome and glomerulonephritis (GN) have been observed. ANCA associated GN is a rare manifestation of SARS-CoV-2 infection that must be differentiated from ATN. Only two cases of ANCA associated vasculitis have been reported. They were both male and presented with ANCA associated GN responsive to immunosuppressive therapy.

Case Description: Case of a 65 year old female patient with medical history of asthma and dyslipidemia presented to the hospital with complaints of recurrent painless hematuria. Physical examination was unremarkable. Initial laboratory work up was remarkable for acute kidney injury accompanied by the presence of pyuria, hematuria and proteinuria. There was evidence of leukocytosis and anemia. PCR test for COVID19 came back positive. Renal imaging showed thickening of the urothelium at the renal pelvis with parenchymal echogenicity. After multiple efforts there was no significant improvement.

PO0125

AKI Secondary to Atypical Hemolytic Uremic Syndrome Caused by COVID-19

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Introduction: Atypical Hemolytic Uremic Syndrome(aHUS) can be triggered by viral infections. So far there has been little data on COVID 19 infection-causing aHUS. We present one such case of acute kidney injury(AKI) secondary to aHUS with COVID-19 infection and its outcome.

Case Description: A 55-year-old woman presented with altered mental status and shortness of breath from 2-3 days. The patient tested positive for the COVID-19 virus. Labs showed creatinine of 4.8g/dl from a baseline of 0.8g/dl, with a hemoglobin of 8.9g/dl and a platelet count of 20,000/uL. Peripheral smear showed evidence of a large number of schistocytes and thrombocytopenia. Haptoglobin and reticulocyte counts were 28mg/dl, reticulocyte count 3.8% respectively. In view of her symptoms and laboratory findings, there was high suspicion for Thrombotic thrombocytopenic purpura (TTP). Her PLASMIC score was 6. Treatment with plasma exchange therapy (PEX) and steroids was initiated but there was no significant clinical improvement. An ADAMSTS13 level was sent prior to the initiation of PEX and resulted at 65%, ruling out the diagnosis of TTP. Due to lack of evidence of TTP eculizumab was started for suspected aHUS. She responded remarkably well (within days) with mentation returning to baseline, hemoglobin stabilizing, platelet slowly trending towards normal and peripheral smear, labs showing no signs of hemolysis, and an improvement in her RFP. At 5 month follow-up, the patient eventually progressed to end-stage renal disease had to be placed on regular dialysis.

Discussion: AHUS is a rare variety of thrombotic microangiopathy(TMA) which results in a classic triad of Coombs negative hemolytic anemia, renal injury, and thrombocytopenia. aHUS has a mortality rate of 25%. 50% of patients eventually progress to ESRD or have irreversible brain damage. Multiple triggers have been identified including various non-enteric infections, viruses, drugs, malignancies, transplantation, pregnancy, and other underlying medical conditions. At the time of writing this case report, there is only one other case report of COVID-19 virus-induced aHUS resulting in AKI. In aHUS renal damage is thought to be caused by microthrombi formation in the kidney vasculature. Endothelial damage is further escalated by anaphylatoxins produced by complement activation. aHUS induced AKI is an alternate mechanism for COVID -19 to cause AKI requiring eculizumab for optimal treatment.

PO0126

Cryoglobulinemia in the Setting of COVID-19 AKI

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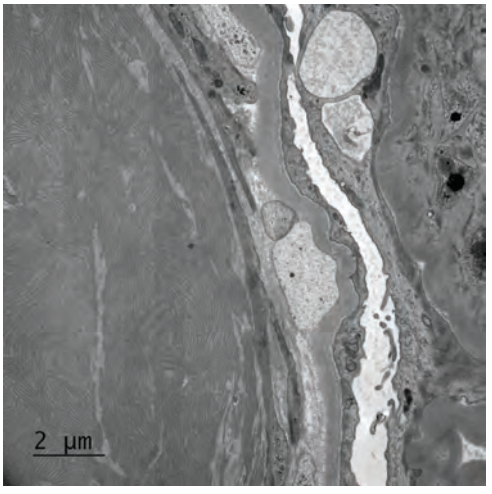
Introduction: COVID19 is due to SARS-CoV-2 a single stranded RNA virus with respiratory and epithelial cell targets. As COVID19 has reached pandemic proportions, complicating AKI is common. Pathogenesis is varied and multifactorial but acute tubular injury is most common. Glomerular pathology is possible but not well defined.

Case Description: 66YOM with HTN, Stage III CKD, & COVID19 hypoxemic respiratory failure complicated by AKI & nephritic syndrome. Cr peaked at 5mg/dL. He required CRRT for volume overload & acidosis. Labs showed low C3 & type I cryoglobulinemia. IgGλ monoclonal protein on SPEP. Extensive cryoglobulinemic GN on renal bx with IgGλ immunofluorescence. Negative Congo red stain. Microtubular deposits indicative of cryoglobulins on EM. He received pulsed solumedrol then 5 sessions of PLEX. Renal recovery with good urine output, dialysis discontinued. Cr down to 2.2mg/dL post PLEX.

Discussion: Cryoglobulinemia is due to cold immunoglobulin precipitation. Type I is associated with malignancy or hematologic disease and Types II & III have infectious triggers. Our patient had Type I IgGλ cryoglobulinemia without evidence of malignancy. BM bx had 10% abnormal plasma cells, perhaps due to plasma cell dyscrasia of cryoglobulinemia. A prior case series reported COVID19 incident MGUS. Patients had monoclonal IgGλ or IgGκ but no mentioned renal injury. They hypothesized gammopathy due to immune hyperactivation. Expounding, our patient's renal manifestations fit a Hemophagocytic Lymphohistiocytosis pattern so we hypothesize they are due to COVID19 associated hyperinflammation and cytokine release. Our case illustrates the benefit of biopsy to identify additional treatment options and the reality that timely biopsy can't always be safely obtained. In COVID19 patients respiratory or hematologic status can make biopsy unsafe which may limit defining associated glomerular pathology.



PO0127

Antibody and T Cell Reactivity Response After SARS-CoV-2 BNT162b2 mRNA Vaccine in Hemodialysis Patients: A Single-Center Experience from Sweden

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Background: The immune system is affected by uremia. Patients with end-stage kidney disease (ESKD) on hemodialysis treatment (HD) are vulnerable to infections, may have suboptimal response to vaccination and are at increased risk of contagious infections due to many health care contacts. They also have a high mortality from Covid-19 infection.

Methods: In 50 patients (mean age 69.4 years, 62% men) with ESKD and HD at Uppsala Academic Hospital, Sweden, administration of vaccine began in late Dec 2020 and the immune response was followed up four months later, in April/May 2021. IgG antibody test against Covid-19 (SARS-CoV-2) was performed against the nucleocapsid antigen (anti-N), positive only after illness, and against Spike antigen (anti-S) positive both after illness and after vaccination (quantitative method in routine diagnostics at the department of microbiology, Uppsala). T-cell reactivity testing against the Spike protein using ELISPOT technology measuring Interferon-gamma activity was performed at ABC-labs, Solna.

Results: Out of 50 patients IgG antibodies to anti-S were detected in 37 (74%), 5 (10%) had a limit response and 8 (16%) were negative after two doses of vaccine. T-cell responses were detected in 29 (58%) and in 21 (42%) no response was detected. Of the 37 patients with antibody responses to anti-S, 25 (68%) also had a measurable T-cell response, 2 (40%) of 5 with limit value for antibody response and 2 (25%) of 8 had no antibody response. 27 (54%) had both an antibody and T-cell reactivity response. IgG antibodies to anti-N indicating a previous Covid-19 disease after 2 doses of vaccine were detected in 7 (14%) patients. 3 patients (6%) had tested PCR-Covid-19 positive before vaccination, 2 (4%) became positive between doses one and two. 4 (8%) had positive tests after two injections and all of them developed a mild disease.

Conclusions: A majority of patients with ESKD and HD develop a B- and/or T-cell response after vaccination against Covid-19 but approx. 20 % had a very limited immunological response. In a clinical setting it is justified to measure the antibody response after vaccination to identify patients are not protected and where to need to take other measures to protect them from infection. In these patients, a third vaccine dose with another type of vaccine could be justifyable.

Funding: Clinical Revenue Support

PO0128

COVID-19 mRNA Vaccine-Associated Autoimmunity Presenting as Minimal Change Disease and Membranous Nephropathy

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Background: Vaccine-triggered complications, including autoimmune diseases and minimal change disease (MCD), were reported during recent COVID-19 vaccine rollout. Anti-nephrin autoantibodies were described in nephrotic syndrome (NS) with kidney biopsy (Kbx)-proven MCD. Therefore, we examined patients with COVID-19 vaccine-associated NS for anti-nephrin autoantibodies.

Methods: 5 patients presenting with nephrotic-range proteinuria 1-3 weeks after COVID-19 vaccine and a KBx were identified (3 Pfizer/BioNTech, 2 Moderna). Past medical history and lab tests including serum creatinine (sCr), urine protein-to-creatinine ratio (UPCR), and serological workup were recorded. KBx were routinely evaluated by light microscopy (LM), immunofluorescence microscopy (IF), and electron microscopy (EM), followed by confocal examination of relative IgG and nephrin localization in all patients; serological studies for anti-nephrin antibodies using human glomerular extract and recombinant nephrin extracellular domain were performed using plasma available on 2 patients.

Results: In all patients, sCr was 0.5-1.2 mg/dl and UPCR 4.5-7.6 g/g. 1 patient had MCD in remission diagnosed 6 months prior; others had no relevant PMH. All workup was negative, except low positive ANA in 2 patients. On KBx, diagnosis of MCD was made in 4 and stage I membranous nephropathy (MN) in 1 patient(s) (serum albumin 2.0-2.4g/dl in MCD and 3.6g/dl in MN patient(s)); all had mild chronic changes. All 4 MCD patients had fine granular punctate podocyte staining for polyclonal IgG colocalizing with nephrin by IF and diffuse FPE by EM; in 1 patient plasma was saved during NS and was serologically positive for anti-nephrin. The MN patient had 3+ fine granular IF staining for polyclonal IgG and PLA2r along GBMs with sparse superficial subepithelial electron-dense deposits on EM, and was serologically negative for anti-nephrin. All MCD patients were successfully treated with oral glucocorticoids, while the MN patient was monitored closely under RAAS blockage.

Conclusions: COVID-19 mRNA vaccines can trigger de-novo or relapsing anti-nephrin- and PLA2r-mediated NS, thus adding both autoimmune-mediated podocytopathies to vaccine-induced complications. Temporal association is essential for diagnosis; prompt accurate diagnosis benefits treatment and response.

Funding: Private Foundation Support

PO0129

Real-World Effectiveness and Immunogenicity of BNT162b2 in Dialysis Patients

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Background: BNT162b2 (Pfizer/BioNTech) is a SARS-CoV-2 vaccine that received an emergency use authorization from the US Food and Drug Administration. Clinical trials in the general population demonstrated that BNT162b2 reduced risk of COVID-19 by 95%, however, dialysis patients were not represented in these trials. Here, we estimated the effectiveness and SARS-CoV-2 antibody response among real-world dialysis patients who were vaccinated with BNT162b2.

Methods: Patients included in this analysis were adults dialyzing at a large dialysis organization. For the effectiveness analysis, patients who began a BNT162b2 vaccination series (January-March 2021) were matched (with replacement) to up to 4 previously unvaccinated controls based on age, diabetes status, sex, race, body mass index, date of first vaccine, US state of residence, and prior known COVID-19 diagnosis. Vaccine effectiveness was estimated by calculating the hazard ratio (HR) for time to polymerase chain reaction confirmed infection between vaccinated and unvaccinated patients over 3 follow-up intervals: days 1-21, 22-42, and ≥43 after first dose of vaccine. Immunogenicity was measured in a subset of consented patients who completed the 2-dose BNT162b2 vaccination schedule. Blood samples were collected approximately 28 days after the second dose of BNT162b2, and indirect chemiluminescence immunoassays were used to measure immunoglobulin G (IgG) antibodies against SARS-CoV-2. Samples with a reading of >1 arbitrary unit (AU) were considered IgG+.

Results: We identified 12,169 patients who received BNT162b2 and were matched to 44,377 unvaccinated controls. The HRs and 95% confidence intervals (CI) were 0.84 (0.68, 1.03), 0.61 (0.40, 0.93), and 0.21 (0.13, 0.35) during 1-21, 22-42, and ≥43 days postvaccination, respectively. Among the 344 patients with postvaccination antibody measurements, 98.0% (95% CI: 95.2%-99.2%) were IgG+ (median: 63.3 AU of IgG).

Conclusions: Our results indicate that BNT162b2 is effective in preventing SARS-CoV-2 infection in dialysis patients. Moreover, antibodies to SARS-CoV-2 were detected in nearly all patients vaccinated with BNT162b2 in whom antibodies were measured.

PO0130

Early Humoral Responses of Hemodialysis Patients After COVID-19 Vaccination with BNT162b2

Claudius Speer, Louise Benning, Christian Nusshag, Florian Kälble, Paul Schnitzler, Martin G. Zeier, Christian Morath, Caner Süsal, Katrin Klein. *University of Heidelberg, Heidelberg, Germany.*

Background: Patients receiving hemodialysis are at high risk for both SARS-CoV-2 infection and severe COVID-19. A life-saving vaccine is available, but sensitivity to vaccines is lower in dialysis patients. Little is yet known about antibody response after COVID-19 vaccination in this vulnerable group.

Methods: In this prospective study, we included 22 dialysis patients and 46 healthy controls from Heidelberg University. We measured anti-S1 IgG with a threshold index for detection >1, neutralizing antibodies, and antibodies against different SARS-CoV-2 fragments 17–22 days after the first and 18–22 days after the second dose of BNT162b2.

Results: After the first vaccine dose, 4/22 (18%) dialysis patients compared with 43/46 (93%) healthy controls developed positive anti-S1 IgG, with a median (IQR) anti-S1 IgG index of 0.2 (0.1–0.7) compared with 9 (4–16), respectively. SARS-CoV-2 neutralizing antibodies exceeded the threshold for neutralization in 4/22 (18%) dialysis patients compared with 43/46 (93%) in healthy controls, with a median (IQR) percent

inhibition of 11 (3–24) compared with 65 (49–75), respectively. After the second dose, 14/17 (82%) of dialysis patients developed neutralizing antibodies exceeding the threshold for viral neutralization and antibodies against the receptor-binding S1-domain of the spike protein, compared to 46/46 (100%) of healthy controls, respectively. The median (IQR) percent inhibition was 51 (32–86) compared to 98 (97–98) in healthy controls.

Conclusions: Patients receiving long-term hemodialysis show a reduced antibody response to the first and second doses of the mRNA vaccine BNT162b2. The majority (82%) develop neutralizing antibodies after the second dose, but at lower levels than healthy controls.

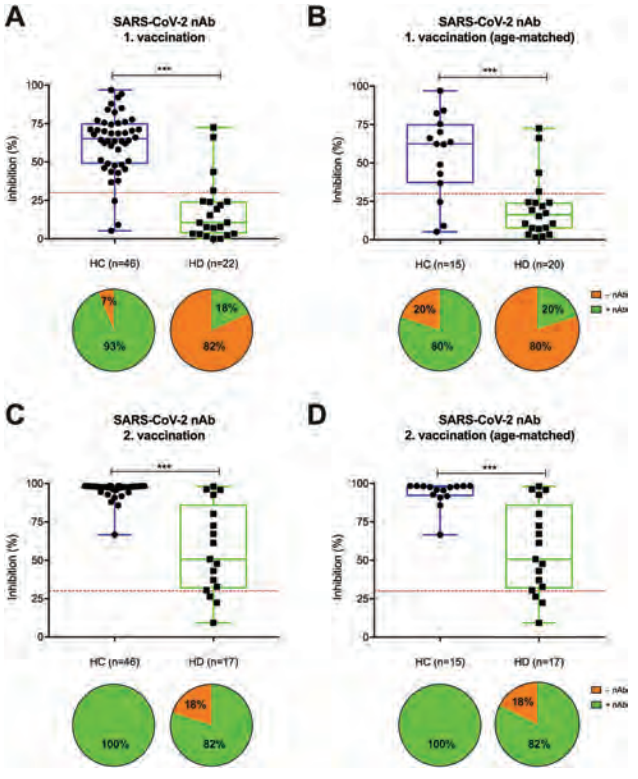

Figure 1

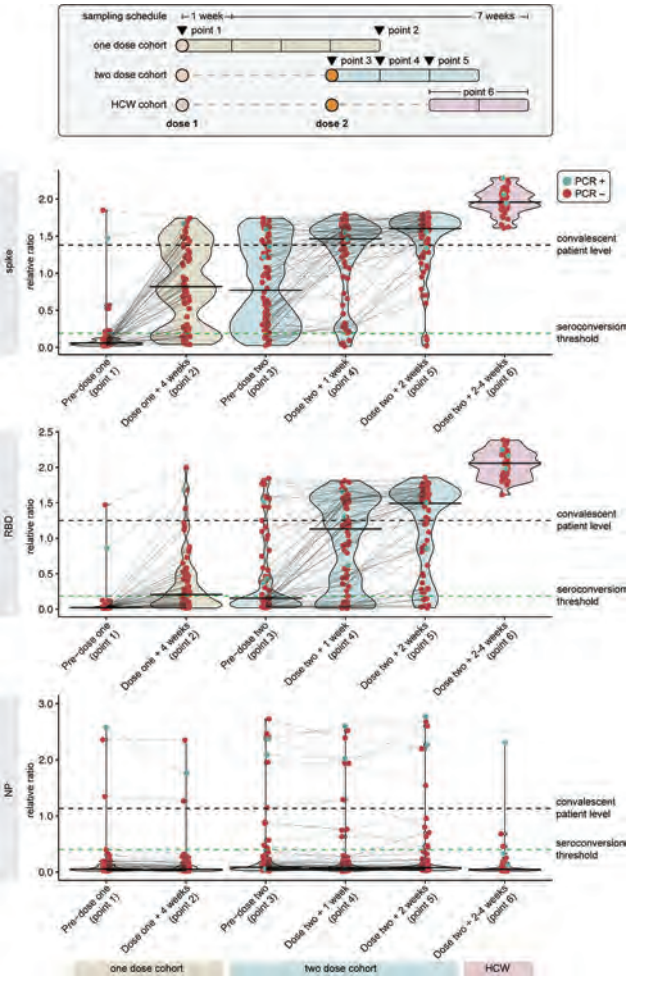

Figure 1: SARS-CoV-2 IgG Spike, RBD, and NP Antibody Response Following One Versus Two Dose BNT162b2 Vaccine in Hemodialysis Patients.

PO0131

Humoral Response to the BNT162b2 Vaccine in Hemodialysis Patients

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Background: Hemodialysis (HD) patients have high mortality from COVID-19 and immunity following vaccination remains uncertain. This study evaluated SARS-CoV-2 antibody response in HD patients following BNT162b2 COVID-19 vaccination compared to health care workers (HCW) and convalescent serum.

Methods: This single centre observational cohort study enrolled 142 HD patients and 35 HCW receiving the BNT162b2 vaccine. SARS-CoV-2 IgG antibodies to the spike protein (anti-spike), receptor binding domain (anti-RBD), and nucleocapsid protein (anti-NP) were measured in 66 HD patients receiving one vaccine dose, 76 HD patients receiving two vaccine doses, and 35 HCW receiving two vaccine doses.

Results: In HD patients receiving a single BNT162b2 dose, seroconversion occurred in 53/66 (80%) for anti-spike and 35/66 (55%) for anti-RBD by 28 days post dose, but only 15/66 (23%) and 4/66 (6%), respectively attained a robust response defined as reaching the median level of anti-spike and anti-RBD in convalescent serum. In patients receiving two doses of BNT162b2 vaccine, seroconversion occurred in 69/72 (96%) for anti-spike and 63/72 (88%) for anti-RBD by 2 weeks following the second dose while 52/72 (72%) and 43/72 (60%) reached median convalescent serum levels of anti-spike and anti-RBD. In HCW, 35/35 (100%) exceeded median levels of anti-spike and anti-RBD in convalescent serum 2-4 weeks post second dose.

Conclusions: This study found poor immunogenicity 28 days following a single dose of BNT162b2 vaccine in HD patients, supporting adherence to recommended vaccination schedules, and avoiding delay of the second dose in this population.

Funding: Government Support - Non-U.S.

PO0132

Comparative Effectiveness of Ad26.COV2.S vs. BNT162b2 for the Prevention of SARS-CoV-2 Infection Among Dialysis Patients

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Background: Elsewhere, we have demonstrated that the BNT162b2 vaccine (Pfizer/BioNTech) is highly effective in reducing risk of COVID-19 among real-world dialysis patients. Because individual vaccines may be differentially available (and acceptable) to patients, it is important to understand the comparative effectiveness of other agents, such as Ad26.COV2.S (Janssen).

Methods: This was a retrospective real-world comparative effectiveness study comparing two vaccination strategies ("use Ad26.COV2.S" versus "use BNT162b") among adult patients dialyzing at a large dialysis organization. Patients receiving Ad26.COV2.S were matched 1:1 to those initiating a BNT162b2 series based on age, race, US state of residence, calendar week of first vaccine receipt, and prior history of COVID-19. Follow-up time began the day after the first vaccine dose. The outcome of interest was the comparative rate of polymerase chain reaction-confirmed SARS-CoV-2 infections considered over 3 follow-up intervals: days 1-21, 22-42, and ≥ 43 post vaccination.

Results: There were 2683 matched pairs of patients who received a first dose of each vaccine. During days 1-21, the incidence rate was 1.26 infections per 1000 patient-weeks (pt-wks) among BNT162b2 recipients and 1.26 among Ad26.COV2.S recipients (incident rate difference [IRD]: 0.00; 95% confidence interval [CI]: -1.10, 1.10). During days 22-42, the incidence rate was 0.93 infections per 1000 pt-wks among BNT162b2 recipients and 0.40 among Ad26.COV2.S recipients (IRD: -0.50; 95% CI: -1.40, 0.30). After day 43, the incidence rate was 0.50 infections per 1000 pt-wks among BNT162b2 recipients and 0.50 among Ad26.COV2.S recipients (IRD: 0.00; 95% CI: -0.8, 0.8). Results were nearly identical when considering only patients without a prior history of COVID-19.

Conclusions: In a large contemporary cohort of dialysis patients, a "use Ad26.COV2.S" strategy versus a "use BNT162b2" strategy would be expected to yield no difference in additional cases of SARS-CoV-2 infections. Given similar effectiveness, vaccine allocation should be based on availability and logistical considerations.

PO0133

Predictors of Response to SARS-CoV-2 Vaccines Among Maintenance Dialysis Patients

Caroline M. Hsu,[1] Daniel E. Weiner,[1] Gideon N. Aweh,[2] Harold J. Manley,[2] Vladimir Ladik,[2] Jill M. Frament,[2] Dana Miskulin,[1] Doug Johnson,[2] Eduardo K. Lacson.[1,2] *[1]Tufts Medical Center, Boston, MA; [2]Dialysis Clinic Inc, Nashville, TN.*

Background: Vaccines against SARS-CoV-2 are highly effective in the general population; however, their efficacy may be diminished in maintenance dialysis patients, a population particularly vulnerable to COVID-19. We assessed vaccine response in a national sample of maintenance dialysis patients.

Methods: Using retrospective clinical data, we assessed seroresponse to vaccine among maintenance dialysis patients cared for at 130 Dialysis Clinic, Inc (DCI) facilities. Via a clinical protocol available to early vaccinating facilities, antibodies against SARS-CoV-2 spike antigen were semi-quantitatively assessed beginning with the monthly blood draw at least two weeks after completion of a SARS-CoV-2 vaccine series. Vaccine response was defined as a titer ≥2 U/L, and logistic regression analysis was used to identify characteristics associated with response. Patients with history of COVID-19 prior to antibody assessment were excluded.

Results: Among 1,352 patients, 996 (74%) had a serologic response. Serologic response differed significantly by vaccine type: 314/386 (81%) among BNT162b2/Pfizer recipients, 615/655 (94%) among mRNA-1273/Moderna recipients, and 67/311 (22%) among Ad26.COV2.S/Janssen recipients. Age greater than 75, lack of hepatitis B immunity, immune-modulating medication, lower serum albumin, and COPD were associated with vaccine non-response (**Figure**).

Conclusions: Serologic response to mRNA vaccines is robust among chronic dialysis patients, and the use of mRNA vaccines should be promoted aggressively in this vulnerable population. High rates of non-response to the Janssen vaccine warrant further study. Future research should evaluate the potential role for boosters and whether seroresponse corresponds with protection from COVID-19.

Funding: NIDDK Support

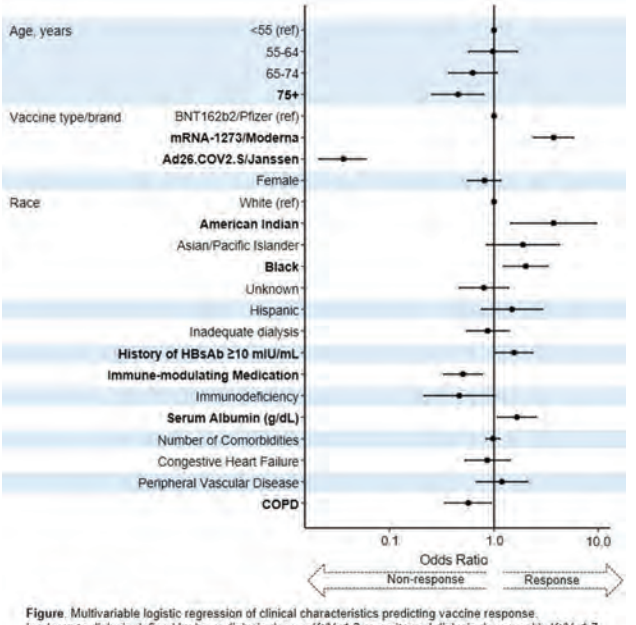

Figure. Multivariable logistic regression of clinical characteristics predicting vaccine response. Inadequate dialysis defined by hemodialysis dose spKt/V<1.2 or peritoneal dialysis dose weekly Kt/V<1.7 HBsAb hepatitis B surface antibody

PO0134

Humoral Responses to Single-Dose BNT162b2 mRNA Vaccination in Dialysis Patients Previously Infected with SARS-CoV-2

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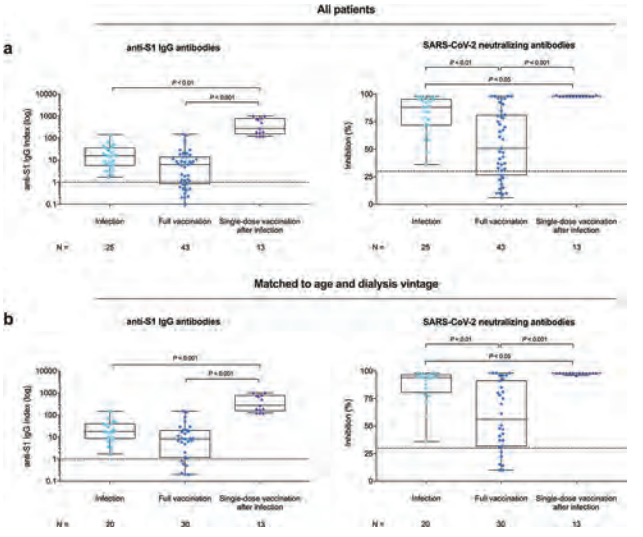
Background: Seroconversion rates following infection and vaccination are lower in dialysis patients compared to healthy controls. There is an urgent need for the characterization of humoral responses and success of a single-dose SARS-CoV-2 vaccination in previously infected dialysis patients.

Methods: We performed a dual-center study with 43 dialysis patients after BNT162b2 vaccination and 25 dialysis patients after PCR-confirmed COVID-19. Single-dose vaccination was performed in 13 previously infected patients. Anti-S1 IgG, neutralizing antibodies, and antibodies against various SARS-CoV-2 epitopes were measured 6 weeks after the first vaccination or onset of COVID-19 and 3 weeks after single-dose vaccination.

Results: Previously infected patients without vaccination showed a significantly higher neutralizing capacity than patients vaccinated twice (median (IQR) percent inhibition 88.0 (71.5–95.5) vs. 50.7 (26.4–81.0); P=0.018). After one single vaccine dose, infected individuals generated 15- to 34-fold higher levels of anti-S1 IgG than age- and dialysis vintage-matched patients after infection or two-time vaccination with a median (IQR) index of 274 (151–791) compared to 18 (8–41) and 8 (1–21) (for both P<0.001). With a median (IQR) percent inhibition of 97.6 (97.2-98.9), the neutralizing capacity of SARS-CoV-2 antibodies was significantly higher in previously infected patients compared to other groups (for both P<0.01). Bead-based analysis showed high antibody reactivity against various SARS-CoV-2 spike protein epitopes after single-dose vaccination in previously infected patients.

Conclusions: Single-dose vaccination in previously infected dialysis patients induced a strong and broad antibody reactivity against various SARS-CoV-2 spike protein epitopes with high neutralizing capacity.



PO0135

Anti-Spike Antibody Responses in Hemodialyzed Patients Vaccinated with Anti-COVID-19 BNT162b2 mRNA Vaccine

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Background: Patients under hemodialysis are at higher risk of developing severe complications upon SARS-CoV-2 infection and were prioritized in the Portuguese vaccination campaign.

Methods: We performed a longitudinal analysis of antibody responses upon vaccination with BNT162b2 mRNA (Pfizer/BioNTech, Comirnaty) in a cohort of 156 hemodialyzed patients. Direct ELISA was used to quantify IgG, IgM and IgA anti-full-length Spike antibody levels against calibrated sera from naturally infected patients at three points: day of the first vaccine dose (t0); 3 weeks later (day of the second dose, t1), and 3 weeks after the second inoculation (t2) for 143/156 patients. Anti-n was also measured in t0 and patients anti-n positive were excluded.

Results: We observed that 90.9% of the patients developed anti-spike IgG antibodies after the second vaccine dose (t2). Seroconversion was remarkably low at t1 after the first vaccine dose with only 29.4% of patients developing anti-spike IgG antibodies. In addition to positivity, the second vaccine dose markedly increased IgG antibody levels. IgA levels were also higher at t2 with 83.9% of the patients achieving positivity while IgM positivity only reached 29.4%. Age showed a significant negative effect on the humoral response at t2 for anti-Spike IgG and for IgM, particularly over 60 years. Further analysis revealed that nine patients under immunosuppression therapies showed significantly lower humoral response along the vaccine schedule (p=0.005 at t1; p=0.008 at t2). Interestingly, the inability to develop anti-HBs antibodies upon hepatitis B vaccination frequently found in hemodialyzed patients was not correlated with lack of responsiveness to SARS-CoV-2 vaccination.

Conclusions: The large majority hemodialyzed patients showed a significant humoral response to BNT162b2 mRNA vaccination, but a sizable proportion of patients showed low antibody levels when compared to responses in the general population (medRxiv 2021.03.19.21253680).

Age Group (years)	27-49	50-59	60-69	70-79	80-89	90-93
IgG (median)	2.27	2.09	2.07	1.84	2.00	0.54
IgG (IQR)	(2.1-2.4)	(1.9-2.3)	(1.8-2.2)	(1.6-2.2)	(1.6-2.2)	(0.38-1.9)

PO0136

How Well Do Hemodialysis Patients Respond to the BNT162b2 mRNA COVID-19 Vaccine?

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Background: Hemodialysis patients as well as healthcare workers are considered to be in a high-risk category for SARS-CoV-2 infection and a priority for vaccination.

Methods: In a single-center out-patient hemodialysis unit, 46 healthcare workers and 216 patients were vaccinated simultaneously with BNT162b2 (BioNTech-Pfizer) vaccine. They received two doses, 21 days apart. The primary objectives were to evaluate the safety and efficacy of the vaccine.

Results: There were no major adverse events in either group. Lymphadenopathy was reported by some health workers. All (100%) individuals in the healthcare workers group developed a positive antibody response (anti-S IgG) after the second dose compared with 91.7% of patients. Among patients there was a significant negative correlation between anti-S levels and age after both, the first dose (R= -0.176, p=0.01) and the second dose (R= -0.193, p=0.005); there was also a significant negative correlation between anti-S and Charlson Comorbidity Index adjusted for age after both, the first dose (R= -0.150, p=0.028) and the second dose (R= -0.163, p=0.018). Finally, a negative correlation between anti-S and Body Mass Index was found after the first dose (R= -0.140, p=0.04). No correlations were found with dialysis vintage, Kt/V, or diabetes.

Conclusions: Following vaccination, patients had a significantly lower anti-S response than healthcare workers. Age, Charlson Comorbidity Index and Body Mass Index negatively impacted the humoral response. However, with more than 91% response we believe that vaccination can be recommended strongly in the hemodialysis population.

PO0137

Real-World Effectiveness and Immunogenicity of mRNA-1273 in Dialysis Patients

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Background: mRNA-1273 (Moderna) is a SARS-CoV-2 vaccine that received an emergency use authorization from the US Food and Drug Administration. Clinical trials in the general population demonstrated that mRNA-1273 reduced risk of COVID-19 by 94.5%, however, dialysis patients were not represented in these trials. Here, we estimated the effectiveness and SARS-CoV-2 antibody response among real-world dialysis patients who were vaccinated with mRNA-1273.

Methods: Patients included in this analysis were adults dialyzing at a large dialysis organization. For the effectiveness analysis, patients who began an mRNA-1273 vaccination series (January-March 2021) were matched (with replacement) to up to 3 previously unvaccinated controls based on age, diabetes status, sex, race, body mass index, date of first vaccine, US state of residence, and prior known COVID-19 diagnosis. Vaccine effectiveness was estimated by calculating the hazard ratio (HR) for time to polymerase chain reaction confirmed infection between vaccinated and unvaccinated patients over 3 follow-up intervals: days 1-21, 22-42, and ≥43 after first dose of vaccine. Immunogenicity was measured in a subset of consented patients who completed the full, 2-dose mRNA-1273 vaccination schedule. Blood samples were collected approximately 28 days after the second dose of mRNA-1273, and indirect chemiluminescence immunoassays were used to measure immunoglobulin G (IgG) antibodies against SARS-CoV-2. Samples with a reading of >1 arbitrary unit (AU) were considered IgG+.

Results: We identified 23,037 patients who received mRNA-1273 and were matched to 64,243 unvaccinated controls. The HRs and 95% confidence intervals (CI) were 0.96 (0.79, 1.16), 0.51 (0.34, 0.75), and 0.27 (0.17, 0.42) during 1-21, 22-42, and ≥43 days postvaccination, respectively. Among the 329 patients with postvaccination antibody measurements, 96.0% (95% CI: 93.3%-97.9%) were IgG+ (median: 100.5 AU of IgG).

Conclusions: Our results indicate that mRNA-1273 is effective in preventing SARS-CoV-2 infection in dialysis patients. Moreover, antibodies to SARS-CoV-2 were detected in nearly all patients vaccinated with mRNA-1273 in whom antibodies were measured.

PO0138

Fewer ESKD Dialysis Patients (pts) Reach Antibody (AB) Levels Consistent with Neutralizing Titers When Vaccinated with Ad26.COV2.S Compared with mRNA COVID-19 Vaccines

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Background: The COVID-19 viral vector (VV) vaccine's single dose and routine storage requirements may be preferred to the mRNA-based vaccine's 2 doses and low temperature storage requirements. We report an interim analysis of a quality improvement project performed at 2 Arizona dialysis clinics comparing the AB response to VV vaccine with mRNA vaccine in ESKD pts.

Methods: Pts received either the VV vaccine (Ad26.COV2.S) administered in the dialysis clinic or mRNA vaccines (BNT162b2, mRNA-1273) administered in the community. AB response was assessed with remnant blood and a semi-quantitative chemiluminescent assay for IgG directed against the receptor binding domain of the SARS-CoV-2 spike antigen. Values >7.0 Index produce plaque reduction neutralization test (PRNT50) titers greater than 1:80 dilution recommended by the FDA standard for measuring neutralizing titer.

Results: AB response was evaluated at an average of 22 days post vaccination (≥14 days post Ad26.COV2.S or post 2nd mRNA vaccine). 36/45 pts (80%) who received the VV vaccine failed to develop an AB index >7 after ≥14 days post vaccine compared to 5/31 pts (16%) who received an mRNA vaccine (84% achieved AB index >7); all 5 pts had no prior COVID-19 history. Of pts receiving the VV vaccine with prior history of COVID-19, 22% of pts had AB index <8 after 14 days post vaccine. 41 pts receiving the VV vaccine had additional AB measurements in the next 14-37 days (ave 26 days after prior measure). In 34 pts with no prior history of COVID-19, 3 pts achieved AB index >7 in the recent sample and had previously been < 1 (n=1) or 1-7 (n=2), bringing the total number with AB > 7 from 2 to 5 (15%). AB levels remained unchanged in pts with a prior history of COVID-19 (n=9). No demographic or laboratory differences were observed.

Conclusions: Our data support the contention that the available VV-based vaccine against the SARS-CoV-2 virus is not effective in producing AB response in most ESKD pts especially when compared to an mRNA counterpart. If AB indices predict immunity and other studies support our findings, alternative vaccination strategies in ESKD pts vaccinated with VV vaccines is needed.

Funding: Commercial Support - Fresenius Medical Care

PO0139

Humoral Response to Pfizer BNT162b2 in Peritoneal and Hemodialysis Patients: A Comparative Study

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Background: Generalized immunization against COVID19 has become the cornerstone in prevention of Sars-CoV-2. Maintenance dialysis patients (MDP) are at higher risk of both exposure and mortality. Efficacy and security of Pfizer BNT 162b2 vaccine is well documented for the general population, but not in MDP, particularly in peritoneal dialysis (PD) patients. This study aims to compare humoral response between HD and PD patients.

Methods: Observational prospective study including MDP on HD or PD program from a Portuguese middle-sized Nephrology Center, who received Pfizer-BNT162b2. Specific anti-Spike IgG was measured as arbitrary units per milliliter (AU/mL) on two separate occasions, corresponding to the first and second doses' humoral response. The two groups were compared both for absolute value and number of non-responders (NR) after both inoculations. Demographic data was also obtained and compared.

Results: Of 73 patients enrolled, 67 were eligible for the final study: 42 HD and 25 PD patients. PD group developed significantly higher antibody titers both after first (Med 5.44 vs 0.99; p<0.01) and second dose (Med 170.43 vs 65.81; p<0.01). HD status was associated with non-responding after the first dose (Phi=0.383; p<0.01), but not after the second one (p=0.08). Age, Charlson Comorbidity Index and dialysis vintage were lower in the PD group (p<0.01; p=0.02; p<0.01, respectively).

Conclusions: This study demonstrated a better humoral response to immunization with Pfizer BNT162b2 in PD patients, when comparing to HD patients, after both inoculations. Both groups showed substantial humoral response after just one dose of the vaccine. Older age and higher comorbidity burden may explain the relative immunogenicity deficit.

PO0140

Time-Dependent Evolution of IgG Antibody Levels After First and Second Dose of mRNA-based SARS-CoV-2 Vaccination in Hemodialysis Patients: A Multicenter Study

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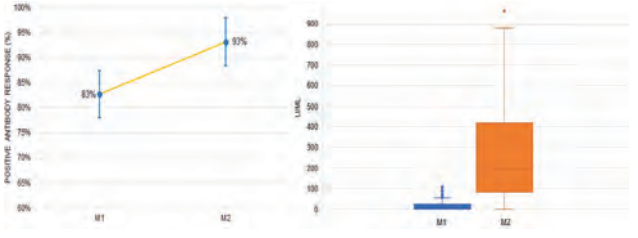
Background: Vaccination programs are essential for the containment of the COVID-19 pandemic, which has affected significantly the hemodialysis population. Early reports suggest a reduced immunologic response to COVID-19 vaccines in dialysis patients, in spite of a high degree of seroconversion. We aimed to identify risk factors for a reduced efficacy of an mRNA vaccine in a cohort of hemodialysis patients.

Methods: In a multicenter study, including 294 Portuguese hemodialysis patients from multiple centers who had received 2 doses of BNT162b2 with a three week interval, IgG-class antibodies against the SARS-CoV-2 spike protein were determined 3 weeks after the first dose (M1) and 6 weeks after the second dose (M2). The threshold for seroconversion was 10UR/mL. Demographic and clinical data was retrieved from a quality registry. Adverse events were registered using a questionnaire.

Results: At M2, seroconversion was 93.1% with a median antibody level of 197.5U/mL (1.2-3237.0) and a median increase of 180.0U/mL (-82.9-2244.6) from M1. Age (beta -8.9; 95%CI: -12.88 to -4.91; p<0.0001), ferritin >600ng/mL (beta 183.93; 95%CI: 74.75 to 293.10; p=0.001) and physical activity (beta 265.79; 95%CI: 30.7 to 500.88; p=0.03) were independent predictors of SARS-Cov-2 antibody levels after two vaccine doses. Plasma albumin >3.5g/dL independently predicted the increase of antibody levels between both doses (OR 14.72; 95%CI: 1.38 to 157.45; p=0.03). Only mild adverse reactions were observed in 10.9% of patients.

Conclusions: The COVID-19 vaccine BNT162b2 is safe and effective in hemodialysis patients. Besides age, iron status and nutrition are possible modifiable modulators of the immunologic response to COVID-19 mRNA vaccines.



Positive IgG spike protein antibody response and antibody levels after BNT162b2 vaccination, just before (M1) and six weeks after (M2) the second administration of the vaccine.

PO0141

Antibody Response to COVID-19 Vaccine in Peritoneal Dialysis (PD) Patients: A Single-Center Study

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Background: In initial published reports of dialysis patients, response to COVID-19 vaccination tends to be lower as compared to general population. To date, these studies were primarily focused on hemodialysis (HD) patients. We studied the factors associated with COVID-19 vaccine humoral response in PD patients.

Methods: Our research setting was a single-center academic institution in New York City. We included patients on PD who received the COVID-19 vaccine. Response was assessed at a median of 4 weeks after completing the full vaccination series by measuring semiquantitative COVID-19 spike protein total antibody (Ab) level using a chemiluminescent sandwich immunoassay. Chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables were used to compare characteristics among patients who did and did not have an Ab response.

Results: Of 111 patients on PD in our center, 64 (58%) received COVID-19 vaccine as of April 2021 and had Ab levels checked. A total of 60/64 (94%) of patients had a positive Ab response and 4/64 (6%) did not mount a response. IgG levels in positive responders were a median of 11.5 (interquartile range, 1.9 – 20). Lower Kt/V was associated with a positive Ab response (p = 0.045) and type of vaccine was associated with an Ab response (p = 0.028). Age, BMI, diabetes, hypertension, lymphocyte count, or residual Kt/V were not statistically significantly associated with Ab response to the vaccine (Table 1).

Conclusions: In conclusion, the vast majority of patients on PD developed positive Ab response to the COVID-19 vaccine. While a small sample size limited our statistical power, our results show promising COVID-19 vaccine effectiveness among patients on PD.

Table 1. Characteristics of patients on PD by COVID-19 Ab response

Variable	Total Sample (n = 64)	Antibody Response to COVID-19 Vaccine (n = 60)	No Antibody Response to COVID-19 Vaccine (n = 4)	p-value
Age	64 [52.5 – 72.5]	64 [51.5 – 73]	63 [59.5 – 64.5]	0.77
Body mass index (BMI)	26.2 [23.3 – 30.1]	26.1 [23.1 – 30.5]	28.5 [26.6 – 29.5]	0.53
Diabetes	16 (25%)	14 (23%)	2 (50%)	0.23
Hypertension	60 (94%)	56 (93%)	4 (100%)	0.59
Absolute lymphocyte count (x 10^3 per µL)	1.1 [0.9 – 1.7]	1.1 [0.9 – 1.6]	1.5 [1 – 1.9]	0.48
Total Kt/V	2.04 [1.75 – 2.4]	1.96 [1.73 – 2.26]	2.49 [2.44 – 2.93]	0.049
Residual Kt/V	0.38 [0 – 0.72]	0.37 [0 – 0.64]	0.75 [0.35 – 1.56]	0.18
COVID-19 Ab Positive prior to Vaccine	11 (17%)	11 (18%)	0 (0%)	0.89
Pfizer	51 (80%)	49 (82%)	2 (50%)	0.028
Moderna	11 (17%)	10 (17%)	1 (25%)	
Johnson & Johnson	2 (3%)	1 (2%)	1 (25%)	
COVID-19 Ab titer	11.5 [1.9 – 20]	11.5 [1.9 – 20]	—*	—

Continuous variables presented as median [interquartile range].
*Antibody titers not checked.

PO0142

Breakthrough COVID-19 Infection in Hemodialysis Patients Following mRNA-1273 (Moderna) Vaccine Administration

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Background: Patients on maintenance hemodialysis are highly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We recently reported that 95% (58/61) hemodialysis patients developed anti-receptor binding domain (RBD) IgG antibody following the 2-dose Moderna vaccine administration. The incidence of breakthrough COVID-19 infection in hemodialysis patients following vaccination is not known.

Methods: All hemodialysis patients (n=61) received the 2-dose Moderna vaccine series. Anti-RBD IgG titer was measured at 1-, 2-, 4- weeks after the 1st vaccine dose. The 2nd vaccine dose was administered 29±3.9 days after the 1st dose. Anti-RBD IgG titer was measured at 1-week following the 2nd vaccine dose. Nasal swabs were performed every 2-weeks to detect SARS-CoV-2 RNA as part of routine surveillance. Additionally, nasal swab tests were performed if patients exhibited signs or symptoms suggestive of COVID-19. Patients were followed for 2-months following the 2nd vaccine dose administration.

Results: Three patients tested positive for SARS-CoV-2 RNA following vaccination. Of these 3 patients, 2 patients tested positive at day-7- and at day-12 following the 1st vaccine dose respectively. Both these patients presented with symptoms of fever and dyspnea, and both had undetectable anti-RBD IgG titer at the time of COVID-19 diagnosis. A third patient tested positive for SARS-CoV-2 RNA on routine nasal swab surveillance test at day-40 following the 2nd vaccine dose administration. At the time of the test, the patient had a positive anti-RBG IgG titer. The patient remained asymptomatic and had an uneventful course. Viral genome analysis revealed that the infection was due to the B.1.526 SARS-CoV-2 variant, also known as the New York variant.

Conclusions: Breakthrough COVID-19 infections were rare in fully vaccinated hemodialysis patients up to 2-months following the Moderna vaccine administration. One case of SARS-CoV-2 breakthrough infection was due to the B.1.526 variant.

PO0143

Rapid Decline in Antibody Levels After Initial High Response in ESKD Patients Vaccinated with mRNA COVID-19 Vaccines

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Background: Vaccine unresponsiveness and rapid AB level decline after successful vaccination have been barriers to antiviral strategies in ESKD populations. We report an interim analysis of a quality improvement project characterizing the temporal AB response to COVID-19 vaccination across 7 dialysis clinics in MA.

Methods: Chronic dialysis pts received 2 doses of mRNA vaccine at prescribed intervals. AB response was measured in remnant blood with semiquantitative chemiluminescent assay detecting IgG AB directed against receptor binding domain of S1 subunit of SARS-CoV-2 spike antigen (Siemens); AB index ≥1 was considered reactive. AB index >7 produce plaque reduction neutralization test (PRNT50) titers >1:80 dilution recommended by FDA standard for measuring neutralizing titer.

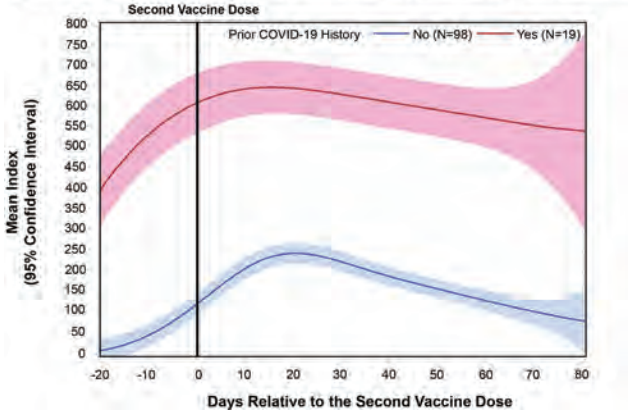
Results: 211 pts received the 2-dose mRNA vaccine (mRNA-1273, 1 given BNT162b2). On average (ave) AB peaked at day 19 post 2nd vaccine; peak index was >7 for 97% of pts. Pts with AB peak >7 had higher serum albumin vs pts with AB peak ≤ 7 (3.8 vs 3.4 g/dl). Among pts with AB measured after peak AB index (n=188),

ave AB index decreased by 125 (46% reduction) over an ave 46 days. Ave decreases from peak were 51% in pts with no prior COVID-19 history (n=162) and 20% in pts with COVID-19 history (n=26); illustrated in subset with ≥5 AB measurements ≥ 45 days post 2nd vaccine dose (n=114, Figure). No symptomatic COVID-19 cases were reported.

Conclusions: mRNA-1273 is a highly reactive vaccine producing reactive AB in all, and >7 index in 97% of vaccinated ESKD pts. However, if AB index confers immunity, blunted and rapid decline of circulating AB may place ESKD pts at risk of future COVID-19 infection. Monitoring post-vaccination AB levels may be important for ESKD pts (especially hypoalbuminemic pts) and may guide future vaccination requirements.

Funding: Commercial Support - Fresenius Medical Care

Figure 1. Temporal Antibody Response in ESRD Patients Vaccinated Against COVID-19



PO0144

Immunogenic Response of Hemodialysis Patients to COVID-19 Vaccine: A Multicenter Study

Avital Angel-Korman,[1,2] Tal Brosh-Nissimov,[1,2] Adi Leiba.[1,2] *[1]Samson Assuta University Hospital, Ashdod, Israel; [2]Ben Gurion University, Faculty of Health Science, Beer-Sheva, Israel.*

Background: The use of the mRNA-based vaccine BNT162b2 against COVID-19 has shown great success preventing SARS-CoV-2 infection in the general population. Limited data exist regarding its effectiveness in patients requiring dialysis. Dialysis patients have reduced immune response following different types of vaccines including Hepatitis B vaccine. We aimed to asses humoral response and the factors associated with it in a large and diverse maintenance hemodialysis (MHD) patient population.

Methods: SARS-CoV-2 Anti-spike, anti-nucleocapsid and neutralizing antibody (Ab) levels of 424 MHD patients from 13 nationally spread dialysis units in Israel were compared with 155 control subjects (dialysis patients' family members and dialysis units health care workers). Patients' history, dialysis treatment details and Hepatitis B Ab (HBsAb) levels were obtained from dialysis units medical records.

Results: Our study included 400 MHD patients and 141 controls (58% males, 42% females), excluding 24 MHD and 14 control samples from anti-N positive cases, signifying previous SARS-CoV-2 infection. Anti-S antibodies developed in 89.3% of MHD patients and 99.3% of controls, ($p<0.01$) after a median time of 82 and 89 days from second vaccine dose for MHD and controls, respectively. Median anti-S titer was significantly lower in MHD patients compared with controls (median 194, IQR 118-242 vs. 69, IQR 33-119; $p<0.001$) and correlated well with the level of neutralizing Ab titers in the study group as compared to control group (median 16, IQR 8-64 vs. 256, IQR 64-516; $p<0.001$, respectively). Notably, age was higher in MHD patients than controls (median 72, IQR 63-80 vs. 49, IQR 38-58, $p<0.01$) which likely contributed to the association with anti-S titers ($p<0.01$, $r=0.44$) as well as neutralizing Ab titer levels ($p<0.01$, $r=0.42$). Sex, dialysis vintage and etiology of ESRD were not significantly associated with anti-S positivity or titer levels. Interestingly, there was a significant correlation, between anti-S and HBsAb positivity ($p<0.01$) though campatability was low ($r=0.18$).

Conclusions: MHD patients have lower seroconversion rate, lower anti-S and neutralizing Ab levels after BNT162b2 vaccination. HBsAb levels may potentially be used as a marker for estimating the level of humoral response following COVID-19 vaccine. To our knowledge this is the largest cohort of MHD patients studied thus far.

PO0145

Extremely Low Humoral Immune Responses to BNT162b2 Vaccine in Nursing Home Residents Undergoing Hemodialysis

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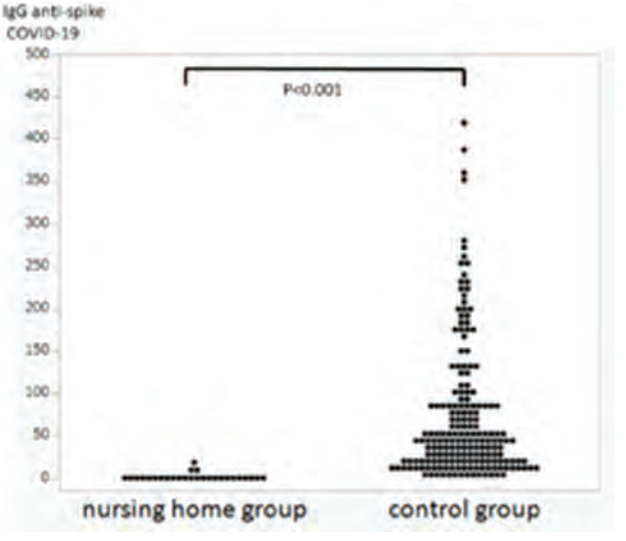
Background: As coronavirus disease 2019 (COVID-19) can cause lethal outcomes in hemodialysis (HD) patients, they should be protected effectively by vaccination. HD patients are known to have a weak immune response to vaccines, and the seropositive rate three week after first vaccination (BNT162b2 Pfizer) is around 35%. However, its efficacy among elderly HD patients remains unknown. We aimed to evaluate spike antibody levels of nursing home residents on long-term maintenance HD after the BNT162b2 vaccine, comparing those of health care workers.

Methods: Between April and May 2021, HD patients from a nursing home (nursing home group) and health care workers (the control group) who received BNT162b2 were included. Those with a prior history of COVID-19 were excluded. IgG anti-spike against COVID-19 were measured by Elecsys Roche (cut off index <1.0) 3 weeks after the first injection.

Results: The study included 27 nursing home residents on HD and 191 care workers, and 2 care workers were excluded due to a prior history of COVID-19. The nursing home group were 84±9 years old and 41% male, and the median of HD vintage was 51 months (IQR 28-119), and the control group were 45±14 years old and 29% male. Only 6 patients in the nursing group were confirmed as seropositive (22%), whereas the rate of responder in the control group was 99% ($p<0.001$). Notably, the IgG levels of 20 patients in the nursing home group were under the detectable level (<0.4). In contrast, the median of the IgG levels in the control group was 42 (IQR 18-87). Moreover, the prevalence of adverse reactions, such as developing fever, in the nursing home group was low compared to the control group ($p<0.001$)

Conclusions: The seropositive rate after BNT162b2 in elderly HD patients was quite low owing to poor immune responses. To prevent a COVID-19 outbreak in nursing homes, IgG levels against COVID-19 in elderly residents on HD should be paid attention to.



PO0146

No Antibody Response to Viral Vector SARS-CoV-2 Vaccine but Subsequent Conversion After COVID-19 Infection in an ESKD Patient

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Introduction: ESKD patients generally have low response rate to vaccines. Early data suggests that viral vector SARS-CoV-19 vaccine is less effective than its mRNA counterparts. This case illustrates AB non-response to a viral vector based SARS-CoV-19 vaccine (Janssen) with subsequent AB response to mild clinical COVID-19 in an ESKD patient.

Case Description: 84 year old male on HD for 12 years. He had a prior response to the Hepatitis B vaccine with a recent titer >10 IU/L. SARS-CoV-19 AB (IgG AB to the spike protein) was being checked monthly as part of an observational cohort. SARS-CoV-19 AB was (-) 1 month prior to receiving a viral vector-based vaccine. The AB was rechecked 1 month after the vaccine and remained (-). He was soon after admitted for GI bleed and tested positive for COVID-19 by PCR nasal swab on routine hospital screening. On discharge, he was asymptomatic but was hypoxemic requiring oxygen. 17 days after hospital discharge, SARS-CoV-19 by nasal PCR remained positive and AB titer was detectable at 1.3 U/L. Both were checked again 1 week later, viral PCR remained (-) with further increase in AB to 2.3 U/L. A titer of >2.0 U/L has been reported as protective. He was no longer hypoxemic by that time.

Discussion: SARS-CoV-19 AB was measured longitudinally in this elderly HD patient. AB titer to the spike protein was negative 4 weeks after receiving a viral vector-based SARS-CoV-19 vaccine. He was relatively immunocompetent based on prior AB response to Hepatitis B vaccination. He became SARS-CoV-19 AB (+) 2.5 weeks after mild COVID-19 infection. Most studies on SARS-CoV-19 vaccination in ESKD have focused on mRNA vaccines, which show a reasonably high AB conversion rate after the second injection. We do not know if lack of detectable spike protein AB after vaccination necessarily precludes resistance to infection, nor do we know if this patient's eventual seroconversion was due only to his COVID-19 infection or simply a slow response to the vaccine. There is evidence in the general public that efficacy of the viral vector-based SARS-CoV-19 vaccine may be lower than that of mRNA vaccines. With ESKD patients more susceptible to infection and less able to mount AB's to vaccines, this case supports the use of mRNA SARS-CoV-19 vaccines preferentially in the ESKD population if AB seroconversion is the targeted intermediary outcome.

PO0147

ESKD Immunoglobulin Response at 3 Months Post COVID-19 Vaccination

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Background: End stage kidney disease (ESKD) patients (pts) remain at high risk for COVID 19 infection. Inadequate post infection antibody response is reported in 10-11% of pts[1]. Current data is limited on ESKD post vaccination (vac)[2] We report 3-month (mo) post vac response of ESKD pts receiving 2 doses of either Moderna or Pfizer vaccines.

Methods: Twenty- six of 42 stable ESKD pts completed 2 doses of either Moderna or Pfizer vaccination at Salem VAMC or at their nursing home facility during mo 01/02-2021. 17/42 were not vaccinated (7 declined, 2 with COVID 19 infection, 6 acutely hospitalized) during that time. Antibody immune response testing using ADVIA Centaur COV2G automated 2-step sandwich immunoassay using indirect chemiluminescent technology and designed to detect the SARS-CoV-2 surface spike protein receptor binding domain (S1RBD) was completed in 05/2021. Measures obtained included reactivity to total SARS CoV-ab (IgM+ IgG) and IgG separately.

Results: Please see table 1 for results

Conclusions: ESKD vaccine response to COVID 19 after 3months was 96% for total immunoglobulin response (IgM and IgG) and 87.5% for total IgG antibody response compared to no reactivity in those nonvaccinated patients. Age and presence of diabetes did not significantly affect immune response. Approximately 12.5 % of patients had nonreactivity to IgG antibody after 3 months. Patients not developing an IgG response by 3 mo were found to have underlying immunosuppressive disease. ESKD with COVID 19 infection maintained IgG reactive response 3 months after active disease. Nonreactivity was seen in those neither infected nor vaccinated, suggesting that these patients have likely not been exposed to COVID 19 viral infection.

Funding: Veterans Affairs Support

Results: Table 1 Demographic and 3 Month Antibody Response of COVID 19 vaccination in ESKD Patients

Total n=42 40 males, 2 females	Mean age 71 (years) Range 42-90 years	DM present N=16	SARS CoV2 Ab total reactive n=24 Nonreactive N=10	SARS CoV2 Ab IgG reactive n=22 Nonreactive n=10
Vaccinated n=26 25 males, 1 female)	71	10/26 (38%)	Reactive n=23 Of tested 24 (96% reactive) Nonreactive 1/24 (4%)	Reactive n=21/24 tested (87.5%) Nonreactive 3/24 (12.5%)
Not vaccinated n=14 (13 male, 1 female)	70	6/15 (40%)	Reactive 0 /14 (0%)	Reactive 0 ((0%)
COVID 19 infection- (not vaccinated) n=2	48	0 (0%)	Reactive n=2 2/2 (100%) Nonreactive n=0 (0%)	Reactive n=2 2/2 (100%) Nonreactive n=0 (0%)
Vaccinated not tested n=2	72	N=1/2 (50%)	Not tested	Not tested
Non Vaccinated-not tested n=5	69	N=3/5 (60%)	Not tested	Not tested

PO0148

The SARS-CoV-2 Vaccine Response in ANCA-Associated Vasculitis

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Background: The development of efficacious vaccines against COVID-19 is an overarching achievement of modern medicine. This efficacy, however, may not be achieved in patients on immunosuppression. We looked to ascertain humoral response and tolerability of these vaccines in patients with ANCA associated vasculitis(AAV) treated with B-cell depleting agents

Methods: AAV patients who completed 2 doses of BNT162b2 or mRNA-1273 or a dose of JNJ-78436735, subsequently screened for spike protein antibody against SARS-CoV-2 were included in the study. Clinical details, demographics and immunosuppression regimes were ascertained, with primary outcome being humoral response to SARS-CoV-2.Statistics included Fischer's exact test and Wilcoxon rank sum test.

Results: Forty-eight patients with a mean age of 67y(35% female) completed vaccine series with BNT161b2(n=19), mRNA-1273(n=25) and JNJ-78436735(n=4). Vaccine associated side effects occurred in 27% of patients after 1st dose, with 39% after the 2nd dose. Spike protein antibody was tested at a median of 31 days after vaccination- 30(61%) patients had demonstrable antibody. All patients (n=44) other than 4 post-transplant patients, were treated with Rituximab- only 17/44(39%) developed an antibody response. In the setting of rituximab treatment, absence of seroconversion post vaccination was associated with vaccine type, duration elapsed since last rituximab dose (figure 1), low IgM level and absence of B-cell reconstitution (all stastically significant). Two patients without serologic response had severe COVID–19 infection

Conclusions: This data demonstrates that majority of patients treated with rituximab lack demonstrable serologic response, with risk of severe COVID-19 infections despite vaccination. Confirmation of B-cell reconstitution before vaccination may have a bearing on serological conversion. It is imperative that authorities consider these factors while designing vaccination schedules and provide recommendations for booster doses in this vulnerable population

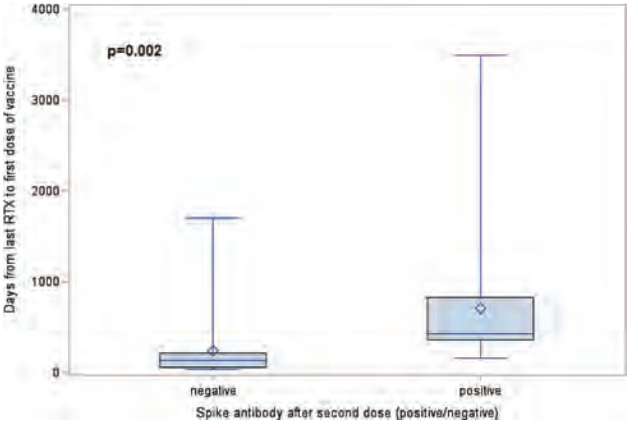


Fig 1

PO0149

Durability of SARS-CoV-2 Spike Antibody Levels in Dialysis Patients After COVID-19 Infection

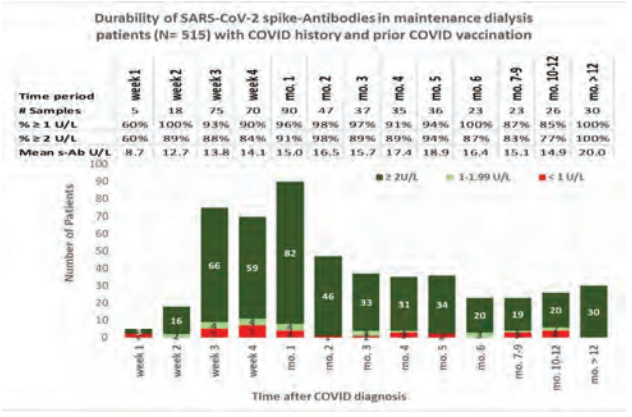
Harold J. Manley,[1] Caroline M. Hsu,[2] Gideon N. Aweh,[1] Daniel E. Weiner,[2,1] Jill M. Frament,[1] Vladimir Ladik,[1] Doug Johnson,[1] Eduardo K. Lacson.[1,2] *[1]Dialysis Clinic Inc, Nashville, TN; [2]Tufts University School of Medicine, Boston, MA.*

Background: Durability of SARS-CoV-2 receptor-binding domain spike antibody (RBD s-Ab) levels among patients receiving dialysis after COVID-19 [WDE1] is unknown[EL2] beyond 6 months. We describe the persistence (index value ≥ 1 and ≥ 2 U/L) of semi-quantitative RBD s-Ab levels in dialysis patients over 14 month period.

Methods: All maintenance dialysis patients (≥18 years old) within Dialysis Clinic, Inc. 260 clinics in 28 states with COVID-19 infection history and RBD s-Ab levels determined between Jan 1 and May 23, 2021 were included. On the day of RBD s-Ab level determination, patient demographics (age, sex, race, modality, ESKD vintage) and days since COVID-19 diagnosis were determined. Patient RBD s-Ab levels obtained after COVID-19 vaccination were excluded.

Results: A total of 515 patients, mean age 62±14 years, 57% male, 46% White, 94% HD and vintage 4.6±4.4 years[EL1], [HJM2] had 835 RBD s-Ab levels assessed at a median of 59 days (range 0-422 days) post COVID-19 diagnosis. RBD s-Ab levels were assessed 1, 2 or ≥3 times in 64%, 18% and 18% patients, respectively. Only 32 (6.2%) patients had undetectable RBD s-Ab on the last draw. A cross sectional summary of the last available RBD s-Ab levels suggests that titers remain detectable for long duration (Figure[EL3] [HJM4]). In patients (N=186; 36%) with multiple RBD s-Ab levels (mean 28±15; median 28 days between levels), subsequent values were higher, lower [EL5] [HJM6] or unchanged 7%, 16% and 77% of time[EL7], respectively.

Conclusions: Most maintenance dialysis patients sampled developed SARS-CoV-2 RBD s-Ab after COVID diagnosis, and durability extends up to 14 months. Further elucidation of longitudinal RBD s-Ab values post-COVID-19 infection as well as after completing vaccination for SARS-CoV-2 is needed.



PO0150

COVID-19 Vaccine and Multiple Viral Infection: Cross-Reaction?

Jose Rivera Sepulveda, Elizabeth Pabon-Vazquez. *Mayaguez Medical Center, Mayaguez, Puerto Rico.*

Introduction: The COVID-19 pandemic has brought a lot of challenges in the medical and educational field. Every day, new facts and knowledge are published about the pathophysiology, treatment, and prognosis of COVID-19 patients. In addition, community response to vaccination and vaccine side effects has been one of the major talking points in social media. The general public wants to fully understand if the vaccine really provides immunity and possible side effects of its use.

Case Description: Under this premise, a 36 y/o female patient with a past medical history of type 2 diabetes mellitus, hypertension and obesity came to emergency department 2 days after she received the second dose of Moderna COVID-19 vaccine, and developed non-quantified fever, general malaise, vomiting and watery diarrhea. Associated symptoms were scattered non-blanching maculopapular rash from head to shoulders to mid back and abdomen, pustules inside ear and decrease urine output. Patient was unable to urinate for at least 48hrs. Laboratory bloodwork was remarkable for hyponatremia, hypochloremia, high anion gap metabolic acidosis and creatinine clearance of 18ml/min. Hepatic enzymes were more than five times elevated, and total bilirubin was elevated as well. Urinalysis reported proteinuria, positive leukocytes esterase, few calcium oxalate crystals and many urate amorphous sediment. Patient was convinced that symptoms were related to COVID-19 vaccination. Etiology of symptoms remained unclear at admission, for that reason she was admitted and received isotonic IV fluids. Further laboratory bloodwork reported elevated LDH, creatinine kinase and hypertriglyceridemia. In addition, infectious disease workup was performed, in which HAV, VZV, EBV, CMV IgM were positive. Patient received inpatient supportive care for five days. Renal function normalized, rash improve and the patient was discharged home with close follow up.

Discussion: There are different reasons that could explain patient's acute kidney injury. From dehydration to sepsis is the spectrum of differential diagnosis in this patient. The renal function recovery after hydration, clearly suggest pre-renal injury. Viral infection could be the primary reason of her dehydration. However, the event of vaccination, could not be completely ruled out. Was the vaccine a catalyst for viral infection? Or was the vaccine a confounder in this patient's renal failure?

PO0151

Five-Month Impact of Tozinameran (BNT162b2) Vaccine on Kidney Transplant and Dialysis Patients: Serology and Clinical Outcomes

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Background: Dialysis-treated (DT) and kidney transplant (TX) patients face higher morbidly and mortality risks than the general population during COVID-19 pandemic. Determining humoral response and associated COVID-19 morbidity after vaccination will guide risk assessment and changes in vaccination policy in this vulnerable population.

Methods: Prospective cohort study up to 5 months follow-up after Tozinameran or SARS-CoV-2 infection. Primary outcomes: qualitative and quantitative anti S1/S2 antibody (ABs) and disease rates during follow up. Anti-SARS-2 IgG ABs were quantified using LIAISON SARS-CoV-2 S1/S2 IgG (DiaSorin) immunoassay in serum of TX, DT and treating team at our hospital. Demographics and clinical data were collected from participants files.

Results: 174 DT patients (40% women, age 65±15 years) 253 TX patients (33%, 53±14 years) and 71 control participants (65%, 44±14 years) were recruited. 3 months or more after vaccination we detected anti S1/S2 ABs in 81% of DT (95%CI, 72-90%), 43% of TX (95%CI, 29-57%) and 100% of controls. After COVID-19 respective rates were 94% (95%CI, 83-100%), 75% (95%CI, 60-90%) and 100%. Quantitative titers were in line with qualitative ones. Predictors of negative serology were older age, diabetes, cancer history, lower lymphocyte count and lower vitamin D. Peritoneal dialysis predicted higher titers compared to hemodialysis. In TX, hypertension and higher levels of immnosupression predicated lower titers. Vaccination was associated with fewer subsequent COVID-19 infections (HR=0.23, 95% CI 0.05-0.99, p<0.05). Higher antibody titers associated with fewer events, HR 0.41/unit increase in $\log_{10}$ titer (p<0.05).

Conclusions: Patients with ESRD, particularly TX, mounted delayed and diminished antibody response to vaccination, and lesser response was associated with more infections. Thus, measures to protect non-responsive patients are urgently required.

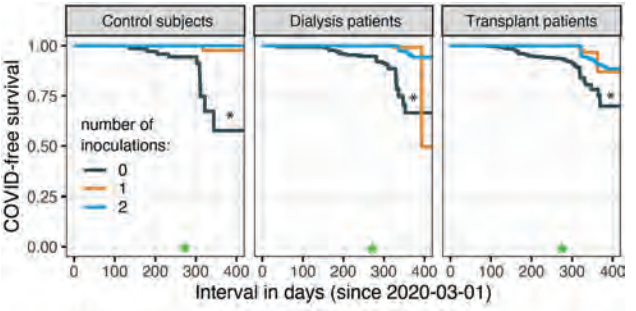

Figure: KM curves depicting COVID-19 infections according to vaccination status in all participants separated by study group. Vaccination began at ~day 270 (green symbol). * denotes p<0.05 for the comparison between 2 and 0-1 inoculations.

PO0152

Antibody Response Post SARS-CoV-2 Vaccination in Kidney Transplant Recipients

Maria Butiu, Nicolae Leca, Ramasamy Bakthavatsalam. *University of Washington, Seattle, WA.*

Background: This project aims to analyze the proportion of patients who did not develop antibodies following COVID-19 vaccination and to ensure that the immune stimulation secondary to the vaccine is not associated with clinical rejection and DSA development.

Methods: Samples collected from COVID-19 vaccinated kidney transplant recipients from 3/1/21-4/26/21 were tested for DSA and COVID-19 antibodies using a multi-antigen detection Luminex platform (BioRad). The following were tested: receptor binding domain IgG, spike 1 IgG, spike 2 IgG, nucleocapsid IgG.

Results: 94 patients were included in this study. 57% had no antibodies post second dose of COVID-19 vaccination. This number decreased to 52% when looking at samples collected >2 weeks after the final vaccine dose. Of all positive patients, 19% showed evidence of previous COVID-19 infection based on nucleocapsid positivity, which if excluded from the cohort analysis, lead to a higher rate of patients not responding to the vaccine. We did not observe a correlation between antibody positivity and demographics or clinical characteristics. Only 2 patients developed new DSA post-vaccination(avg MFI 1600). No episodes of clinical rejection were noted. 10 patients provided multiple samples, of which 5 had positive antibodies with an average decrease of 17 U/mL for S1 IgG per week.

Conclusions: When excluding patients previously infected with COVID-19, the rate of positive antibody formation post vaccine is 35%. More research needs to be done to understand the correlation of antibody response and protection against COVID-19 infection.

Variables	Negative CoV-2 Antibodies	Positive CoV-2 Antibodies			P value
		S1+/S2 -	S1+/S2 +	S1-/S2+	
No. Patients	32 (52%)	20 (66.7%)	30 (48%) 9 (30%)	1 (3.3%)	
Age Category					
18-39	0 (0%)	4 (80%)	5 (100%) 1 (20%)	0 (0%)	0.1166
40-59	7 (64%)	3 (75%)	4 (36%) 1 (25%)	0 (0%)	
>=60	25 (54%)	13 (61.9%)	21 (46%) 7 (33.3%)	1 (4.8%)	
Sex					
Male	15 (51%)	9 (64.3%)	14 (49%) 4 (28.6%)	1 (7.1%)	1
Female	17 (53%)	11 (73.3%)	15 (47%) 5 (33.3%)	0 (0%)	
Race					
White	23 (52%)	13 (61.9%)	21 (48%) 7 (33.3%)	1 (4.8%)	0.4759
Black or African American	3 (75%)	1 (100%)	1 (25%) 0 (0%)	0 (0%)	
Asian or Pacific Islander	5 (38%)	6 (75%)	8 (62%) 2 (14.3%)	0 (0%)	
American Indian or Alaska Native	1 (100%)	0 (%)	0 (0%) 0 (%)	0 (%)	
Years post transplant					
<1 year	13 (59%)	5 (55.6%)	9 (41%) 3 (21.4%)	1 (7.1%)	0.3108
>1 year	19 (47.5%)	15 (71.4%)	21 (52.5%) 6 (42.9%)	0 (0%)	
Vaccine					
Moderna	14 (44%)	10 (55.6%)	18 (56%) 7 (38.9%)	1 (5.6%)	0.1266
Pfizer	16 (59%)	9 (81.8%)	11 (41%) 2 (18.2%)	0 (0%)	
Johnson&Johnson	2 (100%)	0 (0%)	0 (0%) 0 (0%)	0 (0%)	
cPRA pre-transplant					
0	26 (53%)	15 (65.2%)	23 (47%) 7 (30.4%)	1 (4.3%)	0.908
<50	2 (40%)	2 (66.7%)	3 (60%) 1 (33.3%)	0 (0%)	
>50	4 (50%)	3 (75%)	4 (50%) 1 (25%)	0 (0%)	
Matintenance immunosuppressant regimen					
Antimetabolites	28 (53%)	17 (68%)	25 (47%) 7 (28%)	1 (4%)	0.3525
No Antimetabolites	4 (44%)	3 (60%)	5 (56%) 2 (40%)	0 (0%)	

Demographics and Clinical Characteristics

Antibody Type	Avg. Titer for S1+/S2-	Avg. Tier for S1+/S2+
RBD IgG (U/mL)	303	686
S1 IgG (U/mL)	212	556
S2 IgG (U/mL)	N/A	27

Average Antibody Titers

PO0153

Comparison of Safety and Outcomes Related to Remdesivir Use Among Dialysis Patients Hospitalized with COVID-19

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Background: Use of remdesivir in the treatment of dialysis patients with Coronavirus Disease 2019 (COVID-19) has been limited due to inconclusive data regarding safety outcomes among patients with severe renal impairment. For this reason, the FDA has not recommended remdesivir use in patients with eGFR < 30 ml/min per 1.73 m^2. We sought to evaluate outcomes among dialysis patients with COVID-19 who received remdesivir in a real-world setting.

Methods: We conducted a retrospective study of patients on hemodialysis or peritoneal dialysis hospitalized with COVID-19 between 5/1/2020 - 1/31/2021 within the integrated health system of Kaiser Permanente Southern California. Patients with a COVID-19 International Classification of Diseases (ICD)-10 code: U07.1 and laboratory confirmed SARS-CoV-2 infection within 14 days prior to admission date to two days after admission date were included. The primary endpoint was 30-day all-cause mortality. Secondary endpoints were intensive care unit (ICU) stay, and evidence of acute liver injury defined as AST and/or ALT values >5x upper limit of normal.

Results: A total of 486 patients (407 hemodialysis and 79 peritoneal dialysis) met inclusion criteria. Among those, 112 patients (23%) were treated with remdesivir, with median treatment time of 4 days (IQR: 2-5). Mean age was 63.8 years with 63.8% male and 63.0% Hispanic patients. There were 80.2% of patients who received treatment with steroids during hospitalization. Relative risk (RR) for all-cause 30-day mortality was 0.74 (95% CI: 0.52-1.05) in remdesivir treated patients compared to untreated patients. Acute liver injury occurred in 1.8% and 2.4% of remdesivir treated and untreated patients, respectively. ICU admissions occurred in 14.3% of remdesivir treated and 16% of untreated patients.

Conclusions: Among dialysis patients hospitalized with COVID-19, treatment with remdesivir was not associated with worse outcomes in terms of liver injury or ICU admission, and demonstrated a trend (26% lower risk) toward decrease in 30-day mortality, though no statistical significance was found due to insufficient power.

PO0154

Outcomes Associated with Tocilizumab Use in Patients with COVID-19 Infection Complicated by Severe AKI Requiring Continuous Renal Replacement Therapy

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Background: The percentage of critically ill amongst COVID-19 infected patients stands at 5%. The incidence of acute kidney injury in those patients varies according to risk factors. A little is known about the use of Tocilizumab in patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT)

Methods: This is a retrospective study of 22 COVID-19 patients. Patients were between 18 and 80 years old, had proven COVID-19 infection, were admitted to the ICU between April 1 and July 15, 2020, received CRRT and Tocilizumab parenterally. Other therapies included antivirals, hydroxychloroqine and convalescent plasma. We reported biochemical outcomes related to cytokine storm as well as clinical outcomes; Those included ventilator dependence, renal outcomes, length of hospital stay and mortality

Results: 21 out of 22 patients were males. Median age was 56 years. 14 patients had hypertension and 13 had diabetes mellitus. All patients had cytokine storm on admission (elevated IL-6 and CRP levels). At the completion of the follow up (average 44.4 days), 20 out of 22 patients experienced improvement in IL-6 and CRP levels. 11 patients died. 13 experienced improvement in oxygen requirements including 9 who were succesfully extubated. 13 were still on CRRT (including 10 patients who died) while 9 patients became dialysis independent (5 had complete recovery of kidney function and 4 developed chronic kidney disease). There was no reported side effect from using tocilizumab

Conclusions: Tocilizumab can be considered in critically ill COVID-19 patients with severe AKI and cytokine storm. No dose adjustment is needed in patients on CRRT. Further studies are required to confirm our results.

Table 1. Demographics and laboratory findings

Patient	AGE (Years)	SEX	Fever	Cough	Admission Creatinine µmol/L	Hematuria	Proteinuria	Lymphopenia	Lactate on admission mmol/L	Procalcitonin on admission mcg/L	D-Dimer on admission mcg/L	Fibrinogen on admission g/L	Ferritin on admission mcg/L
1	43	M	Y	Y	269	N/A	N/A	Y	3.16	32.7	>4	6.24	844
2	59	M	Y	Y	62	Y	Y	Y	1.48	0.96	0.69	6.59	2226
3	46	M	Y	Y	132	N/A	N/A	Y	1.85	>100	3.79	7.14	5490
4	51	M	Y	Y	116	Y	Y	Y	1.22	2.45	>4	7.06	748
5	56	M	N	N	116	N/A	N/A	Y	1.57	1.61	>4	6.06	573
6	67	M	Y	Y	115	Y	Y	Y	2.9	0.88	>4	6.62	1148
7	52	M	Y	N	62	Y	Y	Y	2.07	1.77	>4	>8	1142
8	79	M	Y	Y	82	Y	Y	Y	2.51	0.18	>4	N/A	1260
9	51	F	Y	N	58	Y	Y	Y	1.42	0.41	0.77	5.87	1515
10	80	M	Y	Y	75	N	Y	N	1.63	0.09	0.35	5.89	556
11	64	M	N	N	758	Y	Y	N	1.19	9.84	>4	6.97	2429
12	42	M	Y	Y	399	Y	Y	Y	1.40	14.26	>4	3.78	738
13	34	M	N	N	470	Y	Y	Y	0.85	8.9	2.64	6.96	2937
14	44	M	N	N	149	Y	N	Y	1.8	0.96	>4	2.51	2519
15	62	M	Y	Y	260	Y	Y	Y	1.01	11.89	2.66	>8	500
16	65	M	Y	N	66	Y	Y	Y	1.59	0.32	0.5	5.34	1644
17	55	M	Y	Y	389	N/A	N/A	Y	7.10	75.45	>4	>8	5112
18	46	M	Y	Y	60	Y	Y	Y	0.94	0.47	>4	6.26	1406
19	70	M	Y	Y	71	Y	Y	Y	1.61	0.21	2.49	>8	710
20	44	M	Y	Y	88	Y	Y	Y	1.19	0.57	>4	6.12	3486
21	68	M	Y	N	67	Y	Y	Y	1.06	0.11	0.66	5.71	790
22	52	M	Y	N	48	Y	Y	Y	2.31	0.17	>4	3.26	1613

Table 1: Y=Yes, N=No, N/A=Not available, lymphopenia (White cells <1500/mm^3)

PO0155

Safety of Bamlanivimab Monotherapy Administered in Dialysis Centers to Hemodialysis Patients for COVID-19

Katherine L. Mckeon,[1] Scott Sibbel,[1] Karl Wendt,[1] Nicole Macioce,[2] Francesca Tentori,[1] Steven M. Brunelli,[1] Irina Goykhman,[2] George R. Aronoff.[2] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: Bamlanivimab (Eli Lilly) is an intravenously administered monoclonal antibody that was granted an emergency use authorization (EUA) by the US Food and Drug Administration for the treatment of mild to moderate COVID-19 on 09 Nov 2020.

On 16 Apr 2021, the EUA was revoked over concerns of resistance among SARS-CoV-2 variants. Between 01 Jan and 16 April 2021, physicians at DaVita dialysis clinics were able to order bamlanivimab (700 mg) treatment during dialysis for nonhospitalized hemodialysis patients who tested positive for SARS-CoV-2 infection and met the eligibility criteria. Here, we report safety data among dialysis patients who received bamlanivimab as a monotherapy for COVID-19.

Methods: Bamlanivimab was administered intravenously as a single dose over the course of 60 minutes during a regularly scheduled hemodialysis session. All patients were monitored for at least 1 hour after bamlanivimab administration. All facilities were required to have emergency medications on-site, and staff were trained to identify and treat potential reactions. A serious adverse event was considered if a patient developed anaphylaxis or any condition requiring use of an epinephrine injection (1:10,000 IM) or albuterol, was sent to the emergency department, or was hospitalized after bamlanivimab administration. An adverse event was considered if a patient developed fever, chills, hives, rash, hypotension, headache, nausea, fatigue, dizziness, angioedema, muscle pain, or throat irritation.

Results: 264 patients with newly diagnosed SARS-COV-2 infections received a single dose of bamlanivimab at DaVita. Among all patients who received the drug, 46% were female and the mean age was 60 years. On average, patients were followed for 64 days postinfusion. There were 0 adverse events or serious adverse events documented in the 1-hour postadministration observation window.

Conclusions: Bamlanivimab was found to be safe in dialysis patients.

Patients	264
Days postadministration, mean ± SD	63.5 ± 23.9
Age, years, mean ± SD	60.3 ± 14.4
Female sex, n (%)	121 (45.8)
Severe adverse events within 1-hour postadminstration, n (%)	0 (0.0)
Adverse events within 1-hour postadminstration, n (%)	0 (0.0)

Abbreviations: SD, standard deviation

PO0156

Intravenous Immunoglobulin: Answer to COVID-19?

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Introduction: Traditionally intravenous immunoglobulin (IVIG) has been used for immunodeficiency disorders. It has been also used in certain autoimmune and infectious diseases. IVIG has several immunomodulatory and anti-inflammatory effects. Here, we are reporting a case where IVIG was used for BK viremia in a patient with COVID-19 pneumonia who showed dramatic recovery of COVID-19 symptoms and laboratory parameters.

Case Description: Our patient is a 55-year-old African American male who received simultaneous pancreas and kidney transplant in April 2019 with induction immunosuppression with thymoglobulin and was on chronic immunosuppression with Tacrolimus and Mycophenolic mofetil. His Post-transplant course was complicated by BK viremia and presumed BK nephropathy after 2 months. His immunosuppression was gradually tapered off but his viremia was persistent despite being off Mycophenolate and low target goal of Tacrolimus. Patient partially responded to high dose IVIG so we decided to continue monthly high dose IVIG with daily Leflunomide. Later in April 2021, patient was admitted with COVID-19 symptoms with normal oxygen saturation at room air. His clinical condition worsened over the following 4-5 days in the form of hypoxic respiratory failure requiring high flow oxygen supplements and Acute Kidney injury (AKI) with nephrotic range proteinuria and gradual rising inflammatory markers. Patient was about to be transferred to the Intensive Care Unit as his clinical condition was worsening and refractory to the traditional treatment with steroid and antibiotics. On day 10 he received his monthly due dose of IVIG therapy (0.5 gm/kg of body weight for 4 consecutive days). His COVID symptoms started to improve from day 2 of the treatment. His inflammatory markers were dramatically down trended over the next 3-4 days post IVIG. He was discharged home with oxygen therapy (3L/min) by the day 5 post treatment with IVIG with recovering AKI.

Discussion: Few international studies have reported that initiation of high dose IVIG as adjuvant treatment for COVID-19 disease in selected patients may result in early clinical and laboratory recovery. The studies are limited due to the small sample size and patient selection criteria. Although our patient exhibited dramatic recovery, randomized clinical trial needs to be done to explore more about effect on COVID-19 pneumonia and COVID-19 associated AKI.

PO0157

CytoResc, or CytoSorb for COVID-19 Patients with Vasoplegic Shock: A Prospective Randomized Pilot Study

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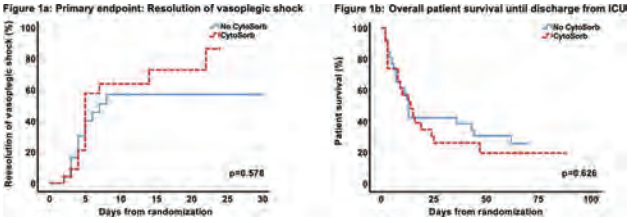
Background: Several observations indicate a hyperinflammatory state in severely ill COVID-19 patients as target for therapeutic interventions. The aim of this study was to investigate the effect of extracorporeal cytokine elimination by CytoSorb on COVID-19 associated vasoplegic shock.

Methods: In this prospective randomized pilotstudy patients with vasoplegic shock requiring norepinephrine >0.2 µg/kg/min, CRP >100 mg/L and indication for kidney replacement therapy were randomized 1:1 to receive CytoSorb treatment for 3-7 days or standard of care. The primary endpoint was time until resolution of vasoplegic shock (freedom of vasopressor therapy for at least 8 hours to sustain a MAP ≥65mmHg). Data were analyzed using Cox-regression and Kaplan-Meier curves.

Results: From November 2020 - March 2021 50 patients were enrolled. Of these 23 patients received CytoSorb treatment, 26 patients received standard of care and 1 patient had to be excluded due to withdrawal of informed consent. The median age was 61 (IQR 58-65) years in the CytoSorb group and 66 (IQR 60-71) years in the control group. Patients were predominantly male (CytoSorb 91.3% vs. control 76.9%). Comorbidities and indicators for disease severity were well balanced. The primary endpoint was reached in 13/23 patients (56.5%) in the CytoSorb and 12/26 patients (46.2%) in the control group after a median of 5 (IQR 4-5) and 4 days (IQR 3-5), respectively (Figure 1a). The Cox-regression analysis for the primary endpoint showed no statistically significant difference between the groups with and without adjustment for the predefined additional variables age, gender, ECMO-therapy or time from beginning of shock until study inclusion. ICU-mortality was high with 18/23 (78%) deaths in the CytoSorb and 19/26 (73%) deaths in the control group (Figure 1b).

Conclusions: In this pilot trial in severely ill COVID-19 patients CytoSorb treatment did neither lead to a faster resolution of vasoplegic shock as compared to standard of care, nor was it associated with altered mortality.



PO0158

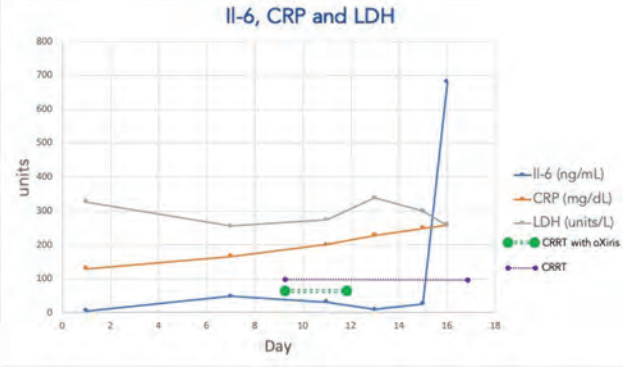
CRRT with the oXiris Filter Attenuates IL-6 in a Patient with Severe COVID-19

Jennifer C. Tang, Thanh Cao. *Keck Hospital of USC, Los Angeles, CA.*

Introduction: SARS-CoV-2 infection can result in ARDS and multiorgan dysfunction. The pathophysiology underlying Covid-19 includes a hypercoagulable state and a cytokine release storm with upregulation of IL-6, IL-10, and TNF-alpha, which are associated with ICU admission, ARDS, AKI, and increased mortality. While there are no proven treatments for this cytokine storm, tocilizumab, has shown promise in studies against severe Covid-19, suggesting that cytokine removal via blood purification products like oXiris may help achieve immune homeostasis.

Case Description: A 70-year-old male status post DDRT in 2016 presented with fevers, malaise, and dyspnea. He tested positive for SARS-CoV-2 and was admitted requiring high-flow nasal cannula with a rate of 50L/min and FiO2 of 90%. Urinalysis revealed pyuria, hematuria, and proteinuria. Labs revealed a creatinine of 2.4 and a BUN of 61 as well as a CRP of 130, ESR of 65, D-dimer of 1048, LDH of 325, ferritin of 3891, and IL-6 of 5.6 consistent with severe Covid-19. An ultrasound of his allograft kidney was normal. The patient then went into PEA arrest and was intubated with decreasing urine output, therefore was initiated on CRRT with an oXiris filter for 48 hours followed by a M150 filter. His P/F ratio increased and his IL-6 and SOFA score decreased while on the oXiris filter, however both CRP and LDH increased. After switching filters, the patient's P/F ratio quickly declined with a rapid increase of IL-6. Ultimately, the family decided to withdraw care.

Discussion: The oXiris filter could potentially manage the cytokine storm seen in Covid-19 as it is the only filter shown to remove cytokine and endotoxins, improve renal function, and have antithrombogenic properties as it is grafted with heparin. It is an AN69-based oXiris membrane treated on the inside with a high concentration of polyethyleneimine (PEI) binding cytokines and endotoxins. Given the impact of Covid-19, more studies must be done to assess if oXiris may serve as an effective treatment.



Graph demonstrating Day of Admission vs IL-6, CRP, and LDH.

PO0159

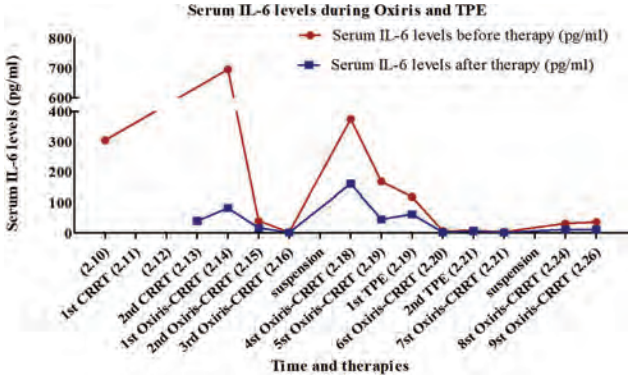
Blood Purification in a Critically Ill COVID-19 Patient with Cytokine Storm: A Case Report

Wenya Cao. *Dialysis Department of Nephrology Hospital, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Introduction: Cytokine storm syndrome (CSS) is a common and severe cause of mortality among critically ill COVID-19 patients. BPTs, especially continuous renal replacement therapy (CRRT), may work by removing cytokines and blocking the cascade of inflammation and thus preventing the progression of CSS. However, the efficacy of Blood purification therapies (BPTs) in patients with complications of CSS but without AKI(Acute kidney injury) is still controversial.

Case Description: We report the case of a 66-year-old female who had severe COVID-19 without AKI. After admission, the patient's condition progressed rapidly to severe respiratory failure and heart failure, and she had been treated with venous-venous extracorporeal membrane oxygenation (VV-ECMO). Meanwhile, the level of interleukin-6 (IL-6) increased rapidly and reached 304.8 pg/ml. Although there was no kidney impairment in our patient, CRRT was initiated to reduce the levels of cytokines in circulation, while the decrease in IL-6 in serum and dialysate was not significant. Oxiris-CRRT was then introduced and there was a significant decline in serum levels of IL-6 after 3 Oxiris-CRRT sessions. However, when we stopped Oxiris-CRRT after the third treatment, the serum levels of IL-6 were elevated again 12 hours after the suspension of Oxiris-CRRT Subsequently. Therefore, the patient received 6 additional Oxiris-CRRT sessions until the serum IL-6 levels of 2.67 pg/ml. After 144 days of hospitalization, including 2 CRRT sessions, 9 Oxiris-CRRT sessions and 2 therapeutic plasma exchange (TPE) sessions, she completely recovered (shown in Fig. 1).

Discussion: In our patient, BPTs, especially Oxiris-CRRT, showed unique superiority and application value in the clearance of excess plasma cytokines, promoting a smooth recovery, which suggests that even if AKI does not occur, it is beneficial to use BPTs to prevent the progression of CSS in COVID-19 patients.



IL-6 levels gradually decreased to normal levels after 9 sessions of Oxiris-CRRT and two sessions of TPE.

PO0160

COVID-19 vs. Bloodstream Purification: A Targeted Therapy

Sean Barnett. *Brooke Army Medical Center, Fort Sam Houston, TX.*

Background: The use of bloodstream purification has been well studied in bacteremia but the emergence of COVID found a new target. Using blood purification in the fight against COVID we have found a potential treatment for viremia and pneumonia, cytokine storm and decompensation, and superinfections in COVID. When used at the appropriate time, blood purification has the potential to prevent further organ injury.

Methods: The following case series is an individual clinical observation of patients withing the PURIFY NIH funded clinical trial.

Results: 28M w/o significant PMHx, transferred to BAMC for ECMO due to severe COVID. He initially improved, but decompensated with MRSA bacteremia, was ECMO/CRRT and quadruple pressor dependent. He was treated with the Seraph for bloodstream purification and was off all vasopressors within 6 hours. He recovered, and was ultimately discharged without ECLS depdence. 64 M w/ CAD and CKD was admitted for mild COVID PNA requiring minimal o2. On hospital day 9-11 he decompensated ultimately requiring intubation and vasopressor support with AKI and oliguria. He was treated with the Seraph for 16 hours and was off vasopressors within 10 hours, urine output recovered within 24 hours, he was extubated in 48 hours and discharged from the ICU after 96 hours. 52 M w/ CKD/COPD/CHF/CAD admitted for mild COVID PNA, decompensated on day 12, required intubation / vasopressor support / CRRT, treated for 24 hours on CRRT with the Seraph Filter and was off vasopressors with returning renal function within 24 hours. 64 M w/ CKD/CHF/CAD admitted for NSTEMI and cardiogenic shock, found to be non-obstructive and likely viral cardiomyopathy due to COVID. He was started on dobutamine / levophed and IABP. Due to oliguria he was treated with CRRT and Seraph for blood purification. Within hours he was off vasopressors, no longer needing IABP after 24 hours, and ultimately recovered renal function within 48 hours.

Conclusions: While further study is needed, the use of blood purification for specific targets in COVID appears to have incredible benefits. Due to documented pathogen removal (bacteria/fungi/virions) it is likely beneficial treatment for any bloodstream infections, but especially in the susceptible COVID population it seems to have miraculous benefit. The Seraph also appears to mitigate organ injury from the cytokine storm in COVID due to attenuation of the cytokine storm.

Funding: Other U.S. Government Support

PO0161

Hemoperfusion with Seraph® Filter Late in the Course of Severe COVID-19 Pneumonia

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Introduction: Severe COVID-19 infection is often associated with uncontrolled cytokine response and a milieu of circulating inflammatory markers. Cytokine adsorption with viral binding of SARS-CoV-2 has been utilized in severe COVID-19 cases under emergency use authorization by the FDA. Evolving observations of its use showed reduction in inflammatory markers; improvement in hemodynamics; reduction of vasopressor requirements and oxygen support; and avoidance or reduction of time on mechanical ventilation. We report a case of hemoperfusion utilizing the Seraph® filter as a last resource in a patient with life-threatening COVID-19 infection.

Case Description: A 37-year old female with a diagnosis of morbid obesity (BMI 60 kg/m^2) presented to the University of Kentucky hospital with acute respiratory failure from COVID-19 pneumonia. The patient required ICU care, mechanical ventilation and eventually extracorporeal mechanical oxygenation (ECMO) on day 5 of her hospital stay. Despite aggressive COVID-19 management, her condition gradually worsened. On day 15 of her hospital stay, extracorporeal sorbent hemoperfusion via Seraph® filter was delivered through PrismaFlex® in tandem with the ECMO circuit. Her serum IL-6 levels dropped from 154 pg/ml to 29 pg/ml, and C-reactive protein from 317 mg/L to 294 mg/L within 2 hours of treatment completion. She had intermittent fevers up to 40C, especially in the 48 hours prior to treatment which resolved right away with hemoperfusion and she remained afebrile for the next 72 hours. There was, however, no significant change in her hemodynamics and overall clinical status and the patient remains on ECMO and mechanical ventilation at the time of this report (Day 34).

Discussion: This case exemplifies that hemoperfusion therapy delivered late in the course of severe COVID-19 disease is still effective in decreasing circulating inflammatory markers, but may not be effective in significantly and positively affecting clinical outcomes. Although circulating inflammatory markers could be used to guide eligibility for hemoperfusion therapy, timing of hemoperfusion should be considered in clinical trials to effectively test the potential of this intervention to ameliorate clinical outcomes in susceptible populations.

PO0162

Direct Hemoperfusion Using a Polymyxin B-Immobilized Polystyrene Column for COVID-19

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Background: The involvement of increased cytokine levels in severe COVID-19 has been noted, and anti-inflammatory therapy including corticosteroids or anti-human interleukin (IL)-6 receptor monoclonal antibody is expected to be effective in such patients. Direct hemoperfusion using a polymyxin B-immobilized polystyrene column (PMX) is a treatment that selectively adsorbs endotoxins; it is also expected to adsorb a variety of endogenous substances.

Methods: The patients (N=22) included were those whose respiratory samples tested positive for SARS-CoV-2 upon real-time reverse transcription-polymerase chain reaction (RT-PCR) and underwent PMX during hospitalization at National Center for Global Health and Medicine, Tokyo, Japan between January 30 2020 and April 30, 2021. PMX was considered when an image of pneumonia consistent with COVID-19 was obtained on chest CT and the P/F ratio was less than 300. Demographic data, information on clinical symptoms, and laboratory data were collected.

Results: On day 15 of first PMX treatment, disease severity decreased in 63.6 % of the patients. P/F ratio increased and there was a downward trend in urine β2-microglobulin on days 4 and 8. Cytokine level measurement pre- and post-PMX revealed a downward trend in interleukin-6 levels and decreased levels of the factors involved in vascular endothelial injury, including vascular endothelial growth factor. There were 43 PMX, of which nine and five caused an increase in inlet pressure and membrane coagulation, respectively. When the membranes coagulated, the circuitry needed to be reconfigured.

Conclusions: PMX is expected to become a therapy to address medical needs and prevent the exacerbation from moderate to severe condition in COVID-19.

PO0163

Plasma Exchange to Treat Patients with Severe COVID-19

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Background: The clinical spectrum of coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to critical illness and death in up to 89% of mechanically ventilated patients. Therefore, new therapeutic strategies are needed. Recent evidence

suggests a multi-level inflammatory syndrome in some of the most critically ill patients with overlapping features of other hyperinflammatory or autoimmune diseases. Thus, plasma exchange (PE) has become a subject of controversy as potential therapy in these patients. Here, we report the results of the so far largest cohort of critically ill COVID-19 patients treated with PE.

Methods: All critically ill COVID-19 patients treated with PE at Heidelberg University Hospital were analyzed between April and December 2020. Disease course and outcomes were compared with a standard care control group matched for age, sex, and disease severity. Changes in laboratory and clinical parameters were studied longitudinally. Kaplan-Meier and Cox regression analyses were performed.

Results: In total, 28 critically ill COVID-19 patients were treated with an average of 3 PE procedures per patient. No relevant complications occurred during PE therapy. Inflammatory markers and biochemical indicators of end-organ damage and endothelial activation were significantly reduced during PE. These laboratory changes were accompanied by normalization of body temperature, improved pulmonary function, and reduced vasopressor demand. Most importantly, the laboratory and clinical improvements were maintained after the last PE. In contrast, most parameters in the control group did not improve significantly over seven days, although baseline clinical and laboratory parameters were comparable in both groups. Kaplan-Meier analysis showed improved 30-day survival in the PE group compared to the control group (67.9% vs. 42.9%, p=0.044). In a multivariable analysis, the hazard ratio for death was 0.27 (95% CI 0.11-0.68, p=0.005) with PE versus standard care.

Conclusions: Our data further suggest that PE represents a potential therapeutic strategy for a subset of severe COVID-19 cases. The observed PE-related effects appear to go beyond a purely artificial improvement in blood parameters and may indicate a reversal of the complex COVID-19 immunopathology. Randomized controlled trials are urgently needed.

PO0164

COVID-Related Renal Thrombotic Microangiopathy: Role of Plasma Exchange

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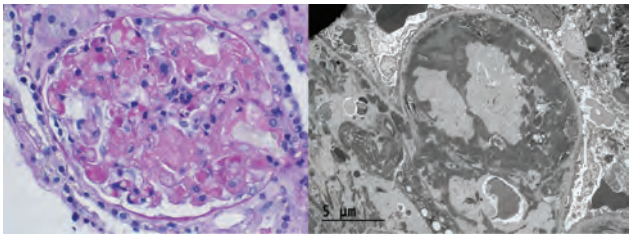
Introduction: The most common COVID-19 associated glomerular diseases are COVID associated nephropathy (COVAN) and Thrombotic Microangiopathy (TMA). Other less common glomerular diseases associated with COVID reported are antineutrophil cytoplasmic antibody (ANCA) vasculitis, anti-glomerular basement membrane (Anti GBM) antibody disease, podocytopathies, and IgA nephropathy. We report a case of TMA due to COVID-19 infection.

Case Description: A 67-year-old woman with asthma was admitted for COVID related respiratory failure and was noted to have acute kidney injury with anemia and thrombocytopenia. She was hypertensive and urine analysis was notable for hematuria and proteinuria. ANA, ANCA, Anti GBM, Coombs, ADAMTS13, disseminated intravascular coagulation panel, serum immune fixation and free light chains, cryoglobulins, and infectious work up were unrevealing. Complement C3 and C4 were low, lactate dehydrogenase and bilirubin were high, haptoglobin was undetectable, and schistocytes were seen on peripheral smear which raised concern for thrombotic microangiopathy. Renal function deteriorated rapidly with ensuing anuria prompting initiation of dialysis. Kidney biopsy confirmed acute thrombotic microangiopathy. She was started on plasma exchange (PLEX) for COVID related thrombotic microangiopathy and she started producing urine with rapid improvement in creatinine (Cr) after two treatments. Cr was down to 3.11mg/dL from a peak of 7.45 mg/dL after PLEX and normalized at discharge. The patient is currently being monitored with renal panel and complete blood picture every three months, as an outpatient.

Discussion: COVID is known to cause TMA that is presumed to be secondary to endothelial dysfunction and complement activation. There are no standard guidelines for treatment. Terminal complement blockade was not used in our patient. Our case demonstrates the efficacy of PLEX in the treatment of COVID related TMA. Early recognition and treatment is crucial and may reduce morbidity and mortality.



PO0165

Sustained Low-Efficiency Dialysis vs. Continuous Renal Replacement Therapy in Critically Ill COVID-19 Patients

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Background: Acute kidney injury among patients with COVID-19 infection is a poor prognostic indicator. There is limited evidence to guide the nephrology community if there are any risk or advantages of using sustained low-efficiency dialysis (SLED) or continuous renal replacement therapy (CRRT). We aim to evaluate the clinical outcomes of COVID-19 patients receiving renal replacement therapy in the intensive care unit (ICU).

Methods: This is a retrospective chart review of adult patients with COVID-19 admitted to ICU in the state of Qatar who had 1)acute kidney injury and 2)received renal replacement therapy between February to August of 2020. We evaluated clinical characteristic, severity of illness, mortality, and renal outcomes at 30 days.

Results: Among 127 patients with acute kidney injury requiring dialysis in ICU, 16 patients were on CRRT, 68 patients were on SLED, and 43 patients were on combination. We did not observe significant difference among age, gender, ethnicity or baseline creatinine. Most common indication for indication of dialysis was volume overload followed by acidosis in all three groups with serum creatinine of 264umol/L vs 499umol/L vs 351umol/L in CRRT, SLED and CRRT+SLED, respectively. Inflammatory markers, Pressore requirement and APACHE II score were similar between all groups. 30-day Survival was 23%, 50% and 9%. Among 34 patients on SLED who survived, 6 were dialysis dependent post COVID-19 infection.

Conclusions: Acute kidney failure in critically ill COVID-19 patients is associated with high mortality. A lower mortality, but high morbidity is observed in patients receiving SLED in critical care setting. Further investigation of SLED in COVID-19 should be considered.

PO0166

Detection of SARS-CoV-2 in Dialysis Effluent on a Peritoneal Dialysis Program in Mexico City: Four Cases

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Introduction: Since the rapid spread of the COVID 19 pandemic, it is crucial to identify possible sources of transmission of the SARS-COV-2 virus in order to perform procedures safely. There has been interest to identify the presence of SARS-CoV-2 in different compartments including peritoneal compartment. SARS-CoV-2 was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in dialysis effluent on a few single cases while other authors have reported negative results. Peritoneal membrane pores have a diameter of 20-40 nm while the SARS-CoV-2 virion diameter is between 60 to 140 nm, theoretically the virion could reach the peritoneal cavity by hematogenous diffusion or through the dialysis catheter after contact contamination.

Case Description: We report dialysis effluent findings of four patients, two women and two men, with an age range of 35 to 64 years and different comorbidities including: diabetes mellitus, hypertension and obesity. They were diagnosed with COVID-19 using RT-PCR assay on nasopharyngeal samples or by tomography findings. RT-PCR samples of peritoneal effluent were obtained with a length of stay on peritoneal cavity of 6 hours, without centrifugation of the sample. Three patients were positive for presence of SARS-CoV-2 on nasopharyngeal sample and dialysis effluent, while the fourth patient was negative in both samples despite having tomography findings suggestive of COVID-19 infection. It should be noted that in the 3 patients that had a positive RT-PCR on both nasopharyngeal and peritoneal effluent, samples were obtained within the first 7 days following the onset of symptoms associated with COVID-19 and on the fourth patient the peritoneal effluent sample was obtained 12 days after initial symptoms. All patients presented with acellular peritoneal fluid. No abdominal symptoms were reported.

Discussion: Presence of SARS-CoV-2 on peritoneal fluid continues to be a subject of debate. Peritoneal effluent sample-drawing procedure has not been standardized, which may explain the inconsistent results noted by different authors. The positive results of the RT-PCR for SARS-CoV2 on peritoneal effluent must be confirmed on a larger sample. Although based on a small group, these findings should prompt to consider these fluids as potentially infective.

PO0167

A Comparison of Clotting Rate During Hemodialysis in COVID-19 Patients Receiving Anticoagulant vs. No Anticoagulant in an Inpatient Setting

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Background: Anticoagulant use during hemodialysis is a standard practice in both outpatients and inpatients setting. In an inpatient setting with heightened acuity of illness, the potential for bleeding attributable to anticoagulant is concerning. Hospitals have started applying an anticoagulant free HD protocol with success. COVID-19 patients showed a degree of systemic hypercoagulability with unique features, including a consumptive disseminated intravascular coagulation coexisting with hyperfibrinolysis and increased bleeding risk. Maintaining circuit patency and avoiding bleeding risk has been challenging. Data regarding anticoagulant in COVID-19 patients who received hemodialysis is limited. This study's primary objective is to compare hemodialysis clotting rate in COVID-19 patients who received anticoagulant versus those without anticoagulant.

Methods: Retrospective chart review for all COVID-19 patients who received hemodialysis at Banner Medical Center Tucson Campus Between November 2020 and January 2021. Primary outcome was clotting rate during hemodialysis. CRRT was excluded.

Results: 330 total patients observed, 56% sessions in the ICU unit and 44% in the medicine unit. 57% were AKI and 43% were ESRD. Anticoagulant use was 38.5% (heparin IVP during hemodialysis was 12%, continuous systemic heparin was 16% and others (warfarin, DOAC, Argatroban, etc) was 11%). Clotting rate was 12%. Other characteristics can be seen on the table 1. There was no difference in the clotting rate between group with anticoagulant versus without anticoagulant (8% vs.15%, p value 0.06). Multivariable logistic regression for clotting outcome showed that compared to no-anticoagulation, systemic heparin continuous infusion decreased clotting by 83% (OR 0.17, 95% CI 0.04- 0.77, p-value=0.02) and others anticoagulant decreased clotting by 91% (OR=0.09, 95% CI 0.01-0.85); compared to AV fistula, temporary dialysis catheter increased clotting by 2.9x (OR 2.9, 95% CI 1.10-7.44, p-value=0.03); and every 10 increase in platelet count increased clotting by 4% (OR 1.04, 95% CI 1.01-1.07, p value =0.01)

Conclusions: No anticoagulation and temporary catheters carry high risk for clotting in patients with COVID undergoing iHD. Continuous heparin should be considered.

PO0168

Divergence Between Serum Creatinine and Cystatin C in Estimating Glomerular Filtration Rate of Critically Ill COVID-19 Patients

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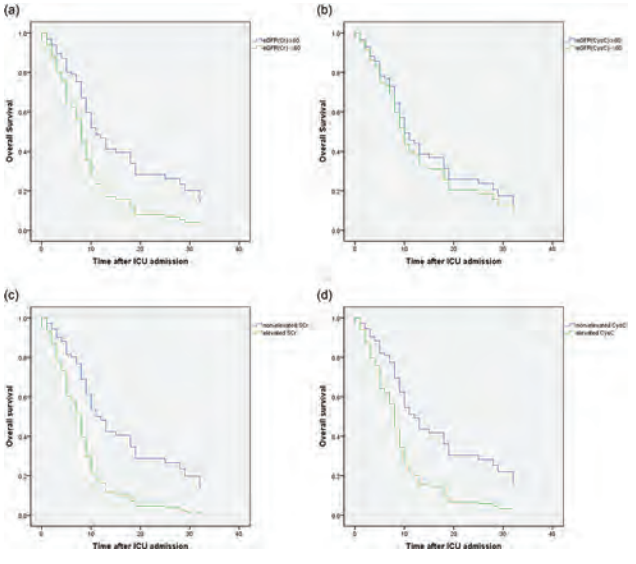
Background: The clinical use of serum creatine (sCr) and Cystatin C (CysC) in kidney function evaluation of critically ill patients has been in continuous discussion. The values of estimated glomerular filtration rate calculated by sCr(eGFRcr) and CysC (eGFRcysc) of critically ill COVID-19 patients were investigated in this study.

Methods: This is a retrospective, single-center study of critically ill patients with COVID-19 admitted in Intensive Care Unit (ICU) at Wuhan, China. Control cases were moderate COVID-19 patients who were matched in age and sex at a ratio of 1:1. The eGFRcr and eGFRcysc were compared. The association between eGFR and death were analyzed in critically ill cases. The potential factors leading to the divergence between eGFRcr and eGFRcysc were explored.

Results: A total of 76 critically ill COVID-19 patients were concluded. The mean age was 64.5±9.3 years and the male : female ratio was 49:27. At ICU admission, their eGFRcr (85.45 (IQR 60.58-99.23) ml/min*1.732m^2) were much higher than eGFRcysc (60.6 (IQR 34.75-79.06) ml/min*1.732m^2). About 50% of them showed eGFRcysc < 60 ml/min/1.73 m2 while 25% showed eGFRcr < 60 ml/min/1.73 m^2 (c^2=10.133,P=0.001). This divergence was not observed in control group. The potential factors influencing the divergence included serum interlekin-6(IL-6)level, tumor necrosis factor(TNF-α) level as well as APACHEII. Reduced eGFRcr (<60 mL/min/1.73 m2) was associated with death(HR=1.939,95%CI 1.078-3.489, P=0.027).

Conclusions: The eGFRcr was higher than eGFRcysc in critically ill cases. The divergence might be affected by the inflammatory condition. Reduced eGFRcr predicted in-hospital death. In these patients, we advocate for caution when using eGFRcysc.

Funding: Private Foundation Support



The Kaplan-Meier survival curves for critically ill patients divided by reduced eGFRcr (a), reduced eGFRcysc (b), elevated sCr(c) and elevated CysC (d).

PO0169

Serum Sodium and Patient Symptoms in COVID-19 Hospitalizations

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Background: Disorders of serum sodium (SNa) are common in hospitalized patients with COVID-19 and associated with longer length of stay and inpatient mortality. However, the association of SNa with patient-reported outcomes is not clear.

Methods: The Brigham and Women's Hospital COVID-19 Registry is a prospective cohort study of consecutive, adult patients admitted with confirmed SARS-CoV-2 infection (n=809). We examined the association of SNa (continuous and tertiles) at admission with: 1) patient symptoms obtained from detailed chart review; and 2) in-hospital mortality using unadjusted and adjusted logistic regression models. Covariates included demographic data and comorbidities. Only index admissions were considered.

Results: Mean age was 60 years, 48% were male, and 35% had diabetes. The most frequent symptoms were cough (64%), fever (60%) and shortness of breath (46%). In adjusted models, higher SNa (per mmol/L) was associated with lower odds of GI symptoms (OR 0.96; 95%CI 0.93-0.99), higher odds of confusion (OR 1.08; 95%CI 1.40-1.13) and higher odds of in-hospital mortality (OR 1.06; 95%CI 1.02-1.11). Compared with the lowest tertile, the highest tertile of SNa was associated with a lower odds of GI symptoms and anosmia/ageusia, and higher odds of confusion and in-hospital mortality (Table 1).

Conclusions: In this prospective cohort study of hospitalized patients with COVID-19, hypernatremia is associated with higher odds of confusion and in-hospital mortality, but lower risk of GI symptoms and anosmia. The presence of dysnatremia may help identify higher-risk patients with COVID-19 and prompt ascertainment of patient symptoms, both of which may improve patient-centered approaches to care.

Table 1

Variable	Frequency	SNa (mmol/L)	SNa Tertiles		
Symptoms	N, (%)	(N=809)	Tertile 1	Tertile 2	Tertile 3
			(N=368)	(N=298)	(N=143)
Cough	513 (64.2)	0.98 (0.95-1.01) p=0.11	REF	1.05 (0.75-1.47) p=0.78	0.95 (0.62-1.45) p=0.81
Fever	483 (59.8)	0.99 (0.96-1.02) p=0.34	REF	0.94 (0.67-1.32) p=0.73	0.79 (0.52-1.20) p=0.27
Shortness of Breath	456 (56.4)	1.01 (0.98-1.04) p=0.63	REF	1.14 (0.82-1.58) p=0.42	1.21 (0.80-1.83) p=0.37
Sore Throat	107 (13.3)	1.0 (0.95-1.05) p=0.94	REF	1.01 (0.63-1.61) p=0.97	0.89 (0.47-1.66) p=0.71
Rhinitis	90 (11.1)	1.01 (0.96-1.06) p=0.78	REF	1.26 (0.76-2.07) p=0.37	1.07 (0.55-2.08) p=0.85
Malaise Myalgia	446 (55.1)	0.99 (0.96-1.02) p=0.61	REF	0.98 (0.71-1.35) p=0.9	0.91 (0.60-1.37) p=0.65
Chest Tightness	130 (16.1)	1.02 (0.97-1.06) p=0.45	REF	1.56 (0.99-2.44) p=0.05	1.28 (0.71-2.32) p=0.41
Gastrointestinal Symptoms	301 (37.2)	0.96 (0.93-0.99) p=0.01	REF	1.05 (0.76-1.46) p=0.76	0.53 (0.34-0.84) p=0.01
Confusion	104 (12.9)	1.08 (1.4-1.13) p=<0.00	REF	1.09 (0.61-1.95) p=0.76	4.11 (2.4-7.21) p=<0.00
Headache	103 (12.9)	0.97 (0.92-1.02) p=0.2	REF	1.34 (0.83-1.53) p=0.23	0.77 (0.39-1.53) p=0.46
Anosmia or Ageusia	93 (11.5)	0.95 (0.90-1.00) p=0.06	REF	1.10 (0.68-1.78) p=0.69	0.33 (0.13-0.81) p=0.02
In-Hospital Mortality	144 (17.8)	1.06 (1.02-1.11) p=<0.00	REF	1.22 (0.75-1.99) p=0.43	2.76 (1.63-4.67) p=<0.00

PO0170

Lower CD3 and CD4 Counts in Kidney Transplant Recipients Who Did Not Respond to COVID-19 Vaccination

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Background: Kidney transplant recipient's response rate to COVID-19 vaccination is reportedly less than 54% after the 2nd dose, significantly lower than general population and dialysis patients, reported as between 85-90% and 95-100%, respectively.

Methods: We studied SARS-CoV-2 anti-spike IgG levels in our kidney transplant recipients after their COVID-19 vaccination using the OrthoV IgG platform.

Results: 69 kidney transplant recipients received a SARS-CoV-2 vaccine (47 Pfizer, 20 Moderna and 2 Johnson and Johnson) at a median 36 months after transplantation (range, 3 months to 22 years). 61% were male, 39% Black, 29% Hispanic with a median age of 60 (range 22-82). 72% were deceased-donor kidney transplant recipients. 23 patients had previous history of COVID-19 diagnosed by SARS-CoV-2 PCR and/or anti-nucleocapsid antibody and 21 of those patients (91%) developed anti-spike IgG after 1st or 2nd dose with a median level of 13.2 (11.2-16.2). 46 patients without history of previous COVID-19, 17 (37%) developed anti-spike IgG at a median of 28 days (range 10-72) after the second vaccine dose with a median level of 5.7 (1.22-15.4). Patients who didn't develop anti-spike IgG tended to be older, of African-American descent, on MMF > 1 g/day, have lower CD3 and CD4 counts.

Conclusions: In summary, most kidney transplant recipients without history of COVID-19 did not produce anti-spike IgG after being fully vaccinated and it is associated with augmented immunosuppression, lower T cell counts, African-American race and older age.

	Anti-Spike IgG NEGATIVE (N = 29)	Anti-Spike IgG POSITIVE (N = 17)	p-value
Mean age (SD) years	63 (9)	53 (18)	0.04
Sex (male), %	62%	47%	0.32
African American Race, %	52%	18%	0.03
Mean time after transplant (SD), months	53 (41)	71 (67)	0.32
Mean BMI (SD), kg/m^2	29.1 (6)	31.2 (8)	0.32
MMF > 1 g/day, %	69%	29%	0.01
Mean CD3 count (SD), cell/μL	777 (604)	1183 (631)	0.04
Mean CD4 count (SD), cell/μL	375 (334)	630 (374)	0.03
Mean CD8 count (SD), cell/μL	377 (363)	496 (349)	0.3
Mean IgA levels (SD), mg/dL	210 (199)	204 (115)	0.89
Mean IgM levels (SD), mg/dL	69 (45)	110 (92)	0.1
Mean IgG levels (SD), mg/dL	1324 (964)	1024 (415)	0.16
Mean eGFR (SD), mL/min	53 (42)	71 (67)	0.32

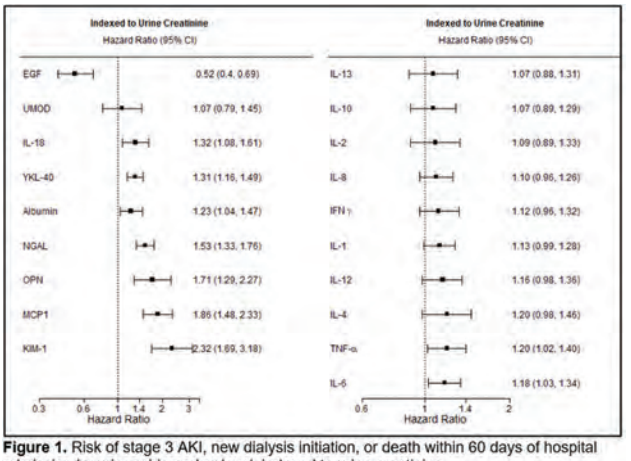

Figure 1. Risk of stage 3 AKI, new dialysis initiation, or death within 60 days of hospital admission by urinary biomarker level, indexed to urine creatinine.

PO0171

Prognostic Significance of Urinary Biomarkers in Patients Hospitalized with COVID-19

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Background: Acute kidney injury (AKI) is common in patients with COVID-19 and associated with poor outcomes. Urinary biomarkers have been associated with adverse kidney outcomes in other settings and may provide additional prognostic information in patients with COVID-19.

Methods: We evaluated 19 urinary biomarkers of injury, inflammation, and repair in patients hospitalized with COVID-19 at 2 academic medical centers between April and June 2020. We associated biomarkers with a primary composite outcome of KDIGO stage 3 AKI, requirement for dialysis, or death within 60 days of admission. We also compared various kidney biomarker levels in the setting of COVID-19 versus other common AKI settings.

Results: Out of 157 patients, 24 (15.3%) experienced the primary outcome. Two-fold higher levels of neutrophil gelatinase-associated lipocalin (NGAL) (HR: 1.53; 95% CI: 1.33-1.76), monocyte chemoattractant protein (MCP-1) (HR: 1.86; 95% CI: 1.48-2.33), and kidney injury molecule-1 (KIM-1) (HR: 2.32; 95% CI: 1.69-3.18) were associated with highest risk of the primary outcome. Higher epidermal growth factor (EGF) levels were associated with a lower risk of the primary outcome (HR 0.52; 95% CI: 0.40-0.69). Individual biomarkers provided moderate discrimination and biomarker combinations improved discrimination for the primary outcome.

Conclusions: Urinary biomarkers are associated with severe kidney complications in patients with COVID-19 and provide valuable information to monitor kidney disease recovery and progression.

Funding: NIDDK Support

PO0172

Urine Test Predicts Kidney Injury and Death in COVID-19

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Background: Kidney injury is a common feature of COVID-19 infection, but serum creatinine (SCr) is not a sensitive or specific marker of kidney injury. We hypothesized that measurement of molecular markers of tubular injury can diagnose COVID-19 associated kidney injury and predict a poor prognosis.

Methods: This is a prospective cohort study of 444 consecutive COVID-19 patients in a New York City Emergency Department recruited in March and April, 2020. Urine and blood were collected simultaneously at hospital admission (median time of day 0, IQR 0-2 days) and within 1 day of a positive SARS-CoV-2 test in 70% of patients. Urine NGAL and KIM-1 assays were blinded to clinical data. Primary outcomes included the diagnosis of Acute Kidney Injury (AKI) as defined by AKIN criteria, as well as its duration and severity. Secondary outcomes included death, dialysis, shock, respiratory failure, and length of hospital stay. Kidney biopsies from COVID-19 patients were examined for biomarker gene expression.

Results: Elevated urinary NGAL (uNGAL) levels were associated with SCr based AKI (267±301 vs. 96±139 ng/mL, P=1.6x10^{-10}). uNGAL level >150 ng/mL had 80% specificity and 75% sensitivity to diagnose AKIN stage 2 AKI or higher. Higher uNGAL levels were associated with sustained AKI [aOR per SD of uNGAL (95%CI): 2.67 (1.81-4.06), P=1.8x10^{-6}], need for dialysis (aOR: 3.67 (1.89-7.57), P=2.2x10^{-4}), shock (aOR: 1.64 (1.26-2.15), P=2.9x10^{-4}), prolonged length of stay (aHR: 1.22 (1.09-1.36), P=4.8x10^{-4}), and death [aOR=1.62 (1.19-2.24), P=2.5x10^{-3}], independent of baseline SCr and pre-existing co-morbidities. These associations were also preserved after adjusting for proteinuria measured in the same urine sample. NGAL is typically transcribed by distal nephron segments but in COVID-19 kidney biopsies with widespread histopathologic acute tubular injury (ATI), NGAL mRNA expression included proximal tubules.

Conclusions: Elevated uNGAL in patients admitted with acute COVID-19 was associated with the development of AKI, increased severity and duration of AKI, the degree of histopathological acute tubular injury, shock, prolonged hospitalization, need for dialysis, and death.

Funding: NIDDK Support

PO0173

Readmissions After AKI in Colorectal Carcinoma Are Associated with Adverse Outcomes: Findings from the National Readmission Database

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Background: Acute kidney injury (AKI) is common in critically ill cancer patients with poor outcomes. Colorectal carcinomas (CRC) are frequently associated with AKI, due to complications of disease or treatment. AKI in CRC remains a well-known but under-represented topic in current literature. We aim to analyze and quantify the impact, healthcare burden, readmission rates and predictors of metastatic CRC with AKI.

Methods: We conducted a retrospective cohort study of the 2017 National Readmission Database (NRD) of adult patients readmitted within 30 days after an index admission for AKI with a concomitant diagnosis of CRC. ICD 10 codes were used to identify diagnoses and procedures.

Results: A total of 2,239 patients with metastatic colorectal cancer were admitted with AKI. The 30-day readmission rate was 27.9%. Main causes for readmission were sepsis, progression of malignancy, hypovolemia and recurrent AKI. Readmitted patients were associated with higher in-hospital mortality (0.1% vs. 1.5%; p<0.01), mechanical ventilation need (4.7% vs 1.5%; P<0.01) and chronic kidney disease (CKD) diagnosis (44.6% vs 36.1%; P<0.01). The total health care in-hospital economic

burden of readmission was $32.3 million in total charges and $7.8 million in total costs. After adjusting for age and comorbidities, independent predictors of readmission were disposition against medical advice, HIV, CKD, and sepsis. Preventive factors for readmission were found to be radiation therapy and peripheral parenteral nutrition.

Conclusions: AKI in metastatic CRC has a high rate of readmissions, with poor outcomes in morbidity, mortality and costs making it a significant healthcare burden. Among common causes of readmission, potentially targetable causes include hypovolemia and sepsis while among readmission predictors, CKD and sepsis warrant further attention. Abovementioned preventive predictors consolidate the importance of combination therapy and supportive care in CRC.

Predictors of Readmissions

Variable	Adjusted odds ratio (95% confidence interval)	P value
Comorbidities		
HIV	2.95 (1.58-5.49)	<0.01
CKD	1.46 (1.10-1.93)	<0.01
Radiation therapy	0.59 (0.14-0.39)	<0.01
In-Hospital Complications		
Sepsis	2.19 (1.01-4.84)	0.05
In-Hospital Procedures		
Peripheral parenteral nutrition	0.33 (0.07-0.56)	<0.01

PO0174

Risk for AKI in the Outpatient Setting

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Background: Risk-factors for acute kidney injury (AKI) in the hospital have been well studied. Yet, tools for identifying outpatients at high risk for AKI are not available.

Methods: A development cohort for modelling risk of AKI without concurrent or subsequent hospitalization was defined by repeated primary care encounters in an urban healthcare system. An external validation cohort was similarly defined in the Veterans Health Administration. Logistic regression with bootstrap sampling for backward stepwise covariate elimination was used to develop a model for outpatient AKI in an 18-month outcome period. The model was then transformed into two binary tests to identify high-risk patients: one for research and another for clinical care.

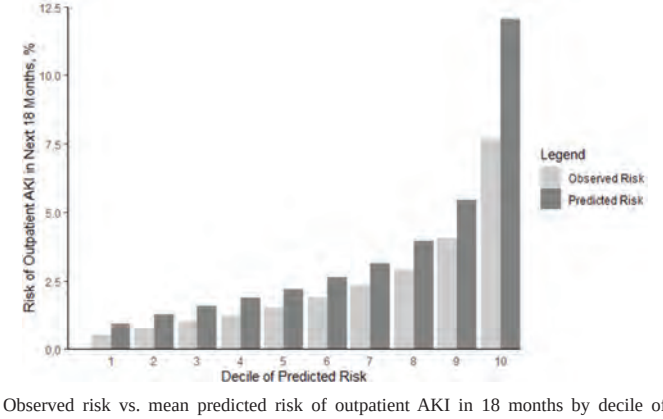
Results: Outpatient AKI occurred in 4611 of 152,371 (3.0%) and 115,744 of 4,864,576 (2.4%) patients in the development and validation cohorts, respectively. The model C-statistics were 0.72 (95% CI: 0.71-0.73) and 0.72 (95% CI: 0.72-0.72) in the development and validation cohorts. The research test had sensitivity of 0.21 (95% CI: 0.21-0.21) and specificity of 0.95 (95% CI: 0.95-0.95). The clinical test, with a lower test-positivity threshold, had sensitivity of 0.49 (95% CI: 0.49-0.50) and specificity of 0.81 (95% CI: 0.81-0.81).

Conclusions: The outpatient AKI-risk prediction model performed well in both continuous and binary forms.

Performance in the validation cohort of two binary tests for outpatient AKI in 18 months

Statistic	Research Test	Clinical Test
Threshold for test-positivity (a)	≥9.5% (b)	≥4.5% (b)
Sensitivity	0.210 (95% CI: 0.208-0.213)	0.494 (95% CI: 0.491-0.497)
Specificity	0.952 (95% CI: 0.951-0.952)	0.806 (95% CI: 0.806-0.807)
Positive predictive value	0.096 (95% CI: 0.094-0.097)	0.058 (95% CI: 0.058-0.059)
Negative predictive value	0.980 (95% CI: 0.980-0.980)	0.985 (95% CI: 0.985-0.985)
Percent of cohort "positive" by the test	5.2%	20.0%

(a) Derived in the development cohort (b) P <0.001 for predicting outpatient AKI in the validation cohort



Observed risk vs. mean predicted risk of outpatient AKI in 18 months by decile of predicted risk in the validation cohort.

PO0175

Additive Harmful Effects of AKI and Acute Heart Failure on Mortality in Hospitalized Patients

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Background: Organ crosstalk between kidney and heart has been suggested. This study aimed to investigate the additive effect of both conditions on mortality.

Methods: We retrospectively recruited 102,721 hospitalized patients for 5 years. Acute kidney injury was diagnosed with serum creatinine-based criteria, and acute heart failure with International Classification of Diseases code, within two weeks after admission. Primary outcome was all-cause mortality.

Results: Among the 5,316 (5.2%) patients who died, 20.5% died within 1 month. Hazard ratio for 1-month mortality was 23.25 in patients with both conditions, 13.47 for acute kidney injury only, and 2.76 for acute heart failure only. The relative excess risk of interaction was 8.01, and it was more prominent in patients aged <75 years, and those without chronic heart failure.

Conclusions: Acute kidney injury and acute heart failure had a detrimental additive effect on short-term mortality in hospitalized patients.

Results of analyses on interaction, where AKI and AHF are the two exposures of interest to mortality within 1 month

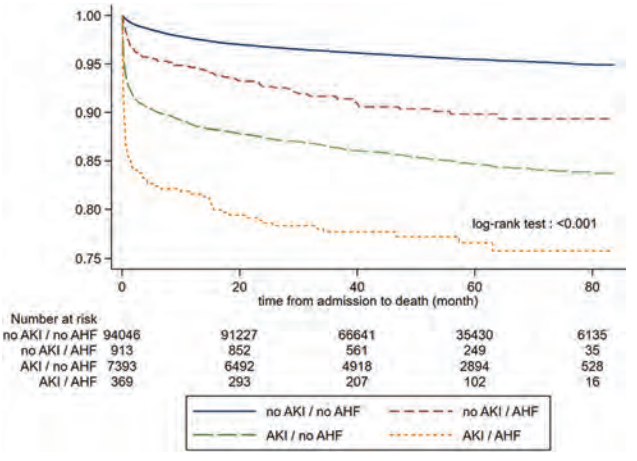
	No AKI		AKI		HRs (95% CI) for AKI within strata of AHF
	n	HR (95% CI)	n	HR (95% CI)	
No AHF	494894,046	1.000 (Ref)	523/7,393	14,846 (12,957-17,010)	14,846 (12,957-17,010)
AHF	218/913	3.292 (2,042-5.308)	53/369	28,591 (20,478-39,917)	14,425 (12,627-16,479)
HRs (95% CI) for AHF within strata of AKI		3.292 (2,042-5.308)		2.168 (1.624-2.895)	

Relative excess risk of interaction (95% CI) = 11.453 (2.386-20.520); P = 0.013.

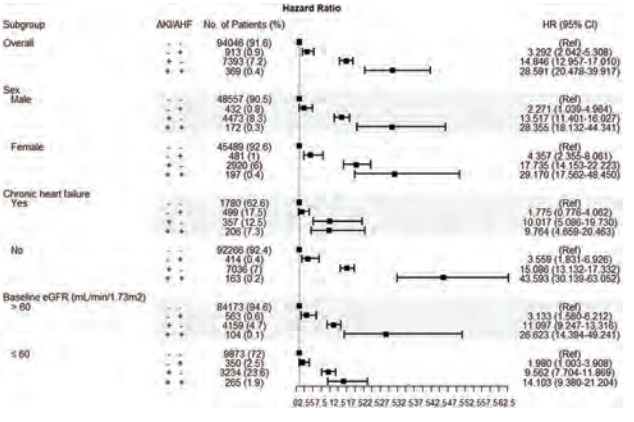
Attributable proportion due to interaction (95% CI) = 0.401 (0.208-0.594); P <0.001

Synergy index (95% CI) = 1.710 (1.224-2.388); P = 0.002.

AKI, acute kidney injury; AHF, acute heart failure; HR, hazard ratio; CI; confidence interval.



Kaplan-Meier curves for death by groups, based on presence of AKI or AHF



HRs of death within 1 month in subgroups

PO0176

Clinical Trajectories of AKI and Clinical Outcomes in Acute Decompensated Heart Failure

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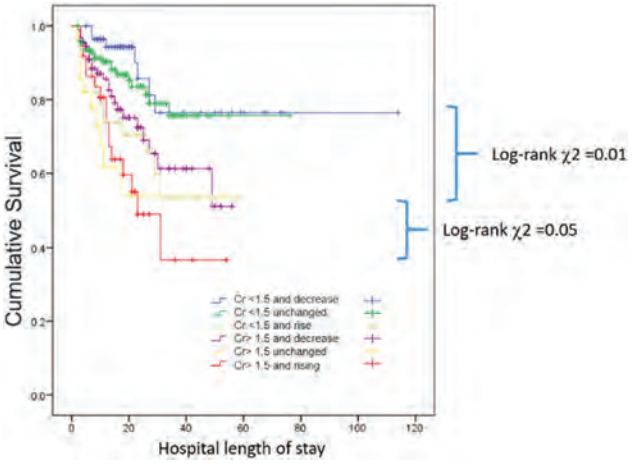
Background: Cardiorenal syndrome (CRS) is a pathophysiologic disorder of the heart and kidneys, with both acute and chronic dysfunction. CRS type 1 is characterized by an acute cardiac disease leading to AKI.

Methods: This is a retrospective cohort study from Jan 2017 to Dec 2018 in 3rd level center in Mexico City. The objective was to describe the incidence and outcome of AKI in patients with CRS type 1. We divide AKI's trajectory into: ascending and descending AKI, also we used a creatinine (Cr) cut-off point of 1.5mg/dl and identified 6 trajectories. We used a Logistic regression analysis (LRA) for in-hospital mortality and length of stay.

Results: 404 patients were included. Mean age 58.9 ±16.5 years, 60% were men, 27% had DM, 45% had hypertension. The incidence of AKI was 60.9% and mortality was 22%. Severe AKI in 25.5%, 36 (8.9%) required kidney replacement therapy. The incidence of ascending AKI was 29.7% and mortality In this group was 46.7%. AKI's six trajectories are shown in Figure 1. In LRA for the whole cohort, PASP >40mmHg (OR 4.82 CI 2.0-11.6 p=<0.001), NT-proBNP >10000 (OR 3.26 CI 1.61-6.57 p= 0.001), ascending AKI (OR 4.08 CI 2.11-7.88 p=0.04) were associated with mortality. In LRA for ascending AKI, BUN/Cr ratio >25 (OR 1.59 CI 1.00-2.54 p=<.001) and neutrophil/lymphocyte ratio (NLR) >6.5 (OR 2.64 CI 1.65-4.23 p=<0.001) were associated with in-hospital mortality.

Conclusions: The incidence and mortality of AKI in patients with decompensated heart failure is high. Patients with ascending AKI had a significant increase in mortality and descending AKI had a better prognosis. Different Cr trajectories indicate different outcomes, the group of patients who at the time of admission had Cr >1.5mg/dl and presented a rise during hospitalization had a worse outcome. NLR>6.5 and BUN/Cr ratio >25 are predictors of mortality.



PO0177

National Epidemiology of Community-Acquired AKI

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Background: Community-acquired acute kidney injury (CA-AKI) is AKI that develops outside of the hospital and is the most common form of AKI globally. National estimates of CA-AKI in the US are absent due to lack of integrated health data and limited availability of outpatient lab data. In this study, we leverage data from the Veterans Health Administration (VA) to estimate CA-AKI incidence and risk factors.

Methods: We constructed a retrospective cohort using national VA administrative and lab data to assess the cumulative CA-AKI incidence among active VA primary care users in 2013-2017. Veterans who did not have recorded outpatient serum creatinine (SCr) and those with a history of severe kidney disease (≥ Stage 5 or kidney transplant) were excluded. CA-AKI was defined as ≥ 1.5 fold relative increase in outpatient SCr or inpatient SCr (≤ 24 hours from admission), from a reference value defined as the preceding outpatient SCr ≤ 12 months prior. A Cox model was used to estimate the association between CA-AKI risk and baseline variables capturing socio-demographics and comorbidities, accounting for repeated measurements among Veterans.

Results: Of approximately 2.5 million eligible Veterans in each analysis year, the cumulative incidence of CA-AKI was approximately 2% each year and declined slightly over time (2.0, 2.0, 2.0, 1.9, and 1.6% in 2013-2017, respectively). Of these, 79% were Stage 1 AKI, 15 % were Stage 2, and 6% were Stage 3 across all years. Only 26% of CA-AKI was observed in the inpatient setting. Veterans with CA-AKI (vs. no CA-AKI) more likely to be older, male, Black race, with greater comorbidity. After adjustment, increasing age, female sex, Black race, Hispanic ethnicity, diabetes, heart failure, hypertension, alcohol use, HIV/AIDs, metastatic cancer, and sickle cell anemia were all associated with increased CA-AKI risk (HR >1.15).

Conclusions: CA-AKI affects approximately 1 of every 50 US Veterans and is most common in the outpatient setting, with less than a third observed in the inpatient hospital setting. Reliance on inpatient evaluation of AKI likely results in significant under-recognition and missed opportunity to prevent and manage the substantial long-term consequences of AKI.

Funding: NIDDK Support

PO0178

National Practice Patterns in the Care of Pediatric AKI Survivors

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Background: Acute kidney injury (AKI) affects 5-10% of all children admitted to the hospital and is associated with adverse outcomes such as increased risk of recurrent AKI, incident and progressive chronic kidney disease (CKD) and death. However, few guidelines exist to optimize post-AKI care. In this study, we surveyed pediatric nephrologists to determine their practice patterns in the care of AKI survivors.

Methods: We administered an email survey to members of the Pediatric Nephrology Research Consortium (PNRC) throughout the US & Canada. Participants were asked questions regarding their practice characteristics, frequency of care of post-hospital AKI survivors and perceptions regarding provider roles in post-AKI outpatient care. Participants were also asked questions regarding the content of their AKI care, patient counseling and disease monitoring.

Results: Of the 52 respondents, most practiced in an academic setting (96%) for <20 years (83%) and reported caring for >10 AKI survivors each year (69%). The majority of respondents (64%) felt pediatric nephrology should always be involved in AKI follow-up care; 33% felt only for ≥ Stage 2 AKI. Most (73%) felt nephrology care was no longer needed when clinical concerns resolved; 60% when eGFR returns to normal; 46% when urine protein/creatinine (UPC) ratio is normal. Most respondents listed professional conferences (79%) and peer-reviewed articles (87%) as information sources. For mild AKI, 60% of participants repeated a creatinine test after 1 month following discharge; 25% reported checking within 1 week of discharge. In severe AKI, tests were repeated within 1 week (67%). Most reported measuring blood pressure, serum creatinine & UPC at follow-up (>90%). Respondents endorsed counseling patients on risk of recurrent AKI (69%), incident hypertension (92%), incident CKD (81%) and NSAID avoidance (85%). Overall, 90% of respondents felt comfortable managing AKI follow-up in pediatric patients.

Conclusions: Pediatric nephrologists were generally confident in their ability to counsel and manage pediatric AKI survivors. Most felt AKI care required pediatric nephrology input and reported providing education about AKI consequences. Whether primary care providers endorse similar confidence and co-management perceptions requires further study.

Funding: Other NIH Support - This work was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number R38HL143612

PO0179

AKI Stage Is a Poor Predictor of Long-Term Cardiovascular Outcomes

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Background: Trials to improve long-term outcomes in post-AKI patients have enrolled patients primarily based on AKI stage; however, whether AKI stage is a reasonable predictor of cardiac morbidity and mortality is unknown. We developed predictive models for MACE readmissions in post-AKI patients and determined the utility of AKI stage within these predictive models.

Methods: VHA patient data for inpatient admissions was obtained between 2013 and 2018. AKI was defined as a creatinine increase of ≥0.3 mg/dL from baseline. The primary outcome was subsequent hospitalization for congestive heart failure (CHF), myocardial infarction (MI), or stroke (MACE), with follow-up of at least 2 years. Over 50 variables were considered for inclusion in the final model. Bootstrap modeling was used to determine the outcomes of 100 stepwise regressions using random sampling with replacement. Variables included in more than 60 were included in a final model using Cox regression censored for mortality. If not selected, AKI stage was forced into the model. Due to the association between cardiac disease and the primary outcome, and in order to evaluate risk factors for de novo cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease.

Results: A total of 241,781 Veterans with AKI were included. AKI stage did not meet selection criteria for either model. In patients without pre-existing cardiac disease, the final model included age, sodium, bilirubin, chronic lung disease (CLD), complicated diabetes mellitus (CxDM), atrial fibrillation (A-Fib), and proteinuria. AKI stage 3 (HR 1.12, CI 1.08-1.16) compared to AKI stage 1 was a weak predictor of subsequent MACE events. Similarly, in patients with prior cardiac disease, the final model included age, blood urea nitrogen, white blood count, CHF, MI, CLD, CxDm, A-Fib, cardiomyopathy, cardiac device, sleep apnea, complicated hypertension, valvular disease, major electrolyte abnormalities, and proteinuria. AKI stage 3 was again a weak predictor (HR 1.065, 1.03-1.10).

Conclusions: While AKI stage is commonly used to enroll patients into AKI survivorship clinics, it was not found to be a strong independent predictor of MACE events among post-AKI Veterans. Our findings may inform risk stratification for post-AKI follow up.

PO0180

Urinary Oxygen Partial Pressure to Monitor AKI Risk

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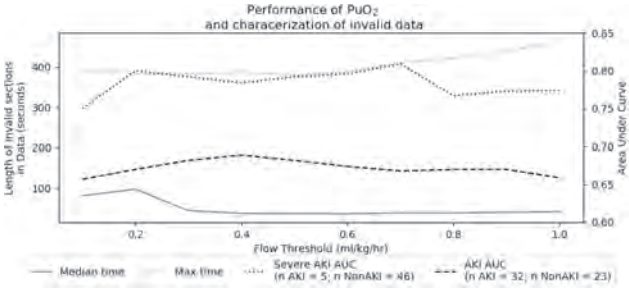
Background: In a prior study, we showed that patients who developed acute kidney injury (AKI) had lower mean urinary oxygen partial pressure (PuO_2) following cardiopulmonary bypass (CPB). However, PuO_2 is unreliable when urine flow is low and little is known about the distribution of urine flow intraoperatively. The objective of this research was to determine the distribution of the length of sections of unreliable PuO_2 data due to low flow.

Methods: Following IRB approval and informed consent, a device that measures PuO_2 and urine flow was placed in cardiothoracic surgery patients. PuO_2 and urine flow (sampled at 1 Hz) were deemed not reliable when urine flow was below a threshold. Patients who did not meet a percent valid data threshold were excluded. Mean PuO_2 following CPB and the maximum and median length of sections of invalid data were calculated. Data were generated for a percent valid data threshold of 30 % and urine flow rate thresholds of 0.1 to 1 mL/kg/hr at 0.1 increments. Patients who met the KDIGO criteria for AKI were compared to non-AKI patients. In addition, patients with Stage 2 or 3 AKI based on the KDIGO serum creatinine criteria were assigned to the Severe AKI group and were compared to patients with stage 1 or no AKI. The area under the curve (AUC) of a receiver-operator (ROC) plot of mean PuO_2 estimating AKI development was calculated for each comparison.

Results: AUC was 0.69 for AKI when the flow threshold was 0.4 ml/kg/hr. The average for all patients of the median and maximum length of invalid data was 37 seconds and 387 seconds, respectively. For Severe AKI, the AUC was 0.81 for a flow threshold of 0.7 ml/kg/hr. As the maximum length of invalid data sections increases the AUC decreases.

Conclusions: Sections of unreliable PuO_2 data are sufficiently short and do not significantly impact the performance of PuO_2 as a marker of AKI when a urine flow threshold is used to filter the data. The data demonstrate the feasibility of measuring PuO_2 to monitor AKI risk during cardiothoracic surgery. Further research is needed to determine if intraoperative PuO_2 can reduce the incidence of AKI.



AUC of mean PuO2 and distribution of length of invalid data sections

PO0181

Serum Trace Metal Changes Could Potentially Indicate Kidney Damage in Rats with Cisplatin-Induced Kidney Injury

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Background: Cisplatin (CDDP), a widely used anticancer drug, is known to exhibit nephrotoxic adverse effects. Nephrotoxicity is a dose-limiting toxicity. Therefore, the early detection of cisplatin-induced nephrotoxicity is crucial. Certain trace metals reportedly change with kidney injury, although their relationship with CDDP-induced kidney injury remains unclear. Therefore, in this study, we investigated the trace metal changes after cisplatin treatment in rats.

Methods: Eight-week-old male Wistar-ST rats were divided into a control and a CDDP group (n = 6 for both), treated intraperitoneally with saline or CDDP 3 mg/kg, respectively. On day 0 and 5, we took serum samples and measured the SCre and BUN levels. The kidneys were obtained on day 5 and subjected to histological studies using HE staining. The serum samples were used for the comprehensive measurement of nine different trace metal types (Mn, Fe, Co, Ni, Cu, Zn, As, Se, and Mo) by ICP-MS. The statistical analysis was performed using Student's *t*-test.

Results: The SCre and BUN levels significantly increased in the CDDP group compared with those in the control group ($P<0.01$). The HE staining showed that the proximal tubular injury in the CDDP group was severe compared to that in the control group. Three out of nine serum trace metals, Co, Ni and Cu, were significantly high in the CDDP group compared with those in the control group ($P<0.01$).

Conclusions: Co, Ni, and Cu increased after the CDDP treatment. The measurement of such elements could be useful for the detection of CDDP-induced nephropathy.

PO0182

Identifying Factors Associated with Clinically Adjudicated Drug-Induced AKI in Children

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Background: Drug-induced acute kidney injury (DI-AKI) affects up to 33% of hospitalized children. Clinical adjudication of DI-AKI is challenging since AKI is multifactorial. We report clinical variables that influence ascertainment of DI-AKI cases and inter-rater reliability (IRR) of existing causality assessment tools (CAT) for adverse drug events.

Methods: We analyzed data from the DIRECT study, an international, multi-center, observational cohort study of clinically adjudicated pediatric cases of AKI stage 2 associated with nephrotoxic medication (NTMx) exposure. Each case was adjudicated by two pediatric nephrologists using CAT. A third adjudicator acted as the tiebreaker. IRR was calculated using Krippendorff's alpha. We developed variables to capture exposure to NTMx and serum creatinine trends. We constructed a multivariable logistic regression model with clinically adjudicated DI-AKI as the outcome and clinical variables as predictors.

Results: 115 (86.5%) out of 133 children were adjudicated as DI-AKI. The mean age was 12.2 ± 4.5 years, and the most frequent NTMx: vancomycin (43.6%), piperacillin/tazobactam (32.3%), and non-steroidal anti-inflammatory drugs (18.8%). AKI risk factors were comparable between clinically adjudicated DI-AKI and Not DI-AKI groups. Past medical history of malignancy, increased vascular capacity (i.e., sepsis or hypotension), and severe AKI treated with dialysis made DI-AKI adjudication less likely. Longer duration from the start of drug exposure to AKI onset made DI-AKI adjudication more likely. The IRR of the Liverpool ($ka = 0.35$) and the Naranjo ($ka = 0.31$) CAT were poor.

Conclusions: DI-AKI adjudication is a complex and multifactorial process. Current CAT appear to be unreliable. Development of CAT specific to DI-AKI is needed to perform robust outcomes research.

Funding: Other NIH Support - International Serious Adverse Events Consortium, National Library of Medicine (Grant #T15LM011271).

PO0183

Clinically Distinct Subtypes of AKI on Hospital Admission Identified by Machine Learning Consensus Clustering

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Background: Patients with acute kidney injury were clustered at hospital admission into clinically distinct subtypes using an unsupervised machine learning approach. Mortality risk was assessed among these distinct clusters.

Methods: Consensus clustering analysis was performed on demographics, principal diagnoses, comorbidities, and laboratory data on 4,289 hospitalized adult patients with acute kidney injury at admission. The standardized difference of each variable was calculated to identify each cluster's key features. We assessed the association of each cluster with hospital and one-year mortality.

Results: Consensus clustering analysis identified four distinct clusters. There were 1,201 (28%) patients in cluster 1, 1,396 (33%) patients in cluster 2, 1,191 (28%) patients in cluster 3, and 501 (12%) patients in cluster 4. Figure 1 illustrates cluster differences. Figure 2 highlights associated increased mortality in clusters 2, 3, and 4.

Conclusions: Our study demonstrated the use of machine learning consensus clustering analysis to characterize a heterogenous cohort of patients with acute kidney injury on hospital admission into four clinically distinct clusters with different associated mortality risks.

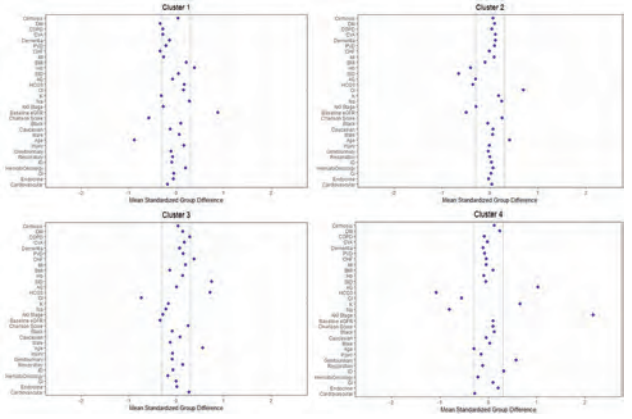

Figure 1: Standardized differences across clusters

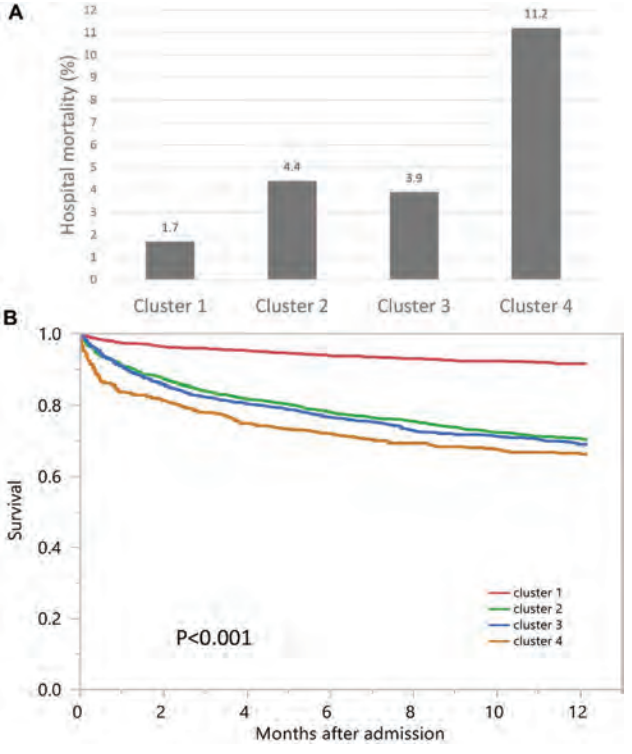

Figure 2: Hospital and One-Year Mortality among Different Clusters with Admission AKI

PO0184

Severe Kidney Injury Requiring Continuous Renal Replacement Therapy: Correlation of Mean Platelet Volume with Mortality at Multiple Time Intervals

Sean Pickthorn, Nathaniel Hocker, Lewis Mann, Ravinandan Venkatasubramanian, Meenakshi Sambharia, Jonathan Nizar, Benjamin R. Griffin. *The University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: Platelet decreases after continuous renal replacement therapy (CRRT) initiation are common and associated with increased mortality. Platelet activation during CRRT due to shear forces and membrane interactions may be associated with subsequent platelet loss. The degree of platelet activation can be approximated with mean platelet volume (MPV), as activated platelets undergo degranulation which increases their size. While MPV values at CRRT initiation correlate with mortality, MPV changes following CRRT initiation are unknown. We hypothesized that MPV would increase following CRRT initiation and correlate with mortality.

Methods: Adult patients admitted to the University of Iowa between January 1, 2019 and December 31, 2020, were included in this retrospective analysis. Patients were excluded if they survived <48 hours while on CRRT, or if fewer than two values were available for MPV. MPV was collected at the time of CRRT initiation and at 24, 48, and 72 hours. The primary outcome evaluated was in-hospital mortality. The final regression models were adjusted for age, sex, race, illness severity, and days of CRRT therapy.

Results: A total of 190 patients (81 survivors and 109 non-survivors) were included. MPV was significantly higher at each timepoint (24, 48, and 72 hours) in the full cohort compared to CRRT initiation, and increased by a greater amount over time in non-survivors than survivors. MPV at 72 hours was independently associated with in-hospital mortality after adjustments for covariates (OR 1.76, CI 1.15-2.69, p=.01).

Conclusions: MPV increased after CRRT initiation, especially in non-survivors, and MPV at 72 hours was independently associated with in-hospital mortality. These findings suggest that platelet activation temporally related to CRRT initiation may play a role in platelet loss and mortality in this population. Future studies will evaluate more direct measures of platelet activation in patients on CRRT and the impact of platelet activation blocking agents in this population.

PO0185

Recovery After AKI: Goals of an AKI!Now Workgroup

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Background: The American Society of Nephrology recently established the AKI!Now initiative. AKI!Now aims to promote excellence in the prevention and treatment of AKI by transforming the delivery of AKI care to improve clinical and patient-centered outcomes. Herein, we describe the focused efforts of AKI!Now on "recovery after AKI."

Methods: Three core objectives were identified in the domain of AKI recovery: 1. To determine areas of priority for mechanistic research focused on recovery after AKI. It is expected that these would include a variety of experimental models suitable for various AKI etiologies and disease severities. 2. To benchmark existing strategies to care for patients after AKI including integrated insights from primary care providers, nephrologists, other subspecialty health care professionals. 3. To facilitate implementation and testing of interventions designed to limit short- and long-term complications of AKI and promote recovery. Dialysis dependent and independent AKI survivors should both be considered for these interventions and clinical trials.

Results: The AKI!Now initiative will highlight and clarify challenges and opportunities to improve care after AKI. This work will also inform who is followed after AKI and by whom (i.e., primary care and/or nephrology), options for care delivery (i.e., in-person versus telehealth), and potential practices to improve outcomes (i.e., role of ACEi/ARB and SGLT2 inhibitors after AKI, physical/cognitive rehabilitation). The stakeholder relationships formed, including those with patients, healthcare professionals, industry, and academia, will facilitate a collaborative research and practice agenda necessary to understand and outline best practices after AKI.

Conclusions: Survivors of AKI are a high-risk and growing population, and AKI is associated with worse long-term outcomes than an acute myocardial infarction. However, how to care for patients after AKI remains ill-defined with substantial practice variation. This represents an opportunity for the "recovery after AKI" workgroup of AKI!Now to provide leadership by raising awareness and promoting strategies focused on equitable and effective post-AKI care throughout the American Society of Nephrology and wider nephrology community.

PO0186

Exploration of the Mitochondria Genes Alteration in AKI

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Background: Acute kidney injury (AKI) is one of the most common complications in clinic, especially in critical ill patients. Recently, the fundamental function of mitochondria in acute kidney injury and repair have gradually been noticed while the mechanism still unclear. Therefore, we aimed to identify the change pattern of mitochondria alteration associated gene in AKI through Gene Expression Omnibus (GEO) database analysis and AKI animal model verification.

Methods: A total of 1893 genes involved in mitochondria function and metabolism were screened from Gene Ontology (GO) database and defined as GO terms in mitochondria metabolism. Meanwhile, 2 studies invested transcriptome differences in renal ischemia reperfusion injury (GSE98622 and GSE99703) were extracted from GEO database. By crossing GO terms and 2 datasets from GEO database, 69 and 62 mitochondria metabolism genes were identified in GSE98622 and GSE99703 separately. Among which, 23 genes were overlapped in 2 datasets and verified by real-time PCR in 2 kinds of AKI model (ischemic renal reperfusion injury model and cisplatin induced AKI model).

Results: Through GO and KEGG enrichment analysis, these differentially expressed genes (DEGs) were allocated to peroxisome, butanoate metabolism, arginine and proline metabolism, neurotrophin signaling pathway and metabolic pathways. Protein-protein interaction analysis demonstrated that Hao2, Acsm3, Amacr, Aadat may play vital roles of mitochondrial regulation in AKI. The results of real-time PCR shown that 3 genes were significantly increased in both two kinds of AKI model (Arg2, Clu, Lgals3) and 12 genes were decreased (Aadat, Acsm3, Agps, Ak4, Amacr, Bdh1, Gatm, Hao2, Isoc2b, Mpv17l, Nat8f1, Nudt19), while others were not altered in animal model or had no consistency changes between 2 kinds of AKI model.

Conclusions: We have identified 23 DEGs were associated with mitochondria metabolism in I/R AKI by using bioinformatic technology. Among these genes, GO and KEGG analysis suggests that the DEGs are mainly enriched in lipid metabolism, amino

acid metabolism pathway and tightly associated with peroxisome. Furthermore, 15 DEGs were revalidated in kidney of two kinds of AKI mouse model (I/R AKI and Cisplatin-AKI).

Funding: Government Support - Non-U.S.

PO0187

Artificial Intelligence in AKI: Goals of an AKI!Now Workgroup

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Background: In 2019, the American Society of Nephrology established *AKI!Now,* a collaborative initiative to promote excellence in the prevention, diagnosis, and treatment of Acute Kidney Injury (AKI). Here, we describe the ongoing efforts of the *AKI!Now* workgroup focused on Artificial Intelligence (AI) to improve the quality, accessibility, affordability, and equity of AKI care.

Methods: The workgroup has outlined objectives in 3 key domains: *1. Patients*. Input in designing and implementing fair and equitable AI tools and identifying clinical scenarios based on personal and caregiver experience that could be improved with AI *2. Clinicians*. Input in the design, value, and implementation of fair and equitable AI tools and identifying clinical uncertainties that may benefit from new AI tools *3. Researchers*. Evaluation of current AI tools, with a focus on removing implicit bias; development of novel, feasible, and effective AI tools to address gaps identified by patients and clinicians; and development and implementation of AI methods along with novel sensors for more sensitive assessment of kidney function and injury to advance the science of AKI

Results: This project, with involvement from a multi-disciplinary group of stakeholders, will yield efficient and effective use of AI for quality improvement in AKI care. Specific deliverables include 1) Risk-stratification and prediction tools; 2) Intelligent alert tools; 3) Decision support for bundled care compliance; 4) Decision support for implementing pragmatic clinical trials, among others. Importantly, this work will fill gaps in validating available AI tools and develop many desired AI tools that do not exist. These coordinated efforts are expected to deliver highly useful AI tools that could improve AKI care, research and reduce associated costs.

Conclusions: The *AKI!Now* workgroup on AI is committed to improving value care in AKI and encourages engagement and collaboration with patient, provider, researcher, and industry stakeholders. We seek to improve the care provided to the growing and susceptible AKI population, along the entire lifespan.

PO0188

Incidence of AKI in Individuals Treated with Lithium

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Background: Lithium has been linked to acute kidney injury (AKI) at toxic blood levels but the risk of AKI has otherwise not been well studied. Interestingly, lithium has been shown to protect against tubular injury in experimental AKI models. The aim of the study was to examine the risk of AKI in individuals treated with lithium.

Methods: This was a retrospective cohort study of all individuals treated with lithium in Iceland in 2003–2018. A control group comprised patients with affective disorders (ICD 10 codes F30-F39) attending the outpatient clinic of the Mental Health Services at Landspitali–the National University Hospital in 2014–2016, who had never used lithium. Clinical and laboratory data, including ICD-9 and ICD-10 codes and serum creatinine (SCr) values, were obtained from nationwide electronic medical records. Individuals with <2 SCr values available were excluded. AKI was defined using the SCr component of the KDIGO criteria. Multivariable logistic regression was used for the analysis.

Results: The lithium-treated group consisted of 2682 individuals, of whom 2310 (86.1%) were included in the study. Of those, 297 (12.9%) developed AKI. Of 1426 individuals in the control group, 1218 (85.5%) were included and 97 (8.0%) developed AKI. Lithium use was not an independent risk factor for AKI (OR 0.93, 95% CI, 0.72–1.20; Table). When lithium users were analyzed separately, lithium intoxication (OR 2.34, 95% CI, 1.33–4.09), duration of lithium therapy (OR 1.01, 95% CI 1.00–1.01) and mean lithium concentration (OR 1.22, CI, 1.14–1.30) were all significant risk factors for development of AKI.

Conclusions: Our findings suggest that lithium use does not affect the incidence of AKI after controlling for important covariates. However, lithium intoxication, time on lithium therapy and blood lithium concentration are associated with increased risk of AKI.

Funding: Government Support - Non-U.S.

Factors associated with AKI; multivariable logistic regression.

	Odds ratio	95% confidence interval
Sex, women	1.41	1.12 - 1.77
Age	1.01	1.00 - 1.02
Initial eGFR	0.98	0.98 - 0.99
Hypertension	1.44	1.07 - 1.93
Cardiovascular disease	1.23	0.95 - 1.58
Diabetes	1.82	1.25 - 2.60
CKD	0.94	0.68 - 1.32
Lithium use	0.93	0.72 - 1.20

PO0189

Healthcare Analytics with Time-Invariant and Time-Variant Feature Importance to Predict Hospital-Acquired AKI

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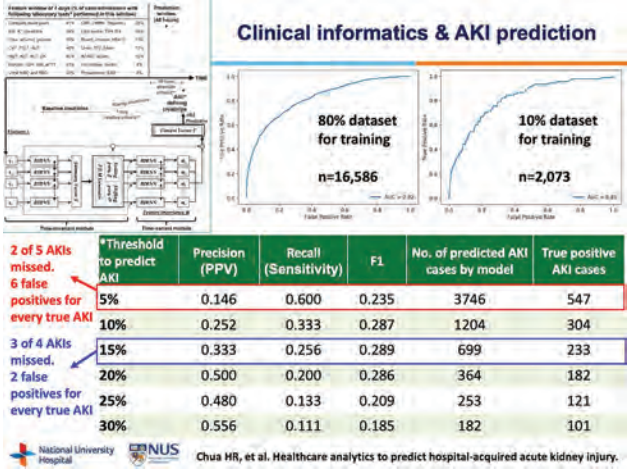
Background: Acute kidney injury (AKI) develops in 4% of inpatients and is a marker of clinical deterioration and nephrotoxicity. AKI onset is highly variable in hospital which makes it difficult to time biomarker assessment in patients for preemptive care. We applied machine learning to electronic health records and predict hospital-acquired AKI by a 48-hour lead time, with aim to create an AKI surveillance algorithm that is deployable in real-time.

Methods: The data was sourced from 20,732 case-admissions in 16,288 patients over one year in our institution. We enhanced our bidirectional recurrent neural network with a novel time-invariant and time-variant module to capture clinical features temporal to AKI in cases. Time-series features included laboratory parameters that preceded a 48-hour prediction window before AKI onset; the latter's corresponding reference was the final in-hospital serum creatinine performed in cases without AKI.

Results: The cohort was of mean age 53(±25) years, of whom 29%, 12%, 12%, and 53% had diabetes mellitus, ischemic heart disease, cancers, and baseline eGFR <90 mL/min/1.73m^2, respectively. There were 911 AKI episodes in 869 patients. We derived and validated an algorithm in the testing dataset with an AUROC of 0.81 (0.78–0.85) for predicting AKI. At a 15% prediction threshold, our model generated 699 AKI alerts with 2 false positives for every true AKI and predicted 26% of AKIs. A lowered 5% prediction threshold improved the recall to 60% but generated 3,746 AKI alerts with 6 false positives for every true AKI.

Conclusions: We generated an accurate algorithm from electronic health records through machine learning that predicted AKI by 48 hours prior. The prediction threshold could be adjusted during deployment to balance an optimal recall with alert-fatigue, while its precision could be augmented by better-timed AKI biomarker assessment in the high-risk cohort identified.

Funding: Government Support - Non-U.S.



PO0190

Urine Biomarkers of AKI in Extremely Low Gestational Age Neonates: A Case-Control Study

David J. Askenazi,[1] Brian A. Halloran,[1] Robert Schmicker,[2] Patrick J. Heagerty,[2] Sandra Juul,[2] Stuart Goldstein,[3] Sangeeta R. Hingorani,[4] Meagan Reagan.[1] *[1]The University of Alabama at Birmingham School of Medicine, Birmingham, AL; [2]University of Washington School of Medicine, Seattle, WA; [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [4]Seattle Children's Hospital, Seattle, WA.*

Background: Urine biomarkers hold promise to diagnose and differentiate AKI. In premature neonates, biomarker evaluation must address normative gestational age (GA) differences.

Methods: We performed a case-control study from neonates enrolled in the Preterm Erythropoietin Neuroprotection Trial (PENUT) to evaluate differences in urine obtained in the first postnatal week between cases and controls. Twenty (N=20) neonates with severe AKI (Stage 2 or 3) were matched with 2 controls (N = 40) who did not have AKI, had the same GA week (rounded down to the nearest week), gender, and BW (+/- 50 g), without replacement. Biomarkers were analyzed on multi-analyte electro-chemiluminescent or single colorimetric ELISA kits. Biomarker were run in duplicates; the average concentration was converted to $\log_{10}$. Days were grouped into day 0-3, 4-6, 7-9, with day of birth was defined as day 0. For each biomarker, the average pairwise difference between cases and controls was calculated. To account for multiple measurements, a linear mixed model framework was employed incorporating a random intercept for match, random effects across day, and a day case status interaction term. The predicted mean differences (95% CI) between cases and controls for each measurement time frame are compared and reported in the figures.

Results: Demographic characteristics were similar between those with and without AKI. The association with case status was modified by day (interaction p-values <0.05) for (Albumin, Clusterin, Creatinine, Cystatin C, epithelial growth factor (EGF), kidney injury marker-1 (KIM1), neutrophil gelatinase associated lipocalin (NGAL), FGF23, Ghrelin, IGFBP7, IL15, MCP1, TIMP2, VEGFA). Figures show a forest plot of the predicted mean differences (case minus control) at days 1 (0-3), 5 (4-6), and 9 (7-9) for each of 21 urine biomarkers. Urine albumin (day 1), EGF (day 1), creatinine (day 5 and 9), Cystatin C (Day 9), KIM-1 (day 9), IL-15 (day 9), and VEGFa (day 5) were significant differences between cases and controls.

Conclusions: Several urine biomarker concentrations differed in extremely low gestational age neonates with severe AKI *vs.* control. Further evaluation of these biomarkers is needed before clinical utility can be addressed.

Funding: Other NIH Support - Recombinant Erthropoietin for Protection of Infant Renal Disease (REPaIReD) Study is an NIH NIDDK funded (R01 DK103608) ancillary study designed to look at kidney outcome in patients enrolled in the Preterm Erthropoietin Neuroprotection Trial (PENUT Trial) which is an NIH NINDS funded (U01 NS077953, U01 NS77955) trial. The clinicaltrials.gov identifier is NCT01378273.

PO0191

Predictors and Outcomes of Post-Left Ventricular Assist Device AKI

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Background: Left ventricular assist device (LVAD) is used to treat advanced heart failure as a bridge to orthotopic heart transplant (OHT) or as destination therapy in patients who are not OHT candidates. With limited donor availability and significant improvement in LVAD outcomes, the number of patients with LVAD implantation as destination therapy has increased. With increased LVAD use, the number of adverse events and complications are expected to increase. Acute kidney injury (AKI) is a frequent complication after LVAD implantation and is associated with high mortality. We studied the predictors of Post-LVAD AKI and the association between AKI and mortality, as well as between AKI and receiving an OHT.

Methods: We conducted a retrospective multi-center study using TriNetX Research Network database, a federated electronic medical records, to identify 486 patients from 24 healthcare organizations from the United States, with no underlying chronic kidney disease (CKD) who had an LVAD implanted between 1/1/2010 and 12/31/2019. Of these, 116 (23.9%) had developed AKI within the first month of the procedure. The baseline characteristics of this group were compared with the 370 patients who had not developed AKI during the first month after LVAD placement.

Results: There was no statistically significant difference between the two groups in regards to age at time of LVAD placement, sex, or ethnicity. Black race was associated with a higher odds of developing AKI (Odds Ratio [OR]: 1.70; 95% Confidence Interval [CI]: 1.11, 2.59). The two co-morbidities most significantly associated with AKI during the first month after LVAD placement were: persistent atrial fibrillation (OR: 3.33; CI: 1.35, 8.22), and a body mass index (BMI) > 50 (OR: 3.86; CI: 2.21, 6.75). During the first year after LVAD placement, 73 patients died and 37 patients received OHT. There was no statistical difference in one-year mortality or likelihood of undergoing an OHT within a year between the AKI and non-AKI groups.

Conclusions: In patients with no underlying CKD, black race, persistent atrial fibrillation, and BMI above 50 increase the likelihood of post-LVAD AKI. Development of AKI post-LVAD implantation in these patients is not associated with changes in one-year mortality or likelihood of receiving an OHT.

PO0192

AKI in COVID-19 Patients and History of Cancer: Role of D-Dimer as a Potential Risk Factor

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Background: New York City (NYC) was the epicenter of the coronavirus disease 19 (COVID-19) pandemic in the United States in the Spring of 2020. Complications of severe COVID-19 infection included ARDS, thrombotic events and acute kidney injury (AKI). Patients with co-morbidities such as diabetes mellitus, heart failure, chronic kidney disease and cancer had higher mortality rates. The rate of AKI in NYC was between 37%-46% in hospitalized patients. In this study we determined the role of coagulation activation as assessed by D-Dimer as a risk factor for AKI in COVID-19 patients with history of cancer.

Methods: We used the MSKCC electronic medical records to obtain patient data. We included all patients above 18 years of age who were hospitalized at MSKCC for COVID-19 infection and had a confirmed positive RT-PCR nasopharyngeal swab test for SARs-CoV2 between March 1, 2020 to May 1, 2020. Patents with ESRD on dialysis were excluded.

Results: We had a total of 361 patients with COVID-19 infection who were hospitalized and of these 25.7% (93/361) required admission to the intensive care unit (ICU). AKI developed in 9% (33/361) of patients and of these 69% (23/33) developed AKI after ICU admission. 26 patients who developed AKI had D-dimer levels checked and 88.4% of these patients had an elevated D-dimer vs 34.5% (67/194) positivity rate for patients with no AKI (p= 1.4e-7). D-dimer and AKI association shown in Figure 1.

Conclusions: The rate of AKI in our population was significantly lower than in general population despite having history of active or treated cancer as a comorbidity. The majority of patients developed AKI after admission to the ICU. An elevated D-dimer was noted in 88.4% of patient who developed AKI and were tested for it. This could make D-Dimer a risk marker for AKI in cancer patients with COVID-19.

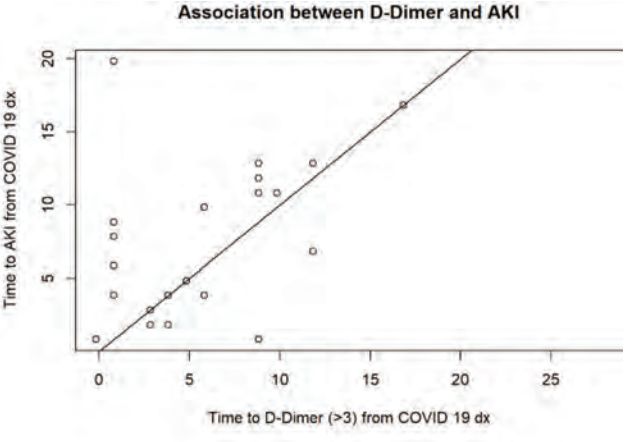

Fig 1.Association between time to elevated D-Dimer and time to AKI after COVID-19 diagnosis.

PO0193

Associations of RAS Inhibitor Suspension During AKI with Mortality in Hospitalized Patients

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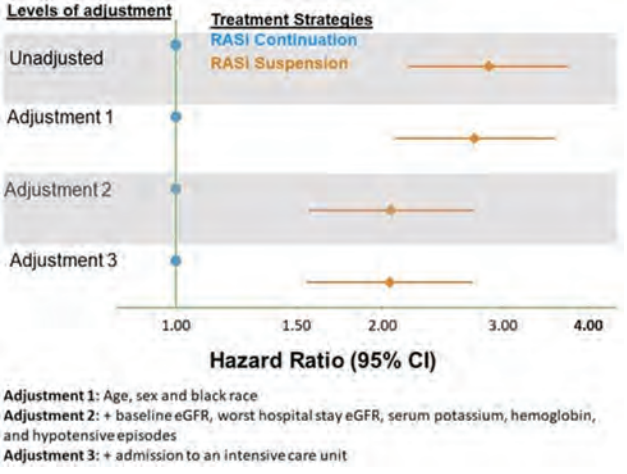
Background: Blockade of the renin-angiotensin system may slow disease progression and prevent mortality in patients with chronic kidney disease. However, it is unclear whether RASi can increase the risk of developing AKI and its complications in hospitalized patients. The aim of the study is to compare mortality of patients with AKI who have discontinued RASi to those who maintained its use.

Methods: We analyzed data from a cohort of hospitalized patients identified by an AKI alert based on KDIGO creatinine criteria, who were on a RASi. From January to December, 2018, suspension of RASi medications was defined by the lack of its prescription until 3 days after AKI alert in their electronic health records. Cox models were used to test the association of RASi suspension with all-cause mortality, adjusting for possible confounders: age, sex, race, baseline and worst achieved GFRs, potassium, hemoglobin levels and episodes of hypotension during the hospitalization.

Results: During hospitalization 1253 patients were on a RASi. After the AKI alert, 493 remained and 760 suspended its use. The median [IQR] follow-up time was 11.9 [7.20-20.8] days. Patient characteristics were similar across treatment strategies. In the suspended group more patients needed dialysis (13% vs 4%) and were admitted to intensive care units (66% vs 55%); mean potassium levels were consistent across groups

(4.45 mg/dL (0.72) vs 4.39 mg/dL (0.67) for the patients who remained on RASi). There was a strong association of RASi suspension with death as shown in the figure.

Conclusions: Among patients with AKI, the strategy of suspending RASi resulted in a twofold higher death rate than for those who remained on the medication, even after adjustment for possible confounders. These findings suggest that an individualized approach to RASi therapy may be warranted in the hospitalized patient with AKI.



Adjustment 1: Age, sex and black race
Adjustment 2: + baseline eGFR, worst hospital stay eGFR, serum potassium, hemoglobin, and hypotensive episodes
Adjustment 3: + admission to an intensive care unit

PO0194

External Validation of Simple Postoperative AKI Risk (SPARK) Classification in Noncardiac Surgery: The NARA-AKI Cohort Study

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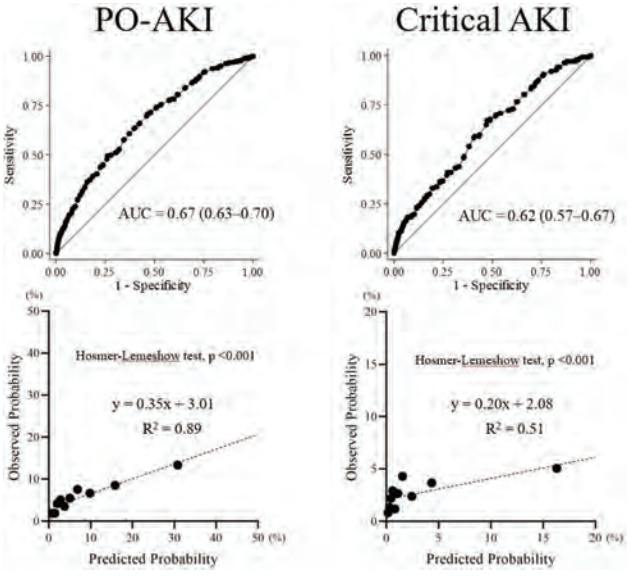
[1]Nara Kenritsu Ika Daigaku, Kashihara, Japan; [2]Nagoya Shiritsu Daigaku, Nagoya, Japan; [3]Nara-ken Sogo Iryo Center, Nara, Japan.

Background: The aim of the present study was to externally validate Simple Post-operative AKI Risk (SPARK) index which was developed to predict post-operative acute kidney injury (PO-AKI) in non-cardiac surgery.

Methods: In a retrospective cohort study, adults with non-cardiac surgery under general anesthesia were included. Those with obstetric or urological surgery, estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2, pre-operative dialysis, expected surgical duration <1 hour, and missing data for analyses were excluded. The exposures of interest were risk factors for AKI included in SPARK index, and outcomes were PO-AKI and critical AKI. The discrimination and calibration of SPARK index were examined with receiver operating characteristic curves and calibration plots, respectively.

Results: Among 5135 subjects, 303 and 137 developed PO-AKI and critical AKI, respectively. Subjects in our cohort were older, and baseline eGFR was lower compared to SPARK cohort. In addition, the proportion of subjects with comorbidities was higher. The incidence of PO-AKI and critical AKI increased as the scores of SPARK index increase. However, areas under the curves for PO-AKI and critical AKI were both suboptimal, and the calibration was poor (Figure). Higher age, diabetes mellitus, expected surgical duration, emergency surgery, renin-angiotensin-aldosterone system blockade use, and hyponatremia included in SPARK index were not associated with PO-AKI in our cohort, resulting in overestimation of predicted probability of AKI in our cohort.

Conclusions: SPARK index is useful in identifying subjects at high risk for developing AKI pre-operatively. However, predicted probability might not be accurate in cohorts including older subjects with more comorbidities.



PO0195

A Risk Score for Major Adverse Kidney Events One Year After AKI

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Background: Epidemiologic evidence suggests that those with AKI are at increased risk of post-AKI kidney disease, higher hospital resource utilization, and deathI. However, literature to support identification of those most at risk of these outcomes is limited. Here we pilot predicting risk of post-AKI MAKE.

Methods: In a cohort of 4.2 million United States Veterans, risks of MAKE within a year of discharge associated with an AKI were detailed using survival regression with inverse probability of treatment weighting. Risk factors for MAKE including demographics, clinical characteristics including diagnoses, medication use, and laboratory tests, as well as hospitalization parameters among those with an AKI were examined, and then a risk score was developed and evaluated following the Framingham Heart risk score algorithm.

Results: In the year after dischrarge form a hospitalization, compared to those without an AKI, those with an AKI were at an increased risk of a subsequent AKI (HR=1.47; 95% CI=1.45-1.49), incident eGFR less than 60 ml/min/1.73 m^2 (1.23; 1.22-1.24), eGFR decline >30% (1.69; 1.67-1.71), receipt of kidney replacement therapy (2.41; 2.28-2.51), and MAKE (1.24; 1.23-1.25). Results were consistent in Fine and Gray competing risk models. Among those with an AKI, predictors of MAKE included age, albuminuria, bicarbonate, blood pressure before and during hospitalization, cardiovascular disease, cancer, chronic lung disease, dementia, diuretic use, baseline eGFR, hematocrit level, NSAID use, obesity, platelet count, pneumonia, serum creatinine trajectory during hospitalization, surgeries, and urinary tract infection. A risk score constructed using these predictors achieved an area under the curve (*AUC*) of 0.72, where corresponding probabilities of having a MAKE within a year of discharge ranged from 7.3% to 59.9% at the lowest and highest risk score values experienced in the cohort. Comparatively, use of KDIGO stage alone marginally predicted future risk of MAKE (0.52). Calibration plots suggested that models were well calibrated.

Conclusions: Use of EHR resulted in a moderate ability to identify those at increased risk of post-AKI MAKE. Further research is needed in identifying those who may benefit from post-AKI care.

Funding: Veterans Affairs Support, Private Foundation Support

PO0196

The Association of Metabolic Acidosis with AKI in Patients with CKD: A Retrospective Cohort Study in Two Cohorts

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Background: Metabolic acidosis in patients with chronic kidney disease (CKD) results from a loss of kidney function. It has been associated with more rapid CKD progression, all-cause mortality, and other adverse outcomes. Whether metabolic acidosis is associated with a higher risk of acute kidney injury (AKI) remains unknown.

Methods: We conducted a retrospective cohort study in 2 North American cohorts (US EMR cohort and Manitoba Claims cohort) using electronic health records and administrative data of patients with CKD Stages G3-G5. The primary exposure was metabolic acidosis (serum bicarbonate between 12 and <22 mEq/L), and the primary

outcome of interest was the development of AKI (defined using ICD-9 and 10 codes at hospital admission or a laboratory-based definition based on KDIGO guidelines). We applied Cox proportional hazards regression models adjusting for common demographic and clinical characteristics.

Results: In both cohorts, metabolic acidosis was associated with AKI: HR 1.565 (95% CI 1.518 – 1.613) in the US EMR cohort and HR 1.652 (95% CI 1.578 – 1.729) in the Manitoba Claims cohort. The association was consistent when serum bicarbonate was treated as a continuous variable, and in multiple subgroup and sensitivity analyses including those adjusting for albuminuria.

Conclusions: Metabolic acidosis is associated with a higher risk of AKI in patients with CKD. AKI should be considered as a safety outcome in studies of treatments for patients with metabolic acidosis.

Funding: Commercial Support - Tricida, Inc.

PO0197

Chikungunya Fever: A Trigger for Different Renal Disorders

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Background: Prevalence of chikungunya fever (CHIK)-related kidney injury (KI) is variable, but data are scarce and limited to the acute phase of the disease. Necropsies performed in fatal acute cases of CHIK show that viral RNA can be found in renal tissue, but clinical and histopathological aspects poorly characterized. This study aimed to describe renal histopathological features and to detect viral antigens in renal tissue in patients affected by CHIK in different phases of infection.

Methods: This was an exploratory study, conducted between 2016 and 2020. Patients followed in six nephrology reference centers due to KI with onset after different phases of CHIK infection were evaluated. These patients had hematuria, proteinuria and/or renal dysfunction after a common history of CHIK infection and were referred for renal biopsy. Viral antigens were investigated by electron microscopy, immunohistochemistry and PCR in renal tissue.

Results: Sixteen patients (aged 10-59years) had KI 0.5 to 24months after CHIK, with predominance of glomerular lesions. Initial creatinine ranged from 0.2 to 22.3mg/dl (median 3.9mg/dl; IQR 1.0-5.5). Proteinuria and hematuria were initially detected in 94% and 81% of patients, respectively. Histopathological findings comprised diagnoses of focal segmental glomerulosclerosis (FSGS) (3), class IV lupus nephritis (3), crescentic glomerulonephritis (2), atypical hemolytic uremic syndrome (aHUS) (2), pauci-immune vasculitis (1), PLA2R-positive membranous nephropathy (2), collapsing glomerulosclerosis (CG) (2). One patient was diagnosed with collagen IV-related nephropathy in renal biopsy performed due to macroscopic hematuria after CHIKV infection. No viral antigens were detected in renal tissue. The 2 patients with aHUS included in the study carry heterozygosis mutations associated with increased risk of developing the disease. *APOL1* high-risk genotypes were identified in 2 patients with CG (G1/G2 and G2/G2) and 1 patient with FSGS (G1/G2). Nine (56%) patients progressed to chronic kidney disease after a median follow-up of 12 months.

Conclusions: Our findings reveal the potential of CHIK virus to directly cause and/or trigger KI. These effects can be translated into a variety of renal lesions potentially with significant severity.

PO0198

Risk Factors and Outcome Variables of Cardiorenal Syndrome Type 1 from the Nephrological Perspective

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Background: In cardiorenal syndrome (CRS) type 1, acute cardiac failure or acute decompensation of chronic heart failure causes acute kidney injury (AKI). Every individual AKI episode increases the risk for chronic kidney disease (CKD) in the long-term. In this study we aimed to evaluate epidemiological characteristics and outcome variables of CRS type 1 individuals from the nephrology perspective.

Methods: The study was performed in a restrospective, observational manner. All AKI patients treated at the Brandenburg Hospital of the Medical School of Brandenburg between january and december 2019 were screened for diagnostic criteria of CRS type 1. Endpoints were in-hospital death, need for dialysis, and renal recovery.

Results: During the screening, a total number of 1,189 subjects were diagnosed with acute kidney injury according to KDIGO. One-hundred ninety-eight (198 - 16.6%) out of these patients were assigned to the diagnosis CRS type 1. The overall in-hospital mortality was 19.2%. Non-survivors were not older than survivors. Nine point six (9.6) % of the patients required dialysis due to AKI, respective individuals were significantly older (84.6 +/-1.4 vs. 77.6 +/-0.7 years; p=0.002). Complete recovery of kidney function was observed in 86 individuals (43.4%), incomplete recovery occurred in 55 patients (27.8%), fifty-seven patients (28.8%) did not revover at all. Age-related differences were not identified. Sixty-four (32.2%) demission letters did not contain any cardiorenal diagnosis at all, nephrology follow-up recommendations were given in only 8%.

Conclusions: The incidence of CRS type 1 is high (~16% of all in-hospital AKI subjects) and the mortality is higher than the average mortality of AKI in general. At the same time complete recovery of kidney function occurs less frequent. The kidney-related follow-up management of CRS type 1 needs to be significantly optimized in order to improve the long-term outcome of affected patients.

PO0199

An Automated, Open-Source Program to Standardize AKI Definition from Time-Stamped Creatinine Data

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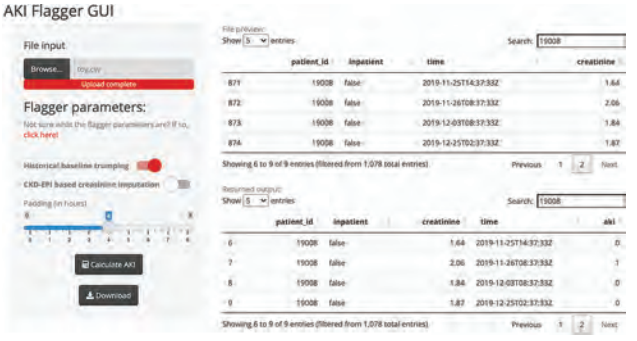
Background: Though KDIGO guidelines specify a definition for AKI based on changes in serum creatinine, operationalizing this definition with real-world data requires multiple assumptions that leads to variation across studies. A standardized AKI flagging tool may increase inter-study validity.

Methods: We develoepd AKIFlagger, an open-source computational tool built in Python, R, and as a web application which implements a standardized AKI definition based on KDIGO guidelines while allowing for variational definitions of baseline creatinine. We applied the AKIFlagger to a dataset of patients hospitalized with COVID-19 while permuting various operational implementations of the guidelines.

Results: We demonstrate that subtle changes in definition can have a large impact on estimates of AKI prevalence and outcomes. Compared to a rolling window approach, using a baseline definition that leverages outpatient creatinine values and or imputes those values based on an eGFR back-calculation increases the size of captured patient populations by 20.7% and 57.1%, respectively. We characterize the predictive value of the different methods of identifying AKI by determining the sensitivity and specificity for stage progression and progression to death or dialysis. The approaches span sensitivities from 0.18 to 0.20 and specificities from 0.90 to 0.95 for stage progression, and sensitivities from 0.71 to 0.85 and specificities from 0.62 to 0.76 for progression to death.

Conclusions: Subtle differences in the definition of AKI can lead to drastic differences in which patient populations are captured by the definition. A standard mechansim to implement the KDIGO criteria is necessary for the field to accurately advance both clinical and basic science research. This standardized tool can be used by researchers to ensure definitions are uniform across studies.

Funding: NIDDK Support



Screenshot of the web interface for AKIFlagger

PO0200

Community-Acquired AKI: A Prospective Case-Control Study

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Background: Acute kidney injury (AKI) represents an abrupt decline in kidney function occurring over hours or days. While hospital-acquired AKI has been extensively studied, data on community-acquired AKI are scarce. The aim of this study was to examine the incidence and causes of AKI among patients presenting to the emergency department (ED).

Methods: This was a prospective case-control study in which serum creatinine (SCr) of all individuals admitted to the ED of Landspitali–The National University Hospital were examined for the presence of AKI. We present data from January 1 until March 3, 2020 and May 19 until September 21, 2020. The study was paused between these periods due to the COVID-19 epidemic. All patients who met the KDIGO criteria for AKI were invited to participate. Randomly selected control cases (1:2) were paired according to age, sex and time of ED admission. Participants answered questions about their medical history and use of medications, including over-the-counter (OTC) drugs. Medical records were reviewed with regard to medical history. Logistic regression was used to identify factors associating with AKI.

Results: A total of 372 persons with AKI were identified, 315 (85%) of whom participated in the study. The mean (±SD) age of AKI cases and controls was 66.6±16.1 years and 66.3±16.2 years, respectively; 46% of cases and controls were female. AKI cases were significantly more likely than controls to have used non-steroidal anti-inflammatory drugs (NSAIDs) (31.1% vs 22.2%, p=0,003) in the week preceding the ED visit, particularly OTC NSAIDs (24.7% vs 16.2%, p=0.001). In the logistic regression analysis, AKI was associated with vomiting (OR 2.40 95%CI 1.74-3.35), diarrhea

(OR 1.35, 95%CI 1.00-1.84), diabetes (OR 1.66, 95%CI 1,17-2,35) and NSAID use (OR 1.60, 95%CI 1.18-2.23), but a statistically significant relationship was not observed for use of ACE inhibitors/angiotensin receptor blockers or diuretics, or a history of hypertension, vascular disease or chronic kidney disease.

Conclusions: These results suggest that volume depletion and the use of NSAIDs play a major role in the development of AKI in the community setting. Frequent use of OTC NSAIDs is a concern and should be addressed in light of serious adverse effects.

Funding: Government Support - Non-U.S.

PO0201

Serum Proteomics Identifies Protein Alterations After Platinum-Based Chemotherapy

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Background: Acute kidney injury (AKI) is a common complication after platinum-based chemotherapy. However, the mechanisms mediating this process remain to be fully understood. Our object was to invest serum proteins variations among patients after receiving platinum-based chemotherapy to provide more evidence of the pathophysiology of chemotherapy induced AKI.

Methods: In this study, serum samples from 10 patients underwent chemotherapy were used and samples before therapy were used as control. Serum proteins were extracted and submitted for LC-MS/MS. Peptides were analyzed for spectral count quantitation. The classification and enrichment analysis of these factors were based on Gene Ontology and Kyoto Encyclopedia of Genes and Genomes.

Results: An overview of GO enrichment showed that organization biogenesis, response to stimulus and immune system process were significantly changed after chemotherapy. Protein binding and transporter activity were the main differences of molecular function in the GO assignments. KEGG analysis revealed that several pathways were highly enriched including infectious disease, immune system, transport and catabolism. After narrowing down the targets and compared with the control status, top 5 significantly up-regulated proteins were HBD, HBB, HBG2, HBA1, TNC and top 5 down-regulated proteins ADAMTS13, FLT4, HRNR, MINPP1 and KRT9. These proteins were mostly involved in immune regulation, cellular component and organization biogenesis.

Conclusions: The serum proteomic is distinct after platinum-based chemotherapy. Inflammation and extracellular related proteins were involved in renal disease.

Funding: Government Support - Non-U.S.

PO0202

Markers of Kidney Tubule Cell Function and Future Risk of Infection-Associated AKI

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Background: Novel biomarkers can quantify kidney tubular functions including proximal tubule reabsorption (alpha 1 microglobulin [a1m]), and tubule protein synthesis (uromodulin [umod]). We have previously reported that abnormalities in these markers at times of health predicted future risk of AKI secondary to volume depletion. Association between tubular function markers and other causes of AKI are uncertain.

Methods: We identified 474 individuals within the REGARDS study who had in-patient admissions for infections and developed AKI (≥ KDIGO stage 1) during 3.8 years follow-up. Cases were matched (1:1) by age, sex, race, and time from baseline to hospital admission to individuals admitted with infection but without AKI. We used stored urine specimens from REGARDS baseline to measure a1m (ELISA) and umod (immunoassay), as well as NGAL (immunoassay) as a marker of tubule injury. Conditional logistic regression evaluated odds of AKI.

Results: Mean age was 70 ± 8 years, 44% were female, 38% were black. Mean baseline eGFR among cases and controls was 71 and 78 mL/min/1.73m^2, respectively and mean albuminuria was 241 vs. 69 mg/g, respectively. Cases were more likely to be taking ACEi, ARB, and NSAIDs. Most had state 1 AKI (92.7%). Higher urine a1m and higher urine umod levels were each associated with higher AKI risk but these associations were attenuated in final models. Results were similar with NGAL (Table). Results were also similar when examining KDIGO stage 2 or greater AKI vs. controls.

Conclusions: At times of health, urine a1m and UMOD are not independently associated with future risk of infection-associated AKI.

Funding: Veterans Affairs Support

Association of tubule cell function markers and future risk of infection-associated AKI

Biomarker (per 2-fold higher)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
a1m	1.49 (1.38, 1.61)	0.97 (0.86, 1.09)
Umod	1.22 (1.04, 1.42)	1.24 (1.00, 1.54)
NGAL	1.60 (1.43, 1.78)	1.01 (0.89, 1.17)

Adjusted for age, urine creatinine, diabetes, SBP, DBP, ACE, ARB, or NSAID use, and baseline eGFR and urine albumin.

PO0203

Circulating Endotoxin Levels Correlate with Kidney and Mortality Outcomes in Critically Ill Patients

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Background: Among the critically ill, sepsis is a common cause of acute kidney injury (AKI). Endotoxin is a component of gram negative bacterial cell walls, and is a potent trigger of AKI in sepsis, but may also be present in non-bacteremic patients. Our aim was to determine correlations between endotoxin levels and AKI and mortality outcomes in incident critically ill patients.

Methods: Patients were recruited from those admitted to intensive care units (ICUs) who were over 18, and who did not have end-stage renal failure requiring dialysis, or were on chronic immunosuppressive medications. Blood endotoxin activity (EA) was measured using the FDA-approved chemiluminescent EA Assay. Blood EA was measured on days 1, 4 and 8 of admission to ICU, and results either categorized as low (0.0-0.39), intermediate (0.4-0.59) or high (≥0.60), or used as a continuous variable in Spearman correlation analysis. Kidney parameters and dispositions were obtained from electronic medical records. AKI was defined as per KDIGO guidelines.

Results: A total of 35 patients were recruited between November 2020 and April 2021, with 4 testing positive for gram negative bacteria. Initial EA levels were 6 (17%), 10 (29%) and 19 (54%) patients with low, intermediate, and high levels, respectively. During the study, 14 patients' EA levels changed such that their categorization either went up (4) or down (9), whilst one patient alternated between intermediate and high levels. When stratified by presence of AKI, no patients with low EA (0/6) developed AKI, whilst 9/13 (71%) of patients with AKI had high EA versus 8/20 (40%) of non-AKI patients who had high EA. All of the patients with low EA were discharged, whereas 3/10 (30%) and 4/18 (22%), respectively, of those with intermediate and high EA expired. When analyzed as a continuous variable, there was a significant positive correlation between initial EA and initial sCr ($r = 0.56$, $p<0.001$). Furthermore, there was a significant correlation between the rates of changes in EA and sCr over time ($r = 0.47$, $p<0.05$).

Conclusions: Endotoxin levels on admission to ICU correlated with kidney function, presence of AKI, and mortality. Changes in EA over time also correlated with changes in kidney function, suggesting that EA may be a potential biomarker in critically ill patients.

Funding: Commercial Support - Dialysis Clinic Inc.

PO0204

Incidence of Hypophosphatemia During Continuous Renal Replacement Therapy: Baseline Data for a Quality Improvement Initiative

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Background: Hypophosphatemia is common among critically ill patients on continuous replacement therapy (CRRT). And low serum phosphorus is associated with difficulty to wean off from mechanical ventilation, longer hospital stays, and death. Our objective was to determine the incidence of hypophosphatemia among individuals receiving CRRT before implementing a phosphate replacement protocol as part of a quality improvement initiative.

Methods: We conducted a retrospective study of electronic health records from the University of Arkansas for Medical Sciences to identify consecutive adults diagnosed with acute kidney injury who received CRRT for at least 24 hours between May 2014 and September 2018. Laboratorial measurements of serum phosphorus collected while on CRRT were examined and hypophosphatemia was defined as levels <2.5 mg/dL.

Results: A total of 685 unique participants received CRRT between 2014 and 2018. On average, 13.2 individuals were started on CRRT every month. Of 685 individuals, 446 were on CRRT for at least 24 hours for a total of 3,328 treatment days. The median number of days on CRTT was 4.3 (2.1-9.2). Those 446 individuals had 2,709 measurements of serum phosphorus. In total, 192 (43%) individuals were diagnosed with hypophosphatemia which occurred with a median time of 63.0 hours after initiation of CRRT. Hypophosphatemia developed in 25% of individuals within the first 2 days after starting dialysis.

Conclusions: Hypophosphatemia occurred frequently, and the incidence peaked at day 3. Although there is no ideal protocol about how to replace phosphate, our findings suggest that replacement should begin early after initiation of CRRT.

PO0205

AKI in Kuwait: Incidence, Causes, Management, and Outcomes – A Prospective Observational Study

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Background: Little is known about AKI epidemiology, causes, management and outcome in Kuwait. We report that.

Methods: Demographics, comorbidities, treatment and 4 weeks outcome data for nephrology referrals for AKI in 7 public hospitals from 1/Jan-30/Apr/2021 prospectively collected and analyzed

Results: Total number of AKI referrals was 1298, that is 3.3% of hospital admissions. Community acquired cases were 12.5%. Males were 57%, mean age 64 (52% > 65), and Kuwaiti citizens 65%. DM affected 71%, HTN 74%, and cardiac disease 36% of patients. Mean baseline eGFR before AKI was 62. Baseline eGFR < 60 seen in 52%, and those compared to patients with eGFR > 60, had mean baseline eGFR of 35 (vs 90), were older (68 vs 60 with 61% above age 65 vs 41%), 81% had DM (vs 60%), 85% had HTN (vs 63%), 46% had cardiac disease (vs 24%). Cause of AKI was pre-renal / ischemic ATN in 87%, COVID-19 related in 8%, contrast-associated in 6%, drug-induced AIN in 5% of cases. Many had more than one possible cause. Sepsis was most common precipitating factor seen in 67% then volume depletion in 50%. Many had more than one factor. IV fluids used in 73% (less in lower eGFR group), IV diuretics in 46% (more in lower eGFR group), IV vasopressors in 40% (less in lower eGFR group) and steroids in 33%. KRT needed in 33%, more in patients who used diuretics or vasopressors. Volume overload and electrolytes / acid-base disorders were most common indication (75% and 79% respectively). CKRT was modality of choice in 85%, however, in 52% of CKRT, conventional HD not used due to lack of dialysate source in some sites. At 30 days, mean eGFR was 42%, with complete recovery in 34%, and 38% failed to recover at all. Death occurred in 31%, 55% had baseline eGFR > 60, and 50% of deaths occurred while still on KRT. Non-survivors were older and had higher use of vasopressors. AKI associated mortality in 25% of total hospital mortality and in 31% of ICU / CCU mortality.

Conclusions: AKI is common. Most cases hospital-acquired. Use of resources (medications, critical care, KRT) and rates of mortality are high. Kuwaiti citizens represent 1/3 of the population and 2/3 of AKI cases and almost 70% of deaths.

PO0206

AKI in the Month of Ramadan

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Background: Fasting in Ramadan from dawn to sunset is one of Islam's 5 pillars. Islamic lunar calendar is 11 days shorter than Gregorian solar calendar, so the start of Ramadan changes every year and hours spent on fasting vary from 12 hours in Australia, to 21 hours in Sweden, with most countries have 11-16 hours of fasting on average. Patients with certain medical illness are exempted from fasting, however, many such patients partake in fasting. The long hours of fasting may be a risk factor for AKI in certain populations. We assess AKI in Ramadan.

Methods: Demographics, comorbidities, treatment, and 4 weeks outcome data for all nephrology consultation for AKI in 4 public hospitals in Kuwait during Ramadan of 2021 (13/April-12/May/2021) prospectively collected and analyzed. We compare AKI in people fasting prior to admission to non-fasting.

Results: Total number of AKI cases in Ramadan was 158, 55% males, mean age 64, and 61% were Kuwaiti citizens. Community acquire cases were 15%. DM affected 75%, HTN 72%, and cardiac disease 25% of patients. Median baseline eGFR before AKI was 66.5. Baseline eGFR < 60 seen in 43%, and those compared to patients with eGFR > 60, had median baseline eGFR of 37.5 (vs 92), were older (69 vs 62), 87% had DM (vs 66%) and 87% had HTN (vs 61%). Cause of AKI was pre-renal / ischemic ATN in 69%, COVID-19 related in 17%. Many had more than one possible cause. IV fluids used in 76%, IV diuretics in 39%, IV vasopressors in 31%, and steroids in 21.5%. KRT needed in 27%. Volume overload and electrolytes / acid-base disorders were most common indication (21% and 19% respectively and 15% had more than one indication. Death within 30 days occurred in 11.4%. Of the total, 24% were fasting before admission, with mean age of 56 (compared to 63 for non-fasting). No significant difference in baseline eGFR between fasting and non-fasting, nor in use of IV fluids, IV diuretics, or IV vasopressors. Dialysis needed in 21% of the fasting group, not significantly different from non-fasting group. Mortality rates were lower but not statistically significant in the fasting group (8% vs 12.5%).

Conclusions: AKI affect both fasting and non-fasting population similarly, with no increased risk of need for dialysis or mortality.

PO0207

Seventy-Two Cases of Metformin-Associated Lactic Acidosis (MALA): Clinical Presentation and Evolution Analysis

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Background: MALA is a complication that continues to occur today. It is important to collect large series of cases to better understand the clinical presentation and evolution of this condition.

Methods: We collected the MALA cases (diagnostic criteria: pH ≤ 7.5; lactate ≥ 5 mmol / L) in a 700-bed tertiary hospital during the period January 2010-December 2020. We analyzed the clinical factors and laboratory tests associated with the presentation of the condition, as well as mortality.

Results: 72 cases were registered (38 men; 52.8%). Average age 76.03 ± 10.37 years. Metformin serum levels were available in 46 patients (mean: 26.41 ± 17.87 mcg / ml; toxic if > 5 mcg / ml). Mean length of stay 11.61 ± 9.7 days. Average Charlson comorbidity index 5.7 ± 1.8 points. Ingested milligrams / day of metformin: 1788.89 ± 395.8. 29 patients had a history of chronic kidney disease (CKD) (40.3% of the total). Cases in the context of acute kidney injury (AKI): 70 (97.2% of the total; 7 KDIGO stage 1 cases, 6 stage 2, 57 stage 3). 90.2% were AKI of prerenal origin. 26 patients required admission to the ICU (36.1%). 10 cases received hemodiafiltration, 26 cases hemodialysis. Mean analytical parameters: pH 7.10 ± 0.19; Lactate 10.12 ± 5.3 mmol / l; bicarbonate 10.94 ± 5.3 mmol / l; GAP anion 27.23 ± 7.6 mmol / l; pCO2 31.9 ± 12.22 mmHg; potassium 6.25 ± 1.42 meq / l; hemoglobin 11.51 ± 2.3 g / dl. Overdose occurred in 17 cases (23.6%). The statistical analysis detected the existence of a linear association between: metformin and peak creatinine levels (Spearman's r 0.48, p = 0.001); metformin levels and pH (Spearman's r -0.37, p = 0.000); metformin and lactate levels (Pearson's r 0.42, p = 0.004); potassium and pH levels (Spearman's Rho 0.35, p = 0.003); Charlson index and number of active drugs (Pearson's r 0.38, p = 0.001). 17 patients died (mortality 23.6%). A multivariate logistic regression model detected pH (OR 0.003; 95% CI 0.00-0.380) and peak creatinine (OR 0.706; 95% CI 0.49-1.008) as the variables independently associated with mortality.

Conclusions: Virtually all cases occurred in the context of severe AKI, the majority of prerenal origin. Mortality was 23.6%. It is necessary to warn patients taking metformin of the clinical situations potentially inducing AKI (especially dehydration).

PO0208

An Analysis of Risk Factors for AKI in Patients with Decompensated Cirrhosis: A 4-Year Retrospective Study, 2012-2015

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Background: Acute kidney injury (AKI) is a common complication in advanced liver diseases. So prevention of AKI occurence in patients with cirrhosis might improve their outcomes. We aimed to determine the risk factors for AKI in patients with decompensated cirrhosis.

Methods: We conducted a retrospective analysis, which was a 4-year study involving 945 patients. AKI was diagnosed based on 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria. The clinical and demographic data of AKI group was compared with other patients by univariate and multivariate regression analyses.

Results: The incidence of AKI in decompensated cirrhosis was 17.7%. Compared with patients without AKI, patients with AKI had higher white blood cell (WBC) count, longer prothrombin time (PT), higher total bilirubin (TBil), higher serum creatinine (SCr) and higher blood urea nitrogen (BUN), but having lower alanine aminotransferase (ALT), lower albumin, lower cholinesterase (ChE), lower estimated glomerular filtration rate (eGFR), lower total cholesterol (TC), lower triglyceride (TG) and lower serum sodium concentration. But no significant differences in platelet (PLT) count and International Normalized Ratio (INR). In the multivariate logistic regression analysis, hypertension (odds ratio [OR]:3.647, 95% confidence interval [CI]:1.546-8.606, *P*=0.003), upper gastrointestinal bleeding (OR:4.957, 95%CI:2.177-11.286, *P*<0.001), SCr(OR:1.019, 95%CI:1.003-1.035, *P*=0.019), WBC(OR:1.147, 95%CI:1.032-1.275, *P*=0.011), PT(OR:1.097, 95%CI:1.004-1.198, *P*=0.04) and eGFR (OR:0.958, 95% CI:0.934-0.983, *P*=0.001) were independent risk factors for occurrence of AKI in patients with decompensated cirrhosis.

Conclusions: We observed that hypertension, upper gastrointestinal bleeding, SCr, value of WBC count, length of PT and eGFR were independently associated with the development of AKI in patients with decompensated cirrhosis. It is, therefore, necessary to apply early intervention in patients with the risks of AKI.

PO0209

Admission Platelet Count Is an Independent Predictor of AKI

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Background: Thrombocytopenia is a recognized marker of disease severity that is associated with higher mortality in patients with sepsis-associated acute kidney injury (SA-AKI). It is plausible that thrombocytopenia is also a predictor of SA-AKI development due to the characterisitic microvascular dysfunction seen in this disease state, but human studies are lacking. In this analysis, we evaluated admission platelet counts and SA-AKI rates in a large VA database of patients with methacillin-resistant staph aureus (MRSA) bacteremia.

Methods: We evaluated patients admitted to 124 VA Hospitals who developed MRSA bloodstream infections during a hospitalization from 2007-2014. Patients were excluded if platelet counts or creatinine values were not available on 2 or more days. Predictor variables were platelet counts <150 and <100 at admission. Primary outcome was the development of in-hospital AKI, defined as a platelet increase of 0.3 mg/dL over 48 hours, or an increase of 1.5x baseline within 7 days. Cox proportional hazard modeling was used to determine the association between predictors and primary outcome, and covariates were chosen using forward stepwise regression. Potential covariates evaluated for inclusion were age, race, admission laboratory values, comorbidities, antibiotic agents, infection location, healthcare utilization prior to admission, and surgical intervention, among others.

Results: A total of 6,765 patients were included, of which 2,656 (39.3%) developed AKI during admission. At admission, 1,633 (24.1%) and 757 (11.2%) had platelet counts <150 and <100, respectively. AKI rates in these pateints were 44.1% and 46.2%, respecitvely. Hazard ratios for AKI were 1.17 (CI 1.07-1.28) in patients with platelets <150, and 1.24 (CI 1.10-1.39) in patients <100.

Conclusions: Platelet counts of <150 and <100 at admission were found to be independent predictors of subsequent SA-AKI development in a large database of patients with MRSA bacteremia. These findings may inform future studies in the prevention and prediction of AKI development.

PO0210

AKI!Now: Defining Excellence in the Prevention of and Care for Patients with AKI

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Background: ASN is committed to define excellence in AKI prevention and care to transform management, reduce morbidity, mortality and improve long-term outcomes. AKI!Now addresses a set of well-defined objectives to achieve those goals.

Methods: The AKI!Now initiative has developed a broad education program that bridges the continuum from basic investigation to clinical studies focused on early recognition, intervention, and effective therapies with a patient-centered focus

Results: *Workgroups and tasks*: **Basic Science: AKI-Specific Early Interventions**: Leverage basic science discoveries to innovate in AKI prevention, diagnosis, and treatment; develop a centralized research portal; promote AKI research and translational initiatives; create a roadmap to facilitate discovery and novel interventions; and enhance communication within the community. **AKI Recognition and Clinical Interventions**: **Artificial Intelligence (AI):** Design fair and equitable AI tools among physicians and researchers; and provide expert input on pathways to implement AI tools in all clinical contexts. **Post-AKI Recovery**: Identify mechanisms of repair to identify treatment strategies to accelerate recovery; prevent adverse outcomes and identify areas of priority research; promote comparative effectiveness research benchmarks; develop, test, and promote strategies to build capacity for post-AKI care. **Public Awareness and Education:** Leverage existing and develop novel education processes for health professionals and patients and multiple resources including the AKI!Now Compendium, focusing on AKI recognition, management, and recovery; collaboratively emphasize the role of continuous quality improvement in AKI recognition and care, and include patients and families in the healing process.

Conclusions: AKI is common, serious, under-recognized across the life span, and associated with severe risk of progressive adverse outcomes. Education at all levels; use of AI to improve pattern recognition, prevention, and management; development of novel specific therapies through better understanding of AKI mechanisms; and appropriate post-AKI recovery care will alleviate the severe short- and long-term individual and societal AKI impacts.

PO0211

Diagnosing and Staging AKI in the Absence of a Baseline Serum Creatinine Value

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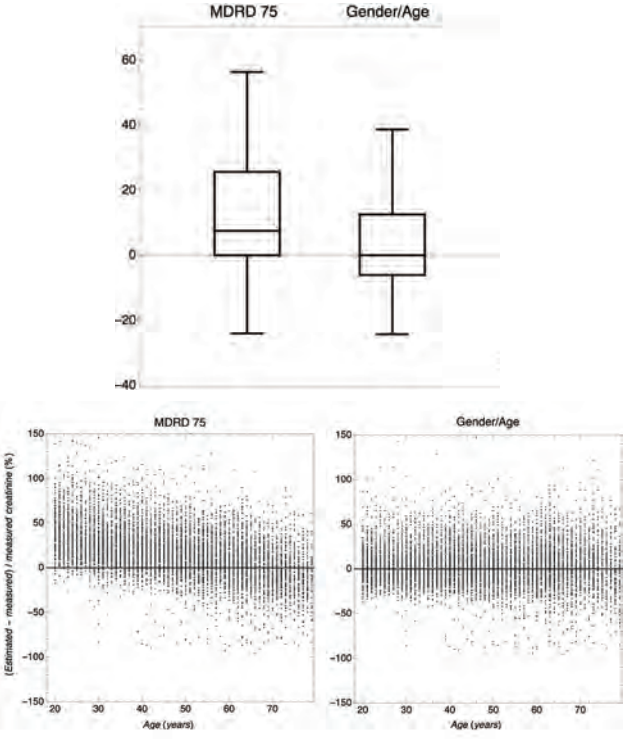
Background: AKI is commonly diagnosed and classified from changes to serum creatinine according to the 2012 KDIGO criteria. When baseline creatinine is missing, the guideline recommends to back calculate it from an assumed MDRD-GFR of 75ml/min/1.73m2. We describe an alternative method.

Methods: From NHANES 2015-2018 data we calculated distribution of serum creatinine values for the adult US population as a whole, and for gender, age and weight subgroups. We then assessed mean values in an external validation cohort (NHANES 2011-14) for performance to predict baseline creatinine in comparison to back calculated MDRD values.

Results: Relative differences between back calculated MDRD and measured creatinine values in the validation cohort show a median bias of +8% and an interquartile precision range of 0% to +26% (Fig 1). Accuracy is rather low, with P15 and P30 values at 42% and 71%. In contrast, our gender/age-based estimation eliminates bias to 0 % and improves precision, interquartile range of -6% to +13% (Fig 1). P15 increases to 58%, P30 to 86%. The relative differences show a clear age dependency for MDRD, that is not present in our gender/age-based estimation (Fig 2). Adding weight categories did not significantly improve our predictions.

Conclusions: We describe a simple method to estimate missing baseline creatinine values for assessing acute kidney injury. Compared with the current standard approach our method shows no bias, more precision and improved accuracy in predicting baseline creatinine on a population level.



PO0212

Premenopausal Age in Females Is Associated with Protection from Development of Postoperative AKI

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Background: Acute kidney injury (AKI) is one of the most common forms of perioperative organ injury. Preclinical and clinical studies examining the influence of sex on AKI have yielded conflicting results. The objective of our study was to determine the association of sex hormones on postoperative AKI. We hypothesized that pre-menopausal-aged females would display lower incidence of postoperative AKI than males of similar age; and the protection would be lost in post-menopausal-aged females.

Methods: This was a retrospective observational study of the Multi-center Perioperative Outcomes Group database. We reviewed surgical patients at 46 institutions between 2013-2019. Our primary exposure was an interaction between age younger or older than 50 years and sex. Our primary outcome was development of AKI by KDIGO criteria. A mixed effects multivariable logistic regression was used to determine the association of sex hormone status with postoperative AKI. Secondary analyses consisted of ascending age groupings over 40 years.

Results: After excluding patients with CKD5 and cardiac, transplant, urologic and obstetric procedures, among 390,382 patients undergoing index surgeries, 25809 (6.6%) developed postoperative AKI. In the adjusted model, the lowest risk of AKI was in women under 50 (OR 1.0), with higher risk in men under 50 (OR 1.90 [1.79, 2.01]; p<.0001), women over 50 (OR 1.51 [1.43, 1.59]; p<.0001), and men over 50 (OR 2.06 [1.96, 2.17]; p<.0001). In the secondary analysis, risk of AKI gradually increased in women as they aged, whereas men had very little change in risk based on age (Fig. 1).

Conclusions: Younger females display a lower risk of postoperative AKI that gradually increases with age. These results suggest that female sex hormones might protect against AKI. To explore this possibility, we are examining the risk of postoperative AKI in patients receiving sex hormone replacement or antagonism at time of surgery.

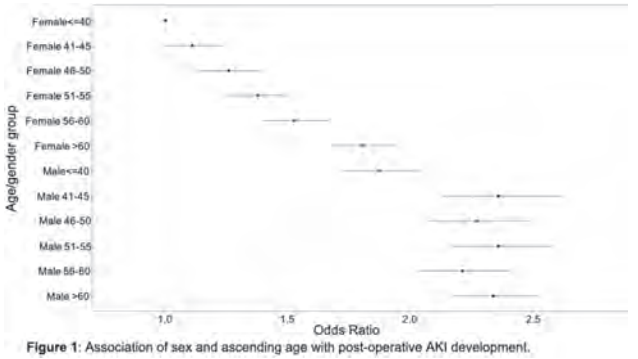

Figure 1: Association of sex and ascending age with post-operative AKI development.

PO0213

Phenotyping Inpatient AKI by Serum Creatinine Trajectory

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Background: Clinical guidelines for risk stratification of acute kidney injury (AKI) do not fully consider characteristics of changes in serum creatinine that may be informative for future risk of adverse outcomes. Identification of patient groups that display distinct patterns in trajectory of SC during an AKI may enhance risk stratification.

Methods: Latent trajectory model identified trajectory patterns of SC in a cohort of United States Veterans hospitalized with AKI. Trajectories and outcome profiles were used to establish AKI phenotypes. Risk factors for phenotypes were examined, and phenotype discrimination in short-term outcomes was assessed vis-à-vis KDIGO stages.

Results: In a cohort of 360,560 US Veterans with a hospitalization with an AKI, we identifyied 6 phenotypes representing distinct patterns in trajectory of SC during hospitalization. Compared to a trajectory with mild changes in SC (59.4% of cohort), moderate (23.1%), and more severe changes (8.7%) with moderate recovery were associated with decreasing odds of non-recovery in SC by discharge (OR=0.52 and 0.25 respectively), higher odds of receipt of kidney replacement therapy (KRT) (3.8 and 13.8) and death within 30-days of hospitalization (1.8 and 2.5). Those whose SC continued to rise during hospitalization (3.86%) had the lowest odds of recovery (OR=0.02) and highest odds of mortality (8.0). Phenotype with highly increased SC with incomplete recovery (2.81%), or very dynamic change in the first few days of hospitalization (2.15%), were associated with higher odds of KRT (57.3 and 89.4, respectively) and lower odds of recovery (0.08 and 0.11). A prior history of chronic kidney disease, albuminuria, and prior AKI, as well as major in-hospital events including sepsis, admission to ICU, and mechanical ventilation, were associated with trajectories with worse outcomes. Discrimination in future outcomes during course of hospitalization suggested that as the hospitalization progressed, phenotypes increasingly provided more information on risk of future outcomes (*C*-statistic: 0.72, recovery; 0.87, KRT; 0.62, death) than KDIGO stages (0.62, recovery; 0.75, KRT; 0.59, death).

Conclusions: Our results suggest that leveraging EHR data to profile changes during the occurrence of AKI in kidney function may enhance risk stratification of AKI patients during the course of the hospitalization.

Funding: Veterans Affairs Support, Private Foundation Support

PO0214

Provider Acceptance of Electronic AKI Alerts in a Cardiac Surgery ICU

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Background: Electronic acute kidney injury (AKI) alerts can improve the rates of detection of AKI, though their effect on improving patient outcomes has been variable. Their focused utilization in cardiac surgery patients, a population at a high risk for both AKI and its complications, is likely to lead to more consistent improvement in outcomes. We implemented AKI alerts in the cardiac surgery ICU of a tertiary care, high volume cardiac surgery center starting July 2020. As electronic alerts can be disruptive to the workflow and lead to alert fatigue, we surveyed health care providers in our cardiac surgery intensive care unit (ICU) regarding their acceptance of these electronic AKI alerts.

Methods: Our AKI alerts used a previously validated logic to trigger an alert when serum creatinine increase by 0.3mg/dL or more within last 52 hours. They were implemented as passive alerts in the EPIC electronic medical record. Alerts were situated in the EPIC storyboard and provided information in the format "Possible AKI Stage X", with the option to get more information by hovering over the alert. The alerts were set to disappear if no further increase in creatinine by at least 0.3mg/dL was noted in next 52 hours. We emailed a validated survey regarding alert usefulness to providers 6 months into the alerts implementation to assess their acceptance.

Results: Out of 19 ICU providers (7 intensivists and 12 advanced practice providers) all but one responded to the survey. 7/18 (38.8%) providers reported that they recognized AKI earlier due to the alert. 16/18 (88.9%) shared that they re-dosed or discontinued medications earlier due to the AKI alert. Majority of participants also reported earlier management of volume status (72.2%), avoidance of iv contrast use (72.2%) and point of care ultrasound use (77.8%) in response to the alert. 15/18 (83.3%) reported satisfaction with the way AKI alerts are displayed and overall satisfaction with the AKI alerts. 16/18 (88.9%) providers reported satisfaction with the duration the alert is displayed for.

Conclusions: Among providers taking care of patients at high risk for AKI, the electronic AKI alert well received. A follow up survey is planned to assess the changes in longitudinal perception of the AKI alert.

Funding: Other NIH Support - The project described was supported by the National Institute of General Medical Services, 5U54GM104942. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH

PO0215

Kratom, an Herbal-Induced Cholestatic Liver Failure, Leads to Cholemic Nephropathy Requiring Liver Transplant and Hemodialysis

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Introduction: Kratom, an herbal supplement, has opioid-like and stimulant effects. Its recreational misuse has increased in the United States (US). Its alkaloid compounds consist primarily of mitragynine and 7-hydroxymitragynine and are metabolized in the liver. Reports have shown many side effects, notably confusion, seizures, coma, and hyperbilirubinemia. Hepatic injury presents as cholestatic liver injury, which has a consequence on renal function. Patients with hyperbilirubinemia, bile casts damage the nephron directly and is known as bile cast nephropathy, a rare or underdiagnosed pathology. We present a case of Kratom usage that play a role in causing cholestatic liver failure, leading to cholemic nephropathy and liver transplant and hemodialysis.

Case Description: A 26-year-old woman with history of Kratom usage presented with complaint of 5-days of abdominal distention and pain, jaundice, and heavy mucosal bleeding. Laboratory testing revealed Na^+ 123 mmol/L, BUN 84 mg/dL, Cr. 6.9 mg/dL, AST 104, ALT 31, total bilirubin 32 mg/dL and ALP 124 units/L, WBC 27.8, platelets 109, and H/H 7.2/20.7, INR 2.23. There was no serology evidence of viral infection. Tylenol and alcohol level were unremarkable. Urinalysis positive for bile acid cast. Abdominal ultrasound and Computed Tomography findings are consistent with liver cirrhosis. She underwent liver transplantation and required hemodialysis due to acute renal failure from profound hyperbilirubinemia.

Discussion: Bile cast nephropathy represents a wide spectrum of disease, ranging from mild reversible to irreversible needing dialysis. It occurs when total bilirubin levels >20mg/dL**,** exceeding the binding capacity of albumin to bilirubin. It causes tubular obstruction and injury, oxidative damages, and ATPase activity. Most of the damage occurs in distal tubules but can occur in the proximal tubules. While kratom has stimulant and opioid-like effects, its use can be hazard to health. There are currently no treatment guidelines for bile cast nephropathy. In irreversible nephropathy in cirrhotic patient, patient may be evaluated for both liver and kidney transplant. Renal replacement therapy has no role in treating bile cast nephropathy directly. Clinicians should keep cholemic nephropathy as a differential diagnosis in patient with hyperbilirubinemia and be aware of the increasing consumption of kratom in the US.

PO0216

Dietary Hyperuricemia Causes Nephropathy in a Cancer Patient

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Introduction: Hyperuricemia is associated with several diseases including kidney disease. Everyday drinks (sodas/juices) have very high fructose content, contributing to hyperuricemia through various mechanisms. Here we present a case of a cancer patient with Acute Kidney Injury (AKI) secondary to hyperuricemia in the setting of a sudden high intake in fructose rich drinks.

Case Description: A 49-year-old Asian man with history of myelofibrosis, coronary artery disease and chronic kidney disease stage 2, was admitted for AKI. He was recently admitted for septic shock due to scrotal abscess and discharged to a nursing home for wound care. He endorsed recent high intake of sodas and juices, due to dislike of food at the nursing home. His creatinine at previous admission was 1.1–1.4 mg/dl (similar to his baseline). His urinalysis (UA) routinely did not show uric acid crystals, and uric acid levels were within reference range. One week prior to admission, his creatinine was 1.97 mg/dl and UA showed occasional uric acid crystals. At current admission, creatinine was 3.02 mg/dl with uric acid level of 23.3 mg/dl, and UA showed uric acid crystals. He received 3 doses of 3 mg Rasburicase (9 mg total) the first day, after which uric acid level improved to 6.4 mg/dl, and creatinine dropped to 2.14 mg/dl. Three days later his creatine improved to 1.76 mg/dl, and repeat UA did not show uric acid crystals. A week after discharge, his creatinine was at baseline and uric acid level was normal. By the time visual examination of urine could be done, uric acid level had normalized.

Discussion: It is known that fructose is the only carbohydrate that increases uric acid levels. Fructose-induced hyperuricemia results from an increased degradation of purine ribonucleotides and causes increased purine synthesis. Hyperuricemia is common in patients with hematological malignancies with or without chemotherapy. Our patient had a hematological malignancy and endorsed drinking large amounts of soda and juice. Given many patients drink fructose rich drinks daily, it is imperative that the dangers of this dietary habit are highlighted, both to physicians and patients. Cancer patients can benefit from nutrition education and dietary modifications prior to and during chemotherapy to avoid hyperuricemia and renal failure. Dietary counselling can help avoid need for hospitalization as well as use of expensive uric acid lowering agents.

PO0217

Turmeric-Associated Oxalate Nephropathy

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Introduction: Turmeric contains Curcumin which has anti-inflammatory properties that may be beneficial in patients with osteoarthritis, hyperlipidemia, pruritus, and Rheumatoid Arthritis. Thus it's a popular herbal supplement. Here we present a rare case of severe acute kidney injury (AKI) due to calcium oxalate nephropathy in a patient with heavy turmeric consumption.

Case Description: An asymptomatic 69 year male with no significant past medical/surgical history was evaluated for a spike in Creatinine from 1.2 to 3.1mg/dl over a few months. There was no history of drug/NSAID use, contrast exposure, or other nephrotoxins. He did mention taking Turmeric 2g daily for the past 2 years. There was no personal or family history of nephrolithiasis. Urine sediment was bland. Serum C3, C4, ANA, ANCA, anti-GBM, anti-dsDNA, hepatitis B&C screen, SPEP&UPEP were negative. Kidney Biopsy revealed widespread calcium oxalate deposition in tubules(Renal Oxalosis-Hyperoxaluria) with diffuse acute tubular injury. Turmeric was discontinued, but the patient soon started on dialysis. 24h urine oxalate was elevated; serum oxalate was also high at 14micromol/L. Genetic testing(AGXT mutation) for primary hyperoxaluria(PH) is pending, but lack of recurrent nephrolithiasis or nephrocalcinosis or systemic oxalate deposition and only marginally high S.oxalate make PH less likely.

Discussion: Although many herbal remedies have shown promising results, these supplements often evade the rigorous standards that conventional therapies are subject to. Turmeric has long been used for anti-inflammatory & analgesic benefits and recently was publicized as an immunity booster and studied for prophylactic and therapeutic use in COVID. Compelling evidence for its efficacy comes from osteoarthritis trials, but recommendations for safe daily allowances aren't elucidated. Contrarily, turmeric has demonstrated increased urine oxalate excretion, a known cause of oxalate stones and, presumably, oxalate deposition in tubules. Hyperoxaluria mainly occurs secondarily in malabsorption syndromes. Loss of oxalate-degrading gut flora from antibiotics contributes and PH, a disorder of oxalate overproduction, is a rare cause. Several factors can interplay, but the contribution of oxalate-rich food like spinach, starfruit, and in this case, turmeric is indisputable. We recommend a high suspicion index and a thorough medication review in patients with severe AKI.

PO0218

Chronic Tubulointerstitial Nephropathy and Nephrotic Range Proteinuria in a Patient with an Underlying Eating Disorder

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Introduction: Eating disorders in particular atypical anorexia nervosa; binge eating/purging type, have been reported as an established cause of CKD with chronic tubulointerstitial nephritis as a prominent histopathological feature seen on kidney biopsy.

Case Description: A 40-year-old woman with hypertension, generalized anxiety and an eating disorder was referred to our clinic for new onset nephrotic range proteinuria and elevated serum creatinine (SCr). Patient endorsed remote NSAID use without any recent use. Physical exam notable for uncontrolled hypertension and bilateral lower extremity edema. SCr was elevated at 2.33 mg/dl, higher than 1.6 mg/dl two months prior to evaluation. Urinalysis showed proteinuria and trace hematuria but was otherwise unremarkable. Spot urine TP/CR was elevated at 9.4 gm/gm. Serologic work up including PLA2R antibody levels, ANA, ANCAs, Hep B surface antigen were negative. Serum immunofixation did not reveal any monoclonal bands. Renal sonogram showed bilateral echogenic kidneys with no renal artery stenosis or hydronephrosis. Of note, patient presented with severe hypokalemia (2.2 mmol/L) and hypomagnesemia (0.8 mg/dl), which were found to be chronic. Electrolyte derangements were attributed to purging disorder in the past, however she adamantly denied active purging or diuretic/laxative abuse. She also denied taking any herbal medications. A kidney biopsy showed widespread fibrosis and advanced global and segmental glomerulosclerosis (more than 50% of gloemruli) with diffuse chronic tubulointerstitial nephropathy (TIN). The tubules also revealed microcystic dilatation with several simple cysts. CKD and TIN were most likely secondary to underlying eating disorder. Lithium exposure can have a similar pattern on histology, however there was no history of lithium use as confirmed by prior providers. Given the chronicity, she was initiated on dialysis. A Renasight genetic test revealed no genetic abnormalities explaining the above findings

Discussion: Diffuse TIN with glomerulosclerosis and widespread fibrosis can be associated with anorexia nervosa. Clinicians should be aware of the potential implications of kidney disease in patients with eating disorders. Early recognition and referral to Nephrologists can help improve outcomes by preventing irreversible kidney damage.

PO0219

BK Polyomavirus Nephritis in a Low-Risk Native Kidney: A Case Report

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Introduction: BK viremia has increased prevalence in solid organ transplant, particularly renal transplant recipients. BK nephropathy in native kidney is rare, but has been reported after hematopoietic stem cell transplant (HSCT).

Case Description: 74-year-old male with Grade 2 Follicular lymphoma (in complete remission for 2 years after obinutuzumab, bendamustine, & venetoclax), complicated by hypogammaglobinemia receiving IVIG (IgG 751mg/dL) & chronic lymphopenia (absolute lymphocyte 152 cells/uL) who was evaluated for acute kidney disease. Patient's baseline creatinine was around 0.8 mg/dL & progressively rose to 4mg/dL over a period of 6 months despite IV hydration for intermittent mild diarrhea. Urinalysis had no proteinuria or hematuria. Serologic workup for systemic lupus erythematosus and other autoimmune disease, monoclonal gammopathy, sarcoid was unrevealing. Kidney biopsy revealed polyomavirus nephritis with acute tubular injury & severe interstitial fibrosis with tubular atrophy. Serum BK PCR showed 1.3 million copies. The patient continued on IVIG increasing the frequency to every 3 weeks and started on a course of fluoroquinolones but with ultimate progression to chronic kidney disease.

Discussion: BK virus infections in immunocompetent individuals typically occur early in childhood (asymptomatic or mild respiratory illness). Following primary infection, BK virus remains in a latent state in the urothelium & renal tubular epithelial cells. Most cases of BK Polyomavirus nephritis occur in renal transplant recipients. Risk factors for BK Polyomavirus nephritis in native kidneys include non-renal solid organ transplant as well as HSCT, chronic lymphocytic leukemia, AIDS, and congenital dysgammaglobulinemia. Clinical presentation is nonspecific and includes varying degrees of renal failure without fever, leukocytosis, hematuria or proteinuria. Incidence of renal failure is dependent on the degree of glomerular inflammation caused by proinflammatory cytokines, influx of immune effector cells, BK virus lytic replication, and lysis of renal tubular epithelial cells that can lead to renal fibrosis. Treatment agents include leflunomide, cidofovir, fluoroquinoles and IVIG but the success has been limited. This case highlights that BK nephropathy may develop in the native kidney other than HSCT. Chronic lymphopenia & hypogammaglobinemia likely predisposed our patient despite his ongoing infusion of IVIG.

PO0220

Interaction of Blood Urea Nitrogen and Tryptophan in Predicting Mortality in a Trauma-Induced Model

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Background: Multiple Organ Failure (MOF), often precipitated by Acute Respiratory Distress Syndrome (ARDS) brought on by trauma-induced injury, is a significant cause of death in military and civilian life. Furthermore, in ARDS, Acute Kidney Injury (AKI) is the most frequent organ failure affecting almost 50% of the patients, increasing the mortality rate. Therefore, understanding the molecular difference between survivors and non-survivors can significantly reduce the mortality burden.

Methods: A porcine MOF model (n =17) was developed using pulmonary contusion injury at Dr. Batchinsky's laboratory. In this model, n=10 are survivors, and n=7 are non-survivors with mortality at 3, 6, and 9 hours. Serum was employed for Amino acid metabolites using the Zip-Chip platform for mass spectrometry. A Cox proportional hazard analysis was employed to quantify the association of survival with the metabolite concentration. Serum blood urea nitrogen (BUN) was measured using the assay kit, and baseline BUN was correlated with baseline tryptophan level using a linear model.

Results: In survival analysis, survivors and non-survivors were partitioned by the mean metabolite concentration. The group with increased tryptophan concentration had a better chance of survival than the group with a reduction of tryptophan from the baseline. Furthermore, when associating the tryptophan level with the BUN, there is an opposite trend between the two groups. In the survivors, higher tryptophan is positively associated with increased BUN, whereas in the non-survivors, there is a negative correlation indicating that lower tryptophan coupled to high BUN increases the risk of mortality. Additionally, linear regression model showed a significant association of tryptophan and BUN with survivors and non-survivors.

Conclusions: Survival analysis indicated that a decrease in serum tryptophan level is a strong risk factor for mortality. Since tryptophan metabolism is associated with renal failure in AKI settings, we investigated serum tryptophan association with BUN. Non-survivors have a strong negative association of tryptophan with BUN, suggesting that combination of BUN and tryptophan could improve mortality risk prediction in early time-point in trauma-induced model.

Funding: Other U.S. Government Support

PO0221

Performance of Validated Indices for Risk of Death for Patients with AKI Requiring Dialysis: A Systematic Review and Meta-Analysis

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Background: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is associated with high morbidity and mortality. Multiple mortality indices have been developed, however, the most optimal index for predicting survival in AKI requiring RRT is unknown. **Objective:** To assess performance of validated mortality indices for patients with AKI requiring RRT.

Methods: Design, setting, participants and measurements: Systematic review and meta-analysis following the PRISMA guidelines. Multiple databases (MEDLINE, Embase, Central Register of Controlled Trials, Cochrane, and Scopus) were searched from inception to Jan 31 2019. **Selection Criteria:** Studies evaluating the performance of validated mortality indices in adult AKI patients requiring RRT were included. Studies not separating AKI patients requiring RRT or used validated indices only as covariates were excluded. Articles were screened and data extracted in duplicate. Risk of bias was assessed using the PROBAST tool. Pre-planned random effects meta-analysis was performed stratified by index, population, renal specific vs. general mortality index, and predictive window.

Results: Of 10,115 articles screened, 37 (2 development, 21 validation and 14 combined) were included totaling 35 different indices tested in 11,142 patients. Average age was 60.8 years with 34.6% women. Predictive windows ranged from ICU to 60-day survival. The most used indices were APACHE II, Liano, SOFA, and SAPS II. Meta-analysis by index showed overall discrimination area under the curve (AUC) of 0.69 (95% CI 0.67-0.71) with high heterogeneity (I^2 =82.37) with highest AUC for APACHE III 0.73(0.66-0.8) Liano 0.73(0.68-0.78) and MODS 0.71(0.62-0.80).

Conclusions: There is insufficient discrimination and heterogeneity in the performance of prognostic indices for AKI requiring RRT. Additional studies are needed to optimize mortality prediction in this population.

Funding: NIDDK Support, Other NIH Support - NIA k23 AG051679

PO0222

Detection and Diagnosis of AKI in the Emergency Department

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Background: Acute kidney injury (AKI) represents an abrupt decline in kidney function occurring over hours or days and is associated with inferior clinical outcomes. In recent years, new definitions of AKI based on changes in serum creatinine (SCr) have gained acceptance, but awareness by primary care and emergency physicians may still be limited. The aim of this study was to use diagnosis codes to examine the detection of AKI among patients who presented to the emergency department (ED).

Methods: This was a prospective case-control study in which SCr of all individuals admitted to the ED of Landspitali–The National University Hospital in Reykjavik were examined by the research team for the presence of AKI. We present data from January 1 until March 3, 2020, from May 19 until September 21, 2020 and from February 1 until May 1, 2021. The study was paused between these periods due to COVID-19 outbreaks. All patients who met the KDIGO criteria for AKI were invited to participate. Clinical information and ICD-10 diagnoses were obtained from participants and from electronic medical records. ICD-10 codes N17 (acute kidney failure) and N19 (unspecified kidney failure) were used as indicative of a confirmed AKI diagnosis.

Results: A total of 527 cases of AKI were identified, 445 (84%) of whom participated in the study. The mean (±SD) age of AKI cases was 67.2±16.8; 47% were female. Of the AKI cases, 104 (23.4%) had a documented diagnosis of AKI in the ED. No difference was found between women and men (20.9% and 23.9%, respectively; p=0.85) and no difference was observed between different age groups (18-49 years 23.9%, 50-69 years 21.7% and >70 years 21.7%). Of 39 (8.7%) participants with pre-existing diagnosis of chronic kidney disease (CKD), 38.5% had a documented AKI diagnosis compared with 21.9% of those without history of CKD (p=0.003). Participants with stage 3 AKI had a documented diagnosis in 48.0% of cases, 25.2% of those with stage 2 AKI and 15.1% of cases with stage 1 AKI.

Conclusions: AKI appears to be seriously underdiagnosed in the ED. While multiple factors may affect the use of diagnosis codes, lack of awareness of recent AKI guidelines among emergency physicians may play an important role. Measures must be taken to improve the diagnosis and documentation of AKI in the ED.

Funding: Government Support - Non-U.S.

PO0223

Risk Factors for AKI in the Intensive Care Unit

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Background: Acute Kidney Injury (AKI) is defined by a sudden decrease in glomerular filtration rate. It currently represents a global public health issue as it is associated with short and long-term morbidity and mortality. In the Intensive Care Unit (ICU) there is an overall incidence of AKI ranging from 20-50% and a mortality rate from 15-60%. Its development leads to increased length of stay and costs. The main objective of this proposed study is to identify risk factors associated with the development of acute kidney injury in a community hospital and a tertiary hospital in Puerto Rico. Also, to investigate if there is a relationship between AKI, length of stay and mortality.

Methods: This retrospective case control study included patients 18 years of age or older admitted to the ICU between January 2015 to December 2016. Patients with chronic kidney disease (CKD) stage 4 or 5, maintenance renal replacement therapy (RRT), or AKI before ICU admission were excluded. The population was divided between patients with AKI and patients without AKI. AKI was diagnosed according to KDIGO criteria. Demographic (age, gender) and clinical data (comorbid conditions, APACHE II score, sepsis or septic shock, vasopressors status, mechanical ventilation, creatinine levels, urine output, nephrotoxic drugs, RRT use, and mortality) was collected from medical records.

Results: Among 121 patients included (median age 54.40, 50% male), 44.6% were diagnosed with AKI and 3.31% underwent RRT. All 7 patients with diagnosed Chronic Obstructive Pulmonary Disease (COPD) had AKI during ICU stay (p-value 0.0024). Diuretics, aminoglycosides, and amphotericin B had a statistically significant relationship with AKI (p-value 0.012, 0.002, and 0.050 respectively). Mechanical ventilation, vasopressor use, sepsis or septic shock and mortality also had a statistically significant relationship with AKI (p-value 0.013, 0.002, 0.018 and <0.0001 respectively).

Conclusions: In our study AKI had a statistically significant association with COPD, diuretics, aminoglycosides, amphotericin B, mechanical ventilation, vasopressors, sepsis or septic shock and mortality. Nephrotoxic agents described as statistically significant are modifiable risk factors to be considered in their administration. This study aids in the characterization of an epidemiologic pattern on ICU patients for future applicability.

PO0224

Evaluation of Chosen Biochemical Parameters in Diagnosis of AKI in Course of Burn Disease

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Background: Burn disease after severe thermal injury often causes multi-organ damage, included AKI. Diagnosis of AKI based on standard renal biomarkers seems to be not optimum, because of its too late beginning. The aim of the study is evaluation of non-renal biochemical parameters as early prognostic factors of AKI in this group of patiens (pts).

Methods: 33 adult pts; 11(33,3%) females, 33(66,7%) males; were hospitalised after severe burn injury. Mean age was 48,3(±18,8) years. None of the pts presented symptoms of chronic kidney disease. Biochemical parameters - platelets count (PLT); serum concentration of albumin (ALB), sodium (Na), potassium (K), urea (U), creatinine (Cr); glomerular filtration ratio (GFR), serum activity of asparagine transaminase (AST) and creatine phosphokinase (CK); blood gas tests and urine sodium excretion - were measured at each patient once daily till 7th day. The results were presented as a mean value with standard deviation or median with interquartile range. AKI criteria were based on RIFLE/AKIN scale. Relationship between parameters and AKI risk were analysed with chi-square test and presented as relative risk (RR) with 95% confidence level, p-value significant level was <0,5.

Results: Biochemical symptoms of AKI were confirmed in 15 (60,6%) pts. AKI developed at the beginning of hospitalisation, on the1st day – 10 (30,3%) pts and 2rd day – 4 (12,1%) pts. Non-normative levels of biomarkers were reported in the same time: low PLT count - average 91,6(±42,7) x10^9/l in 5 (15%) pts; low ALB concentration – avg. 2,4(±0,7) g/dl in 32 (97%) pts; high K concentration – avg. 6,1(±0,7) mmol/l in 14 (42,4%) pts; high activity of AST – avg. 73(40,5÷141,5) U/l in 21(63,6%) pts and CK – avg. 429,0(242,0÷4720,0) U/l in 21 (63,6%) pts and metabolic acidosis with low pH - avg. 7,22(±0,08) in 19 (57,6)%, pts. The significant relationship between parameters and the risk of AKI was confirmed: high activity of CK (RR 2,86; p=0,047) and AST (RR 2,73; p=0,034), and low concentration of ALB (RR 2,63; p=0,012).

Conclusions: AKI is a frequent and important problem in burned patients, occurred in the first days after injury as a part of multi-organ dysfunction. Non-renal biochemical parameters as serum concentration of ALB, activity of CK and AST can be useful early biomarkers of AKI after massive burn injury.

PO0225

Intravenous Administration of Vitamin B Complex Improves Renal Recovery in Patients with AKI

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Background: Preclinical studies have identified NAD^+ augmentation as a potential strategy for the prevention and treatment of AKI. NAD^+ is the final metabolized form of vitamin B3 (niacin). Since there is no availability of niacin in the country; we tested if I.V. vitamin B complex (vitamin B1, B6 and B12) could improve renal recovery in patients with AKI. By oxidation, vitamin B6 (pyridoxine) through the pathway of pentose phosphate lead to the formation of NADPH an analog of NAD^+.

Methods: We conducted randomized, blind, placebo-controlled study in hospitalized patients with AKI (NCT04893733). During the study I.V. vitamin B complex or placebo was given twice a day for 5 consecutive days. For AKI management in each patient, a protocol-based approach was used (STOP AKI protocol from the ISN 0by25 trial https://doi.org/10.1371/journal.pmed.1003408). We evaluated if vitamin B complex could improve renal recovery and if it could reduce *de novo* CKD incidence or CKD progression.

Results: From September 2020 to May 2021, 191 patients were enrolled in this ongoing RCT with 160 patients completing the follow-up by day 7 and 91 patients completing the follow-up by 3 months. Peak sCr was higher in patients randomized to vitamin B complex (2.8 ±1.2 vs. 2.2 ±1.3 mg/dl; p = 0.006). A higher pecentage of patients randomized to vitamin B complex arm had severe AKI (stage ≥ 2) 74% vs. 43% randomized to placebo; p = 0.011. The drop in sCr values by day 7 was higher in the vitamin B complex group (1.01 vs. 0.65 mg/dl; p < 0.001). No differences were found in the percentage of patients with complete recovery (54.3% vs. 45.6%; p=0,268), partial recovery (25.9% vs. 25.3%; p = 0.930) and non-recovery (19.8% vs. 29.1%; p = 0,168). At 3 months, the incidence of *de novo* CKD and CKD progression was not different in both arms (23.9% vs. 20%; p = 0.652 and 28.2% vs. 26.6%; p = 0.865 respectively). No difference was found in mortality rate at day 90 (vitamin B complex 31.1% vs. placebo 28.2%; p = 0.544).

Conclusions: The administration of vitamin B complex could potentially accelerate renal recovery in patients with AKI by day 7, reducing the percentage of patients who will not recover renal function after an AKI episode. No differences were found in terms of CKD progression or de novo CKD. The preliminary data of our ongoing study warrants future studies to validate these findings.

PO0226

GDF-15 Predicts In-Hospital Mortality of Critically Ill Patients with AKI Requiring Continuous Renal Replacement Therapy: Results from a Prospective Randomized Controlled Trial

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Background: Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine that is positively associated with inflammation. This study evaluated the association between GDF-15 and in-hospital mortality among patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: Among the multicenter prospective CRRT cohort between 2017 and 2019, 66 patients whose blood sample was available were analyzed. Patients were divided into three groups according to the GDF-15 concentrations. In-hospital mortality was compared using Cox proportional hazards regression model.

Results: The mean age was 67.7 ± 14.3 years and 47 (71.2%) were male. The median GDF-15 level was 7865.5 pg/mL (496.9 pg/mL in the healthy control patients). Baseline characteristics were not different among tertile groups except the severity scores (Acute Physiology and Chronic Health Evaluation II [APACHE II] and Sequential Organ Failure Assessment [SOFA]) and serum lactate level, which were higher in the third tertile. After adjusting for confounding factors, the patients with higher GDF-15 had significantly increased risk of mortality (second tertile: adjusted hazards ratio [aHR], 3.67; 95% confidence interval [CI], 1.05–12.76; *P*=0.041; third tertile: aHR, 6.81; 95% CI, 1.98–23.44; *P*=0.002). Furthermore, GDF-15 predicted in-hospital mortality (area under the curve, 0.710; 95% CI, 0.585–0.815) better than APACHE II and SOFA scores (Figure 1).

Conclusions: Serum GDF-15 concentration was elevated in AKI patients requiring CRRT, higher in more severe patients. GDF-15 is a better independent predictor for in-hospital mortality of critically ill AKI patients than the traditional risk scoring system such as APACHE II and SOFA scores.

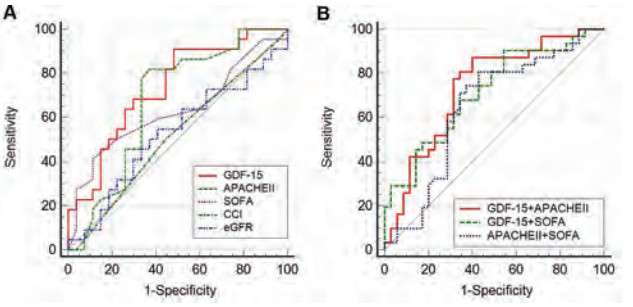

Figure 1. Receiver operating characteristic curves of prognostic predictors for in-hospital mortality.

PO0227

The Effect in Renal Function and Vascular Decongestion in Type 1 Cardiorenal Syndrome Treated with Two Strategies of Diuretics: A Randomized Trial

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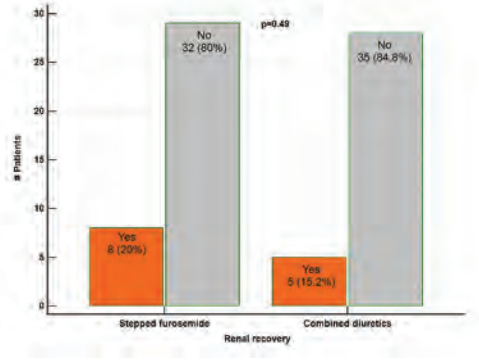
Background: In cardiorenal syndrome 1 (CRS1), is probable that sequential blockage of the renal tubule with combined diuretics (CD) will obtain similar benefits compared with stepped-dose furosemide (SF)

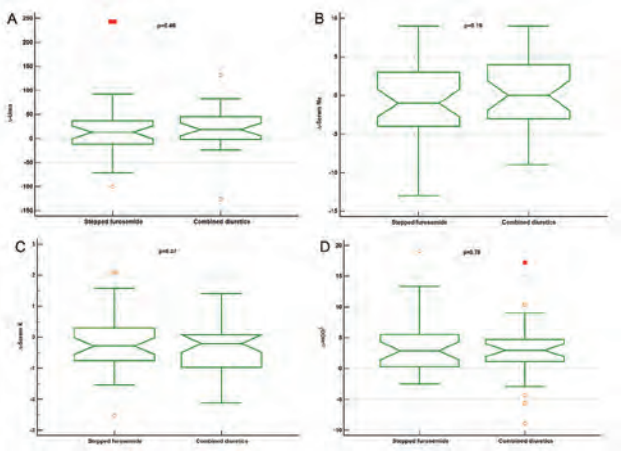
Methods: In a double-blind randomized controlled trial of CRS1 patients were allocated 1:1 to SF or CD. The SF group received a continuous infusion of furosemide 100mg during the first day, with daily incremental doses to 200 mg, 300 mg and 400 mg. The CD group received a combination of diuretics, including 4 consecutive days of oral chlorthalidone 50 mg, spironolactone 50 mg and infusion of furosemide 100 mg. The objectives were to assess renal function recovery and vascular decongestion.

Results: From July 2017 to February 2020, 80 patients were randomized, 40 to SF and 40 to CD group. Groups were similar at baseline and had several very high-risk features. Their mean age 59 ± 14.5 years; 37 were men (46.2%). Primary endpoint occurred in 20% of the SF group and 15.2% of the DC group (p = 0.49). All secondary and exploratory endpoints were similar between groups. Adverse events occurred frequently (85%) with no differences between groups (p = 0.53).

Conclusions: In patients with SCR-1 and a high risk of resistance to diuretics, the use of CD compared to SF offers the same results of renal recovery, diuresis, vascular decongestion and adverse events, and it can be considered an alternative treatment.

Figure 2. Primary endpoint Renal function recovery (*sCr return to baseline value*) in 80 patients with cardiorenal type 1 syndrome according to allocation groups.





PO0228

Restriction of Sulfur-Containing Amino Acid Intake for Prevention of AKI in Cardiac Surgery: UNICORN, a Randomized, Controlled, Double-Blinded Trial

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Background: Acute kidney injury (AKI) can result in short- and long-term complications and increased mortality. Nonetheless, preventive and therapeutic strategies are lacking. Protein restriction has been shown to protect from organ failure in mice and this protection depended on restriction of sulfur-containing amino acids (SAA). The UNICORN study aims to evaluate the impact of restricting SAA intake by replacing milk-derived dietary protein by collagen prior to cardiac surgery on AKI.

Methods: In this single-center, randomized, controlled, double-blinded trial 115 patients scheduled for cardiac surgery, were assigned in a 1:1 ratio into a LowS group (SAA depleted formula diet) or a regular formula diet (control group, CG) for 7 days prior to surgery. The primary endpoint was incidence of AKI within 72 hours after surgery (KDIGO), secondary endpoints included increase of serum creatinine at 24h, 48h and 72h as well as safety parameters. Quantitative variables were analyzed with t-test or nonparametric methods, while categorical variables were evaluated by means of Chi-Square or Fisher's test.

Results: Baseline characteristics: LowS serum creatinine 1.0 mg/dl[0.34] vs. CG 0.85 mg/dl[0.42]; LowS 77% male vs. CG 54%; age: LowS 67y[IQR: 13] vs. CG 69y[12], body weight: LowS 88 kg[20] vs. CG 78kg[18], crossclamp time: LowS 67min[32] vs. CG 68min[35]). Patients in the LowS group had a 77,6% reduction in SAA as compared to CG. There was no difference in the primary endpoint between the groups (LowS AKI incidence 23% vs. CG 16%; p=0.37). Likewise, no differences were observed with respect to secondary endpoints (AKI during hospitalization, creatinine at 24h, 48h, 72h after surgery). Subgroup analysis focusing on age, gender, body mass index and markers of organ damage did not reveal any between-group differences.

Conclusions: In this first-in-humans translational clinical trial, dietary SAA restriction before cardiac surgery did not result in a lower incidence of AKI. However, larger studies are needed to confirm this finding.

Funding: Commercial Support - Fresenius Kabi

PO0229

Use of Peritoneal Dialysis for the Treatment of AKI Was Associated with Lower Risk for 30-Day All-Cause Mortality During the COVID-19 Surge

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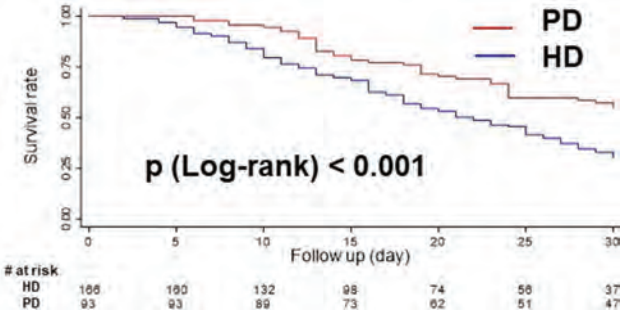
Background: To offset resource constraints that limited the capability to deliver hemodialysis (HD) during the COVID-19 surge, nephrologists in New York City (NYC) rapidly incorporated peritoneal dialysis (PD) for the treatment of acute kidney injury (AKI), which was rarely used in the United States. This study aims to compare the in-hospital all-cause mortality between AKI patients who received PD versus HD during the COVID-19 pandemic.

Methods: In a retrospective observational study, we collected data on 259 patients with AKI who required kidney replacement therapy (KRT) in four medical centers of NYC during the Spring 2020. Patients who had ever received PD were included in the PD group (n=93), and patients who only received intermittent HD or continuous KRT were included in the HD group (n=166). Kaplan-Meier survival curves, log-rank test and Cox regression were used to compare survival between PD and HD groups.

Results: For the entire cohort, the mean age was 61±11 years; 31% were women; 96% had confirmed COVID-19. Median follow up was 21 days (IQR 12-30). Mortality was lower in PD group compared to HD group (43% vs. 60%, p=0.01). Time-dependent analyses showed that PD group was at a lower risk for mortality compared to HD group (p<0.001 for Log-rank test; Figure). After adjusting for age, sex, BMI, comorbidities, oxygenation on admission, mechanical ventilation, prone positioning, steroid use and C-reactive protein, the PD group remained to have a lower risk of mortality compared to the HD group with a HR of 0.45 (95% CI: 0.27-0.77, p=0.003).

Conclusions: Compared to HD, the use of PD for the treatment of AKI was associated with lower mortality in this cohort of patients treated during the COVID-19 pandemic in the Spring of 2020. Our findings demonstrate that rapid implementation of PD for the treatment of AKI was feasible and may be lifesaving.



PO0230

Association of an AKI Follow-Up Clinic with Patient Outcomes and Care Processes: A Propensity-Matched Cohort Study

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Background: Survivors of AKI are at higher risk of chronic kidney disease and death, but few patients see a nephrologist following hospital discharge. Our objectives were to determine whether an AKI Follow-up Clinic is associated with changes in care processes and a reduction in major adverse kidney events in comparison to survivors of AKI who received usual care.

Methods: We identified all patients ≥ 18 years of age who survived a hospitalization with AKI from February 1, 2013 to September 30, 2017 and visited our hospital's AKI Follow-up Clinic within 6-months of hospital discharge. We used propensity scores to match each patient to 4 patients in the region who received usual care. We randomly assigned the control group index dates to ensure these patients were alive and could have received follow-up care. The primary outcome was time to a major adverse kidney event, defined as death, chronic dialysis, or CKD (newly sustained eGFR < 60mL/min/1.73m^2 or a sustained decrease in eGFR ≥ 25% from baseline). We also measured processes of care after AKI, which included nephrologist visits and serum creatinine/proteinuria testing.

Results: We matched 170 AKI Follow-up Clinic patients to 680 patients who received usual care. Approximately 75% in each group had KDIGO stage 2-3 AKI, with similar mean eGFR [SD] at baseline (64.6 [25.1] versus 64.2 [27] mL/min/1.73m^2) and hospital discharge (49.6 [24.6] versus 49.0 [28.1] mL/min/1.73m^2). The AKI Follow-up Clinic group had more nephrology visits per patient-year (1.4 [3.1] versus 0.7 [1.5]), with a greater proportion completing serum creatinine (94% versus 84%) and proteinuria (49% versus 25%) tests within 90-days of hospital discharge. Care in the AKI Follow-up Clinic was not associated with time to a major adverse kidney event (HR=0.90, 95% CI 0.72-1.13), but it was associated with a decreased risk of death (HR=0.55, 95% CI 0.37-0.82).

Conclusions: The AKI Follow-up Clinic was not associated with a decreased risk of major adverse kidney events, possibly due to an increased risk of CKD from more serum creatinine testing. The association with reduced mortality warrants confirmation in randomized controlled trials.

Funding: Government Support - Non-U.S.

PO0231

Risk Factors for Long-Term Mortality Following AKI

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Background: Acute kidney injury (AKI) occurs in over 20% of hospitalized patients and is associated with increased long-term mortality. The purpose of this study is to identify risk factors for mortality following a hospitalization with AKI in US Veterans.

Methods: AKI was defined as a creatinine increase of ≥0.3 mg/dL at or after admission to a VA hospital between 2013 and 2018. The primary outcome was mortality, with follow-up ranging from 2-7 years. Over 50 variables were considered for inclusion in the final model, including demographics, comorbidities, and laboratory data. Bootstrap modeling was used to determine the outcomes of one hundred stepwise regressions using random sampling with replacement, and those included in more than 60 of the 100 models were evaluated in a final model using Cox regression. Given that over a quarter of post-AKI mortality is due to cardiac disease, separate models were constructed for patients with and without pre-existing cardiac disease at baseline.

Results: A total of 241,781 Veterans with AKI were included. There were 47,390 deaths out of 139,144 (34%) in the non-cardiac group, and 54,384 deaths out of 102,637 (53%) in the cardiac disease group. The final Cox regression models for each population are given in **Table 1**. Harrell's Concordance values were 0.67 and 0.66, respectively. Cardiac comorbidities were major predictors of mortality in the cardiac group. Notably, kidney metrics such as admission creatinine and discharge creatinine were not selected for inclusion, and AKI stage was not a strong predictor in the non-cardiac model where it was included.

Conclusions: We report factors in AKI survivors that predict long-term mortality among US Veterans. Mortality was significantly higher in the cardiovascular disease group, and cardiovascular history was a major risk factor. Variables related to creatinine values or AKI stage were not strong predictors of mortality.

Non-Cardiac Disease (N = 139,144)				Cardiac Disease (N = 102,637)			
Parameter	Hazard Ratio	Confidence Interval	p-value	Parameter	Hazard Ratio	Confidence Interval	p-value
Age (per 10 years)	1.62	1.61-1.64	<.001	Age (per 10 years)	1.53	1.51-1.54	<.001
BUN 40-79 mg/dL	1.37	1.34-1.40	<.001	BUN 40-79 mg/dL	1.45	1.40-1.50	<.001
BUN > 80 mg/dL	1.34	1.29-1.40	<.001	BUN > 80 mg/dL	1.69	1.62-1.77	<.001
Chronic Lung Disease	1.35	1.32-1.37	<.001	Chronic Lung Disease	1.26	1.23-1.28	<.001
Atrial Fibrillation	1.12	1.09-1.15	<.001	Atrial Fibrillation	1.06	1.04-1.10	<.001
Mild Proteinuria	1.15	1.13-1.17	<.001	Mild Proteinuria	1.04	1.01-1.06	.001
Heavy Proteinuria	1.13	1.10-1.16	<.001	Heavy Proteinuria	1.06	1.04-1.10	<.001
Peripheral Vascular Disease	1.11	1.09-1.14	<.001	White Blood Count	1.003	1.001-1.005	<.001
Sodium <119 mmol/L	1.17	1.09-1.24	<.001	Bilirubin	1.11	1.10-1.11	<.001
Sodium 120-134 mmol/L	1.06	1.06-1.10	<.001	Congestive Heart Failure	1.31	1.28-1.34	<.001
Sodium >155 mmol/L	2.11	1.94-2.28	<.001	Cardiomyopathy	1.07	1.04-1.10	.001
AKI Stage 2	1.11	1.07-1.14	<.001	Cardiac Device	1.12	1.09-1.15	<.001
AKI Stage 3	1.18	1.15-1.22	<.001	Myocardial Infarction	1.04	1.02-1.07	<.001
				Valvular Disease	1.07	1.04-1.10	<.001
				Major Electrolyte Abnormalities	1.16	1.14-1.18	<.001

PO0232

The Clinical Characteristics of Inpatients with AKI and the Risk Factors for Progression to CKD

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Background: To explore the incidence of AKI in hospitalized patients and demonstrate the distributions and clinical characteristics of AKI and the risk factors for progression to CKD.

Methods: Medical records of inpatients were acquired from Nanjing Health Information Platform from January 1 to December 31, 2019. A total of 20258 patients with 2 or more serum creatinine records during one single hospitalization were enrolled. We analyzed the distribution, clinical features, and associated risk factors of AKI. A prospective cohort of 999 AKI patients was followed up for a medium of one year. Multivariable logistic regression was used to analyze the risk factors for the progression from AKI to CKD and a risk predictive model was established accordingly.

Results: Among the enrolled patients, 2194 (10.8%) developed AKI in this study. The prevalence of AKI in medical department, surgical department and ICU were 9.1%, 10.5% and 27.9%, respectively. Compared with the non-AKI group, there were more men and elderly in the AKI group. Patients with AKI were more likely to be complicated with diabetes, hypertension, and CKD. The baseline serum creatinine, uric acid, fasting blood glucose and inflammatory biomarker in AKI group were significantly higher than those in non-AKI group. On the contrary, those with AKI had lower blood lipids, albumin and hemoglobin. The presence of AKI predicted a significant increase in hospitalization cost, duration and all-cause mortality. Furthermore, 110 individuals (11.0%) progressed to CKD in the prospective cohort. Age, AKI stage, hypertension, baseline serum creatinine, uric acid and hemoglobin were found to be independent risk factors for progression to CKD. A risk predictive model of progression from AKI to CKD was established with an area under the ROC curve of 0.822 (95%CI 0.788 ~ 0.877, $P < 0.001$).

Conclusions: Age, AKI stage, baseline serum creatinine, hypertension, hyperuricemia and hypo-hemoglobinemia were independent risk factors for the progression of CKD in AKI patients. Predictive model established using these variables can help us screen those high-risk populations.

Funding: Government Support - Non-U.S.

PO0233

Reduction of Intraoperative Nephrotoxic Antimicrobial Exposure Can Decrease the Severity of Stage of AKI and Improve Renal Recovery in Patients Undergoing Heart Transplantation

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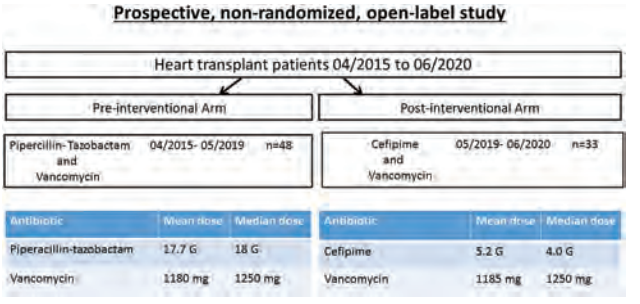
Background: Acute Kidney Injury (AKI) is very common complication post-heart transplant with a reported incidence of approximately 47-76%. Antibiotic combinations, such as piperacillin-tazobactam and vancomycin can cause nephrotoxicity and AKI especially in high doses. The mechanism for this nephrotoxicity is not clear. The purpose of this study was to evaluate the impact of reducing intraoperative nephrotoxic antibiotic exposure on the rate of Acute Kidney Injury and renal recovery in adult patients undergoing heart transplantation.

Methods: This is a single-center prospective study design of all adult patients undergoing heart transplants at Medical University of South Carolina between 4/12/2015 to 5/1/2020. In 06/20/2019, as part of a quality improvement effort to reduce our AKI rate, we changed empiric intraoperative antimicrobial coverage from piperacillin-tazobactam to cefepime while continuing vancomycin use. We collected data using the electronic health record. AKI severity and recovery were extracted for patients exposed to piperacillin-tazobactam and vancomycin or cefepime and vancomycin. AKI was identified using KDIGO serum creatinine criteria. Renal recovery was defined as 25% improvement in serum creatinine within 7 days. We assessed rates of nephrotoxin exposure and KDIGO AKI rates in all heart transplant inpatients for at least 4 years pre-intervention and almost 1 year post-intervention.

Results: While the overall rate of AKI remained the same after the intervention, the rates of severe stage 3 AKI decreased by 32%. Recovery of AKI prior to hospital discharge improved 4-fold in the intervention group (24.0% vs 6.0 %, $P < 0.05$). There was a trend towards less readmissions at 6 months with the intervention group (48.6% vs. 65.9%; p=0.117).

Conclusions: Reduction of nephrotoxic antimicrobial exposure can decrease the severity of heart transplant-related AKI and improve AKI recovery rates.



PO0234

Clinical Trajectories of AKI in Hospitalized Patients

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Background: In surgical sepsis patients, AKI trajectory subgroups have unique physiologic signatures of immunologic and endothelial dysfunction, suggesting potential utility for targeted, therapeutic interventions. It is unknown whether the same phenomena occur among all hospitalized patients. Our objectives are to understand the baseline characteristics of patients who will develop distinct AKI trajectories, determine differences in clinical outcomes, resource use, and long-term survival by AKI trajectory groups defined by persistent kidney injury and renal non-recovery on, and assess the relative importance of AKI severity, duration, and recovery on survival.

Methods: We performed a retrospective study of 156,699 patients admitted to a quaternary care academic hospital between January, 2012 and August, 2019. We used Kidney Disease Improving Global Outcomes and Acute Dialysis Quality Initiative criteria to stage AKI and classify patients as having no AKI, rapidly reversed AKI, persistent AKI with renal recovery, or persistent AKI without renal recovery. Clinical outcomes, resource use, and long-term survival rates were compared among AKI trajectory groups. Cox proportional-hazards regression was used to assess associations between AKI trajectories and time to death while controlling for demographics, Charlson comorbidity score, and provision of mechanical ventilation and ICU admission for two days or greater.

Results: Fifteen percent (54,212/355,678) of the encounters developed AKI. Fifty-eight percent (31,500/54,212) of AKI episodes rapidly reversed within 48 hours; among patients with persistent AKI, two-thirds (14,122/22,712) did not have renal recovery by discharge. One-year mortality was significantly higher among patients with persistent AKI (35%, 7,856/22,712) compared to patients with rapidly reversed AKI (15%, 4,714/31,500) and no AKI (7%, 22,117/301,466). Persistent AKI without renal recovery was associated with approximately five to six fold increased mortality compared to no AKI group, with adjusted hazard ratios of 4.7 and 6.2 for mild and severe AKI.

Conclusions: Among hospitalized patients, persistent AKI and the absence of renal recovery are associated with increased health care resource use and decreased short- and long-term survival. Early identification of patients at increased risk for persistent AKI may facilitate the provision of targeted treatments.

Funding: NIDDK Support

PO0235

Incidence and Prognosis of Different Stages of Acute Kidney Disease: A Single-Center Retrospective Cohort Study

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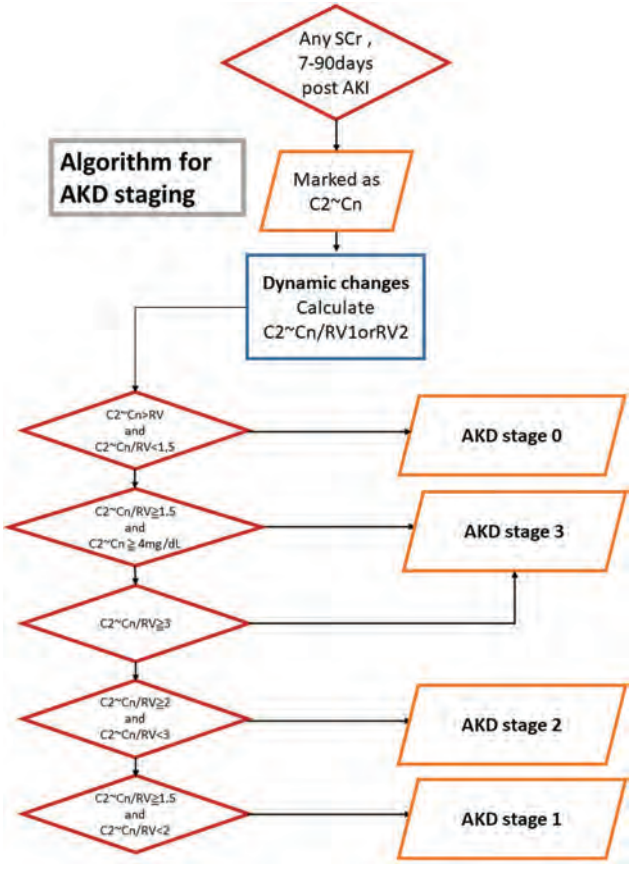
Background: The 16th Acute Disease Quality Initiative (ADQI) recommends that the definitions and staging criteria for acute kidney disease (AKD) be congruent with the stage of AKI. To delineate the prognostic values of the AKD staging system, we constructed a large retrospective cohort and evaluated the disparate outcomes among patients with different stages of AKD.

Methods: This study was a retrospective cohort study including 4,741 adult AKI patients in a single tertiary medical center from 2015 to 2018, with at least 1 serum creatinine measurement between 7 to 90 days after AKI. The 16th ADQI recommendations were used to estimate the proportion of patients at different AKD stages (Figure 1). All patients were followed up for 1 year (study end date, Dec 31st, 2019) to analyze risk factors associated with eGFR decline, initiation of dialysis and in-hospital mortality.

Results: Among the 4,741 AKI patients included in the cohort, AKD stages 1-3 after AKI was common (53% in the CKD group and 51% in the non-CKD group). In the logistic regression model adjusted for demographics and comorbidities and after a 1-year follow-up, AKD stages 1/2/3 (AKD stage 0 as reference group) were associated with higher risks of eGFR decline (AKD stage: Odds ratio, 95% Confidence Interval [95% CI], AKD 1: 2.14, 1.65-2.79; AKD 2: 2.64, 2.01-3.47; AKD 3: 2.90, 2.29-3.66), initiation of kidney replacement therapy, (AKD stage: Odds ratio, 95% CI, AKD 2: 1.88, 1.39-2.53; AKD 3: 8.72, 7.07-10.76), and in-hospital mortality (AKD stage: Odds ratio, 95% CI, AKD 1: 1.79, 1.47-2.18; AKD 2: 3.23, 2.65-3.94; AKD 3: 5.59, 4.69-6.67).

Conclusions: Staging criteria for AKD identified AKI patients at higher risk of kidney function decline, dialysis, and mortality. AKD patients with a more severe stage need to receive intensified care.

Funding: Government Support - Non-U.S.



PO0236

The Quality of Discharge Summaries After AKI

Cameron Giles, Milica Novakovic, Wilma M. Hopman, Samuel A. Silver. *Queen's University, Kingston, ON, Canada.*

Background: Patients who survive acute kidney injury (AKI) are at increased risk of hospital readmission, chronic kidney disease (CKD), and death. However, most patients are unaware they experienced AKI, emphasizing the importance of high-quality communication between inpatient and outpatient health care providers. Our objectives were to determine how often different elements of AKI were mentioned in discharge summaries and to identify predictors of discharge summary quality after AKI.

Methods: We performed a retrospective chart review of 300 randomly selected discharge summaries from 2015 to 2019. We included 150 hospitalizations before and after introduction of a post-AKI clinic in August 2017, with 50 patients from each Kidney Disease Improving Global Outcomes (KDIGO) AKI stage. We assessed each discharge summary for 10 elements, including AKI course and follow-up recommendations. We used multivariable logistic regression to determine predictors of discharge summary quality.

Results: The median number of AKI elements mentioned was 4/10 (IQR, 2-6). Follow-up with nephrology was documented for 33 (11%) patients. AKI-specific recommendations for labs and medication changes were noted in 66 (22%) and 80 (27%) discharge summaries, respectively. The odds of having a higher quality discharge summary (AKI elements ≥4/10) were greater for every increase in baseline creatinine (Cr) of 25 umol/L (OR, 1.86; 95% CI, 1.42-2.43); intrarenal etiology (OR, 2.33; 95% CI, 1.23-4.41); increased AKI severity (stage 3 or kidney replacement therapy (KRT)) (OR, 6.85 and 4.39; 95% CI, 2.83-16.59 and 1.53-12.58, respectively); inpatient nephrology consultation (OR, 10.53; 95% CI, 4.82-22.98); and discharge Cr ≥100% above baseline (OR, 4.88; 95% CI, 1.80-13.26). Discharge summary quality did not improve with the introduction of a post-AKI clinic (OR, 0.76; 95% CI, 0.44-1.31).

Conclusions: Overall discharge summary quality in AKI survivors is poor, improving modestly for patients with baseline CKD, intrarenal etiology, severe AKI, higher discharge Cr, and inpatient nephrology involvement. Most discharge summaries are missing key post-AKI elements, including Cr trajectory and AKI-specific follow-up recommendations, even in patients receiving KRT. These gaps suggest an opportunity exists to improve discharge summary quality and communication post-AKI, especially for patients not assessed by nephrology as inpatients.

PO0237

Risk of Renal Recovery Post Dialysis-Requiring AKI in Critically Ill Transplant Patients Receiving Calcineurin Inhibitors

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Background: The use of the calcineurin inhibitors has led to major advances in the field of transplantation, with excellent short-term graft outcomes. However, these agents are associated with chronic nephrotoxicity and long-term may lead to ESRD. The purpose of this study was to assess the risk of renal recovery at 3 months in critically ill transplant and non-transplant patients who required continuous renal replacement therapy (CRRT) (AKI-D).

Methods: This is a single center retrospective study aimed to assess differences in renal recovery from AKI-requiring dialysis (AKI-D) in both non-transplant patients (CNI - patients) and transplant patients taking calcineurin inhibitors (CNI + patients). Our study was undertaken from 02/2017 to 07/2019 at the Medical University of South Carolina, and our analysis included 153 critically ill patients who received CRRT for AKI-D. Non-renal recovery from AKI-D was defined as ESRD as per KDIGO guidelines. We performed a Cox Hazard Risk Model to asess risk of CNI use on renal recovery at 3 months adjusted for transplant status, mortality at 28 or 90 days, age, sex, hypertension, DM, APACHE score and initial number of vasoactive medication used at that time of CRRT initiation.

Results: CNI users had 61% lower risk of developing end stage kidney disease compared to non-CNI users at 90 days (HR 0.49, p = 0.49, CI 0.07 -3.69) although this risk was not statistically significantly. Interestingly, there was a statistically significant lower rate of 28-day and 90-day mortality in the critically ill transplant AKI-D cohort (21% and 37%, p< 0.05) when compared to the critically ill non-transplant AKI-D cohort (57% and 61%, p<0.05), respectively (see figure)

Conclusions: Even in this small retrospective cohort analysis, critically ill AKI-D patients requiring CNI agents did not have a statistically significant higher rate of ESRD despite CNI use and was associated with a lower 28- and 90-day mortality. More research is required to study the relationship between CNI use on renal recovery.

Outcomes by Transplant Recipient (Yes) vs. Non-Transplant Recipients (No)

Factor	No	Yes	p-value
N	133	20	
Dialysis-free at 2 weeks post-CRRT initiation	24 (37%)	7 (44%)	0.61
Dialysis-free at 4 weeks post-CRRT initiation	33 (50%)	9 (60%)	0.80
Development of CKD at 30days	19 (45%)	4 (44%)	0.97
Development of CKD at 90days	17 (36%)	3 (33%)	0.89
Mortality During Hospitalization	73 (55.7%)	4 (21.1%)	0.005
28-day Mortality	74 (56.5%)	4 (21.1%)	0.003
survival28, mean (SD)	16.669211 (10.908638)	24.578947 (7.1671767)	0.003
90-day Mortality	78 (60.8%)	7 (36.8%)	0.049
survival90, mean (SD)	46.082966 (40.613281)	73.8125 (23.612696)	0.010

PO0238

Outpatient Dialysis Prescription as Predictor and Modifiable Factor for Outcomes of Patients with Dialysis-Requiring AKI

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Background: Patients with acute kidney injury requiring hemodialysis (AKI-D) have poor prognosis. Beginning January 1, 2017, End Stage Kidney Disease (ESKD) facilities were allowed to furnish dialysis services to AKI-D patients. Identifying modifiable predicators of AKI outcomes will allow better care of patients with AKI-D.

Methods: Patients with AKI-D discharged for outpatient hemodialysis (HD) to one of 11 University of Virginia dialysis units from 1/1/2017 to 12/31/2019 (n=274) were followed for up to 6 months. Multinomial logistic regression was used to estimate association between clinical and dialysis factors and outcomes: recovery (patient off dialysis), ESKD, or death at 3 and 6 months. Dialysis data from the first 28 days were analyzed.

Results: Patients were 42% female, 67% Caucasian with mean age 62.8 ± 15.4 years. Comorbidities included diabetes mellitus (42%), hypertension (78%), congestive heart failure (18%), coronary artery disease (27%), prior AKI episode (36%) with pre AKI eGFR 33.8 ± 29.1 ml/min. Median (IQR) number of dialysis sessions was 11 (6-16), lasting 3.6 ± 0.6 hours. Patients declared ESKD had more median drops in blood pressure (BP) (16) than those who recovered (9) or died (10). At 90 days post start of outpatient HD, 45% recovered, 45% were declared ESKD and 9.9% died. Two more patients recovered, 2 patient died with one patient who was initially off HD was declared ESKD by 180 days. Patients with more frequent BP drops had increased odds ratio (OR) of ESKD compared to patients in the lowest quartile. Adjusted odds ratios (95% CIs) for ESKD were 3.8 (1.4 – 9.7, p<0.01) and 2.7 (1.1 – 7.2, p=0.05) for patients in 3rd and 4th quartiles, respectively, adjusting for prior AKI, age, baseline eGFR, hypertension, and UF rate. The magnitude of drop in mean arterial blood pressure was not associated with ESKD or death. Net ultrafiltration (UF) (Liters) and UF rate (ml/kg/hour) were associated with ESKD. OR (95% CIs) 1.6 (1.0 – 2.53, p=0.05) and 1.2 (1.0 – 1.3, P <0.01) respectively.

Conclusions: Optimizing dialysis prescription and close monitoring of outpatient dialysis for patients with AKI-D is crucial and may improve outcomes of these patients

PO0239

Exploratory Diagnostic and Prognostic Biomarkers in Adults with Atypical Hemolytic Uremic Syndrome (aHUS): Analysis of the Phase 3 Study of Ravulizumab (NCT02949128)

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Background: Validated biomarkers for diagnosis and monitoring of patients with complement-mediated thrombotic microangiopathy (CM-TMA) are not clinically available. Characterization of biomarkers in patients with aHUS, a form of CM-TMA, may inform diagnosis, treatment decisions and monitoring for patients with other types of CM-TMA.

Methods: Using data from the phase III study of ravulizumab (terminal C5 complement inhibitor) in adults with aHUS (NCT02949128), baseline (BL; prior to treatment) serum, plasma and urine biomarker levels in patients were compared with levels in healthy volunteers (HV), and evaluated for associations with kidney function (e.g. estimated glomerular filtration rate [eGFR] and urine protein/creatinine [Cr] ratio [UPCR]) at BL and 26 weeks post-treatment initiation. Regression coefficients and p-values (two-sided t-test) are reported.

Results: This analysis included 55 patients: median age 39 (range 19–76) years; 67% female; 53% White, 27% Asian. Specific BL biomarkers were elevated compared with HV, and associations between BL biomarker levels and both BL eGFR and BL UPCR were identified (Table 1). BL plasma complement factor Ba was associated with eGFR changes after 26 weeks of ravulizumab treatment, while urine sC5b-9, sC5b-9/Cr, Ba and Ba/Cr were associated with UPCR changes after 26 weeks of treatment.

Conclusions: The complement biomarkers Ba (plasma and urine) and sC5b-9 (urine) were associated with kidney function in patients with aHUS at baseline and over 26 weeks of treatment with anti-C5 therapy. Such biomarkers demonstrate diagnostic potential in CM-TMA and may predict renal response to terminal complement inhibition.

Funding: Commercial Support - Alexion Pharmaceuticals

Table 1: Baseline biomarkers

Biomarker	Patients with elevated BL biomarker*† % (n/N)	BL biomarker associations with kidney function measures (BL) Regression coefficient (p-value)		BL biomarker associations with kidney function measures (26-week change from BL) Regression coefficient (p-value)	
		eGFR	UPCR	eGFR	UPCR
Urine cystatin C/Cr (ng/mg Cr)	100.0 (36/36)	-0.25 (0.0002)	0.42 (0.0048)	-2.28 (0.4290)	-9.72 (0.2385)
Plasma Ba (ng/ml)	97.7 (42/43)	-0.55 (<0.0001)	1.25 (0.0001)	-13.98 (0.0085)	-27.42 (0.1021)
Urine cystatin C (ng/ml)	97.6 (41/42)	-0.25 (<0.0001)	0.51 (<0.0001)	-0.62 (0.7788)	-7.38 (0.2103)
Urine Ba (ng/ml)	97.5 (39/40)	-0.28 (<0.0001)	0.73 (<0.0001)	1.41 (0.5825)	-16.07 (0.0090)
Urine Ba/Cr (ng/mg Cr)	97.1 (34/35)	-0.31 (<0.0001)	0.77 (<0.0001)	2.40 (0.3957)	-17.28 (0.0110)
Urine sC5b-9**/Cr (ng/mg Cr)	96.9 (31/32)	-0.10 (0.0391)	0.45 (<0.0001)	1.91 (0.3650)	-21.46 (<0.0001)
Urine sC5b-9** (ng/ml)	88.1 (37/42)	-0.12 (0.0021)	0.44 (<0.0001)	-0.79 (0.5862)	-16.03 (<0.0001)
Plasma sC5b-9 (ng/ml)	79.1 (34/43)	0.19 (0.1430)	-0.25 (0.3712)	-3.17 (0.5269)	15.91 (0.1830)

*compared with observed maximum for HV; **urine sC5b-9 is undetectable in HV, therefore HV values were set at ½LLOQ

PO0240

Urinary Follistatin: A Novel Biomarker for Monitoring the Severity of AKI

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Background: Activin A, a member of the TGF-beta superfamily, which was absent in normal kidney, was increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury. However, the role of follistatin, an endogenous antagonist of activins, in the kidney is unknown. To address this issue, we examined the localization of follistatin in normal and ischemic rat kidney, and measured urinary follistatin in both rats and human with AKI.

Methods: Using vascular clamps, renal ischemia was induced for 45 min in 8-week-old male Wistar rats. Localization of follistatin in the kidney and urinary follistatin was examined by immunostaining and ELISA, respectively. Renal tissues of Nephrectomized kidney was used as normal human kidney (Approved number A18-150). Patients with AKI (n=98) and healthy adults (n=10) were enrolled in this study (Approved number A18-081 and A18-089). Serum and urinary follistatin was measured by ELISA. Correlations of urinary follistatin with other clinical parameters were analyzed.

Results: Follistatin was localized in renal tubules of normal rat kidney. Follistatin-expressing cells were positive for NCC and uromodulin, but were negative for AQP1 or AQP2. In contrast, follistatin expression was increased in the inner medulla of the kidney after renal ischemia. Urinary follistatin, undetectable in normal rats, was significantly increased with a peak at 24 h after renal ischemia. Consistent with normal rat kidney, follistatin was localized in renal tubules of normal human kidney. Urinary follistatin, undetectable in healthy adults, was significantly increased in patients with AKI (0.0 ± 0.0 vs. 433.6 ± 190.0 pg/mL, p< 0.05) and was positively correlated with the severity of AKI. Urinary follistatin was significantly increased in patients requiring renal replacement therapy compared to those who did not (911.7 ± 428.3 vs. 94.4 ± 40.0 pg/mL, p< 0.05). There was a significant correlation of urinary follistatin with urinary protein, alpha1-microglobulin, NGAL, but not with serum follistatin.

Conclusions: Follistatin, which is localized in the distal tubules of normal kidney, become detectable in the urine of AKI patients. Urinary follistatin may reflect the severity of acute tubular damage.

PO0241

RBT-1 Safety and Cytoprotective Response Biomarkers in Healthy Volunteers and Subjects with CKD

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Background: RBT-1 (stannous protoporphyrin [SnPP] with iron sucrose [FeS]) is a novel drug designed to precondition organs to prevent acute injury via activation of Nrf2, anti-inflammatory, and iron sequestering pathways. Pretreatment with RBT-1 in several animal models of acute kidney injury (AKI) has demonstrated protection from AKI in conjunction with upregulation of cytoprotective proteins. Here, we report results of a Phase 1b study of RBT-1 that assessed safety and cytoprotective response biomarker induction in healthy volunteers and subjects with stage 3 and 4 chronic kidney disease (CKD).

Methods: Fifty-four (54) subjects (18 healthy volunteers and 36 subjects with CKD) were enrolled and received a single IV dose of RBT-1 (9, 27, 45, 63, or 90 mg SnPP with 240 mg FeS). Plasma heme oxygenase-1 (HO-1), interleukin-10 (IL-10) and ferritin were selected as surrogate measures of organ protective activity. Safety was assessed through Day 29, and cytoprotective response biomarkers were assessed through 168 hours post-dose.

Results: RBT-1 was well tolerated in both healthy volunteers and subjects with CKD. The most common treatment-emergent adverse event was photosensitivity reaction (a known reaction to SnPP), which occurred in 15 subjects (27.8%) and was more commonly observed in the higher dose groups (63 and 90 mg SnPP/240 mg FeS). Photosensitivity was transient and generally mild in intensity. No serious adverse events were reported. RBT-1 induced dose-dependent, statistically significant increases in cytoprotective response biomarkers in both healthy volunteers and subjects with CKD. Peak increases from baseline in healthy volunteers and subjects with CKD were: 386% and 402% for HO-1, respectively; 99% and 332% for IL-10, respectively; and 1552% and 469% for ferritin, respectively.

Conclusions: RBT-1 is well tolerated with a similar safety profile in healthy volunteers and subjects with CKD Stage 3 or 4 and elicits a biomarker response in humans that is associated with RBT-1-mediated organ protection in animal models of AKI. The positive safety and biomarker efficacy data provide a strong scientific basis to study RBT-1 as an AKI prevention strategy in patients undergoing elective cardiac surgery.

Funding: Commercial Support - Renibus Therapeutics, Inc.

PO0242

IL-17 Levels Are Higher in Patients with AKI and Associate with Mortality and Major Adverse Kidney Events

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Background: Inflammatory markers of AKI have garnered attention for having potential to be sensitive biomarkers for AKI prognosis. We demonstrated that TH17 cells are increased in ICU patients diagnosed with AKI vs. those without AKI. The main objective of this study was to examine the association of serum IL-17 with mortality and major adverse kidney events (MAKE) in critically ill patients with and without AKI.

Methods: Multicenter prospective study of 299 critically ill patients with AKI stage 2 or above, and matched ICU patients without AKI. Blood samples were collected within 48 hours after AKI diagnosis (n=153) or within 48 hours of ICU admission in those without AKI (n=146). Serum IL-17a was measured using extremely sensitive ELISA (S-Plex technology; Meso Scale Discovery). Logistic regression was used to examine the association of IL-17 levels with hospital mortality and MAKE at 90 days post-discharge (composite of death, need of renal replacement therapy or inability to recover at least 70% of baseline eGFR).

Results: Patients in the highest tertile of IL-17 were more severely ill than those in lower tertiles, including more frequent AKI (73% vs. 47% vs. 33.3%, p <0.001), more frequent mechanical ventilation (63% vs. 48% vs. 44.4%, p=0.021), and higher APACHE-II scores (19 vs. 15.5 vs. 14, p<0.001). Moreover, patients in the highest tertile of IL-17 had higher rates of inpatient mortality (26% vs. 8% vs. 9.1%, p<0.001) and MAKE-90. In multivariable models, patients in the highest tertile (vs. lowest tertile) had increased risk of hospital mortality (aOR 2.80, 95%CI 1.09-7.20) and MAKE-90 (aOR 3.51, 95%CI 1.72-7.14). Concordant results were obtained when IL-17 was analyzed as a continuous variable.

Conclusions: Higher levels of IL-17 during acute illness were independently associated with hospital mortality and MAKE-90 in critically ill patients with and without AKI. Further studies are needed to validate the use of IL-17 as a surrogate pathobiologic and prognostic marker in this susceptible population.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO0243

Serum Renin and Major Adverse Kidney Events in Critically Ill Patients: A Multicenter Prospective Study

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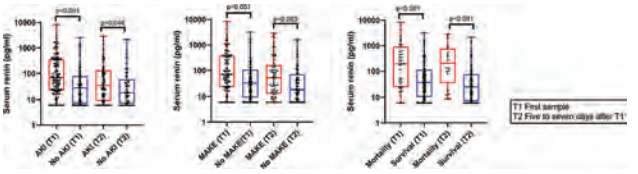
Background: Preliminary studies have suggested that the renin-angiotensin system (RAS) is activated in critical illness and associated with mortality and adverse kidney outcomes. We sought to assess in a larger, multicenter study the relationship between serum renin and Major Adverse Kidney Events (MAKE) in intensive care unit (ICU) patients.

Methods: Prospective, multicenter study at two institutions of patients with and without acute kidney injury (AKI). Blood samples were collected for renin measurement a median of 2 days into the index ICU admission (T1) and 5-7 days later (T2). The primary outcome was MAKE at hospital discharge, a composite of mortality, kidney replacement therapy, or reduced estimated glomerular filtration rate to ≤ 75% of baseline.

Results: Two hundred and eighty patients were enrolled with available blood samples for analysis. Patients in the highest renin tertile were more severely ill overall, and serum renin was significantly higher at both time points in patients with AKI, those who experienced MAKE, and those who died (Fig. 1). In multivariable logistic regression, this initial measurement of renin (T1) was significantly associated with MAKE: third renin tertile OR 2.33 (95% CI 1.01-5.44) and second renin tertile OR 2.51 (1.08-5.80) in reference to the first renin tertile. Similar results were noted for renin's association with hospital mortality. The association of renin with MAKE events in survivors was not statistically significant. The trajectory of the renin measurements between T1 and T2 was distinct when comparing death vs. survival, but not when comparing MAKE vs. those without.

Conclusions: In a broad cohort of critically ill patients, serum renin measured early in the ICU admission is associated with MAKE events at discharge, particularly mortality.

Funding: NIDDK Support, Other NIH Support - NCATS



Serum renin in patients with and without AKI, MAKE, and mortality.

PO0244

Urinary Epidermal Growth Factor and CKD Progression: The ASSESS-AKI Study

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Background: Acute kidney injury (AKI) and chronic kidney disease (CKD) are interconnected syndromes with AKI recognized as a risk factor for CKD incidence or progression. However, biomarkers of repair or resilience, such as epidermal growth factor (EGF), may help better inform this risk, given the limitations of serum creatinine (sCr) in the setting of AKI.

Methods: We enrolled 1,538 hospitalized patients prospectively in the multi-center Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) Study. We measured urinary epidermal growth factor (uEGF) from samples at 3 months post-discharge. The primary outcome was a composite of CKD incidence, progression, or development of end-stage kidney disease (ESKD). We also evaluated change in estimated glomerular filtration rate (eGFR) over time by EGF quartile.

Results: 299 (20%) patients developed the primary outcome at a median of 4.3 years follow-up. Patients in the fourth quartile of uEGF had higher eGFR at baseline and at 3-month follow-up compared to those in quartiles 1-3, as well as significantly lower albuminuria. Each 2-fold higher uEGF level was significantly associated with decreased risk of the composite outcome (HR 0.65; 95% CI: 0.59-0.71). This association remained robust after adjustment for demographic factors, baseline kidney function, urinary albumin, and other urinary biomarkers of injury and inflammation (aHR 0.65, 95% CI: 0.54-0.79). Patients in uEGF quartile 1 had the fastest decline in eGFR (-5.6% per year), compared to patients in uEGF quartiles 2-4 (-3.2, -2.8, -2.3% per year, respectively).

Conclusions: Urinary EGF is a marker of repair after kidney injury, and higher levels of uEGF after discharge are associated with reduced risk of CKD and progression to ESKD in hospitalized patients with and without AKI.

Funding: NIDDK Support

Table 1. Association of kidney outcomes by urinary EGF level at 3-month follow-up

Urine EGF at 3-month follow-up	Range	CKD Incidence, Progression or ESKD				% Change in eGFR over time
		n (%)	Mean (95% CI) event rate per 1,000 py	Unadjusted HR (95% CI)	Adjusted[1] HR (95% CI)	
Continuous[2]	80-54978	299 (19.5%)		0.65 (0.59, 0.71)	0.65 (0.54, 0.79)	
Quartile 1 (n=383)	80 -1441	120 (31.3%)	90.7 (75.9, 108.6)	1.0 (referent)	1.0 (referent)	-5.6/year
Quartile 2 (n=383)	1442 -3185	66 (17.2%)	40.3 (31.7, 51.3)	0.38 (0.28, 0.53)	0.53 (0.34, 0.82)	-3.2/year
Quartile 3 (n=383)	3191 -6469	65 (17.0%)	39.7 (31.2, 50.7)	0.34 (0.25, 0.48)	0.46 (0.27, 0.81)	-2.8/year
Quartile 4 (n=383)	6470 -54978	48 (12.5%)	28.4 (21.4, 37.7)	0.24 (0.16, 0.35)	0.34 (0.16, 0.70)	-2.3/year

1. Adjusted for gender, African American race, ethnicity, smoking status, baseline diabetes mellitus, baseline CKD, sepsis during index hospitalization, AKI during index hospitalization, urine creatinine at 3 months, Urine Albumin 3 months, GFR 3 months, BMI at 3 months, and urine biomarkers at 3 months (NGAL, IL-18, KIM-1, MCP-1, UMOD, YKL-40)
2. log$_2$ transformed

PO0245

Dicarbonyl L-Xylulose Reductase (DCXR) as Surrogate for "Muddy" Brown Granular Casts and Diagnostic Biomarker for Acute Tubular Injury

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Background: Detection of abundant "muddy" brown granular casts (MBGC) during microscopic examination of the urinary sediment (MicrExUrSed) is pathognomonic of acute tubular injury (ATI). Because hospital laboratories do not optimally report MBGC, nephrologists have to independently perform MicrExUrSed. Thus, a diagnostic test to identify MBGC without performance of MicrExUrSed could be clinically useful. Unlike most AKI biomarker discovery approaches, we hypothesized that MBGC-enriched urinary sediment (MBGC-sedi) contains unique proteins that could serve as biomarkers of ATI.

Methods: MicrExUrSed was performed in specimens from patients with acute kidney injury (AKI) seen for nephrology consultation with a suspected etiology of ATI. Specimens from 3 patients containing numerous MBGC (>10 per low power field in >50% of slide) were collected, subjected to low speed centrifugation (100g), proteolytically digested and analyzed by nano-LC tandem mass spectrometry. Identified proteins were quantified by normalized spectral abundance factor (NSAF). Proteins were identified by MASCOT and accepted at <1% false discovery. Presence of proteins in casts was verified by immunofluorescence (IF) and western blotting (WB).

Results: A total of 242 proteins were significantly more abundant in MBGC-sedi specimens respect to the supernatant ($p<0.05$). Among the identified proteins unique to the MBGC-sedi, we selected dicarbonyl L-xylulose reductase (DCXR) as a candidate ATI biomarker because it was the protein with the lowest p value for MBGC-sedi specificity ($p=0.00012$, per NSAF) and only identified in MBGC-sedi. To validate the proteomics, in a separate set of MBGC-sedi specimens from patients with AKI due to ATI ($n = 10$), presence of DCXR was probed by WB and detected in 6 of 7 cases, and DCXR localization within MBGC by IF was verified in 3 of 3 cases.

Conclusions: DCXR is abundant in MBGC-sedi and may be a biomarker of ATI as an etiology of AKI. DCXR is an enzyme expressed in the kidney, primarily localized in proximal tubuli, absent in glomeruli. At the cellular level, DCXR is involved in metabolic and osmotic stress detoxification. We conclude that urinary DCXR is a potential target molecule for ATI diagnosis.

Funding: Other NIH Support - NIH R15DK124846

PO0246

Preoperative Plasma TNFR1, TNFR2, and KIM-1 and Long-Term Adverse Events After Cardiac Surgery: The TRIBE-AKI Study

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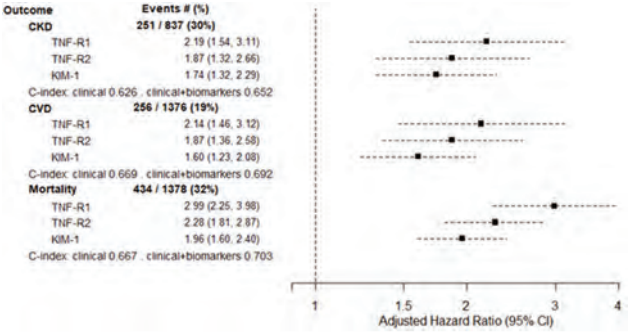
Background: Plasma TNFR1, TNFR2, and KIM-1 have been associated with CKD progression in ambulatory patients with/without diabetes. However, their role as predictors of long-term outcomes and their ability to discriminate such outcomes compared to clinical parameters prior to cardiac surgery is unknown.

Methods: Prospective, multicenter cohort study of high-risk adults undergoing cardiac surgery (2007-2010). We assessed the association between pre-operative levels of TNFR1, TNFR2, and KIM-1 (natural log-transformed) and long-term mortality, CKD (incidence/progression), and cardiovascular (CV) events. We also examined the potential effect modification of DM status on the relationship between these biomarkers and outcomes. C-statistic analysis was used to quantify the discriminatory ability of the biomarkers beyond the clinical model.

Results: 1378 participants (69.1% male) with a mean age: 71.9 ± 9.7, were followed for a median of 5.6 (IQR 4.3-8.6) years. 434 (31.5%) died within the study timeframe, 251 (30%) developed CKD, & 256 (19%) had CV events. After adjustment for covariates, each natural log increase in biomarker concentration was associated with mortality [adjusted HR: TNFR1, 3.0 (95% CI 2.3-4.0); TNFR2, 2.3 (95% CI 1.8-2.9); KIM-1, 2.0 (95% CI 1.6-2.4)]. Similar effect sizes were seen for all 3 biomarkers in their association with CV & CKD events (**Figure 1)**. Baseline DM status did not modify the association between biomarkers and clinical outcomes. The addition of all 3 biomarkers improved discrimination for the 3 outcomes.

Conclusions: Preoperative plasma TNFR1, TNFR2, and KIM-1 were independently associated with long-term outcomes after cardiac surgery and improved discrimination compared to standard clinical models. Pre-operative plasma biomarkers may serve with timely risk-stratification and planning to prevent clinical sequela.

Funding: Other NIH Support - NIH/NHLB institute



HRs were adjusted for age, sex, race, pre-op clinical & kidney-related parameters.

PO0247

Preoperative Biomarkers and Mortality Risk After Cardiac Surgery

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Background: Cardiac surgery patients are at an increased risk for developing adverse outcomes. Preoperative blood and urine biomarkers may help stratify cardiac surgery patients at high risk for mortality.

Methods: The TRIBE-AKI study enrolled 1526 patients undergoing cardiac surgery in the USA and Canada from 2007-2010 and was randomly split into a training and test dataset (70:30). A total of 32 plasma and 17 urine biomarkers were measured preoperatively. The primary outcome was 3-year mortality. Random forest (RF) and LASSO logistic regression models were used to identify top biomarkers. Logistic regression models with the highest performing biomarkers and the Society of Thoracic Surgeons (STS) risk calculator were evaluated and the discriminatory ability was assessed in the test dataset.

Results: Death by 3 years occurred in 163 of the 1526 (10.7%) patients. LASSO logistic regression models retained the STS score and 6 plasma biomarkers (Troponin, IL-6, KIM1, NT-proBNP, TNFR1, YKL-40). The top 6 biomarkers identified by random forest were plasma KIM-1, TNFR1, eGFR, TNF-R2, hsTNT, and urine IL-8. In logistic regression models, the AUC in the test dataset for the STS clinical model was 0.68 (0.61, 0.76) and increased to 0.72 (0.65, 0.79) with the addition of 8 plasma and 2 urine biomarkers (plasma Troponin, IL-6, KIM-1, NT-proBNP, TNFR1, YKL-40, hFABP, TNFR2, and urine IL-8 and albumin; $p=0.24$).

Conclusions: The addition of biomarkers improved discrimination for 3-year mortality prediction minimally beyond clinical characteristics alone. The clinical utility of measurement of biomarkers pre-operatively prior to cardiac surgery is suspect.

Funding: NIDDK Support

PO0248

Considerations in Controlling for Urine Concentration in Performance of Biomarkers of AKI

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Background: Urine biomarkers are often indexed to urine creatinine (UCr) to control for urine concentration. Whether the biomarker-outcome associations are altered using this or other approaches, such as indexing to urine osmolality (UOsm), in AKI patients has not been examined.

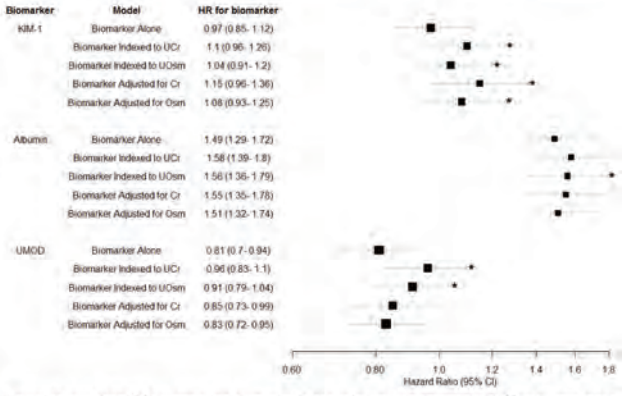
Methods: We studied 769 hospitalized patients with AKI enrolled in the multicenter prospective Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Study. Using Cox proportional hazards regression, we assessed urine biomarkers' associations with a composite outcome of incident chronic kidney disease (CKD) and CKD progression using four approaches to account for urine concentration: indexing to UCr or UOsm and adjusting for UCr or UOsm as covariates.

Results: 207 (27%) participants developed composite CKD outcome at median follow-up of 4.7 years. UCr and UOsm during hospitalization were inversely associated with developing CKD (HR 0.84, 95% CI 0.73-0.96 for UCr; HR 0.81, 95% CI 0.71-0.93 for UOsm). Figure 1 shows the hazard ratio of urine biomarkers collected during hospitalization with the composite CKD outcome using the four approaches to account for urine concentration. The association between urine kidney injury molecule-1 (KIM-1), albumin and CKD strengthened after indexing to or adjusting for UCr or UOsm, but uromodulin's (UMOD) inverse association with CKD was blunted after indexing to UCr or UOsm.

Conclusions: UCr and UOsm, potential markers for tubular health, are both associated with lower risk of developing CKD in hospitalized AKI patients. Indexing to UCr or UOsm strengthens the biomarker- CKD associations for urine KIM-1 and albumin, but attenuates UMOD's inverse association with CKD.

Funding: NIDDK Support

Figure 1. Hazard ratio of urine KIM-1, albumin and UMOD collected during hospitalization in AKI patients with composite CKD outcome using different approaches to account for urine concentration.



* p value less than 0.01 comparing biomarker's association with composite CKD outcome when urine creatinine or osmolality is accounted for versus biomarker alone.
All urine measurements were converted to log-2 base normally distributed Z score.
HR reflects change per 1 SD increase of biomarker on its log-2 scale.
Abbreviation: KIM-1, kidney injury molecule-1; UMOD, uromodulin

PO0249

Clinical Factors Affecting Continuous Renal Replacement Therapy Circuit Life Span

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Background: CRRT is a useful dialysis modality in hemodynamically unstable patients. But despite use of anticoagulants, clotting of CRRT circuit frequently occurs, which reduces the efficiency of dialysis. In the study, we aim to investigate the clinical factors contributing to CRRT circuit clotting.

Methods: The medical records of total 119 critically ill patients requiring CRRT were reviewed retrospectively. We investigated the clinical factors affecting the time from CRRT start to first dialysis circuit clotting, and the proportion of dialysis circuit changes due to clotting to total circuit changes during entire CRRT periods.

Results: Un-tunneled femoral hemodialysis catheter had a shorter time to first circuit clotting (22.8 vs. 32.1 hours, p=0.013), and a higher rate of circuit clotting (69.3 vs. 52.6 %, p=0.043) than jugular catheter. The time to first circuit clotting had a negative correlation with norepinephrine dosage (r= -0.335, p=0.002) and serum creatinine level (r= -0.402, p<0.001), while it had a positive correlation with arterial blood ionized calcium (r=0.273, p=0.017). In multiple regression analysis, it was confirmed that high norepinephrine dosage and high serum creatinine contributed to circuit clotting, and of which serum creatinine was the most significant contributing factor to circuit lifespan (Table 1). During entire CRRT periods, the proportion of dialysis circuit changes due to clotting was well negatively correlated with the time to first circuit clotting (r= -0.460, p<0.001), and total duration of CRRT application (r= -0.306, p=0.006). However, neither transfusion nor CRRT parameters such as blood flow and filtration fraction had no relationship with circuit survival.

Conclusions: Conclusively, in regard to CRRT circuit lifespan, femoral hemodialysis catheter, high norepinephrine dosage, and especially high serum creatinine level contributed to CRRT circuit clotting.

Multiple regression analysis on the time to first CRRT circuit clotting

Model 2	B	Std. Error	Beta	t	p value
(Constant)	34.979	4.420		7.941	0.000
NE dosage	-0.164	0.069	-0.296	-2.368	0.022
Serum Cr	-3.007	1.359	-0.281	-2.246	0.029

Std: standard; NE: norepinephrine; Cr: creatinine

PO0250

CRRT Dose Variation Across Multiple ICUs: A Single-Center Study

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Background: Continuous Renal Replacement Therapy (CRRT) is increasingly a cornerstone of critical care provision in Intensive Care Units (ICUs) but variation in utilization and differences in culture of practice impact percentage of dose delivered, bearing on outcomes. Efforts to establish timing for initiation, modality, and type of anticoagulation continue, but standardizing local practice may be a more feasible route to improvement, through establishing standards across units and measuring adherence to those standards.

Methods: Our single center quality improvement study aimed to assess differences in CRRT utilization, clotting events, percent CRRT dose delivered, and other contributors to differences in CRRT delivery. This initial study is part of a long-term quality improvement project to identify routes to improve CRRT dose delivery and further evaluate CRRT modalities best suited to different ICU environments. We tracked "clotting events," "filter life," and "percent dose delivered," to assess unit specific practice patterns and outcomes. Our study was undertaken from 02/2017 to 07/2019, and includes 150 ICU patients who received CRRT across our system's 5 adult ICUs.

Results: We found CRRT delivery ranging from 92.7% to 96.4% of prescribed dose across our ICUs, with 12,745 hrs of CRRT delivered out of 13,575 hrs CRRT prescribed, and a weighted mean of ~7.8 hrs undelivered CRRT per patient for all patients in the study; average <0.05 hrs undelivered CRRT/patient/day. Undelivered CRRT ranged from 3.4 hrs/patient in the Medical ICU to 13.1 hrs/patient in our Cardio Vascular ICU; the use of a smaller French catheter size for the patients on a specialty surgical ICU, and interruptions for surgical procedures, accounted for the greatest deviation from the mean for undelivered CRRT; significant inter-unit variability of delivered CRRT dose per patient was also noted.

Conclusions: Increased clotting events and decreased percent dose delivery were associated with the use of smaller catheters, and significant variation in average undelivered hours of CRRT per patient across the different units, both of which highlighted the need for shared institutional standards and more frequent measuring of adherence to those standards to improve overall CRRT delivery.

Funding: Clinical Revenue Support

PO0251

Prediction of the Clinical Outcomes in Patients with CRRT Using Body Composition Monitoring: A Machine Learning Approach to a Multi-center Cohort Study

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Background: Fluid balance is a critical predictor of patient outcomes with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). However, accurate assessment and application of fluid balance monitoring for predicting clinical outcomes in these patients were inconclusive.

Methods: In a multicenter cohort study, a total of 784 patients with severe AKI requiring CRRT were recruited, and body composition monitoring (BCM) using InBody® was performed on patients who started CRRT at nine tertiary hospitals in Korea from 2017 Nov to 2019 Nov. The comparison for sequential changes of total body water was performed between the survivor and non-survivor groups using mixed-effects linear regression analysis. Machine learning algorithms were used for the modeling to predict mortality.

Results: Of the 784 patients (mean age: 63.5 years), 521 (66.4%) were male. The mean APACHE II score was 29.2 ± 10.3 in the non-survivor group and 26.5 ± 9.0 in the survivor group. There were no significant differences in the volume status assessed by body weight and BCM at baseline. After adjusting for confounding factors, the survivor group had a marginal benefit from fluid balance in a mixed-effects linear regression (p=0.074). From a range attribute of the decision tree model for predicted mortality, platelet count was found in the first node in the late mortality group (survival duration > 60 days). Patients with survival duration under 60 days showed increased mortality, according to the SOFA score, serum sodium, bilirubin, and target clearance in a decision tree model (AUC=0.957)(Figure 1).

Conclusions: These machine learning approaches showed that conventional parameters for predicting clinical outcomes were interrelated as notable risk factors for mortality augmented by BCM in CRRT patients.

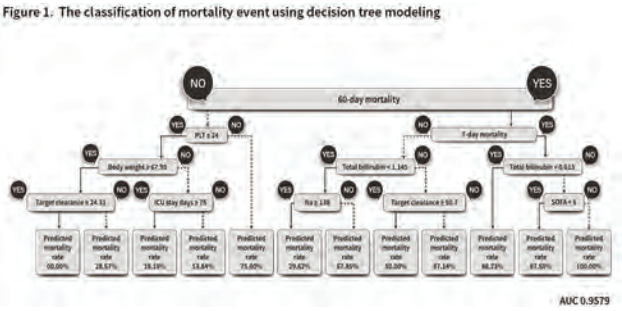

Figure 1. The classification of mortality event using decision tree modeling

PO0252

Optimal Cefepime Dosing Regimens in Obese Critically Ill Patients with AKI Receiving Continuous Renal Replacement Therapy

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Background: Cefepime can be removed by continuous renal replacement therapy (CRRT) due to its pharmacokinetics. Physiologic alterations in obesity and critical illness commonly impact the pharmacokinetics of antibiotics and may result in suboptimal dosing. The information regarding drug dosing in this population is relatively limited. The objective of our study is to determine the appropriate dosing of cefepime in obese critically ill patients receiving continuous renal replacement therapy (CRRT).

Methods: All necessary pharmacokinetic and pharmacodynamic parameters from obese critically ill patients were obtained to develop one-compartment mathematical models with first-order elimination. Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2 according to WHO classification. Cefepime concentration-time profiles were calculated to determine the efficacy based on the probability of target attainment (PTA) of both pharmacodynamics targets of 70% T> MIC and 70% T> 4MIC for Gram-negative infections. A group of 10,000 virtual patients was simulated and tested using Monte Carlo simulations for each dose in the models. The optimal dosing regimens or the "successful dose" were defined as the lowest daily dose that achieved target PTA in at least 90% of the virtual patients.

Results: Our results showed the highest FDA-recommended dosing of cefepime at 2000 mg every 8 hours for patients receiving CRRT with an effluent rate of 25 mL/kg/h cannot achieve at least 90% of PTA for Gram-negative infection due to pseudomonas aeruginosa with an MIC of 8 mg/L. In addition, when a higher effluent rate of 35 mL/kg/h and an aggressive pharmacodynamic targets were applied, the % PTA decreased. The successful dose (3000 mg loading dose on day 1 followed by 2500 mg every 8 hours) was far exceeded the maximal FDA-approved doses.

Conclusions: Using cefepime in obese critically ill AKI patients receiving CRRT with traditional dosing of 2000 mg every 8 hours cannot be recommended as an empiric therapy due to suboptimal efficacy. The MIC target and replacement fluid rate directly impact the pharmacodynamic outcome.

PO0253

Molecular Adsorbent Recirculating System (MARS) Therapy and Outcomes at Mayo Clinic Florida: A Single-Center Experience

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Background: Molecular adsorbent recirculating system (MARS) is an extracorporeal multi-integrative system, combining the processes of continuous veno-venous hemodiafiltration (CVVHDF) and adsorption, that provides rescue support in fulminant hepatic failure. The use of albumin dialysate within the circuit provides effective removal of circulating toxins which accrue from hepatic failure. Our primary aim was to characterize a cohort of patients who received MARS therapy and renal events, given limited data to date.

Methods: Patients initiating MARS in a tertiary care setting from January 2010 through December 2020 were assessed for treatment indications, transplantation, renal replacement therapy (RRT), renal recovery, and death. Data was collected using the REDCAP software.

Results: During the study period, 49 adult patients (67.3% female; 75.0% White; median age 55 years) received MARS therapy during the study period. Indications included hepatic encephalopathy (55.1 %), primary dysfunction of liver transplant (14.3%), bridge to liver transplant (HRS) (12.2%), acute intoxication or overdose (i.e. acetaminophen) (8.2%), and intractable pruritis in cholestasis (2.0%). A majority (73.4%) of patients received 3 or more MARS treatments (median 3; range 1-10). Following MARS, nearly three-fourths (71.4%) of the cohort required Continuous veno-venous hemofiltration (CVVH) due to acute kidney injury. However, 37.1% recovered renal function prior to discharge. 23 (46.9 %) patients died prior to hospital discharge. Twenty (40.8%) patients received liver transplant during hospitalization. Among those who received liver transplant, a majority (75%) required RRT post transplantation.

Conclusions: MARS therapy though most commonly provided for hepatic encephalopathy is associated with high morbidity and acute kidney failure requiring CVVH. About half may recover renal function sufficient to come off renal replacement therapy but mortality rates are high for all MARS patients.

PO0254

The Temporal Relationship Between Ultrafiltration and Mortality in Continuous Renal Replacement Therapy

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Background: In acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), studies suggest that higher ultrafiltration rate (to a point) is associated with reduced mortality, but fluid gain is associated with increased mortality. However, the impact of the timing of net ultrafiltration rate (NUF) on mortality is unknown. Here we evaluated whether the relationship between NUF and mortality is mediated by temporal factors.

Methods: Adults requiring CRRT at the University of Iowa from 2019-2020 were included. Patients were excluded if they survived less than 48 hours on CRRT. Cumulative fluid volume was collected at CRRT initiation and at 24, 48, and 72 hours after initiation. NUF was calculated for each day on therapy by taking the difference in cumulative volume between timepoints and dividing by patient weight. The primary outcome was in-hospital mortality. Covariates were age, gender, BMI, illness severity, CRRT days, volume at CRRT initiation, and comorbidities.

Results: A total of 200 patients met inclusion criteria. Neither NUF from CRRT initiation to 24 hours, nor NUF from 48 to 72 hours, differed significantly between survivors and non-survivors. Strikingly, however, NUF from 24 to 48 hours was strongly statistically associated (**Table 1**), and remained independently associated after adjustments for covariates.

Conclusions: A temporal relationship was observed between NUF and in-hospital mortality in AKI-CRRT patients. NUF from 24-48 hours was a strong predictor of mortality, but outside of this interval no association was observed. Modern fluid resuscitation strategies emphasize the importance of timing and of appropriate de-resuscitation. A similar paradigm may be advisable in CRRT, but further studies are needed.

Table 1. Net ultrafiltration rate by day in survivors and non-survivors

In-hospital Mortality		NUF*: Initiation to 24 Hours	NUF*: 24 to 48 Hours	NUF*: 48 to 72 Hours
Survivors (N=85)	Median, mL/kg/day	5.4	14.2	6.5
	Interquartile Range, mL/kg/day	-10.3 to 17.7	-0.1 to 27.1	-1.0 to 22.8
Non-Survivors (N=115)	Median, mL/kg/day	-0.3	2.4	1.7
	Interquartile Range, mL/kg/day	-20.1 to 14.2	-17.3 to 14.8	-7.4 to 16.7
Total (N=200)	Median, mL/kg/day	1.3	6.6	4.7
	Interquartile Range, mL/kg/day	-13.4 to 16.1	-9.6 to 19.3	-5.6 to 19.6
P-value		.28	.001	.56

* By convention, positive NUF means greater fluid loss, and negative NUF mean an overall fluid gain;

NUF - net ultrafiltration

PO0255

Kinetic Estimated Glomerular Filtration Rate May Be a Useful Tool to Guide Hemodialysis Discontinuation

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Background: There are no objective criteria for the discontinuation of renal replacement therapy (RRT) in patients who have acute kidney injury (AKI). It is unknown if Kinetic Estimated Glomerular Filtration Rate (KeGFR) can be used as assessment of renal recovery in patients who underwent RRT.

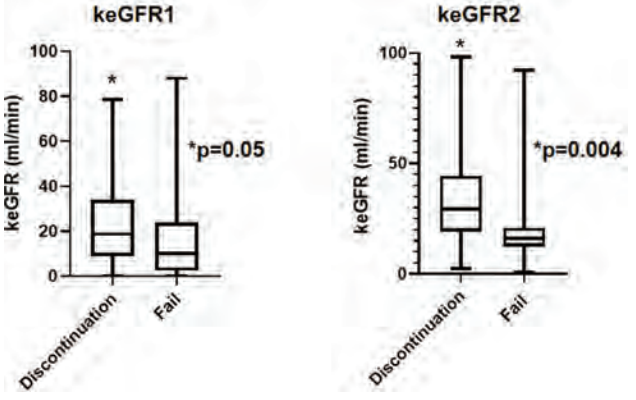
Methods: All critical patients in Hospital das Clínicas during September 2020 to May 2021 who started hemodialysis due to AKI and remained free of RRT for at least 2 consecutive days were included. Patients who stopped RRT due to decision for exclusive palliative care or hemodynamic instability were excluded. Patients were divided in two groups: Success group (free from RRT for 7 consecutive days after their last RRT session) and failure group. Discontinuation day was defined as the second day without RRT. Variables were expressed as median (25th and 75th percentile) and categorical data as percentage. Mann Whitney test was used. Statistical significance was defined as $p<0.05$.

Results: 72 patients were enrolled. COVID19, ischemia-reperfusion and sepsis were the main causes of AKI (37%; 28,7%; 24,6%, respectively), with no difference in prevalence between groups. Success group (n=47) presented higher KeFGR on the day of discontinuation (keGFR1) and in the day after (keGFR2) when compared to failure group (n=25): KeGFR1: Success: 18.76ml/min vs. failure: 10.21ml/min, p=0.05. KeGFR2: Success: 29.38ml/min vs. failure: 16.03ml/min, $p<0.05$. Success group had lower non-

renal SOFA score at discontinuation (4 vs. 6; p<0.05) and higher urine output (1600 vs. 725; p<0.05) when compared to failure group. There was no difference in diuretic use.

Conclusions: KeGFR is higher in patients who succeed in stopping RRT and it may be an useful tool for decision-making. Supported by FAPESP.

Funding: Government Support - Non-U.S.



PO0256

Survival Comparison Between Continuous Venovenous Hemodiafiltration (CVVHDF) and Continuous Venovenous Hemofiltration (CVVH) for Septic AKI

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Background: The mortality rate of septic acute kidney injury (AKI) remains high despite improvements in renal replacement technology. Adding dialysis to continuous veno-venous hemofiltration (CVVH) can increase survival in these patients, although hemofiltration leads to better clearance of inflammatory mediators in sepsis than hemodialysis. We tested whether continuous veno-venous hemodiafiltration (CVVHDF) is more effective than CVVH with the same net effluent according to body weight in intensive care unit (ICU) patients with septic AKI.

Methods: CVVHDF was performed using a Prismaflex (©Baxter International, Deerfield, IL, USA) with a blood flow rate (BFR) of 150 ml/min at a dialysate flow rate 20 ml/kg/hour, in addition to a replacement fluid flow rate of 20 ml/kg/hour. In contrast, the replacement fluid flow rate of CVVH was 40 ml/kg/hour. The patient's removal rate was individually adjusted by attending staff based on clinical status.

Results: In this prospective randomized pilot study, 100 patients were assigned to CVVH (n=47, M:F=25:22, age 64±15 years) or CVVHDF (n=49, M:F=30:19, age 65±11 years). Baseline characteristics including age, sex, body weight, serum creatinine, blood urea nitrogen (BUN), beta-2 microglobulin, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores did not vary between the two groups. There were no significant differences in the reduction ratios of serum creatinine, BUN, beta-2 microglobulin, APACHE II and SOFA scores between the two groups. Seven-, 28-, and 60-day survival also did not vary.

Conclusions: In conclusion, CVVH and CVVHDF led to similar clearance of waste products and survival at the same net effluent in this study. Future large-scale randomized prospective studies will be needed to confirm these results in critically ill patients with septic AKI.

Outcomes by treatment groups

	CVVHDF group	CVVHF group	p-value
Total CRRT days	8.5±8.9	7.4±8.0	0.57
Total ICU days	15.8±18.2	15.8±15.5	0.99
Renal recovery at hospital discharge (%)	31	20	0.29
Survival (%)			
7 days	67	70	0.82
28 days	47	45	1.00
60 days	31	25	0.64

CRRT, continous renal replacement therapy; CVVHDF, continous veno-venous hemodiafiltration; CVVHF, continous veno-venous hemofiltration; ICU, intensive care unit.

PO0257

Systematic Review of the Effects of High-Volume High-Flow (HVHF) in Pediatric Sepsis

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Background: Pediatric sepsis is a significant public health issue. This condition is exacerbated by the presence of excess serum creatinine and inflammatory cytokines that lead to deleterious effects upon the body. The current standard of care involves the use of continuous kidney replacement therapy to remove harmful cytokines until the body returns to homeostasis. In order to promote faster clearance and reduced stay in the ICU, high volume high flow has been posited as a potential new modality of choice. However there is a paucity of studies to fully elucidate its benefits.

Methods: A literature search was done using PubMed/Medline and Embase. Keywords used while conducting the literature search were, "hemofiltration OR haemofiltration OR hemodiafiltration" AND "high-volume". The literature was reviewed by two independent reviewers, who independently assessed the quality of randomized controlled trials by using the Cochrane risk of bias tool for RCTs And Newcastle Ottawa Scale (NOS) for assessing the quality of non-randomized controlled trials. Data was combined from studies with similar design.

Results: The primary endpoint of all cause mortality was found to be reduced by 40% across all of the pooled studies. For secondary endpoints, significant reductions of serum creatinine were found after 24 and 48 hours of use compared to the current standard of care. Additionally, duration of ICU stay and treatment course was found to be significantly shorter in HVHF patients than the current standard of care. Finally the rate of adverse effects were analyzed and there was no difference in the proportion of patients developing hypokalemia, hyperkalemia, hypernatremia or hyponatremia. The proportion of patients developing hyperglycemia was higher in patients undergoing HVHF whereas the proportions of patients developing bleeding was significantly less in patients undergoing HVHF. One study reported a total number of adverse events between the two groups which were significantly lesser in patients undergoing HVHF.

Conclusions: HVHF shows promise as a modality to treat pediatric patients with sepsis. In order to confirm the benefits of this modality, future studies need significantly more patients for analysis.

PO0258

AKI and Hospital-Acquired Sepsis in Critically Ill Children: A Retrospective Single-Center Study

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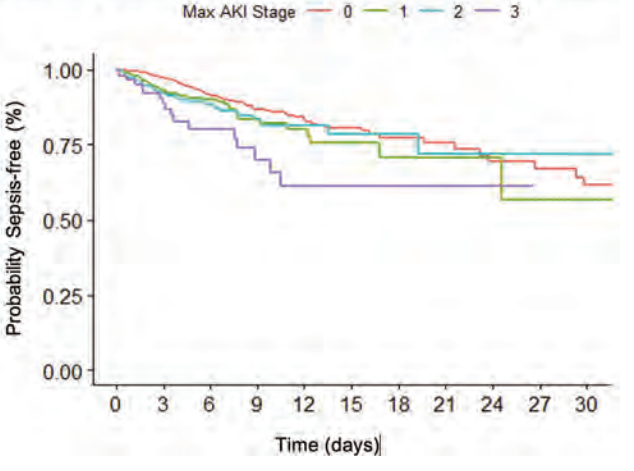
Background: Acute kidney injury (AKI) is common among critically ill children and is associated with an increased risk for de novo infection, however little is known about the temporal relationship between AKI and risk for subsequent infection. The objective of this study was to describe the risk of developing hospital-acquired sepsis over time following AKI onset.

Methods: We conducted a single-center retrospective cohort study of critically ill children admitted to the pediatric and cardiac ICUs at a tertiary pediatric care center in the United States. The cohort included children, ages birth to 18 years, without a diagnosis of chronic kidney disease, primary immunodeficiency, or sepsis within the first 48 hours of hospital admission. The relationship between the primary exposure (AKI) and primary outcome (development of hospital-acquired sepsis) was assessed using Cox proportional-hazards models using AKI as a time-varying covariate.

Results: Among the 5695 children included in the study, hospital-acquired sepsis was more common in the 1153 children that developed AKI (n=117, 10.7%) than in the 4542 children that did not develop AKI (n=210, 4.6%). Over a median follow-up of 3.1 days, the development of AKI was associated with an increased risk for development of hospital-acquired sepsis with an adjusted HR of 1.41 (95% CI 1.11-1.80, p=0.005). The median time from AKI onset to sepsis was 2.6 days (IQR 1.5 – 4.7). Among the 117 children who developed hospital-acquired sepsis following AKI (from 48 hours after hospital admission through hospital discharge or 30 days), 80.3% of children developed sepsis within 7 day and 96.6% within 14 days of AKI onset.

Conclusions: AKI is an independent risk factor for de novo infection. Children with AKI are at highest risk for developing hospital-acquired sepsis within 14 days following AKI onset.

Figure 1. Adjusted probability of hospital-acquired sepsis according to maximum stage of AKI by Kaplan-Meier Analysis.



PO0259

Disseminated Intravascular Coagulation Is Associated with AKI in Pediatric Severe Sepsis

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Background: Exact mechanism of pediatric septic acute kidney injury (AKI) remains unknown. Coagulation pertubations like disseminated intravascular coagulation (DIC) are frequent in sepsis and associated with organ dysfunction. The link between DIC and septic AKI has not been adequately explored in pediatric patients.

Methods: Single center cohort study of pediatric patients with severe sepsis Jan 2017-Apr2018. Primary outcome was AKI (per Kidney Disease Improving Global Outcomes creatinine criteria), primary exposure was DIC (per International Society of Thrombosis and Haemostasis criteria).

Results: 287 patients were enrolled, median age 7.3 (IQR 1.6-14.5) years; 58% had AKI, 34% had DIC. Pediatric risk of mortality score was 8 (IQR 4-13), 57% were mechanically ventilated and 67% were on vasopressors. DIC prevalence was 52% in AKI pts vs 19% in no AKI pts (p<0.001). DIC score was higher in AKI (4.27 (IQR3.85- 4.67) vs 2.25 (IQR1.92- 2.58) in no AKI (p<0.001)). In adjusted analysis controlling for severity of illness, mechanical ventilation, and vasopressor use, DIC presence (aOR 2.6 (95%CI 1.45-4.67)) and DIC score (aOR 1.33 (95% CI 1.17-1.51)) were both independently associated with AKI.

Conclusions: DIC is very common in pediatric septic AKI. Severity and presence of DIC are both independently associated with septic AKI. Mechanistic contribution of coagulation perturbations to septic AKI and identification of potential modifiable factors require further study.

PO0260

Midterm Renal Outcomes and Renal Recovery in Pediatric Continuous Renal Replacement Therapy

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Background: Most pediatric continuous renal replacement therapy(CRRT) outcome studies focus on crude mortality. Recent data highlighted incomplete recovery and dialysis dependency in pediatric acute kidney injury treated with dialysis. We described midterm outcomes and renal recovery in pediatric CRRT.

Methods: Multicenter cohort study between 2/14-2/20. Primary outcome was Major Adverse Kidney Events at 90 days(MAKE90), secondary outcome was renal recovery (noMAKE90 in survivors).

Results: 419 patients received CRRT for 9 days (IQR3-21) (age 93 mo (17-180), 51% male). PELOD2 was 9(7-14), 55% were ventilated, 67% were on vasoactives. 276(66%) patients had MAKE90 (61% dead, 21% dialysis dependent, 18% persistent renal dysfunction). ICU admission reason, peak mean airway pressure, thrombocytopenia, and leukopenia were associated with MAKE90. Urine output at CRRT start was independently associated with renal recovery, each ml/kg/h was associated with 47%(95%CI 12-235%) increased odds of renal recovery.

Conclusions: Majority of pediatric CRRT patients develop MAKE90. Worse lung disease requiring higher respiratory support is independently associated with MAKE90, while admissions for metabolic/endocrine reasons are more likely to survive with intact renal function. Urine output at CRRT start is an independent predictor of renal recovery among pediatric CRRT survivors.

MAKE90 and Renal Recovery In Survivors

MAKE90				
Covariate	Unadjusted OR	95% CI	Adjusted OR*	95% CI
Age	1.00	0.99-1.00	1.01	0.99 -1.01
PELOD-2	0.99	0.97-1.02	0.97	0.82- 1.13
%fluid overload	0.99	0.66-1.49	0.98	0.59- 1.61
Thrombocytopenia (<100k)	2.09	1.33-3.30	2.04	0.73-5.74
Leukopenia(<4k)	2.80	1.37-5.72	1.57	0.45- 5.51
Mean airway pressure, cm H20	1.16	1.06-1.27	1.15	1.04- 1.28
ICU admission reason Metabolic/endocrine	0.22	0.05-0.94	0.10	0.02-0.56
ICU admission reason Renal	5.00	1.45-17.27	1.37	0.18-10.55
Renal recovery among survivors				
Age	0.99	0.99-1.00	1.00	0.99-1.00
PELOD-2	1.03	0.99-1.06	1.02	0.93-1.12
%fluid overload	0.99	0.62-1.57	0.94	0.37-1.57
Vasoactive infusion	0.57	0.31-1.05	0.52	0.27-1.01
Urine ourput (ml/kg/h) at CRRT start	1.47	1.05-2.06	1.62	1.12-2.35
Leukopenia at CRRT start	0.43	0.17-1.07	0.47	0.18-1.27
Thrombocytopenia at CRRT start	0.60	0.36-0.99	0.56	0.27-1.14

*All controlled for each other

PO0261

AKI and Mortality in Patients Prescribed Immune Checkpoint Inhibitor Therapy

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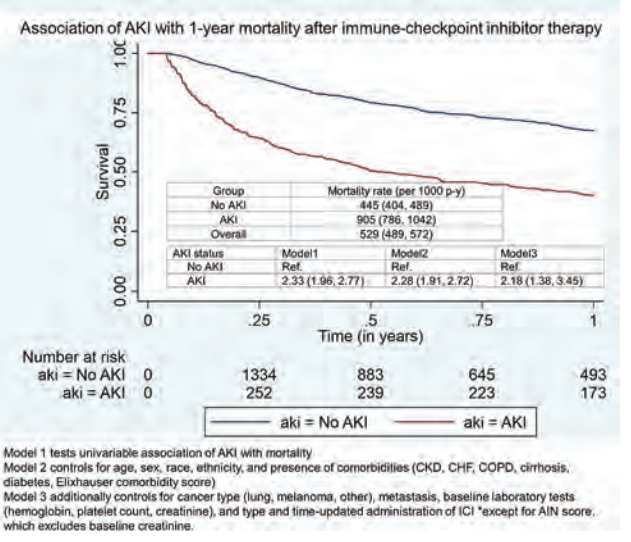
Background: In patients on immune checkpoint inhibitor (ICI) therapy, acute kidney injury (AKI) is relatively common, and can occur from tubular injury or pre-renal azotemia unrelated to ICI use, or from off-target immune activation resulting in acute interstitial nephritis (AIN). The association of AKI and its specific etiologies with mortality is not known.

Methods: In participants initiated on ICI between 2013-2019, we tested the association of serum creatinine-based AKI with mortality up to 1 year after therapy initiation using Cox proportional hazard models controlling for demographics, comorbidities, cancer type, severity, therapy, and baseline laboratory values. In patients with AKI, we tested the association of AKI severity, AKI duration, and, using a validated risk score, AIN risk with mortality.

Results: Of 2,207 patients initiated on ICI therapy, 549 (25%) developed AKI. Mortality rate was higher in those who developed AKI (905 vs. 445 per 1000 person-years). AKI was independently associated with higher mortality [adjusted HR, 2.18 (95% CI, 1.38-3.45)] and this hazard was highest in the first month after AKI [9.7 (7.8-12.1)] and progressively diminished to the background rate by four months. Among patients with AKI, mortality was higher in those with severe AKI [2.03 (1.01-4.11)] and longer duration AKI [2.58 (1.01-6.60)], but lower in those with the highest likelihood of AIN [adjusted HR highest vs. lowest tertile, 0.07 (0.02-0.29)].

Conclusions: We noted that occurrence of AKI was independently associated with higher mortality in patients treated with ICI. Among patients with AKI, mortality was higher in those with severe AKI and longer duration AKI, but lower in those with features suggestive of AIN.

Funding: Other NIH Support - R01DK113191, R01DK128087, P30DK079310, and K23DK117065



PO0262

Sodium-Glucose Cotransporter 2 Inhibitors and the Risk of AKI in Older Adults with Type 2 Diabetes

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Background: We compared the association of AKI with the initiation of a sodium-glucose cotransporter-2 inhibitors (SGLT-2i) to the initiation of a dipeptidyl peptidase 4 inhibitor (DPP-4i) or a glucagon-like peptide 1 receptor agonist (GLP-1RA) in adults aged ≥ 66 years with type 2 diabetes (T2D).

Methods: In this nationwide cohort study, we used Medicare fee-for-service from 2013 to 2017 to identify older adults with T2D. SGLT-2i initiators were 1:1 propensity score (PS)-matched to DPP-4i or GLP-1RA initiators, in two pairwise comparisons. More than 100 variables were used in the PS model, including demographic characteristics, comorbid conditions, medication use, and health care utilization. The primary outcome was a hospital discharge diagnosis of AKI in the primary or secondary position. Cox proportional hazards regression models were used to generate hazard ratios (HRs) in PS-matched groups.

Results: A total of 68,130 and 71,477 SGLT-2i new users were PS-matched to new users of DPP-4i or GLP-1RA (**Table**), respectively. The risk of AKI was lower in the SGLT-2i group than the DPP-4i group (HR 0.71, 95% CI 0.65-0.76) or the GLP-1RA group (HR 0.81, 95% CI 0.75-0.87), over a median follow-up of 181 days.

Conclusions: Among older adults with T2D, initiating an SGLT-2i was associated with a reduced risk of AKI compared to initiation of a DPP-4i or GLP-1RA.

Table. Selected baseline characteristics of SGLT-2i versus DPP-4i and SGLT-2i versus GLP-1RA cohorts after PS-matching

Characteristic	SGLT-2i versus DPP-4i (Cohort 1, n=68,130 pairs)		SGLT-2i versus GLP-1RA (Cohort 2, n=71,477 pairs)	
Age, mean (SD), years	71.9 (5.1)	71.8 (5.2)	71.9 (5.1)	71.9 (5.2)
Male	34,244 (50.3%)	34,157 (50.1%)	33,174 (46.4%)	33,190 (46.4%)
White	56,252 (82.6%)	56,245 (82.6%)	59,366 (83.1%)	59,070 (82.6%)
Acute kidney injury	2,225 (3.3%)	2,225 (3.3%)	2,977 (4.2%)	2,997 (4.3%)
Chronic kidney disease stages 3-5	5,525 (8.1%)	5,498 (8.1%)	8,237 (11.5%)	8,306 (11.6%)
Hypertension	62,857 (92.3%)	62,760 (92.1%)	66,464 (93.0%)	66,512 (93.1%)
Diabetic nephropathy	7,155 (10.5%)	7,046 (10.3%)	9,561 (13.4%)	9,647 (13.5%)
Heart failure	7,481 (11.0%)	7,520 (11.0%)	8,771 (12.3%)	8,788 (12.3%)
Combined comorbidity index (CCI), mean (SD)	1.2 (2.0)	1.2 (2.0)	1.5 (2.1)	1.5 (2.1)
Metformin	53,142 (78.0%)	53,319 (78.3%)	53,957 (75.5%)	53,925 (75.4%)
Insulin	19,153 (28.1%)	18,988 (27.9%)	22,904 (32.0%)	22,818 (31.9%)
GLP-1RA (cohort 1) or DPP-4i (cohort 2)	8,137 (11.9%)	7,595 (11.1%)	26,527 (37.1%)	26,787 (37.5%)
Renin-angiotensin-aldosterone system (RAAS) inhibitors	54,088 (79.4%)	53,823 (79.0%)	57,506 (80.5%)	57,846 (80.9%)
Endocrinologist visit	12,949 (19.0%)	12,520 (18.4%)	15,744 (22.0%)	15,871 (22.2%)
Nephrologist visit	2,955 (4.3%)	2,947 (4.3%)	4,280 (6.0%)	4,341 (6.1%)

Characteristics were measured during the 365 days before treatment initiation, standardized differences < 0.1

PO0263

Urine Sediment Examination: Comparison Between Laboratory-Performed vs. Nephrologist-Performed Microscopy

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Background: Urinalysis is a commonly performed diagnostic test in clinical laboratories and automated urine technology is becoming the standard for providing urinalysis data to clinicians. Time constraints, and use of automated technology has resulted in clinicians no longer performing their own urine sediment exam. We believe that there is a critical value in performing this important unappreciated skill to improve patient care.

Methods: Using our Electronic Medical Records, we identified 140 adult in-patients with acute kidney failure that had urine microscopy with sediment analysis performed both by the laboratory and by a nephrologist within 72 hours of each other. We performed a chart review to determine the following: number of RBCs (≤ 5 or > 5 HPF), number of WBCs (≤ 5 or > 5 HPF), presence of casts (<1 or ≥ 1 LPF), type of casts (hyaline, fine granular, coarse granular, muddy brown, WBC casts, RBC casts and mixed cellular casts), and presence of dysmorphic RBCs. We used Kappa statistics to evaluate agreement between urine microscopy by lab versus by nephrologist reviews.

Results: The reported agreement was moderate for RBCs with 79% of samples in agreement (Kappa 0.54 – 95% CI: 0.39, 0.69), fair for WBCs with 74% of samples in agreement (Kappa 0.39 – 95% CI: 0.23, 0.54), and there was no agreement for casts (Kappa 0). Nephrologist detected 8 dysmorphic RBC's (Kappa 0) while the laboratory did not detect any. Additionally, the laboratory only detected hyaline and fine granular casts, while the nephrologist reported coarse Granular / muddy brown casts, RBC and WBC casts.

Conclusions: Urine sediment exam is an important procedure that provides evaluative information about kidney disease. In our study, we report a disagreement between laboratory vs. nephrologist performed analysis, notably for the recognition of structures that can provide important information in the diagnosis of acute tubular ischemia and glomerulonephritis. This highlights the importance of clinicians continuing to perform sediment exam.

Cast Group – lab review	Cast Group – nephrologist review					
Frequency	No	Hyaline or FG	CG or MBC	RBC	WBC	Total
No casts	22	25	23	0	2	72
Hyaline or FG cast	16	22	23	1	3	65
CG or MB cast	0	0	0	0	0	0
RBC cast	0	0	0	0	0	0
WBC cast	0	0	0	0	0	0
Total	38	47	46	1	5	137
Kappa 0.02 (95%CI:-0.08, 0.11)						

FG: Fine granular; CG: Coarse Granular; MB: Muddy Brown; RBC: Red Blood Cell; WBC: White blood cell

PO0264

Accuracy of Nephrologist Performed Urine Microscopy in Predicting Pathologic Diagnosis in Patients with AKI

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Background: Urinalysis is a commonly performed diagnostic test in clinical laboratories and automated urine technology is becoming the standard for providing urinalysis data to clinicians. Time constraints, and automated technology reporting has resulted in a decline in clinicians performing their own urine sediment exam. We hereby look at the diagnostic accuracy of sediment suggested diagnoses in predicting the respective pathologic diagnoses

Methods: Using our Electronic Medical Records, we identified 33 adult patients with acute kidney injury with documented nephrologist performed urine microscopy and a kidney biopsy within one week of the sediment analysis. We performed chart review to ascertain the suggested diagnosis based on urine sediment analysis and compared it to the respective pathologic diagnoses identified on the subsequent kidney biopsy. We categorized the sediment findings into four categories: Bland, suggestive of acute tubular injury (sATI), suggestive of glomerulonephritis (sGN), and suggestive of acute interstitial nephritis (sAIN). Pathologic findings were categorized into ATI, GN, and AIN.

Results: The cohort demographics consisted of 18 (54.6%) male patients, 23 whites (69.7%), and a mean age of 56.6 years. Sediment analyses was bland in 6 patients (8.45%) with 5 (15.15%) sATI, 22 (66.67%) sGN, and no sAIN cases. All 5 cases with sATI on sediment analysis showed ATI on the kidney biopsy. Similarly, all 22 cases with sGN on the sediment had a pathologic diagnosis consistent with GN on the biopsy. Of the 6 patients with bland sediment analyses, 3 showed ATN pathologically while the other 3 had GN on the kidney biopsy

Conclusions: Urine sediment examination remains an important test than can provide important information about kidney disease. Our data shows 100% agreement between sediment analyses suggestive of ATI or GN and the pathologic diagnoses. This is important in patients in whom a kidney biopsy might be contraindicated precluding the luxury of a pathologic diagnosis. While a suggestive sediment analysis seems to carry a high predictive value, the negative predictive value of a bland sediment was low however. Overall, we believe urine sediment analysis is an important skill for the nephrologist with important patient care implications.

PO0265

Histopathological Confirmation of Acute Tubular Injury in Patients with "Muddy Brown" Granular Casts in the Urinary Sediment

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Background: Microscopic examination of the urinary sediment (MicrExUrSed) can be a useful tool in the differentiation of acute kidney injury etiology. In particular, "muddy brown" granular casts (MBGC) are thought to be pathognomonic for acute tubular injury (ATI). However, the ability of MBGC to predict biopsy-proven ATI has not been formally examined. Thus, we hypothesized that the identification of MBGC by MicrExUrSed can accurately predict a histopathological diagnosis of ATI.

Methods: In a single-center prospective study, we selected cases of patients seen in nephrology consultation who had a urine specimen subjected to MicrExUrSed as part of the clinical evaluation. Within this cohort, we identified cases in which a kidney biopsy was performed within 2 weeks of the MicrExUrSed. Presence of MBGC in those cases was determined. We assessed the performance of identification of MBGC for the diagnosis of biopsy-proven ATI. Sensitivity, specificity, negative predictive values (NPV), and positive predictive values (PPV) of MBGC to diagnose ATI were determined.

Results: Among 371 patients in whom MicrExUrSed was completed, 49 underwent kidney biopsy and were included. Mean age was 61 years, 38% were women. White race accounted for 59% and black race accounted for 33%. Mean serum creatinine was 3.4 mg/dL. Biopsy diagnosis was ATI in 36 (73%) and non-ATI in 13 (27%). Among the 36 cases of biopsy-proven ATI, concomitant glomerular pathology was present in 19 (53%). The sensitivity of MBGC for biopsy-proven ATI diagnosis was 78% (95% CI 61-90%), while the specificity was 100% (95% CI 75-100%). The PPV of MBGC for ATI diagnosis was 100% (95% CI 100%) and the NPV was 62% (95% CI 47-93%).

Conclusions: Our data demonstrate that MBGC on MicrExUrSed are pathognomonic for ATI confirmed by kidney biopsy – with high PPV and specificity of 100%. While MBGC reflect ATI, concomitant glomerular pathology can be present in patients with MBGC in the urine sediment.

PO0266

Feasibility of Point-of-Care Solid Organ Doppler for Assessing Emergency Department Patients with AKI

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Background: Acute kidney injury (AKI) in the emergency department (ED) portends worse in-hospital outcomes for patients. Point-of-care ultrasound (POCUS) can assist with volume assessment, which is critical to diagnose the underlying cause of AKI. We describe clinical and ultrasonographic characteristics of patients with AKI using a

POCUS protocol that examines hepatic, portal and interlobar renal vein spectral Doppler assessment previously described as the Venous Excess Ultrasound (VExUS) protocol which was found to predict AKI after cardiac surgery.

Methods: This is a prospective convenience sample of adult patients presenting to an academic, urban emergency department found to have AKI from September 2020 to May 2021. US images were obtained and interpreted by an US fellowship trained emergency medicine physician under the guidance of a certified vascular US technician. Spectral Doppler assessment of hepatic, portal, and interlobar renal veins were obtained. Hepatic vein dopplers were considered abnormal if the D wave was greater than the S wave. Portal vein Dopplers were considered abnormal if the pulsatility index was greater than 30%. Interlobar renal vein dopplers were considered abnormal if there was phasisity. The diagnosis of AKI was established by Kidney Disease Improving Global Outcomes criteria. The institutional review board approved this study.

Results: Thirty-seven patients were included. Median age was 63 and average BMI 29. 15 experienced stage 1 AKI, 5 had stage 2 AKI, 17 had stage 3 AKI. 7 required dialysis. 36 had an assessment of their inferior vena cava (IVC). 15 had an IVC >15mm with less than 50% respiratory collapse. Of the 15 patients with plethoric IVC assessments, 11 had interpretable hepatic vein Dopplers, 4 were abnormal. 14 had interpretable portal vein Dopplers, 6 were abnormal. 13 had interpretable interlobar renal vein Dopplers, 4 were abnormal. The most common reasons for uninterpretable Dopplers were difficulty holding expiration, arrhythmias and liver cirrhosis or masses.

Conclusions: Our study describes the feasibility of a POCUS assessment using solid organ spectral Doppler for emergency department patients with AKI. Further research is required to understand the test characteristics solid organ spectral Doppler for assessment of this population.

PO0267

Utility of a Point-of-Care Ultrasound Volume Assessment for Emergency Department Patients with AKI: A Pilot Study

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Background: Acute kidney injury (AKI) identified in the emergency department (ED) portends worse in-hospital outcomes for patients. Point-of-care ultrasound (POCUS) for AKI is recommended to rule out obstructive uropathy but does not routinely include volume assessment, which may be informative regarding the underlying cause of AKI. POCUS evaluation of heart and lungs has proven to be useful in assessing intravascular volume status in patients on dialysis and with heart failure. This study aims to describe the clinical and ultrasonographic characteristics of patients with AKI using a POCUS volume assessment.

Methods: This is a prospective convenience sample of adult patients presenting to an academic, urban ED found to have AKI from September 2020 to May 2021. Ultrasounds were performed using 8-point lung, 5-point cardiac, kidney and bladder views. The diagnosis of AKI was established by Kidney Disease Improving Global Outcomes criteria. US images were obtained and interpreted by an US fellowship trained emergency medicine physician. The institutional review board approved this study.

Results: Thirty-seven patients were included. 22 were African American and 20 were male. Median age was 63 and average BMI was 29. Eight had documented CKD, 15 had diabetes, 24 had hypertension and 13 had heart failure. Prior to ultrasound assessment, 24 patients were assessed as hypovolemic, 4 as euvolemic, and 9 as hypervolemic by their emergency physician. Fifteen experienced stage 1 AKI, 5 had stage 2 AKI, and 17 had stage 3 AKI. Seven required dialysis during their admission. Two were found to have a bladder outlet obstruction and 4 were found to have bilateral, moderate to severe hydronephrosis. Thirty-seven had a left ventricular ejection fraction (EF) assessment, 21 had an EF >55%, 10 had an EF 30-55%% and 6 had an EF <30%. Four had right ventricular dilation. Thirteen had bilateral pulmonary B-lines suggestive of pulmonary edema. Thirty-six had an assessment of their inferior vena cava (IVC) and 15 had an IVC >15mm with less than 50% respiratory collapse.

Conclusions: Our study describes the findings of a POCUS volume assessment of ED patients with AKI. Abnormal cardiac and lung findings were common and may be a useful adjunct to IVC, kidney and bladder assessment alone.

PO0268

Addition of High-Dose Furosemide to Norepinephrine During Treatment of Hepatorenal Syndrome Type 1 Augments Diuresis and Does Not Halt Kidney Function Recovery

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Background: Withdrawal of diuretics is recommended as a first intervention in patients with cirrhosis who present with acute kidney injury (AKI) to eliminate prerenal factors. Moreover, diuretics are considered potential trigger for hepatorenal syndrome type 1 (HRS-1). As a result, diuretics are rarely utilized once the diagnosis of HRS-1 is made due to concerns for aggravating the clinical course. We hypothesized that after a prerenal state is ruled out and HRS-1 is diagnosed and properly treated with a vasoconstrictor, i.e., the mean arterial pressure (MAP) is effectively raised, use of diuretics is safe and effective

Methods: We search records of patients hospitalized at Ochsner Medical Center over a 3 year period who received intravenous (IV) furosemide (FURO) while receiving IV norepinephrine (NE) as a vasoconstrictor specifically for treatment of AKI due to HRS-1. We assessed the change in urine output (UOP) and the trajectory of serum creatinine (sCr) values before and after the initiation of NE and before and after the addition of FURO.

Results: A total of 19 patients with HRS-1 received IV FURO [median duration: 2 (1-8) days); median dose: 160 (80-240) mg boluses q6-24 h)] added to IV NE during the study period. Median age was 52 (31-69) years; 89% white race, 53% women, median MELD score 32 (22-41). At the time of initiation of FURO, median sCr was 3.8 (1.7-7.9) mg/dL. Before initiation of any therapy, the median UOP was 275 (10-695) ml/day. NE alone led to a median increase in UOP to 530 (200-2150) ml/day (p=0.013). Addition of FURO to NE induced a subsequent increase in median UOP to 2045 ml/day (p<0.0001), i.e., median gain in UOP of 1605 ml/day. Fifteen (79%) patients treated with NE+FURO [w/median MAP rise 15 (11-24) mmHg] either maintained or improved the sCr trajectory consistent with kidney recovery and not needing dialysis. The magnitude of NE-induced rise in MAP significantly correlated with the average UOP achieved during the days of combined NE+FURO therapy (R=0.48, p=0.03).

Conclusions: In patients with HRS-1 who are adequately treated with NE and achieved an optimal MAP increment, addition of high-dose IV FURO enhances diuresis without negatively affecting recovery of kidney function.

PO0269

Responsiveness to Vasoconstrictor Therapy in Hepatorenal Syndrome Type 1

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Background: We previously reported that raising mean arterial pressure (MAP) during treatment of hepatorenal syndrome type 1 (HRS-1) with vasoconstrictors (VC) is associated with improvement in kidney function. However, the optimal MAP target and factors associated with response to VC remain unclear.

Methods: Records from hospitalized patients with HRS-1 treated with VC without shock were reviewed. We selected those who achieved ≥ 5 mmHg rise in MAP within 48 hours. We examined the relationship between the mean MAP achieved during the 1st 72 hours of VC therapy and the change in kidney function at 7-14 days as determined by serum creatinine (sCr). The primary (1ry) endpoint was > 30% reduction in sCr without need for dialysis or death at day 14. Secondary (2ry) endpoint was change in slope of sCr from positive (worsening) to negative (improving) by day 7.

Results: A total of 74 patients with HRS-1 treated for 2-7 days with either midodrine/octreotide (n=28) or norepinephrine (n=46) were included. Median age was 53 (IQR 46-60), 41% were female and 47% had alcoholic cirrhosis. At start of VC, median MAP was 70 mmHg (IQR 66-73) and median sCr was 3.8 mg/dL (IQR 2.6-4.9). When analyzed based on tertiles of mean MAP increment (5-9, 10-14, ≥ 15 mmHg), there was a significant trend for greater reduction in sCr with greater rise in MAP (ANOVA, p<0.0001). When analyzed based on tertiles of achieved absolute MAP (65-74, 75-84, ≥ 85 mmHg), there was a non-significant trend for greater reduction in sCr with higher absolute MAP (p=0.06). The 1ry and 2ry endpoints were met by 25 (34%) and 42 (57%) patients, respectively. By multivariate logistic regression analysis, mean MAP rise in 1st 72 hrs had an OR 1.18 (95% CI 1.04-1.34; p=0.012) for meeting the 1ry endpoint and an OR 1.22 (95% CI 1.07-1.40; p=0.003) for the 2ry endpoint. Neither age, sex, MELD score, baseline sCr nor baseline MAP were predictive of any endpoint.

Conclusions: Greater magnitude of rise in MAP with VC therapy in HRS-1 is associated with greater improvement in kidney function. Targeting an increment of MAP ≥ 15 mmHg may lead to favorable kidney-related outcomes. No other demographic or clinical variables predicts response to VC therapy, highlighting the need for biomarker development.

PO0270

Rates of In-Hospital Decongestion and Association with Cardiovascular Outcomes Among Patients Admitted for Acute Heart Failure

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Background: Decongestion is an important goal in the management of acute heart failure (HF) among patients with heart failure with reduced ejection fraction (HFrEF), but whether the rate of decongestion is associated with cardiovascular (CVD) outcomes is unknown.

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, we used multivariable Cox regression models to evaluate the association between the rate of in-hospital change in assessments of volume overload, including b-type natriuretic peptide (BNP), N-terminal prob-type natriuretic peptide (NT-proBNP) and clinical congestion score (0-12), as well as change in hemoconcentration including measures of hematocrit, albumin and total protein with risk of the trial's primary endpoint of a composite outcome of CVD mortality or HF hospitalization.

Results: Among 3500 patients with median 10 month follow-up, 1369 (39%) experienced the composite outcome of CVD mortality or HF hospitalization. There were no differences in baseline kidney function between those in the quartile of most rapid decongestion compared to least rapid (mean eGFR 59±23 vs 57±23 ml/min/1.73m^2, respectively). Overall, despite in-hospital eGFR decline with decongestion (-0.2 ml/min/1.73m^2 per day), faster decongestion was associated with decreased risk of both CVD mortality and HF hospitalization (Table).

Conclusions: Among patients with HFrEF admitted for HF, achievement of faster rates of decongestion is associated with reduced risk of CVD mortality and HF hospitalization. Whether this suggests that either more rapid decongestion provides cardiovascular benefit, or whether the ability to rapidly decongest is a proxy for a healthier individual, remains to be further evaluated.

		Quartile 1. Least rapid decongestion	Quartile 2	Quartile 3	Quartile 4. Most rapid decongestion
Volume Overload	BNP	1.00 (1.00, 1.00)	0.69 (0.57, 0.83)	0.62 (0.51, 0.75)	0.46 (0.37, 0.58)
	NT-proBNP	1.00 (1.00, 1.00)	0.98 (0.79, 1.21)	0.78 (0.62, 0.98)	0.52 (0.40, 0.68)
	Congestion Score	1.00 (1.00, 1.00)	0.92 (0.79, 1.08)	0.88 (0.75, 1.04)	0.91 (0.77, 1.09)
Hemoconcentration	Hematocrit	1.00 (1.00, 1.00)	0.90 (0.77, 1.06)	0.82 (0.70, 0.97)	0.71 (0.60, 0.84)
	Albumin	1.00 (1.00, 1.00)	0.96 (0.83, 1.13)	0.82 (0.70, 0.97)	0.75 (0.63, 0.88)
	Total Protein	1.00 (1.00, 1.00)	0.90 (0.77, 1.05)	0.88 (0.74, 1.03)	0.71 (0.59, 0.84)

*Adjusted for: age, sex, race, randomization group (tolvaptan vs placebo), body mass index, medication use (angiotensin converting enzyme inhibitor or angiotensin II receptor blocker, mineralocorticoid receptor antagonist), ejection fraction, New York Heart Association functional class, systolic blood pressure, eGFR at discharge and respective baseline biomarker level

Abbreviations: BNP, b-type natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide; HF, heart failure

PO0271

Effect of Intensive vs. Standard Blood Pressure Targets on AKI and Subsequent Cardiovascular Outcomes and Mortality

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Background: Using linked electronic health record (EHR) data, this study evaluated the effect of intensive vs. standard blood pressure (BP) treatment in SPRINT on acute kidney injury (AKI) and whether incident AKI was associated with cardiovascular disease (CVD) and mortality.

Methods: Inpatient AKI was defined by a) serious adverse event (SAE) reports based on diagnosis codes and admission and discharge notes and b) a 50% or ≥0.3mg/dl increase in creatinine using EHR labs. Outpatient AKI was defined by a 50% increase in creatinine using EHR labs, compared to the most recent creatinine measured in trial follow-up. Cox regression was used to evaluate the effect of intensive BP lowering on the incidence of AKI, and to examine the time-varying association between incident AKI and CVD and mortality.

Results: 3321 participants (1690 intensive vs 1631 standard) had linked EHR data. The mean age was 69 years, 23% were female, and 29% were black. More inpatient AKI events were identified using EHR labs (162 intensive vs 137 standard) as compared to SAE reporting in the trial (87 intensive vs 56 standard). Outpatient AKI similarly occurred more frequently with the inclusion of EHR labs (216 intensive vs 156 standard). Intensive treatment was associated with an increased risk for inpatient AKI based on SAE reports (HR 1.48, p=0.02) and for outpatient AKI (HR 1.36, P=0.004), but not for inpatient AKI based on EHR labs (HR 1.16, P=0.21). Irrespective of the definition, the incidence of AKI was associated with increased risk for all-cause mortality in adjusted analyses, but not with incident CVD. Despite this increased risk, intensive treatment reduced the risk of all-cause mortality (HR 0.57, P<0.001) in this subset of SPRINT participants.

Conclusions: Lab based ascertainment of AKI, facilitated by the EHR, may be more sensitive and less biased than traditional SAE reporting, particularly for open-label trials and for capturing more frequent outpatient AKI events. Given that inpatient and outpatient AKI were associated with increased risk for all-cause mortality, identifying ways to prevent AKI may reduce mortality even further with intensive BP lowering.

PO0272

Fostering Scientific Innovation to Impact AKI: A Roadmap from the AKI!Now Basic Science Workgroup

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Background: The American Society of Nephrology convened a new initiative in 2020, *AKI!Now*, to promote excellence in the prevention and treatment of acute kidney injury (AKI). *AKI!Now*'s interests are broad, spanning molecular and cell biology research through provider education and patient advocacy. Here we describe current efforts of *AKI!Now*'s Basic Science Workgroup to foster innovation in the prevention, diagnosis, and treatment of AKI by leveraging fundamental discoveries. Both in hospitals and the community, the incidence of AKI is high and increasing worldwide. For the individual patient, severe AKI is a life-altering event with profound future consequences. At the societal level, AKI is increasingly recognized as a major public health burden.

Methods: We propose the following goals to promote collaborative and inclusive discovery research that could translate more effectively to our patients:

Results: (1) to develop a centralized portal that provides a living resource for the research community and access to open data sources; (2) to lower entry barriers for researchers interested in AKI by developing interactive educational content; (3) to promote greater collaboration between AKI basic researchers, translational investigators, and researchers in other fields; (4) to articulate a preclinical roadmap that facilitates the development of novel interventions; and (5) to enhance communication around AKI innovation by fostering an open and vibrant community of patients, researchers, clinicians, and other stakeholders.

Conclusions: State-of-the-art medical care of AKI patients remains reactive and supportive. No targeted treatment has yet been identified to prevent this syndrome or hasten the recovery to health. Lowering barriers for new entrants and increasing opportunities for collaborations across a wide spectrum of stakeholders may help promote a culture of innovation to impact AKI.

PO0273

Telenephrology (TN) vs. Face-to-Face (F2F) Visits: A Comparison of Inpatient Nephrology Outcomes and Provider Perspectives

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Background: Clinical outcomes, patient, and provider perspectives on inpatient synchronous telenephrology care remain largely unstudied. In this retrospective study, we compared outcomes in patients who received inpatient synchronous TN plus F2F (cases) versus only F2F (controls) at two Mayo Clinic Health System (MCHS) community hospitals

Methods: Hospitalized adults who had nephrology consults from 3/1/2020 to 2/28/2021 were classified in several diagnoses groups. Logistic regression was used to assess 30-day mortality, readmissions, and hospital transfers. Penalized regression was used in the case of rare events. Negative binomial regression was fit to account for overdispersion in length of hospital stay data. Unadjusted and Adjusted odds ratio with 95% confidence intervals were calculated. We used structured surveys to evaluate the perspectives of non-nephrology hospital providers and tele-nephrologists

Results: A total of 850 patients were included. Mean age was 69 years, 59% were male and 93% white. Cases were more likely to get dialysis after a TN consult; OR: 1.80 (1.00, 3.22). Other outcomes were not statistically different (Table 1). Both non-nephrology hospital providers and tele-nephrologists reported the most frequent reasons for consults were AKI, ESRD, electrolytes, or acidosis. Tele-nephrologists preferred video consults (82%) to phone for communication. More than half (64%) of tele-nephrologists spent less time on TN compared to F2F consults. Non-nephrology hospital providers were very satisfied 10 (48%) and satisfied 6 (29%) with TN response time, and most felt TN was as safe as F2F (67%) and provided them enough information to make patient care decisions (76%)

Conclusions: Outcomes for in-hospital nephrology consults were similar between telenephrology plus face-to-face and face-to-face. Non-nephrology hospital providers and tele-nephrologists had favorable opinions for TN and most thought it is as safe as F2F consults

Table 1: Hospitalized Patient outcomes comparing TN plus F2F versus F2F consults

Outcome	Unadjusted Odds ratio (95% Confidence Interval)	p-value	Adjusted Odds ratio (95% Confidence Interval)*	p-value
Hospital transfer	1.13 (0.36, 3.54)	0.83	1.19 (0.37, 3.82)	0.77
Length of stay	0.94 (0.83, 1.05)	0.27	0.94 (0.84, 1.06)	0.34
30-day Readmission	0.86 (0.53, 1.39)	0.53	0.97 (0.61, 1.52)	0.88
Death within 30 days	0.94 (0.62, 1.42)	0.76	0.90 (0.58, 1.40)	0.63
Dialysis	1.24 (0.88, 1.74)	0.23	1.24 (0.79, 1.94)	0.36

*adjusted for age, Elixhauser, gender, race, diagnosis

PO0274

Renal Cytosolic Phospholipase A2 Mediates AKI in Humans

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Background: Increasing evidence suggests that cytosolic phospholipase A2 (cPLA2) and prostaglandin E2 (PGE2) drive the progression of various forms of kidney disease. Whether renal cPLA2-dependent PGE2 production significantly contributes to the progression of acute kidney injury (AKI) in humans is currently unknown. We compared the lipidomic and metabolomic profile of kidneys from deceased transplant organ donors with or without AKI and used molecular and tissue culture techniques to investigate the role of cPLA2-PGE2 pathway in AKI.

Methods: Kidneys with or without AKI were collected from deceased human transplant organ donors (non AKI: 10 kidneys from 7 donors and AKI: 12 kidneys from 8 donors). We used LC-MS and mass-spectrometry imaging (MSI) to investigate the abundance of relevant metabolites, RT-PCR and Western blotting were used to examine the levels of lipid enzymes and PGE2 levels were investigated by ELISA. To determine whether cPLA2-PGE2 pathway mediates AKI, we stimulated RPTEC and human kidney organ culture using interleukin-1β (IL-1β) and cPLA2 inhibitor and investigated changes in kidney injury markers.

Results: To validate this human model of AKI, kidney injury (KIM-1 and NGAL) and inflammatory (IL-1β and IL-6) markers were significantly higher in kidneys collected from donors with AKI compared to kidneys collected from donors without AKI. Lipidomics showed significantly lower levels of phosphatidylcholine (PC) species (PC 29:1, 31:1, 32:4 and 35:5) and MSI showed significantly higher abundance of arachidonic acid and prostaglandins in kidneys from donors with AKI. Kidneys from donors with AKI demonstrated significant upregulation of cPLA2 mRNA and protein, and higher levels of PGE2, compared to kidneys without AKI. cPLA2 inhibitor significantly reduced PGE2 and kidney injury markers in IL-1β-stimulated RPTEC and human kidney organ culture model.

Conclusions: Lipidomics, MSI and molecular data identify changes in the PC-cPLA2-PGE2 pathway in human kidneys obtained from AKI donors. The inhibition of cPLA2 ameliorates kidney injury *in vitro* suggesting that this enzyme is a key driver of AKI in humans.

Funding: Commercial Support - Astrazeneca UK Ltd, Private Foundation Support

PO0275

Quantitative Proteomics Analysis Identifies Novel Markers of AKI, CKD, and AKI-to-CKD transition in Human Kidneys

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Background: The etiology of AKI is multifactorial and is associated with in-hospital mortality and progression to CKD. Molecular phenotypes that are shared across AKI, CKD and the transition are unclear but may characterize common injury mechanisms that can be targeted for kidney preservation. We hypothesize that molecular interrogation of the kidney tubulointersitium (TI) will identify proteomic signatures that reflect AKI, AKI to CKD transition and CKD progression.

Methods: Frozen kidney biopsies from 4 CKD and 3 AKI patients obtained from recruitment sites in the Kidney Precision Medicine Project were used for this study and compared to nephrectomy controls (n=4). TI was isolated using laser microdisseciton and recovered proteins were submitted for HPLC MS/MS proteomic analysis using Orbitrap eclipse mass spectrometer. Label-free quantification and global normalization of spectral count data was performed to determine changes in protein expression.

Results: Protein signatures demonstrating cell proliferation and migration (MAP1B, PPFIBP1, RASAL1, NT5C2, PITPNM1, S100A4, XRN1, MNDA, SRM, MAMDC2) and extracellular matrix regulatory proteins (VCAN, POSTN, TNC, PXDN, ITGB6, THBS2, FBLN5, COLGALT1) were upregulated in AKI while cell-cell adhesion and extracellular matrix expansion (COL7A1, POSTN, FBLN5, ELN, VCAN, FERMT3, A1BG, MRC1, CP, STAB1, TIMP3, ITIH3, MFAP4, TNC), cell proliferation (MAP1B, PTPRC, NIBAN1, FUBP1, S100A, PPFIBP1, ARHGDIB) and inflammation markers (C2, SAMHD1, IL16, C7) were upregulated in CKD compared to controls. Overall, 57% and 28% of up- and downregulated proteins in AKI, were shared in CKD and may reflect AKI to CKD transition.

Conclusions: Proteomic analysis of the TI identified known and novel markers specific to AKI and CKD. Additionally, activation of common inflammatory and extracellular matrix remodeling proteins in AKI and CKD settings suggests that unified pathways activated in the TI could underlie AKI to CKD progression. The causal role of these candidate markers in the pathogenesis of AKI and CKD needs to be better defined, but if validated, targeting these pathways could help arrest tissue injury and limit disease progression. This work is ongoing.

Funding: NIDDK Support

PO0276

Leishmania infantum-Induced Acute on Chronic Interstitial Nephritis

George Vasquez-Rios,[1] Luis F. Sanchez Russo,[1] Sergio Dellepiane,[1] Fadi E. Salem,[2] Lili Chan,[1] Tonia K. Kim.[1] *[1]Icahn School of Medicine at Mount Sinai Department of Medicine, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Leishmania is an exceedingly rare yet important cause of acute and chronic interstitial nephritis (CIN) that can lead to severe renal dysfunction, necessitating dialysis if unaddressed.

Case Description: A 53-year-old man presented with a progressive rash, cyclic fevers, 20 kg weight loss over 1 year, and prominent hepato-splenomegaly. He resided in Russia and had traveled to South Asia and Africa multiple times. Due to compressive symptoms and pancytopenia, the patient underwent splenectomy and lymph node biopsy which yielded *Leishmania infantum* (Figure 1A). In our institution, he was oliguric and hypertensive. Labs showed Na 129, K 5.3, HCO_3 8.8, BUN 144, Cr 12.6 mg/dL (baseline Cr 0.8 last year), and elevated LFTs. UA showed ATN casts. 24-hour urine protein was 1.8 grams. SPEP/UPEP and K/L ratio were normal. Due to concerns for AIN, CIN, infectious GN vs. amyloidosis, a kidney biopsy was pursued after HD initiation. Biopsy revealed chronic active tubulointerstitial nephritis associated with marked interstitial plasma cell infiltrates and moderate fibrosis without evidence of glomerular disease (Figure 1B). Amphotericin B was started. Steroids were not initiated given moderate fibrosis and risk for blunting response against Leishmania. His rash and LFTs improved rapidly yet, he required HD 3 times a week at discharge. 9 weeks after amphotericin initiation, his HD requirement is now reduced to twice weekly and pre-HD creatinine levels continue to decrease.

Discussion: Leishmaniasis is a rare cause of kidney injury in the US. CIN is the most common underlying pathology in these patients. A high index of suspicion in the appropriate clinical context is necessary to institute timely interventions to prevent long-term sequelae. Patients with visceral leishmania and kidney dysfunction should be evaluated for interstitial nephritis as a potential cause when alternative etiologies have been ruled out.

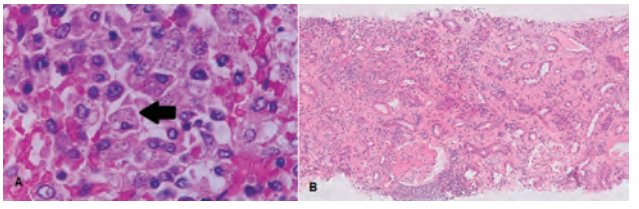

Figure 1: A. Lymph node with Leishmania amastigotes seen as a cytoplasmic organisms in macrophages (arrow) **B.** Kidney biopsy shows diffuse active interstitial inflammation with a background of interstitial fibrosis and frequent tubular injury (H&E).

PO0277

Too Much of a Good Thing: A Case Report of Suspected Acute Tubular Necrosis Potentiated by Hypervitaminosis D

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Introduction: While Vitamin D deficiency is prevalent in the United States, vitamin D toxicity remains a rare pathology. More novel is the incidence of acute kidney injury facilitated by calcitriol toxicity, with a Pubmed search yielding less than twenty results, a majority of which come from foregin journals. Tubular injury propagated by calcitriol has been demonstrated both in vivo, and from biopsies in even fewer case reports.

Case Description: A middle age man presented to the ED after routine labs demonstrated an acute kidney injury approximately four times his baseline creatinine, with mildly elevated hypercalcemia. Creatinine was within normal limits 1 year prior. Workup for his hypercalcemia revealed a markedly elevated 25 vitamin D >480, exceeding the quantifiable limit of the lab equipment. The patient reported a two week history of vitamin D supplementation of approximately 210,000 IU daily. Even with stabilization of his hypercalcemia, fluid resuscitation, and cessation of his supplements, the patient did not recover his baseline kidney function at discharge, nor at follow-up three months later. The patient had no medical history predisposing him to chronic kidney disease, with labs non-contributory for any other nephritic or nephrotic process, but suggesting an intrinsic, tubular pathology. With other etiologies essentially ruled out, in the setting of recent consumption of massive amounts of Vitamin D, the diagnosis of ATN secondary to hypervitaminosis D was suspected.

Discussion: Hypercalcemic AKI, at calcium levels as high as 19.9 mg/dL, typically resolves with treatment within 1-2 weeks; this patient failed to resolve, suggesting an additional insult. In calcitriol-induced AKI, toxicity of excess free Vitamin D metabolites exceeds the capacity of neutralizing vitamin D binding proteins. In vitro, calcitriol potentiates ATP depletion, and cytotoxicity of renal tubular cells even in the absence of hypercalcemia. In vivo, excess calcitriol exacerbates cellular azotemia by 2-3 times even with only modest hypercalcemia. Similar case reports describe biopsy evidence of tubular injury caused by vitamin D toxicity, with recovery of baseline creatinine taking between 3 months to 2 years. As incidence of vitamin intoxication increases, vigilance toward the harms of these supplements are important to recognize in healthy patients presenting with AKI.

PO0278

An Unusual Case of Tubulointerstitial Nephritis with Uveitis (TINU) Syndrome Associated with Alendronic Acid

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Introduction: Tubulointerstitial nephritis and uveitis (TINU) syndrome is rare; while no etiology is identified, in 50% in the remaining it is typically seen with autoimmune or infectious diseases, and medications (nonsteroidal antiinflammatory drugs (NSAIDs)). Bisphosphonate nephropathy has been described causing renal lesions such as collapsing focal segmental glomerulosclerosis, acute tubular necrosis, or very rarely tubulointerstitial nephritis. To the contrary, bisphosphonates are known to cause a variety of ocular side

effects, including uveitis. To our knowledge, TINU syndrome has not been reported with bisphosphonate use.

Case Description: 77 year-old female with a history of hypertension on lisinopril, osteoporosis on alendronic acid for 2 years, baseline creatinine of 0.7 mg/dl, was admitted for worsening renal function. On labs obtained 3 weeks prior to presentation, her creatinine was 1.46 mg/dl. Around that time, she was being treated for an "iritis" episode. Despite holding her lisinopril and alendronate, her creatinine was found to be 3.53 mg/dl 1 day prior to admission. Patient was stable and her exam was unremarkable. Review of system was positive for frothy urine. She denied NSAIDs or antibiotics use. Labs revealed a non-anion gap acidosis and a creatinine of 3.2 mg/dl. Urinalysis showed sterile pyuria and microscopic hematuria; urine protein-creatinine ratio was 1.97. Renal ultrasound was unremarkable. Her autoimmune, infectious, and monoclonal gammopathy workups were negative. A renal biopsy revealed a lymphocytic predominant severe interstitial nephritis with focally destructive tubulitis and edema. During her admission, she developed recurrence of her ocular involvement and was diagnosed with anterior uveitis by ophthalmology. As a result, a diagnosis of TINU syndrome secondary to alendronic acid use was made. Patient was started on 1 mg/kg of daily prednisone and discharged after 5 days of hospitalization. Her creatinine was 1.82 mg/dl 1 week later, and 0.98 mg/dl 3 weeks later.

Discussion: Association of Bisphosphonates use and TINU syndrome has not been reported. Prompt recognition of this rare complication and drug discontinuation are crucial to the management. In our patient, since discontinuation of medication did not improve her renal function, we treated her with steroids, with excellent response.

PO0279

AKI Associated with Hydrophilic Polymer Embolism: A Case Report

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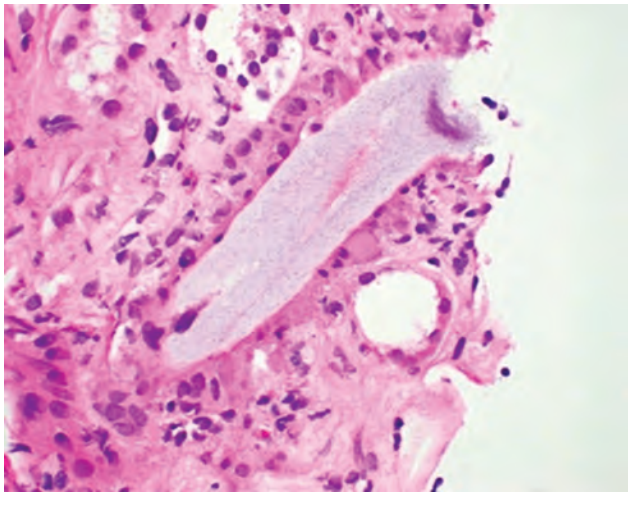
Introduction: Minimally invasive endovascular procedures have become increasingly popular. Technology has improved, allowing the use of hydrophilic polymers to coat surgical tools such as catheters, guidewires, and sheaths to reduce vasospasm and trauma to vessels. However, a complication of using hydrophilic polymers is embolization of the material to distal small arteries, causing ischemia of organs such as the lung, brain and kidneys. Although hydrophilic polymer embolization has recently increased in recognition, only a few cases of renal embolization have been reported.

Case Description: Here we present the case of a 73-year-old male with history of peripheral artery disease and no previous diagnosis of kidney disease who was admitted to the hospital due to acute oliguric acute kidney injury (AKI), four weeks after undergoing an endovascular aneurysm repair with aorto-uni-iliac stent, right femoral endarterectomy and right femoral-popliteal bypass. Laboratory work-up such as complement levels, viral and antibody serologic testing were unremarkable. His hospital course was complicated by anuria, hyperkalemia and hyperphosphatemia. Kidney biopsy (figure 1) showed a foreign material consistent with a hydrophilic polymer embolism, as well as histiocytes with similar ingested foreign material, along with atheromatous emboli, and mild to moderate interstitial fibrosis. Treatment was supportive, including renal replacement therapy (RRT), with improvement in kidney function to the point of having adequate urinary output, no electrolyte derangements and no further need for RRT at discharge.

Discussion: In this case report, we compare our findings to other reported cases of hydrophilic polymer emboli to increase awareness of this under-recognized cause of organ dysfunction.



H&E stain showing arteriole occluded by hydrophilic polymer emboli.

PO0280

A Nutty Case of Oxalate Nephropathy

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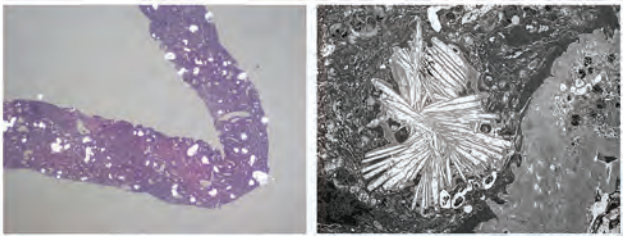
Introduction: Oxalate nephropathy occurs when considerable amounts of calcium oxalate crystals deposit in the renal parenchyma. Excessive dietary intake of oxalate-rich foods (including some associated with healthy eating) in otherwise healthy individuals can lead to secondary oxalate nephropathy. We report a case of severe AKI related to excessive nut consumption.

Case Description: A 41-year-old man with history of Hashimoto's disease and pancytopenia presented to the hospital with 1 week of nausea and vomiting. Evaluation showed AKI with elevated serum creatinine (19.9 mg/dL), BUN (229 mg/dL), hematuria, and proteinuria (urine protein/creatinine ratio 1.6 gm/gm). Serologic workup showed mildly elevated kappa/lambda ratio (3.52) and low C3 (71mg/dL) but was otherwise unremarkable. Serum uric acid was high at 11.6 mg/dL. Renal ultrasound revealed normal kidney size with increased parenchymal echogenicity and punctate echogenic foci bilaterally. A renal biopsy was performed demonstrating widespread oxalate deposition with associated interstitial inflammation and tubular injury. Further history revealed no recent medications, infections, or ingestions, but did uncover a high intake of nuts (~1 pound) daily over the prior 1 year due to their perceived health benefits. He remained hemodialysis dependent on hospital discharge.

Discussion: Secondary oxalate nephropathy can result from increased enteric oxalate availability from dietary consumption. Diagnosis can be delayed when a review of diet and supplements is deferred. It is therefore essential to obtain a detailed dietary and pharmacologic history, particularly in all patients with unexplained kidney disease. Treatment is supportive including decreasing the high oxalate culprit foods in the diet.



H&E (left) and EM (right)

PO0281

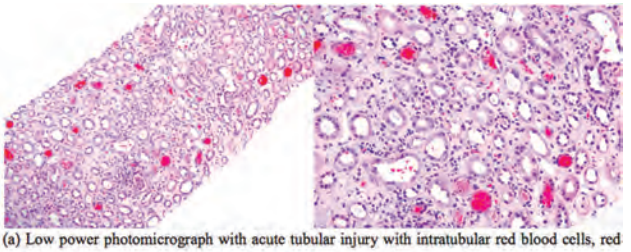
Case Report of Rivaroxaban-Induced Anticoagulant-Related Nephropathy

Remy Fadel,[1,2] Raiya Habib,[4] Patrick D. Walker,[3] Paul A. Alfino,[1,2] Joel D. Murphy,[3] Ayesha Kaleem.[1,2] *[1]North Florida Regional Medical Center, Gainesville, FL; [2]University of Central Florida, Gainesville, FL; [3]Arkana Laboratories, Little Rock, AR; [4]Dow Medical College, Karachi, Pakistan.*

Introduction: Anticoagulant related nephropathy (ARN) is still an under recognized etiology of acute kidney injury (AKI). There are no guidelines for ARN treatment to date and the literature consists mostly of case reports. While early detection of AKI remains the most important treatment, discontinuing the offending agent and antidote administration are also crucial. Other measures utilized include administering fluids and urine alkalinization to minimize red cell precipitation.

Case Description: Our patient is a 63-year-old Hispanic male treated with Rivaroxaban for atrial fibrillation. He started experiencing increased hemorrhaging with progressive worsening kidney function over two months. His serum creatinine (sCr) increased to 3.35mg/dL from 0.83mg/dL. Initial work up only revealed hematuria on a urinalysis. Serologies including auto-immune and hepatitis panels were negative. Subsequently, a renal biopsy done revealed chronic IgA nephropathy and acute tubular injury with prominent RBC casts and intratubular red blood cells. This was suggestive of ARN in the absence of glomerular dysfunction. The causative agent was held and a bicarbonate infusion was initiated. The patient's renal function improved with a most recent sCr of 1.5 mg/dL consistent with an estimated glomerular filtration rate (eGFR) of 50 ml/min/1.73m^2 improved from 19, approximately 7 months after initial treatment.

Discussion: Our case provides another example of ARN and highlights the therapeutic measures utilized. ARN has previously been shown to hasten CKD progression with increased mortality. Early identification and therapeutic management can lead to considerable renal recovery as seen in our patient's case. More studies are needed to further clarify the pathophysiology of ARN and to investigate potential treatments.



(a) Low power photomicrograph with acute tubular injury with intratubular red blood cells, red blood cell casts (hematoxylin and eosin, original magnification x 100). (b) High power photomicrograph with severe acute tubular injury and intratubular fresh red blood cells, red blood cell casts (hematoxylin and eosin, original magnification x 200).

Figure 1. Kidney biopsy specimen under light microscopy

PO0282

The Answer Is in the Urine

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Introduction: Ethylene glycol toxicity carries significant morbidity. Prompt recognition and treatment prevents mortality. Given time needed for confirmatory laboratory testing, high suspicion should be raised in cases of anion gap metabolic acidosis. Here we present a case of ethylene glycol toxicity diagnosed with simple urine microscopy.

Case Description: The patient is a 48-year-old male presented in an obtunded state. Laboratory evaluation was notable for a severe metabolic acidosis with a CO2 <5 mmol/L on basic metabolic panel. Anion gap was unable to be calculated but was at least 27. Serum labs were: Sodium 139 mmol/L, potassium 4.9 mmol/L, chloride 108 mmol/L. Glucose level 144 mg/dL Creatinine 1.14mg/dL and BUN 16 mg/dL, Lactic acid 7.63 mmol/L. ABG showed a pH of 7.14, pCO2 of 11 mmHg, pO2 of 114 mmHg, pHCO3 of 3.6 mmHg, and calculated base excess of -25.0. Measured serum osmolality was 321 mOsm/kg. Calculated serum osmolality was 292 mOsm/kg indicating an osmolar gap of 29 mOsm/kg. White blood cell count was 39.0 x10^3/uL. Ethanol level was <10mg/dL. Volatile acid labs were sent. Unfortunately, these labs required send out to another facility to run which resulted in significant delay. Due to high suspicion of toxic volatile substance ingestion, Fomepizole was administered and a urine sample was viewed under the microscope. Needle shaped crystals were noted to be present. Patient underwent 1 session of hemodialysis and significantly improved clinically. Ethylene glycol level, drawn prior to hemodialysis, came back at 24.9 mg/dL. He received 4 additional doses of fomepizole. He also received high dose thiamine and pyridoxine to enhance the metabolism of ethylene glycol. Labs drawn the following morning resulted in an undetectable ethylene glycol level.

Discussion: Toxic ingestion needs to be considered in any obtunded patient. Workup should include careful assessment of acid-base status and osmolar gap. Prompt Treatment may need to be initiated prior to confirmatory lab results. Simple methods including urine microscopy and fluorescing the urine with Wood's lamp can assist a prompt diagnosis. In our case, crystalluria was present. A teaching point is that the crystals need not be the classic "envelope shape" as a six-sided needle-like structure often occurs as noted in our patient. While labs may confirm the diagnosis, the answer can be found in the urine.

PO0283

AKI: Rare Side Effect of Pemetrexed

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Introduction: Pemetrexed was approved by FDA in 2004 to treat local or advanced metastatic non-small cell lung cancer. It works by disrupting folate dependent processes and in turn preventing cell replication. Folate deficiency leads to increased pemetrexed toxicity. We report a rare and deleterious case of acute kidney injury associated with pemetrexed toxicity.

Case Description: 63-year old male with PMH of stage IV non-small cell lung cancer and HTN presented with acute onset of skin desquamation of his facial, groin and buttocks regions along with severe mouth pain and odynophagia. The chemotherapy regimen was changed from pembrolizumab to pemetrexed two days prior. Severe odynophagia limited his oral intake. His BP on arrival was 86/60 and was fluid resuscitated. CBC was unremarkable except for platelet count of 56,000/uL and absolute neutrophil count of 372 cells/uL. CMP demonstrated BUN of 38mg/dL and serum Creatinine of 4.2mg/dL. His baseline Creatinine one month prior to presentation was .6. MRI of his abdomen was unremarkable. Initial treatment included aggressive fluid hydration, a granulocyte colony stimulating factor (TBO-Filgrastim) and empiric IV antibiotics given the severe neutropenia. Additionally, 5mg of folic acid intravenously was started to counter the anti-folate effects of pemetrexed. Increase in oral intake was encourage and pemetrexed was discontinued. His Creatinine returned to baseline within a few days. After resolution of mucositis, odynophagia and skin desquamation, he was discharged back home with changes to his chemotherapy regimen.

Discussion: Pemetrexed is a second line agent that has been used to treat 84% of the second most common cancer in both men and women in the US. The most common adverse reactions are fatigue, skin desquamation, nausea, stomatitis, neutropenia and pharyngitis. A significantly less common adverse effect is AKI that can occur and if not identified can lead to acute renal failure. In our patient, his AKI is thought to be multifactorial from pre-renal due to decreased oral intake and intrinsic due to the toxicity of pemetrexed. Although aggressive fluid administration is imperative, the anti-folate effects of pemetrexed must be reversed with folic acid in order to prevent the patient from going onto dialysis. Prompt recognition of this adverse effect can lead to suitable treatment and recovery of his kidney function.

PO0284

An Unusual Presentation of Type 1 Cryoglobulinemic GN in Monoclonal Gammopathy of Undetermined Significance (MGUS)

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Introduction: Type I cryoglobulinemia can develop in the setting of monoclonal gammopathy of undetermined significance (MGUS) and can have renal involvement in a third of cases. We present an unusual case of Type I cryoglobulinemic glomerulonephritis (GN).

Case Description: An 83-year-old woman with a history of IgG Kappa MGUS presented with decreased urine output and nausea. During the previous six months, the patient was hospitalized three times for acute kidney injury (AKI) requiring dialysis. Two renal biopsies had been performed during those admissions, which showed GN with scant immune deposit. One glomerulus had intraluminal staining for IgG and Kappa suggesting Type 1 Cryoglobulinemic GN secondary to her MGUS (Figure 1, A-C). She declined chemotherapy at the time, however, each time her renal function improved spontaneously and she was discharged without requiring dialysis. In the ED, her blood pressure was 182/69 but her vitals were otherwise normal. The physical exam was unremarkable. Labs were notable for sodium 122 meq/L, potassium 5.2 meq/L, creatinine 4.5 mg/dL, albumin 3.4 g/dL, low C3 and C4, and positive MPO-ANCA. The urinalysis showed 50 red blood cells, 15 white blood cells, and random urine protein > 2000mg/dL. Other serologic and infectious labs, including serum cryoglobulin, were negative. The renal ultrasound was normal. The patient's renal function worsened and was started on dialysis. This time the patient agreed to chemotherapy and immunosuppression with the aim to prevent further recurrences of AKI. The patient was started on clone-directed therapy with cyclophosphamide, bortezomib, and dexamethasone. Plasma exchange therapy was also performed for the clearance of light chains. The patient's renal function improved and she was discharged without requiring dialysis. Her two-month follow up creatinine was 1.08mg/dL.

Discussion: This case of type 1 cryoglobulinemic GN is unusual in that the patient developed cyclical but self-resolving episodes of AKI-D that was successfully treated with clone-directed therapy.

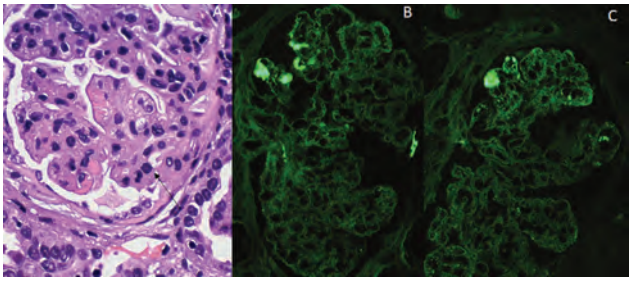

Figure 1. A. Immune Thrombi on H&E

B, C. IgG and Kappa staining on Immunofluorescence

PO0285

A Case of Renal Papillary Necrosis in the Setting of Acute Pyelonephritis and Chronic NSAID Use

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Introduction: Renal papillary necrosis is an ischemic process that affects the renal papillae and inner medulla leading to acute kidney injury. Most common causes include diabetes mellitus often with urinary tract infection, sickle cell anemia, and analgesic use. It is histologically delineated by coagulative necrosis of the renal papilla and medullary pyramids, and potentially acute liquefactive necrosis in the presence of infection. We report a case of renal papillary necrosis in the setting of acute pyelonephritis and chronic NSAID use.

Case Description: A 59-year-old Caucasian male with a history of hypertension, irritable bowel syndrome, hyperlipidemia who presented with 4 days of vomiting, diarrhea, decreased urinary output, and generalized weakness. He endorsed twice daily use of naproxen for the past couple months. Physical examination only notable for dry mucous membranes. Initial work-up demonstrated serum creatinine of 12.7 mg/dL (baseline 1.0 mg/dL), serum sodium level of 123 mmol/L, serum potassium level of 7.4 mmol/L, blood urea nitrogen 147 mg/dL, WBC count 30.5 x10^9/L, and urinalysis with pyuria, microscopic hematuria, and proteinuria. Further work-up showed urine culture

with pan-sensitive Escherichia coli, sub-nephrotic proteinuria, and complete serologic work-up only positive for serum protein electrophoresis. CT abdomen/pelvis without contrast did not demonstrate any hydronephrosis. A native kidney biopsy was performed and revealed diffuse tubulointerstitial inflammation with prominent intratubular white cell casts and areas of confluent parenchymal necrosis consistent with acute pyelonephritis leading to renal papillary necrosis. He completed a 7-day course of ceftriaxone for E. coli urinary tract infection and eventually required hemodialysis with no signs of kidney recovery upon discharge.

Discussion: Renal papillary necrosis is a rare disease entity and is underdiagnosed due to its variable clinical presentation. Unfortunately, it could have potentially fatal outcomes if undiagnosed, which is evident upon reviewing the current literature. By presenting this case, we highlight this unique presentation of renal papillary necrosis in a non-diabetic individual and urge clinicians to have a high index of suspicion and subsequently a low threshold for kidney biopsy to establish a diagnosis and improve patient outcomes.

PO0286

A Rare Case of Evans Syndrome with Systemic Lupus Erythematosus and Pulmonary Nocardiosis

Reddappa Venkata Sai Rakesh Kanipakam. *Brown University, Providence, RI.*

Introduction: Evans syndrome (ES) is a rare autoimmune disorder characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune-mediated thrombocytopenic purpura (ITP). The exact pathophysiology is unknown but is initiated by having autoantibodies attacking body's own red blood cells and platelets.

Case Description: 20-year-old male with history of autoimmune dysregulation including SLE (diagnosed when he was 13), Evan's Syndrome, class 5 lupus nephritis presented to the Hospital for difficulty breathing, dry cough and 30-pound weight loss. He was admitted to ICU for acute hypoxic respiratory failure requiring intubation. His lab work showed anemia, thrombocytopenia, AKI, ANA+, low C3, C4, elevated LDH, high uric acid, UA showing 3+ blood and 6 grams of proteinuria. A chest CT on admission also noted extensive LAD, splenomegaly, ground glass opacities and interstitial prominence in lungs. He underwent a lung biopsy which showed DAH. The patient was also treated with pulsed steroids, plasmapheresis and Cytoxan. He also had MSSA bacteremia treated with antibiotics and rehab course complicated with pulmonary nocardiosis.

Discussion: Although ES is an extremely rare case, it is important to keep broad differentials as renal dysfunction is common from different pathologies. Usually the most common cause of AKI associated with ES is ATN from intravascular hemolysis and had widespread intratubular hemoglobin casts but it is essential to consider other etiologies as in our case of previous lupus flare.

PO0287

Acute Myositis Complicated by Rhabdomyolysis in Setting of COVID-19 Infection in a Patient on Rosuvastatin: A Case Report

Anand Kumar, Anjali Muraleedharan, Yasir Lal. *The University of Texas Medical Branch at Galveston, Galveston, TX.*

Introduction: Viral illnesses are uncommon cause of rhabdomyolysis and AKI. A few cases of rhabdomyolysis have been reported with Covid-19 infection previously. However, Covid-19 presenting solely with rhabdomyolysis in absence of respiratory symptoms is rare. There is also paucity of data supporting steroids use in such cases. We present a case of COVID-19 related rhabdomyolysis who recovered in response to steroid therapy.

Case Description: This is a 78-year-old female with history of dyslipidemia and chronic kidney disease III who presented with generalized weakness and myalgias. Home medications included Rosuvastatin. She was diagnosed with Covid-19 virus. Rosuvastatin was held, however her myalgia muscle weakness worsened, and she was no longer able to stand without support. She denied fever, chills, rash, or respiratory symptoms. At presentation, physical exam revealed diffuse muscle tenderness and diminished strength: 1/5 and 2/5 in proximal bilateral lower and upper extremities respectively. WBCs 11.13, K 5.7, Cr 5.72, ANA, HMG CoA reductase antibody assay and myositis panel (SSA-52, SSA-60, Smith/RNP antibodies, anti-SMRNP, anti-SSA, anti-SSB, & RF) were negative. CK 14, 085 U/L, granular and muddy brown casts on urine microscopy. Lower extremities MRI showed bilateral muscular edema, EMG was consistent with myopathic changes. Muscle biopsy revealed scattered necrotic and regenerating fibers, diffuse type 2 fiber atrophy, and mild neurogenic changes, consistent with rhabdomyolysis. Immunohistochemistry showed rare perivascular B lymphocytes and plasma cells. CK continued to rise and peaked at 89,303 U/L. At that point steroid therapy was initiated. This resulted in a significant improvement in CK and creatinine over the next few days.

Discussion: Viral myositis leading to rhabdomyolysis and AKI as the primary presentation of Covid-19 infection is uncommon. In our case, a short course of steroids, resulted in quick recovery. Early recognition and diagnosis followed by intervention can prevent further muscle and renal damage and can shorten hospital stay and related morbidity significantly. Cureus. 2020 Oct; 12(10): e11186.Ankalesaria et al. Solís, J. G. et al. *The American journal of tropical medicine and hygiene, 103*(3), 1158–1161

PO0288

AKI Induced by Oral Semaglutide Leading to Metformin-Induced Lactic Acidosis

Allyson K. Halderman, Madhu Kandarpa. *Kettering Health Network, Dayton, OH.*

Introduction: Lactic acidosis is a known complication of metformin treatment, especially in the context of elevated creatinine. This is a patient on chronic metformin therapy who developed actue kidney injury and lactic acidosis after intiaition of semaglutide.

Case Description: a 77-year-old male with a history of non insulin dependent type 2 diabetes, hypertension and hyperlipidemia brought in for altered mental status. Patient had been prescribed metformin for years without any complications. Vitals: temp 91.2 F, BP 81/72, RR 25, spO2 98% on room air. Physical examination was unremarkable including no edema however was oliguric. On admission patient had a Na 130 mmol/L, Potassium 6.1 mmol/L, Chloride 76 mmol/L, CO2 5 mmol/L, Anion gap 49 mmol/L, Blood Urea Nitrogen 65 mg/dL, Creatinine (Cr) 6.4 mg/dL (baseline Cr 1.3 mg/dL), lactic acid 22.4 mmol/L and a Venous blood gas pH of 6.8, Ammonia 245 umol/L with normal liver enzymes, COVID PCR negative. CT Abdomen without contrast and Chest x-ray did not show any acute process. Treatment: Patient was admitted to Intensive Care Unit, Semagliptide and Meformin discontinued. He was started on Continuous Renal Replacement Therapy (CRRT) then transtioned to conventional hemodiaylsis. Patient made remarkable recovery. At the time of discharge patient was off diaylsis with Cr 1.1 mg/dL.

Discussion: Semaglutide is a glucagon-like peptide 1 receptor agonist (GLP-1 agonist). GLP-1 agonist's have gained popularity in the outpatient setting for management of Type 2 diabetes mellitis. They carry a low side effect profile including reduced risks of hypoglycemia compared to older treatments. Acute kidney injury requiring diaylsis is listed as a possible adverse reaction, it is rare, usually occurring in the setting of acute dehydration. Reports of AKI requiring dialysis in available studies show incidences near that present in the placebo groups. The high acuity of disease that occurred in the above patient was compounded by metformin toxicity. Many future patients prescribed semaglutide will be on metformin. Information such as this could require physicians to use extra caution as they prescribe this medication combination, especially in the elderly and those at risk for dehydration. Futher studies needed to evaluate possible interval labortory monitoring when patients are initated on this medication combination.

PO0289

Staphylococcus aureus-Associated Infection-Related Glomerulonephritis (IRGN) in an Elderly Male

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Introduction: IRGN commonly occurs in children following Streptococcal upper respiratory tract or skin infections. However, more cases are now being described in adults with symptoms ranging from microscopic hematuria to dialysis dependence. Herein, we describe a case of IRGN in an elderly male in association with a heel ulcer.

Case Description: An 88-year-old man with hypertension, chronic kidney disease stage 3 (baseline creatinine (Cr) 1.6-1.8 mg/dL), rheumatoid arthritis & peripheral artery disease presented with a Cr of 8 mg/dL. 3 weeks prior to presentation, he was hospitalized for a right heel abscess, treated with doxycycline for 5 days & discharged with a Cr of 1.84 mg/dL. Wound cultures grew methicillin sensitive Staphylococcus aureus, E. coli & coryneform bacteria. 7 days after discontinuing doxycycline, he developed oliguria & a pruritic rash on his chest & arms & was readmitted. Urinalysis revealed >50 RBCs, >50 WBCs, 100 protein & few bacteria without casts. Urine protein to Cr ratio was 3.3 g/dL, fractional excretion of sodium was 4.4% & eosinophil count 6.8%. Additional labs included C3 64 mg/dL, C4 32.8 mg/dL & ANA 1:320, with speckled pattern. ESR was 46 mm/hr & CRP was 3.3 mg/dL, with negative blood & urine cultures. Renal ultrasound showed bilateral echogenic kidneys without hydronephrosis. Recent antibiotic use, rash, peripheral eosinophilia & acute kidney injury suggested acute interstitial nephritis. He was started on prednisone 1mg/kg/day. Hemodialysis (HD) was initiated for volume overload & uremic encephalopathy. His kidney function did not improve with prednisone & a renal biopsy was performed. Pathology revealed diffuse exudative glomerulonephritis, prominent C3-only staining, active interstitial inflammation, & subepithelial deposits consistent with IRGN. Despite improved respiratory status with HD, his mental status deteriorated, kidney function did not recover & he died on the 20th day of admission.

Discussion: While prognosis for IRGN is excellent in children with nearly 95% recovery; about half of affected adults become dialysis dependent. Our case is unique as it (a) highlights the need for a high index of suspicion for IRGN in an adult patient recovering from infection & (b) implores nephrologists to have a low threshold to perform a renal biopsy when noticing lack of improvement of AKI.

PO0290

Continuous Renal Replacement Therapy: A Reversible Cause of Thrombocytopenia

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Introduction: Thrombocytopenia is frequently encountered in critically ill patients. Whether present on admission or acquired during hospitalization, inadequate platelet counts are an independent risk factor for patient morbidity and mortality in the Intensive

Care Unit. Continuous renal replacement therapy is a lesser known cause of acquired thrombocytopenia.

Case Description: In this retrospective case series, four patients that developed thrombocytopenia while receiving continuous renal replacement therapy (CRRT) in the Intensive Care Unit were evaluated. The temporal relationship between onset of thrombocytopenia, timing of CRRT, and subsequent trend in platelet counts were analyzed. The patients had a variety of risk factors for thrombocytopenia including septic shock, presence of chronic kidney disease, mechanical support therapies, and anticoagulation with heparin. Despite these characteristics and interventions, each of the patients demonstrated a pronounced drop in platelet count within 72 hours of initiating CRRT, with a subsequent improvement in platelet count following cessation of CRRT.

Discussion: Thrombocytopenia is a complication of critical illness that, in extreme cases, can lead to further cost and resources to evalute and possibly delay necessary intervention. In patients requiring renal replacement therapy, clinicians must be cognizant that continuous modalities are a potential source of thrombocytopenia. Nephrologists are responsible for knowing all potential adverse outcomes of the procedure of dialysis. Educating other health team members of these risks is part of that responsibility.

Data

Hours since CRRT initiation	Platelet Count Patient 1 (per microL)	Platelet Count Patient 2 (per microL)	Platelet Count Patient 3 (per microL)	Platelet Count Patient 4 (per microL)
0	225,000	243,000	225,000	80,000
24	138,000	159,000	112,000	60,000
48	97,000	69,000	77,000	53,000
72	71,000	44,000	58,000	47,000
Hours since CRRT cessation				
0	13,000	44,000	83,000	49,000
24	43,000	58,000	129,000	60,000
48	54,000	67,000	176,000	99,000

CRRT = Continuous Renal Replacement Therapy

PO0291

Successful Utilization of Hemodialysis for Treatment of Vancomycin Nephrotoxicity

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Introduction: Vancomycin is frequently used as empiric antimicrobial therapy for septic shock. At supratherapeutic levels, vancomycin can potentially cause nephrotoxicity. Nephrotoxicity often resolves on discontinuing the medication, but recovery may be prolonged and injury severe, requiring dialysis. The role of hemodialysis is limited, and evidence suggests that standard membrane dialysis provides poor clearance. However, the current use of high flux dialysis can eliminate vancomycin faster, promoting quicker renal recovery.

Case Description: A 49-year-old female admitted for septic arthritis received vancomycin 1.5g q8h and piperacillin/tazobactam. After two days, she developed an oliguric acute kidney injury (AKI). Urine sediment revealed few tubular cells without casts. Vancomycin trough level was 42 ug/ml, and the random level was 101.3ug/ml. We suspected vancomycin toxicity, and for quicker clearance of the drug, we initiated high flux dialysis. She received five sessions of HD, and her random vancomycin level dropped to 18 ug/ml. Gradually her urine output improved with resolution of AKI.

Discussion: Discerning vancomycin nephrotoxicity can be a challenge as higher vancomycin levels can result from decreased GFR from AKI. The rise of creatinine coexisting with elevated vancomycin levels and the absence of an alternative explanation for renal injury supports the diagnosis of vancomycin nephrotoxicity. The odds of developing vancomycin nephrotoxicity are three times higher when combined with piperacillin/tazobactam. Incidence of AKI increases with higher daily dosage (>4g vancomycin/day), higher trough levels (>15 mg/L), and longer treatment time (>1 week). Treatment is aimed at discontinuation of the drug. In severe AKI, with oliguria and poor clearance, strikingly elevated serum vancomycin levels may further escalate the risk of renal injury. In our case, the use of HD to increase the clearance of vancomycin may have expedited renal recovery. Faster removal of vancomycin with HD should be considered in patients with severe AKI.

PO0292

Atypical Hemolytic Uremic Syndrome: A Case Report

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Introduction: Thrombotic microangiopathy is a pathological condition comprised of microvascular thrombosis involving any organ of the body leading to thrombocytopenia, Coombs-negative hemolytic anemia, and end-organ damage. The most common forms of thrombotic microangiopathies are Shiga toxin-producing Escherichia coli mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. The atypical hemolytic uremic syndrome occurs due to genetic and acquired mutations in complement regulatory factors and to complement activation factors in the immune system, mainly the alternative pathway. Clinical manifestations and outcomes differ with the prevalent mutations of the patient. Currently, available treatment modalities are therapeutic plasma exchange and a monoclonal antibody against C5, eculizumab.

Case Description: 43-Year-Old African American female with past medical history hypertension and Diabetes presented with 2-day history of altered mental status. On presentation, she has BP 264/133. Her blood investigations showed acute kidney disease, thrombocytopenia, hemolytic anemia with negative Coombs's test. Coagulation profile was normal. Schistocytes were noted on peripheral smear. Received plasmapheresis for concern of Thrombotic thrombocytopenic purpura with no clinical improvement. Initiated on hemodialysis. Adams TS 13 level returned at 27%, ruling out Thrombotic thrombocytopenic purpura. Genetic complement testing was sent on the patient and was initiated eculizumab for presumed Atypical hemolytic uremic syndrome. After giving eculizumab patient's mental status improved and recovered renal function, came off dialysis. Genetic complement testing is negative however, next generation sequencing revealed no coverage for the CFHAI and' CFHRS genes which may be a risk factor for FH autoantibody development and needs further testing

Discussion: Conclusion: The atypical hemolytic uremic syndrome is a rare disease entity requiring a high index of suspicion to diagnose. It is a diagnosis of exclusion. Early diagnosis with prompt treatment will render a better outcome. The atypical hemolytic uremic syndrome needs to be considered in all patients with thrombotic microangiopathy. Brocklebank V etal, Thrombotic microangiopathy and the kidney. Clin J Am Soc Nephrol. 2018;13(2):300–17

PO0293

A Tricky Diagnosis of Complement-Mediated Thrombotic Microangiopathy

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Introduction: Complement-mediated thrombotic microangiopathy (C-TMA) is caused by inappropriate activation of the alternative complement pathway, usually leading to acute kidney injury (AKI), microangiopathic hemolytic anemia (MAHA), and thrombocytopenia (TCP). Renal biopsy is normally not indicated for diagnosis.

Case Description: A 22 year-old black male was admitted for hypertensive emergency with blood pressure (BP) of 240/140 mmHg, vision loss, and AKI. Ocular exam showed bilateral Frisén Grade IV papilledema. Serum creatinine (sCr) was 4.9 mg/dL (baseline 1.1 mg/dL two years prior) with 4 g proteinuria. Urine microscopy had dysmorphic red blood cells with hyaline and granular casts. Platelet count, hemoglobin, LDH, and haptoglobin were normal. Records showed several years of untreated hypertension; family history was unremarkable. Complement, hepatitis/HIV, ANA, ANCA, anti-GBM, and cryoglobulins were normal. Secondary hypertension workup was negative for endocrine and macrovascular disease. He was treated with antihypertensives and his vision corrected over several days. Renal biopsy showed >50% glomerular obsolescence and 35% interstitial fibrosis/tubular atrophy, with focal arteriolar narrowing and bloodless glomeruli concerning for a subtle TMA. Genetic testing showed a homozygous deletion of CFHR3-CFHR1, confirming C-TMA. Factor H autoantibodies were negative. Therapy was begun with eculizumab, an anti-C5 monoclonal antibody. BP decreased to 120-150/65-90 mmHg and sCr improved to 2.9 mg/dL. He was later switched to ravulizumab for less frequent dosing.

Discussion: This was an atypical presentation of C-TMA without the usual diagnostic clues of TCP or MAHA. Renal biopsy was essential in the eventual diagnosis confirmed by genetic testing. The associations between the genetic variants of C-TMA and specific clinical presentations warrants further investigation. *The views expressed are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense or the United States Government.*

PO0294

Hemolytic Anemia, Thrombocytopenia, and Kidney Injury Associated with Cardiac Procedure: A Diagnostic Dilemma

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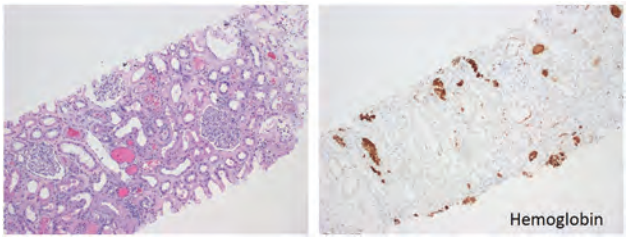
Introduction: Acute intravascular hemolysis is a rare complication of ventricular septal defect (VSD) closure devices; however, profound thrombocytopenia is not typical. We present a case of hemolysis, thrombocytopenia, and kidney failure in a patient with recent VSD closure device placement. Although hemoglobin cast nephropathy (HCN) was considered, the patient was also newly started on ticagrelor, which has been associated with thrombotic microangiopathy (TMA). A biopsy was required for ultimate diagnosis.

Case Description: A 79-year-old woman with recent myocardial infarction (MI) underwent percutaneous coronary intervention and initiation of dual antiplatelet therapy with ticagrelor and aspirin. Subsequently she developed VSD and underwent transcatheter VSD closure device placement. Pre-procedure labs showed normal hemoglobin and platelet levels, but following the procedure she developed progressively worsening jaundice, dark urine, anemia and thrombocytopenia. Peripheral smear revealed numerous schistocytes. ADAMTS-13 activity was 27%, and serotonin release assay was negative. She required initiation of hemodialysis due to anuria. A kidney biopsy was performed, which showed widespread acute tubular injury with hemoglobin casts and without findings of TMA. Hemolysis spontaneously resolved after a few days. The patient remained dialysis dependent at the time of discharge.

Discussion: Intravascular hemolysis can be a rare complication of intracardiac devices as a result of high-velocity turbulent blood flow through the device or a residual shunt causing mechanical erythrocyte fragmentation. HCN can develop as a consequence of intravascular hemolysis. This case was complicated by the recent initiation of ticagrelor, which is associated with TMA. Differentiating between HCN and TMA required a kidney biopsy after careful planning due to ongoing cytopenias.



H&E and Immunohistochemical staining of Hemoglobin casts

PO0295

Patient with Refractory Acquired Thrombotic Thrombocytopenic Purpura Treated with a Novel Agent Caplacizumab

Pranav Sharma, Jonathan Lebowitz. *Rutgers The State University of New Jersey, New Brunswick, NJ.*

Introduction: Acquired or immune-mediated TTP is characterized by thrombocytopenia and anemia caused by autoantibody mediated inhibition of the von Willebrand factor (vWF) cleaving protease, ADAMTS13. This results in a microangiopathic hemolytic anemia and severe thrombocytopenia, resulting in tissue ischemia, multiorgan failure, and, potentially, death. Up until now, treatment for TTP included therapeutic plasma exchange (TPE) and immunosuppression. Recently, caplacizumab, the first targeted nanobody based therapeutic agent that prevents adhesion of platelets to vWF, has been approved for use in acquired TTP. We present a case of acquired TTP that was refractory to high dose, steroids, therapeutic plasma exchange (TPE) and rituximab but responded well to caplacizumab.

Case Description: A 53-year-old man with HIV, complicated by cryptococcal meningitis and PCP pneumonia, intermittent confusion, headache, and multiple falls, presented with anemia, thrombocytopenia, an elevated LDH, and a peripheral blood smear with numerous schistocytes with acute kidney injury with an initial serum creatinine of 1.7 mg/dl which peaked up to 5.5 mg/dl. Further testing revealed a positive ADAMTS13 inhibitor with high titer of 3.4 and less than 5% ADAMTS13 enzyme activity, consistent with TTP. He was treated with high dose steroids, TPE, and rituximab but did not respond. He was initiated on caplacizumab on hospital day 14 and by day 18 his platelet counts began to normalize and mentation improved. He suffered only mild epistaxis as a side effect from caplacizumab. In span of few days, his neurologic symptoms resolved and he was discharged home to complete thirty days of caplacizumab treatment. At the time of follow up, he remained well and continued to have normal ADAMTS13 activity. Kidney function improved post caplacizumab to 0.8 mg/dL.

Discussion: Although conventional therapy has reduced the mortality of TTP, it is not always effective and there are fair number of cases refractory to conventional treatment. Caplacizumab, the first nanobody-based therapeutic agent, has shown marked efficacy in treating TTP and its complications and is a therapeutic option for patients with refractory TTP.

PO0296

Use of Eculizumab in Thrombotic Microangiopathy (TMA) Associated with PM/SCL100 and 75 and RP 155 Antibody-Positive Autoimmune Overlap Syndrome with Renal Crisis

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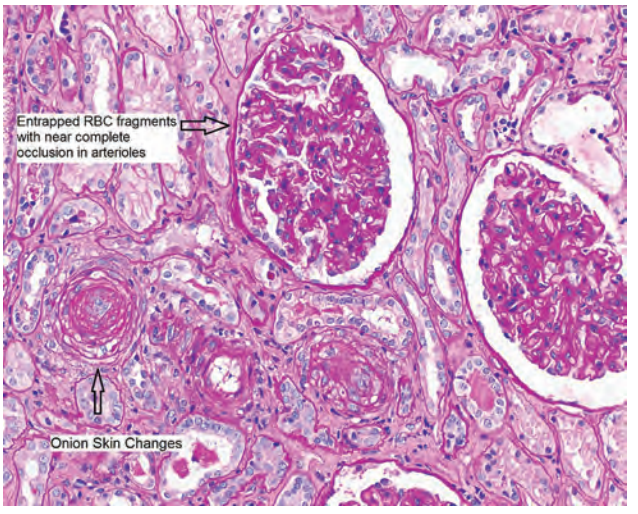
Introduction: TMA with associated PM/SCL100 & 75 and RP 155 antibody positive Autoimmune Overlap Syndrome with renal crisis has a very poor prognosis and limited therapeutic options. Use of Eculizumab has been reported in only a few cases in literature.

Case Description: A 44 years old female with hypertension and Raynaud's phenomenon presented with hypertensive emergency, recent sclerodactyly, hemolytic anemia, thrombocytopenia and renal failure. Routine serum markers including DsDNA Ab, complements, ANCA, SSA, SSB, Scl 70 Ab, Anti-centromere Ab, RNA polymerase 3 Ab, U-3 RNP Ab, lupus anticoagulant, beta 2 glycoprotein Ab and ADAMTS-13 were all negative. Pulse Steroids and plasmapheresis were initiated due to concern of aHUS. Renal biopsy showed onion skinning of arterioles with near complete occlusion of arterioles as shown in the figure. ACEI was added. Later she was found to have positive PM/SCL 100 & 75 and RP 155 antibodies. She was started on Eculizumab secondary to poor hematological response to the above measures. Our patient showed improvement of her thrombotic microangiopathy which helps to support the use of this drug in this rare disorder.

Discussion: Very limited theraputic options are available for cases of Autoimmune Overlap Syndrome. Our use of Eculizumab; an anti-CD5 monoclonal antibody, also supports the benefits of blocking the activation of the classical complement pathyway which may suggest the underline mechanism in this disease process.



PO0297

AKI and Collapsing Focal Segmental Glomerulosclerosis in an Immunocompetent Patient with Cytomegalovirus and COVID-19 Infection

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Introduction: Collapsing Glomerulopathy is a morphological variant of focal segmental glomerulosclerosis (FSGS) characterized by rapidly progressive renal failure and nephrotic range proteinuria. CMV-associated renal infections are usually seen in post-transplant and immunocompromised patients. We present a case of severe collapsing FSGS and acute CMV infection in an immunocompetent host.

Case Description: A 19-year-old woman with HbSS sickle cell disease and infrequent vaso occlusive crisis was hospitalized with febrile illness. During hospitalization she developed non-oliguric acute kidney injury (AKI) and volume overload and started on intermittent hemodialysis. Chest x-ray showed cardiomegaly, pulmonary venous congestion, infiltrates and bilateral pleural effusions. 24h Urine protein was 17,291 mg/24h. Urine and serum myoglobin were elevated. Relevant investigations include positive CMV IgM, CMV PCR 7000 international unit(s)/ml, positive mycoplasma IgM. SARS-CoV-2 RT-PCR & NAT were negative but antibodies were positive. A diagnosis of COVID associated Multisystem inflammatory syndrome in children (MIS-C) was made and she received methylprednisolone. She received piperacillin/tazobactam, azithromycin, ganciclovir, meropenem, and linezolid for CMV infection and pneumonia. Renal biopsy revealed collapsing FSGS, moderate and acute tubular injury, interstitial edema, focal tubular microcysts and podocyte effacement. Renal function improved after ganciclovir therapy and hemodialysis was discontinued. Prednisone and losartan were started for persistent proteinuria.

Discussion: Active CMV infection in immunocompetent hosts is uncommon. The mechanism of CMV associated with collapsing FSGS is unclear as direct viral infection is not always seen on biopsy. CMV is not routinely tested for in immunocompetent patients and should be considered in AKI and nephrotic syndrome with multi-system involvement. Our patient had lung infiltrates and rhabdomyolysis which could be explained by CMV infection. Anti-viral therapy may be effective. As opposed to primary collapsing FSGS steroids are not routinely needed. Some patients have persistent proteinuria and nephrotic syndrome may respond to steroids, with tacrolimus in refractory cases. It is unclear if prior COVID infection or MIS-C contributed to activation of CMV infection and FSGS.

PO0298

Bilateral Hydronephrosis: An Unusual Presentation of a Rare Disease

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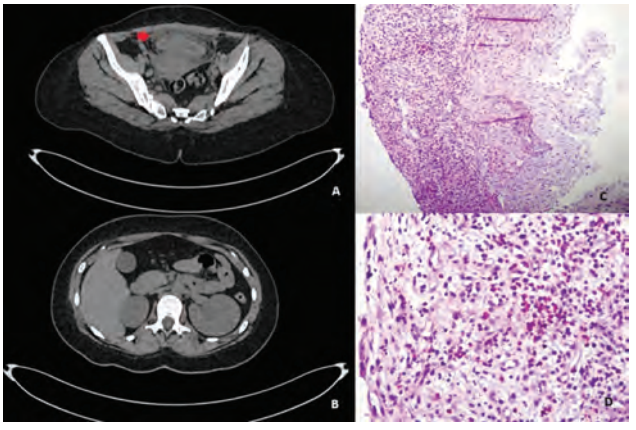
Introduction: Eosinophilic cystitis is a rare disease. Prevalence is equal among gender in adult patients. Patients commonly present urinary frequency, dysuria, hematuria, suprapubic pain and urinary retention. Association with history of allergy and urinary tract infection is variable.

Case Description: 26 years old female presented with bilateral flank pain and dysuria. Labs showed high creatinine and urinalysis was suggestive of a urinary tract infection. CT of the abdomen and pelvis showed bilateral hydronephrosis with no stones (Image A). Diffuse circumferential wall thickening of urinary bladder with extensive perivesical fat stranding (image B). Cystoscopy was performed which revealed diffuse edematous bladder wall including both ureteric orifices. Bilateral retrograde studies confirmed that the obstruction is at the ureteral orifices. JJ stents were inserted bilaterally. Bladder biopsies were taken. Histopathology of the biopsies(image A and B) show denuded urothelium with underlying chronic inflammatory cell infiltrate rich in eosinophils consistent of eosinophilic cystitis. The renal function improved after the procedure. The patient was discharged on antihistamine and a tapering dose of steroid. On follow up, JJ stents were removed and retrograde studies showed normal flow through the ureteral orifices. Serum creatinine is back to baseline and dysuria improved on three months follow up.

Discussion: Eosinophilic cystitis is a rare disease. Association with history of allergy and urinary tract infection is variable. Radiological finding are usually consistent with thickened bladder wall. In a case series of 10 Chinese patients, only one patient had bilateral hydronephrosis. Medical treatment is mainly by non-steroidal anti-inflammatory drugs, corticosteroids, anti-histamines and antibiotics. Surgical modalities of treatment include transurethral resection of the lesions, partial cystectomy or total cystectomy. Response to different modalities of treatment is variable.



PO0299

Treatment of FSGS and Hemophagocytic Syndrome with Tocilizumab

Daniel W. Shields, Michael Dore, Richard A. Plasse. *Naval Medical Center Portsmouth, Portsmouth, VA.*

Introduction: Hemophagocytic syndrome (HPS) is a rare and often life-threatening condition characterized by an overreaction of the immune system. HPS has a variety of triggers including: malignancy, infection, and rheumatologic conditions. Clinically, it is characterized by acute fever, cytopenia, lymphadenopathy, hepatosplenomegaly, intravascular coagulation, hyperferritinemia, and elevated liver associated enzymes. We present a case of reactive HPS complicated by focal segmental glomerulonephritis (FSGS) secondary to a febrile gastrointestinal illness in an otherwise healthy 36 year old male.

Case Description: A 36 year old male presented to the ER with a 3 day history of fevers, nausea, vomiting, and diarrhea. Labs demonstrated hyponatremia to 126 and acute renal injury. He was admitted for presumed viral gastroenteritis and treated supportively. He then developed elevated liver associated enzymes and pancytopenia. An infectious work up was unrevealing. Flow cytometry was negative for lymphoma or leukemia. Ferritin was elevated at 4450 ng/ml. A bone marrow biopsy demonstrated hemophagocytosis. He then developed multiple pulmonary embolisms, lower extremity edema, new onset ascites, and nephrotic range proteinura. A renal biopsy showed diffuse podocyte effacement with rare Focal Segmental Glomerulosclerosis (FSGS) with collapsing features and no immune complexes. His IL-2 soluble receptor was elevated at 2710 µg/mL. He was diagnosed with HPS, started on prednisone 1 mg/kg then transitioned to tocilizumab.

Discussion: The pathogenesis of HPS is excessive activation and proliferation of T lymphocytes and macrophages leading to phagocytosis of hematopoietic cells in the bone marrow and hypersecretion of proinflammatory cytokines causing multi organ dysfunction. Due to the difficulty in diagnosis, the Hscore was developed to estimate the probability of HPS. Our patient's Hscore was 209 equating to an 88-93% probability. Renal dysfunction occurs in ~16% of patients with HPS with symptoms ranging from hyponatremia to renal failure. Nephrotic syndrome is most commonly due to collpasing FSGS. Case reports have demonstrated the use of tocliziumab in the treatment of FSGS from other etiologies, but treatment of HPS and FSGS has not been reported. Our patient had resolution of his nephrotic syndrome with immunosuppressive therapy with steroids and remain in remission on tocilizumab.

PO0300

Transition of Portal Vein Doppler Waveform with Improving Venous Congestion: A Case Study

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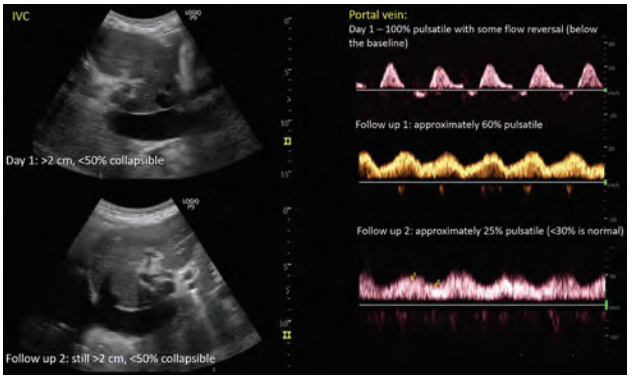
Introduction: The diagnostic accuracy of physical examination, weight, laboratory parameters such as BNP is limited for the assessment of fluid status. Point-of-Care Ultrasonography (POCUS) is emerging as a valuable bedside tool for evaluation of hemodynamics at the bedside. Herein, we present a case which illustrates the practical utility of portal vein Doppler.

Case Description: A 78-year-old woman with a history of heart failure (HF) with reduced EF (<20%) and pulmonary hypertension was brought to the hospital for altered mental status. She was found to have acute kidney injury (AKI) with a serum creatinine of 2.2 mg/dL (baseline ~1.1) and urinalysis was suggestive of UTI. Urine sodium and chloride were <20 mmol/L. Antibiotic therapy was started; AKI was presumed to be secondary to volume depletion as her diuretic regimen was recently intensified. There was no significant weight gain. Admitting physician noted mild pedal edema and no jugular venous distension. NT-pro-BNP level was 8118 pg/mL (last available value 10,537). 1 liter of isotonic fluid was administered, and diuretics were held. Her metal status eventually improved; nephrology consulted for AKI. POCUS-assisted physical examination demonstrated severely impaired left ventricular systolic function, a D-shaped left ventricle suggestive of pressure and volume overload and a plethoric inferior vena cava (IVC) suggestive of elevated right atrial pressure. Portal vein Doppler waveform was pulsatile with intermittent flow reversal consistent with severe venous congestion. Based on these findings, diuretic therapy was restarted. Serum creatinine improved to 1 mg/dL at discharge. While IVC continued to be dilated, portal vein waveform showed consistent improvement during the course of decongestive therapy [Fig.1].

Discussion: While IVC POCUS is relatively easy to perform, it maybe chronically dilated in patients with pulmonary hypertension. Portal vein Doppler offers an additional datapoint to assess the severity of venous congestion and monitor the efficacy of decongestive therapy.



PO0301

Skin Biopsy in Diagnosis of Acute Interstitial Nephritis

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Introduction: Acute Interstitial Nephritis (AIN) is a common cause of Acute Kidney Injury (AKI). It is often caused by drugs, systemic diseases, and infectious diseases. The diagnosis is elusive, as the triad of fever, rash, and peripheral eosinophila is rarely seen. Other diseases, such as atheroembolic renal injury, could present similarly. Hallmark findings on urinalysis (leukocytes, WBC casts) and urine eosinophils are also non-specific. Hence, a definitive diagnosis only comes from renal biopsy. The case presents a patient with AKI and rash, highlighting the utility of skin biopsy in diagnosing AIN as an alternative to renal biopsy.

Case Description: A 72 year old female with a history of hypertension and chronic kidney disease was treated with Keflex in-hospital for a urinary tract infection. Within four days of beginning the medication, she developed a maculopapular rash on the trunk, back, and extremities with AKI (creatinine rose to 3.05 mg/dL, while creatinine on admission around baseline of 1.9 mg/dL). Keflex was discontinued and replaced with Ciprofloxacin. Urinalysis had 2+ proteinuria and 3+ hematuria with 113 red blood cells and 24 white blood cells. Urine eosinophils was positive. Autoimmune workup was unremarkable. Renal ultrasound showed kidneys of normal size and echogenicity. The patient began empiric prednisone 60 milligrams daily. Dermatology performed a skin biopsy showing inflammation consistent with drug eruption. Immunostaining was unremarkable. Meanwhile, the patient's creatinine began to improve after treatment and reached baseline by discharge. The rash also began to improve.

Discussion: AIN is a very common cause of AKI, particularly in the hospital setting. Current lab tests used for workup are neither sensitive nor specific for the disease, often rendering AIN a clinical diagnosis. A definitive diagnosis requires tissue sampling, traditionally via renal biopsy. However, the procedure has particular risks, such as retroperitoneal bleed. In this case, skin biopsy showed inflammation characteristic of drug eruption in a patient with AKI and rash correlating in time with initiation of an antibiotic, lending credence to the diagnosis of AIN. Therefore, in patients with suspected AIN involving skin rash, skin biopsy could prove to be a safer mode of tissue sampling for diagnosis, averting the complications traditionally associated with renal biopsy.

PO0302

Oxandrolone-Induced Acute Tubular Necrosis

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Introduction: Oxandrolone is an anabolic-androgenic steroid (AAS) indicated as adjunctive therapy to promote weight gain in chronic wasting conditions. It is also used off-label by many sports and bodybuilding enthusiasts to increase muscle mass. Common adverse effects include transient elevations in transaminase levels and reduction in HDL cholesterol level. Mostly, kidney complications occur after long-term administration. Renal disorders range from a mild, reversible rise in serum creatinine and BUN to irreversible CKD and FSG. We hereby present a case of acute tubular necrosis in the setting of Oxandrolone use.

Case Description: A 30-year-old previously healthy male presented to the ED with complaints of nausea and vomiting. He reported intentional caloric restriction and intense exercise over the past month, along with using under-the-counter oral Oxandrolone. Labwork revealed AGMA and ketosis (CO2 17.2mmol/L, AG 24.4 mmol/L, β-hydroxybutyrate 48.97 mg/dL) elevated Creatinine (2.8 mg/dL). Glucose, LFTs and CPK were WNL. UA revealed Ketones, Protein 100 mg/dL, RBC 10-25. US and CT of abdomen and pelvis were unremarkable. He was started on IVF and anti-emetics with resolution of symptoms and starvation ketoacidosis. Renal function, however, progressively worsened. BUN/Cr < 20, FeNa 1.4% and no improvement with IVF was consistent with intrarenal etiology. Further work up revealed low C3, normal C4, negative ANA, ANCA, GBM Ab, dsDNA Ab, ASO, LAC, Cryoglobulin, Hepatitis B and Hepatitis C serology. Kidney biopsy was performed given rapid deterioration of renal function with creatinine peak at 6.06. Histology, Immunofluorescence and Electron Microscopy revealed ATN with unremarkable glomeruli. Kidney function gradually improved after 8 days, and patient was discharged in stable condition with follow up with nephrologist.

Discussion: Use of AAS has risen into a worldwide substance abuse problem. Although renal damage secondary to AAS use is rare, they have been demonstrated to cause glomerular damage as FSGS. Tubular injury, however, has only been seldomly reported in the setting of AAS use. Given the rise of uncontrolled use of AAS and the rarity of this type of injury in an otherwise young and healthy population, it is important to inquire further on a possible direct causal relationship. Increased compound risk with commonly coexistent excess creatine and protein intake should also be considered.

PO0303

Pregnancy and Hereditary Thrombotic Thrombocytopenic Purpura: A Case Report

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Introduction: Pregnancy and postpartum have been recognized as periods of high risk for development of thrombotic microangiopathy (TMA). We report a case of hereditary thrombotic thrombocytopenic purpura (TTP) unmasked by pregnancy.

Case Description: A previously healthy 32-year-old Caucasian female G1P1 24 weeks pregnant presented with urinary frequency, dark urine and diarrhea for 1-2 weeks. On initial presentation, blood pressure was at 153/96 mmHg. Labs were significant for a rapidly dropping Hgb with hemolysis, thrombocytopenia with a platelet count of 11, mild transaminitis, and a rising serum creatinine with no antecedent history of renal disease (table 1). Unfortunately, an ultrasound revealed intrauterine fetal demise. She received 2 units of platelets and underwent an uneventful delivery. Following delivery, all parameters including Hgb, platelets and Cr improved (table 1). Two days post-delivery, ADAMTS-13 level returned at <2%. She was started on high dose prednisone and received 4 sessions of plasmapheresis. ADAMTS-13 antibody was later found to be negative.

Discussion: TTP is caused by deficiency of ADAMTS-13 metalloproteinase which cleaves the Von Willebrand factor. Low activity of ADAMTS-13 (20-40%) is seen in patient with preeclampsia, eclampsia, HELLP syndrome and pregnancy associated hemolytic uremic syndrome. The enzyme level will decrease to less than 20% only in pregnancy associated TTP. Though TTP in the general population is mostly immune in nature, 24% of cases of pregnancy associated TTP are hereditary. Delivery has been shown to achieve rapid remission in many cases. Most authorities recommend initiation of plasmapheresis with TMA and pregnancy when platelet count is less than 30 with later addition of steroids when the diagnosis of TTP is confirmed. The response rate to treatment is 80-90%. Immune TTP may reoccur in future pregnancies but hereditary TTP has a 100% risk of relapse with future pregnancies making it essential to differentiate the two entities for appropriate management of future conceptions which requires plasma exchange starting early in pregnancy.

Table 1

	Pre-delivery	Post-delivery	Post-plasmapheresis
Hb (mg/dL)	13.9-->6.9	8.2	11.2
Platelets x10^9/L	11	69	521
LDH (U/L)	1616		
Haptoglobin (mg/dL)	<8		238
Cr (mg/dL)	2.5-->3.7	2.65	1

PO0304

No Tears, Frothy Urine, and Lots of Antibodies: Sjögren Syndrome Presenting as Tubulointerstitial Nephritis

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Introduction: Sjogren's syndrome(pSS) is a systemic autoimmune disease that primarily affects the exocrine glands. Renal involvement is a common finding among patients however, in select patients, worsening renal function precedes these symptoms. Associated pSS renal pathologies include tubulointerstitial nephritis (TIN), glomerulonephritis and renal tubular acidosis. Here we present an unusual case of a patient with worsening renal function as a primary presentation of Sjogren's syndrome.

Case Description: 52 year old woman with no medical illnesses presented with renal impairment and retrospectively reported fatigue, 18lbs weight loss, loss of appetite as well as dry mouth, dry eyes and dysphagia. Labs: Hb 9.4g/dL, BUN 24mg/dL, Cr 1.91mg/dL and random urine protein/creatinine ratio of 2.12mg/g without microscopic hematuria. ESR 94 mm/hr, RF 175 IU/mL and positive ANA with a speckled pattern and titre of 1:1280, normal C3/C4 levels, normal dsDNA, negative hepatitis B&C, negative basement membrane IgG antibodies, negative c-ANCA and p-ANCA. Renal ultrasound showed normal sized kidneys with normal echotexture and renal biopsy revealed interstitial nephritis with moderate to severe activity and mild chronicity. She was diagnosed with tubulointerstitial nephropathy secondary to primary Sjogren's syndrome and was started on 1mg/kg of prednisone along with topical agents for sicca symptoms. After 2 months labs revealed Hb 12.3g/dL, Cr 1.43mg/dL, ESR 22 mm/hr and urine protein/creatinine ratio of 0.358mg/g. She has subsequently been started on a prednisone taper to which she has responded well.

Discussion: TIN is associated with a number of systemic illnesses inclusive of pSS. Renal disease in pSS is as high as 42%, with TIN accounting for approximately 10-20% of cases. TIN usually presents after the initial diagnosis of pSS but in our patient it occurred concurrently with the diagnosis. The renal involvement in pSS is usually chronic and it typically shows monolymphocytic TIN with minimal glomerular involvement. However, there is a wide range of renal pathology including TIN to MPGN, membranous nephropathy, and focal crescentic GN. Even though renal impairment does not typically precede pSS it is imperative to biopsy as early as possible so that treatment can be initiated to prevent chronic disease.

PO0305

Excess Vitamin C Leading to Hyperoxaluria and AKI

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Introduction: Secondary hyperoxaluria is caused by increased ingestion of oxalate or oxalate precursors, increased oxalate enteric absorption due to fat malabsorption, or changes in intestinal microflora and can manifest as end stage renal disease or hypothyroidism.

Case Description: A 55-year-old female with history of hyperparathyroidism and hypothyroidism (not med compliant) presented with myxedema coma secondary to uncontrolled hypothyroidism. Initial workup revealed elevated potassium (7mmol/L), BUN (194mg/dL), SCr (35mg/dL) and TSH (>100uIU/mL). She was given IV levothyroxine, IV liothyronine, insulin, calcium gluconate and hydrocortisone, and started hemodialysis in the setting of acute kidney injury (AKI) with no known underlying CKD, nephrolithiasis or nephrocalcinosis. Autoimmune, gastrointestinal, and hepatobiliary AKI etiologies were ruled out. A renal biopsy revealed renal oxalosis (Fig 1). Investigation of possible secondary causes of renal oxalosis revealed consumption of large quantities of vitamin C in hopes of preserving her health during the COVID-19 pandemic. The patient remained dependent on hemodialysis was discharged on levothyroxine 150mcg sublingual daily followed by nephrology and endocrinology. At time of discharge, TSH remained >100 uIU/mL, but free T4 was 0.86 ng/dL without any hypothyroid symptoms. High dose vitamin C consumption was discontinued.

Discussion: The combination of severe hypothyroidism resulting in myxedema coma and the excessive intake of vitamin C, a precursor for oxalate stones in the kidney, resulted in AKI. However, we believe the severe hypothyroidism was a result of medication noncompliance vs manifestation of systemic oxalosis. We recommend considering secondary oxalosis in cases of dialysis-dependent AKI in the setting of high dose vitamin C consumption or increased exogenous oxalate ingestion and confirming this diagnosis with renal biopsy.

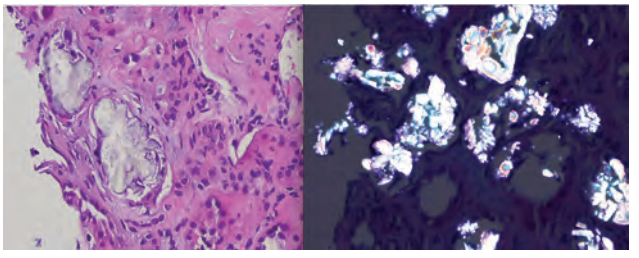

Figure 1: Left: Rhomboid shaped calcium oxalate crystals distending renal tubule with attenuated and disruption of epithelial lining. Right: Calcium oxalate crystals characteristically birefringent under polarized light microscopy.

PO0306

Candida parapsilosis Endocarditis Presenting as Acute Glomerulonephritis: A Case Report

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Introduction: Candida species is an uncommon cause of left sided endocarditis that traditionally associated with high morbidity rate. In a few rare cases, Candida endocarditis has been reported as a cause of infection related GN. Here, we described a case of Candida parapsilosis endocarditis that presented as acute glomerulonephritis.

Case Description: A 52 y.o Caucasian female with history of antiphospholipid syndrome, intravenous drug use history on suboxone who presented with 3 weeks of dyspnea, LE edema and tea colored urine. She was found to have elevation in creatinine to 3.6mg/dL from baseline of 1.08mg/dL. There was no history of fever, chill, night sweats, weight loss. There was a dime sized healing ulcer on the thigh. Due to her high risk thrombotic history, she received heparin for anticoagulation. A urine dipstick showed >300 protein and 3+ blood. A spot urine protein to creatinine ratio was 4.5. The urine sediment showed granular and hyaline casts, many RBC of normal morphology and rare acanthocytes. The C3 level was mildly decreased at 60 and C4 level normal at 14. She had

mildly elevated ANA at 1:80 and negative double strand DNA, smooth muscle antibody level, PR3/MPO and extractable nuclear antigen antibody including SSA/SSB, RnP, Scl-70 and Jo-1 antibody level. A CRP was 33 and ESR was 47. Blood cultures revealed Candida parapsilosis. MRI spine with inflammatory changes of L4-L5 suggesting osteomyelitis. Patient received micafungin but remained persistently fungemic. A TEE revealed a large mitral valve vegetation. While under evaluation for mitral valve surgery, she suffered from a large right MCA stroke and deceased within 48 hours from brain herniation. No autopsy performed due to family's request.

Discussion: Fungal associated GN is a rare clinical entity that usually mentioned only as a foot note in textbooks. The mechanism of kidney injury is likely immune complex deposition. Given the high mortality rate with Candida endocarditis and its associated complications, heightened clinical suspicion and early aggressive treatment with antifungal and surgery are important. Corticosteroid in one case report improved renal function indicating a possible role in patients with controlled infection.

PO0307

Linezolid-Associated Interstitial Nephritis

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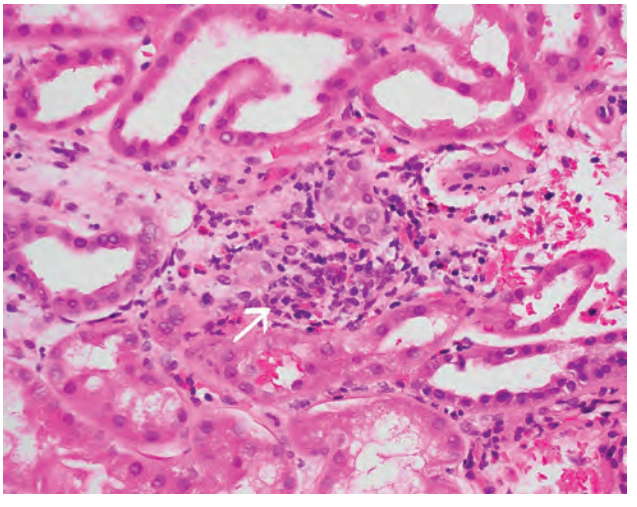
Introduction: Acute Interstitial Nephritis (AIN) accounts for 15-27% of renal biopsies performed for Acute Kidney Injury (AKI). Drug induced AIN remains the most common cause. We present a case of Linezolid induced AIN, a rare entity.

Case Description: Elderly male patient with type 2 diabetes, hypertension and normal renal function was initiated on linezolid for osteomyelitis. Two weeks later, he reported a maculopapular rash on his arms and chest. Labs were significant for a serum creatinine (Scr) of 3.8mg/dl. Immunological and infectious work up for AKI was unremarkable. Scr continued to increase to 7.2mg/dl and absolute serum eosinophil count was 1800 cells/microliter. Interstitial nephritis was suspected and empiric prednisone was initiated. Renal biopsy showed Acute Tubular Injury with Interstitial Nephritis and moderate interstitial fibrosis. The AIN was associated with several eosinophils, and was consistent with a drug induced reaction. Linezolid was stopped, and the patient continued a steroid taper with which SCr improved to 2.0mg/dl and remained stable. The patient did not meet diagnostic criteria for DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) as he had no other systemic involvement, and the rash was not associated with desquamation or infiltration.

Discussion: This patient developed a rash and interstitial nephritis after the initiation of linezolid. He reported no Non-Steroidal Anti-Inflammatory Drug (NSAID) intake and was on vancomycin and piperacillin- tazobactam for less than 48 hours, during which renal function remained stable. Linezolid associated Interstitial Nephritis is rare, and only 4 cases have been reported in the literature. As the prevalence of Methicillin Resistant Staphylococcus Aureus increases, we must be wary of this complication before initiating treatment. Renal function must be monitored, and prompt initiation of steroids can ensure improvement of renal function.



Pathology showing acute interstitial nephritis with eosinophils

PO0308

Rifampicin: An Infrequent Cause of AKI

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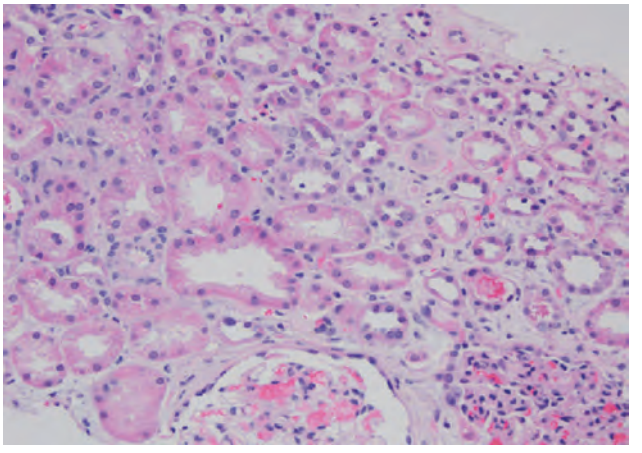
Introduction: Rifampicin is used to treat Mycobacterium infection. Hypersensitivity reaction to rifampicin resulting in acute kidney injury (AKI) is infrequent. Here we describe rifampicin hypersensitivity in a patient presenting with AKI who was treated for Mycobacterium marinum infection.

Case Description: A 43 year old male was treated with Rifampicin for Mycobacterium marinum infection 3 years ago. He recently injured his hand and took two pills of Rifampicin leftover from 3 years ago to prevent another infection. He took them about 12 hours apart and a few hours after taking the second pill he developed severe nausea, vomiting, flank pain and dark colored urine. He presented to emergency department and labs showed elevated LDH(lactate dehydrogenase) and bilirubin, thrombocytopenia, anemia and elevated creatinine. He was transferred to our hospital for further management. Upon arrival creatinine was 7.5mg/dl. Bilirubin had normalized and haptoglobin was in normal range. ADAMTS13 level was 56%. Peripheral smear did not show schistocytes. He underwent kidney biopsy which showed moderate acute tubular injury and focal thrombotic microangiopathy. It was determined that he had AKI from type 2 hypersensitivity to Rifampicin. His creatinine continued to worsen to 18mg/dl before improving. He did not require renal replacement therapy. On follow up three weeks later, his creatinine had improved to 1.7mg/dl.

Discussion: Rifampicin hypersensitivity can manifest with hepatitis, hemolytic anemia and AKI. It is most often seen when the drug is re-administered or used intermittently. The outcome of AKI is usually favorable after discontinuation of the drug, with most patients achieving full recovery within 90 days. As the hypersensitivity reaction is infrequent, prompt recognition and withdrawal of drug is important to prevent irreversible injury.



Renal biopsy showing Acute Tubular Injury.

PO0309

Hypertension Secondary to Obstructive Retroperitoneal Fibrosis

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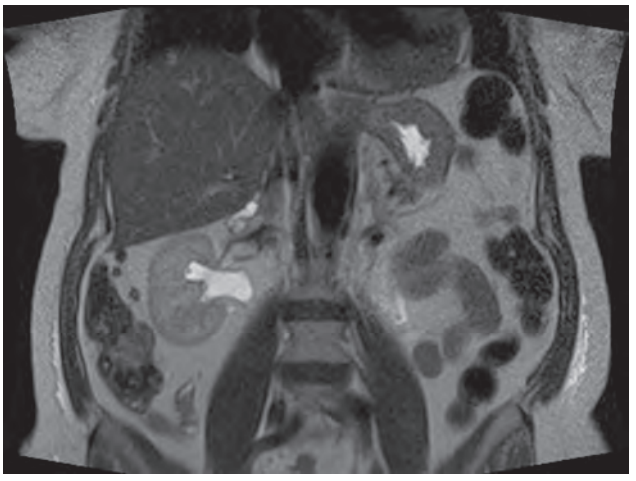
Introduction: Retroperitoneal fibrosis (RPF) has been known to cause ureteral compression leading to obstructive nephropathy. This case details RPF presenting as hypertensive emergency with acute on top of chronic kidney disease.

Case Description: A 62-year-old female with stage 3 chronic kidney disease and essential hypertension (HTN) presented to the emergency room with headache and elevated blood pressure (BP) of 200/121 mm Hg. Physical exam was significant for trace lower edema. Labs showed elevated creatinine at 13.8 (1.08 two months prior) and hyperkalemia, potassium at 5.8. Urine analysis was unremarkable. MRI revealed bilateral hydronephrosis and a soft tissue mass encasing the aortal bifurcation, abutting the ureters concerning for RPF vs. lymphoma. Subsequent MAG 3 showed significantly compromised left renal function. A foley was placed, returning 4.7 liters of urine in 24 hours. Her BP and headache improved with clonidine and nicardipine over the next 48 hours. Upon normalization of her BP and creatinine, patient was discharged. On follow up, CT guided biopsy of her mass confirmed RPF. Extensive workup for etiology was unrevealing, making a diagnosis of idiopathic RPF. Post discharge, a left ureteral stent was placed and repeat imaging after 3 months showed spontaneous regression of the mass with resolving hydronephrosis. The stent was removed, and the patient opted to pursue mycophenolate mofetil therapy to manage her RPF.

Discussion: Rarely detailed in medical literature, RPF induced secondary HTN has been proposed to be mediated by the tubuloglomerular feedback and renin angiotensin and aldosterone axis. Imaging can play a key role in diagnosing RPF. Whilst relieving obstruction can quickly resolve HTN in these patients, glucocorticoids and other immunosuppressive therapies can manage long-term progression.



Soft tissue mass encasing the distal abdominal aorta and aortic bifurcation, measuring 2.3 cm by 5.2 cm by 9.2 cm

PO0310

Precipitous AKI: A Unique Form of AKI by Vancomycin

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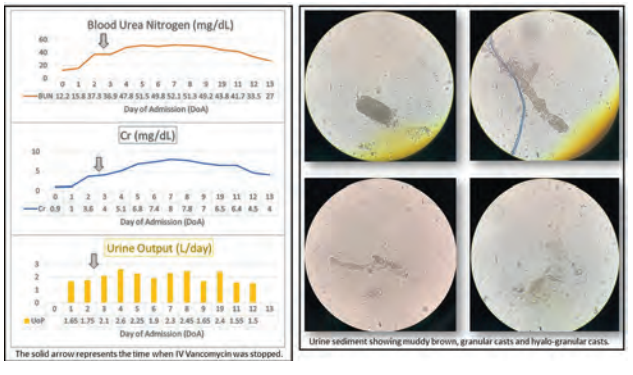
Introduction: Vancomycin-associated acute kidney injury (VA-AKI) is a well-known entity. With improvement in formulations of vancomycin (vanc), its incidence has decreased, however it remains a risk factor of AKI especially when used in combination with other nephrotoxic agents. We present a case of VA-AKI that represents a unique pattern of kidney injury, known as "precipitous AKI".

Case Description: A 23-yr-old male presented to the emergency room with fever & body aches for 1 day. He was getting chemotherapy for acute lymphocytic leukemia; last received cyclophosphamide 10 days ago. He was tachycardic. Physical exam was unremarkable. His absolute neutrophil count was $0.5x10^3$ cells/µl. He was admitted & started on IV vanc & Piperacillin/Tazobactam. On the 4th day of admission (DoA), he developed AKI with rise in blood urea nitrogen (BUN) and creatinine (Cr) to 37mg/dL and 3.6mg/dL, (baseline of 12mg/dL & 0.9mg/dL) respectively. Urine sediment showed granular casts suggestive of tubular injury. Vanc was stopped; until then he had received a cumulative dose of 5grams. Cr peaked to 8mg/dL on the 8th DoA. The rise in BUN was discordant which only rose to 52mg/dL. The patient never developed oliguria either. His BUN and Cr improved thereafter and he was discharged. The BUN and Cr were normal on repeat testing done 2 weeks later.

Discussion: Precipitous AKI is the term coined by Velez et al. which appears to be the first description of this entity. To our knowledge, only a handful of cases have been reported. It is seen in patients who receive high cumulative dose of vancomycin and manifests as rapid rise in Cr (more than 2.5mg/dL in a day) while in other causes of AKI the rise of Cr is between 1-1.5mg/dL. The relative rise in BUN does not match that of Cr. The patients do not develop oliguria, & cystatin C is usually normal:. These observations support the notion that glomerular filtration is not affected, and is postulated to be caused by tubular toxicity that effects the tubular secretion of Cr. Further studies are needed however.



PO0311

Atypical Hemolytic Uremic Syndrome Secondary to Homozygous CFHR1-CFHR3 Mutation

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a disease of complement dysregulation characterized by microangiopathic hemolytic anemia, thrombocytopenia, and multisystem end organ damage commonly affecting the kidneys. About two thirds have identifiable genetic abnormalities. Mutations cannot be identified in 30% of the time. A strong association has been observed between anti-FH autoantibodies and a homozygous deletion of *CFHR1* and *CFHR3*. Factor H autoantibodies can impair complement regulation, resulting in aHUS. We report a case of aHUS secondary to a homozygous CFHR1 – CFHR3 mutation.

Case Description: A 35-year-old gentleman with no significant past medical history presented with acute worsening of his kidney function of unclear etiology (creatinine 2.5mg/dL). Kidney biopsy was performed showing thrombotic microangiopathy without evidence of vasculitis. Two days post-biopsy, he developed acute weakness and slurred speech. MRI of the brain was compatible with multiple acute cerebral infarcts. Initial laboratory values were nonspecific but follow up labs showed evidence of hemolysis with worsening renal function (creatinine 3.8 mg/dL) and thrombocytopenia (platelet count 120,000 from 283,000 per microliter). Further workup showed undetectable haptoglobin, elevated lactic acid dehydrogenase, low C3 levels and normal ADAMS-T13 activity. Given high index of suspicion for aHUS and the absence of other causes of thrombotic microangiopathy, he was started on eculizumab. After 6 doses his renal function improved and repeat MRI showed improving cerebral vasculopathy suggesting that the process was likely thrombotic. The aHUS susceptibility panel was positive for a homozygous *CFHR3-CFHR*1 gene deletion with elevated Factor H autoantibody 74.2 mg/dl (normal 37-68 mg/dl). The patient's renal function stabilized with complete neurologic recovery. He remains on maintenance dose of eculizumab.

Discussion: Atypical HUS is an rare cause of thrombotic microangiopathy. Many cases have identifiable genetic mutations that lead to dysregulation of alternative complement pathway. Delayed or inappropriately treated cases lead to increased morbidity and mortality. Early screening for aHUS related genetic mutations in patients with acute kidney injury and microangiopathic hemolytic anemia is essential for prompt diagnosis of aHUS and help guide treatment duration.

PO0312

A Rare Case of Concomitant Acute Interstitial Nephritis (AIN) and HIV-Associated Nephropathy (HIVAN)

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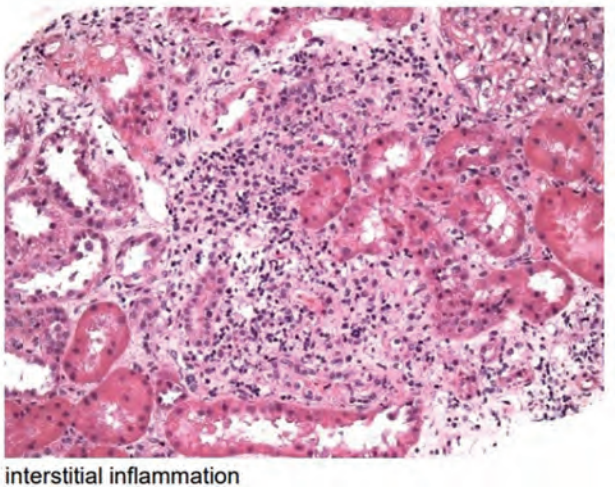
Introduction: HIVAN is characterized by collapsing focal segmental glomerulosclerosis (FSGS), the most common cause of renal dysfunction in HIV patients. Whereas AIN causes only 10% of renal dysfunction in HIV patients and it is usually caused by drugs, infections, or dysimmune syndromes but not as a direct consequence of HIV infection. AIN caused by HIV itself is a rare phenomenon, with only one reported case in the literature. We present a case of AIDS presenting itself as acute renal failure secondary to AIN and HIVAN

Case Description: 51-year-old male with a history of hypertension presented with abdominal discomfort, loss of appetite, and dark brown urine for one week. He denied medication use. Initial laboratory values of serum potassium 8.9 mEq/L, serum creatinine 18 mg/dL, serum bicarbonate 12 mEq/L. CT Abdomen showed no hydronephrosis. He underwent urgent hemodialysis for refractory hyperkalemia. Urinalysis showed pyuria with WBC clumps, and microalbumin-to-creatinine ratio of 27g/dL. Further workup revealed HIV-1 positive with a CD4 count of 5/mL and viral load of 2,680,000 copies/mL. Anti-retroviral therapy was started. Kidney biopsy was consistent with acute intestitial nephritis and collapsing FSGS. IV pulse steroids started for 3 days then oral prednisone with gradual improvement in the clinical status. Unfortunately, his clinical status deteriorated with an acute respiratory failure requiring intubation with multiorgan failure and refractory septic shock that resulted in demise

Discussion: AIN in HIV is rare with few case reports having been published in the literature. In this case, pulse dose steroids were use for treatment with a very limited response. Our aim is to remind physicians that AIN can be found in HIV with or without glomerular disease. More data is needed to establish treatment guideliness and monitor patient closely for treatment response.



PO0313

Unexplained AKI: Never "Brush" Off the Role of a Renal Biopsy

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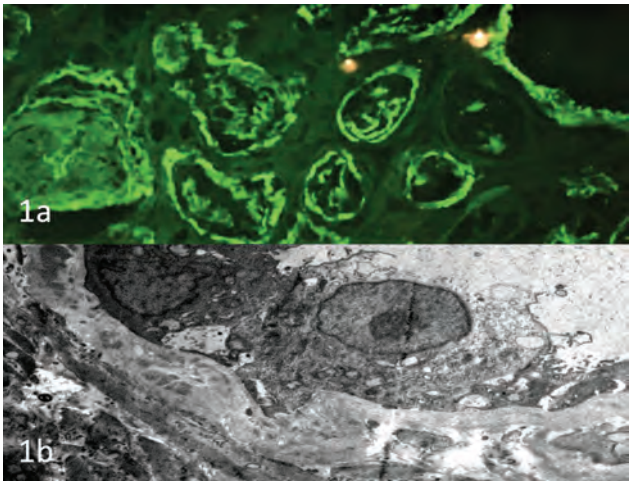
Introduction: Anti-Brush Border Antibody Disease (ABBAD) is a rare condition typically seen in elderly individuals and presents with acute kidney injury (AKI) and sub-nephrotic proteinuria. Patients often progress rapidly to ESKD despite treatment.

Case Description: A 73-y/o man with a PMH of HTN, a-fib and CKD (serum creatinine SCr 1.5 mg/dl 4 mo ago and 2.3 mg/dl 2 mo ago) was found to have a SCr of 3.2 mg/dl. His medications were tamsulosin, apixaban, losartan and metoprolol tartrate. He denied NSAID usage. His vital signs were normal and his physical exam was unremarkable. His urinalysis was significant for 2+ protein without blood. He had an elevated urine protein/Cr ratio at 1.5 g/g. Serological and infectious workups were negative. A renal ultrasound was normal. A renal biopsy demonstrated 50% global sclerosis with remaining glomeruli normal. There was moderate interstitial fibrosis and tubular atrophy. The immunofluorescence and electron micrographs are shown in Fig 1a and 1b. Specific IF staining for lipoprotein-related protein 2 (LRP2) was positive in the tubular basement membrane (TBM), consistent with a diagnosis of ABBAD. Because of his advanced age he was treated with 60 mg of prednisone alone with no improvement.

Discussion: ABBAD occurs from formation of IgG antibodies against low density lipoprotein-related protein 2 (LRP2) megalin which deposit on the tubular BM of the PCT. Because it is so rare, (<20 cases) little is known about the treatment with rare responses to prednisone and cytotoxic agents. It is unknown if rituximab is effective. ABBAD can recur in a renal transplant. Early diagnosis and aggressive immunotherapy would seem prudent. This approach requires a low renal threshold for biopsy in AKI. It is however unknown if early treatment can alter the typical abysmal renal outcome.



1a) IF showing segmental staining with IgG along the tubular basement membrane. 1b) EM showing electron dense deposits along the tubular basement membrane.

PO0314

Vitamin C, CKD, and Roux-en-Y; A Dangerous Combination

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Introduction: Patients who have undergone bariatric procedures can be at increased risk for acute kidney injury (AKI) due to oxalate nephropathy; therefore, it is important that there is an awareness of other risk factors for this condition in this patient population. In particular, high doses of vitamin C should be avoided.

Case Description: A 74-year-old female, who had a Cr of 0.8 mg/dl a year prior, with a history of Roux-en-Y gastric bypass surgery in 2016, recurrent nephrolithiasis, and an atrophic right kidney was advised to go to the hospital after outpatient laboratory data revealed a Cr of 8.7 mg/dl. The patient had been taking Vitamin C 1000 mg daily. An initial evaluation did not reveal an etiology of AKI and her renal function did not improve with 48 hours of IV fluids. Hemodialysis was initiated for uremic symptoms. The patient underwent a biopsy (Figure 1) which showed severe acute tubular injury, mild interstitial fibrosis and tubular atrophy, and significant tubular calcium oxalate crystal deposition. At the time of discharge, she had poor creatinine clearance and remained on hemodialysis.

Discussion: AKI related to oxalate nephropathy can be viewed as a confluence of pre-disposing conditions, risk factors, and exposures. Any single case may have one or more of these issues; this case is remarkable in that it encompasses multiple factors: 1. A pre-existent history of calcium oxalate stones, 2. A markedly atrophic right kidney, with a suspicion of chronic kidney disease and a reduced excretory capacity, 3. Prior Roux-en-Y gastric bypass resulting in increased absorption of oxalate, 4. Supplemental vitamin C intake, 5. Pyridoxine deficiency which limits the body's ability to "detoxify" oxalate. Unfortunately, oxalate nephropathy is associated with poor renal outcomes; therefore, patients with multiple risk factors for this condition should be appropriately counseled and closely monitored.

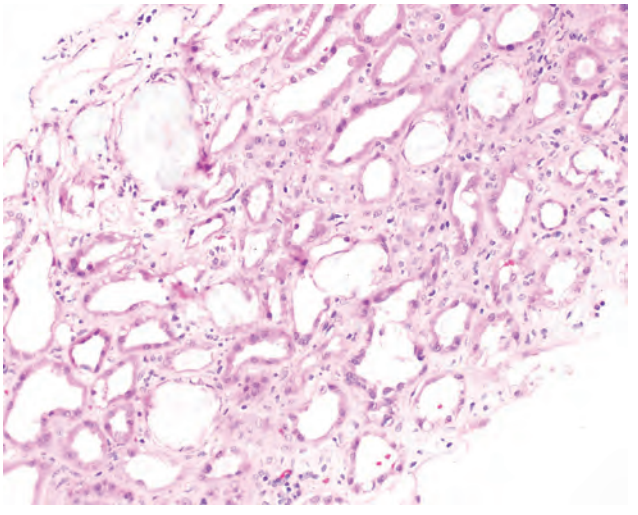

Figure 1: H & E stain

PO0315

Lamotrigine-Induced Acute Interstitial Nephritis

Indraneel Reddy, Abhay D. Patel, Rupesh Raina, Ron Jones. *Summa Health System, Akron, OH.*

Introduction: Medications such as penicillins, cephalosporins, vancomycin, ibuprofen, and ketorolac are the most common cause of acute interstitial nephritis (AIN), accounting for more than 75% of cases. Recently, antiepileptic drugs such as lamotrigine have been reported to cause AIN. Here, we report a case of a 39-year-old female who was on lamotrigine and admitted to the hospital with abdominal pain and acute renal failure.

Case Description: A 39-year-old female with a history of Hepatitis C, history of meth and heroin abuse, overactive bladder, hypothyroidism, and bipolar disorder presented to the emergency department with a week of abdominal pain. In the emergency department, she complained of nausea, constipation, and five days of hematuria. The patient was admitted after labs showed BUN/Cr of 48/3.69. Two weeks prior to presentation, she was started on lamotrigine 100 mg daily, which was held upon admission. Patient was started on IV fluids but her condition acutely worsened with thrombocytopenia, anemia, and leukopenia. She was started on methylprednisolone 500 mg IV daily due to concern for AIN vs vasculitis. Her blood and urine cultures resulted positive for E. coli, and she was subsequently started on IV ceftriaxone. The patient underwent a left kidney biopsy demonstrating AIN without crescentic glomerulonephritis, which was likely an allergic reaction secondary to lamotrigine use. Her biopsy also showed neutrophilic infiltration, likely secondary to pyelonephritis. She was discharged in stable condition on prednisone oral 20 mg daily.

Discussion: In summary, we present an adult patient on lamotrigine who was admitted due to acute renal failure. There have only been four reported cases of AIN induced by lamotrigine use. The patients had few commonalities other than lamotrigine use, but notably half of them were being treated for bipolar disorder. Our patient had a history of drug abuse with uncertainty on last use, which could represent another cause of

her AIN. After cessation of lamotrigine and treatment with methylprednisolone 500 mg IV, her kidney function improved. Renal biopsy confirmed AIN. Our case is significant because it substantiates the use of corticosteroids for management of lamotrigine-induced AIN.

PO0316

A Case of Abrupt Anuria from Bilateral Kinked Ureters

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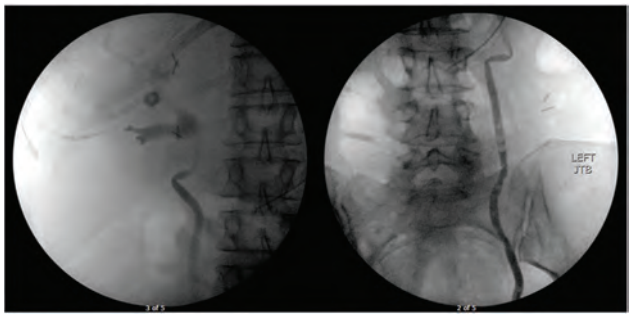
Introduction: Urinary tract obstruction is a well-known cause of reversible AKI. In patients with 2 functioning kidneys, bilateral ureteral obstruction is rare and unilateral ureteral obstruction rarely causes anuria and often does not result in a noticeable worsening of renal function. Here we describe a case of abrupt anuria and severe AKI secondary to bilaterally kinked ureters resembling parenchymal renal failure.

Case Description: A 58-year-old female with metastatic epithelioid mesothelioma underwent debulking peritonectomy, bilateral salpingioopherectomy, and omentectomy with hyperthermic intraperitoneal chemotherapy with cisplatin at 50 mg/m^2. Bilateral ureteral catheters were placed preoperatively to avoid ureteral injury during surgery. The catheters were removed on post-operative day (POD) 0. Post-operative course was initially uncomplicated with stable renal function and more than 2L urine output a day. On POD 2, she was noted to have abrupt anuria despite the presence of a functioning foley catheter. Her creatinine increased from 0.7 mg/dL to 2.3 mg/dL. Renal ultrasound revealed normal sized, echogenic kidneys with mild bilateral hydronephrosis. A CT cystogram with contrast was negative for a urinary leak. On POD 3, she remained anuric. At this point there was concern for a dense ATN caused by cisplatin and initiation of renal replacement therapy was considered. Given a high degree of suspicion for ureteral obstruction, the patient underwent cystoscopy with bilateral retrograde pyelogram revealing significant bilateral ureteral kinking (see image). Bilateral ureteral stents were placed with brisk urine output noted intraoperatively and her renal function improved back to baseline.

Discussion: Obstruction can occur at any point in the urinary tract but tends to only cause anuric AKI with an obstruction below the level of the bladder for patients with 2 functioning kidneys. Obstruction at the level of the ureter generally does not cause anuric AKI except in rare bilateral cases. This case may represent reflex anuria in the setting of a combination of post-operative bilateral ureteral spasm, edema, and kinking.



PO0317

Acute Interstitial Nephritis Secondary to Cocaine Use

Andrea Broka, Marjorie M. Flores chang, Carlos E. Arias Morales, Ahmed Abdurham, Jamil Ibrahim, Bessy Suyin Flores Chang. *SBH Health System, Bronx, NY.*

Introduction: Renal failure resulting from cocaine use disorder is well documented with etiology ranging from rhabdomyolysis, vasculitis, thrombotic microangiopathy and rarely acute interstitial nephritis, although unclear underlying mechanisms

Case Description: 33-year-old African American female with history of bipolar disorder alcohol, crack, cocaine use disorder presented with generalized fatigue and dyspnea for the past 4 days requesting inpatient detox. Home medications were ziprasidone, trazadone, topiramate. No recent history of nonsteroidal anti-inflammatory drugs, antacids or antibiotics. Family history was positive for hypertension only. On exam, vitally stable but, she was lethargic, with fluctuating sensorium and attention, with painful, deep linear nonbleeding lesion on oral mucosa and oliguric. Rest of exam was unremarkable. Her initial work up showed elevated blood urea nitrogen (BUN) 215 mg/dL and serum creatinine (SCr) 19.3 mg/dL, serum bicarbonate of 14 mEq/L, leukocytosis 19.2 x10^3 cells/uL with neutrophilia, normal eosinophil count and elevation of liver enzymes. Creatine phosphokinase was 782, peaked at 2574 and down trending the next day. Urinalysis showed large blood with more than 182 red blood cells/ HPF, 27 white blood cells/HPF, and moderate leukocyte esterase. Protein to creatinine ratio 1.12. Urine drug screen was positive for cocaine. Ultrasound kidney was unremarkable. A panel for autoimmune disease, hepatitis, and human immunodeficiency virus was negative. Initial assessment was acute kidney failure, likely acute tubular necrosis in the setting of cocaine use. She underwent emergent hemodialysis (HD) with improvement on her mental status. Renal biopsy showed diffuse acute tubulointerstitial nephritis, acute tubular injury, focal myoglobin casts and arteriosclerosis with negative immunofluorescence. She was started on IV methylprednisolone 1 g/daily for 3 days and then switched to oral prednisone 1 mg/kg for 8 weeks. HD was discontinued, urine output improved, with complete renal recovery on outpatient follow up

Discussion: We believe that AIN must be in the differential when treating patient with AKI and recent cocaine use, treatment must be started as earlier as possible to prevent progression to chronic kidney disease with fibrosis

PO0318

Uric Acid Crystallopathy Associated with Trimethoprim/Sulfamethoxazole (TMP/SMX) Use in a Patient with Gout

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Introduction: The commonly used antibiotic trimethoprim/sulfamethoxazole (TMP/SMX) is known to cause AKI. AKI induced by TMP/SMX can occur through various mechanisms, such as acute interstitial nephritis, crystalluria, acute tubular necrosis, and "pseudo"-AKI due to inhibition of proximal tubular secretory organic cation transporters by TMP. Here, we present a patient with a history of gout found to have AKI secondary to uric acid crystallopathy in the setting of TMP/SMX treatment.

Case Description: A 69-year-old male with a history of gout, heart transplant, and CKD3a secondary to calcineurin inhibitor toxicity was initiated on inpatient TMP/SMX treatment for *Pneumocystis jirovecii* pneumonia (PJP), with starting dose of 15mg/kg/day orally. 3 days later, creatinine was 3.2 mg/dL, from baseline of 1.6 mg/dL; cystatin C was 4.1 mg/L with an eGFR of 12. Urinalysis revealed pH of 5 and 4+ uric acid crystals. Serum uric acid level was 11.7 mg/dL, with an elevated fractional excretion of uric acid at 17%. Of note, the patient had been off urate-lowering therapy since heart transplant, and had had 3 gout flares in the 6 months prior to presentation. Because TMP/SMX is the preferred treatment for PJP, it was continued. He was given IV bicarbonate to alkalinize his urine; uric acid crystals were no longer present on repeat UA the next day. He was also given rasburicase, which lowered serum uric acid to <0.4 mg/dL. Creatinine began to downtrend 1 week after rasburicase therapy, reaching baseline levels about 3 weeks later, while still on TMP/SMX.

Discussion: Uric acid crystallopathy, uricosuria, and hypouricemia associated with SMX and/or TMP have been previously reported in the literature. It is hypothesized that SMX may inhibit uric acid reabsorption in the proximal tubule, increasing fractional excretion. TMP has also been shown to be uricosuric. Studies to determine whether SMX and TMP inhibit heterologously-expressed urate transporters are ongoing. Patients with a history of gout and a high baseline serum uric acid level may be at higher risk of kidney injury from uric acid crystallopathy when administered TMP/SMX. Thus, it seems appropriate to check serum uric acid levels before initiating TMP/SMX therapy in patients with gout. If serum uric acid level is elevated, concomitant urate-lowering therapy may be renoprotective.

PO0319

Pseudo AKI: When the Kidney Biopsy Doesn't Match the Creatinine

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Introduction: Elevated Creatinine (Cr) without AKI can be seen due to increased production of Cr, interference with the assay, decreased tubular secretion of Cr and urine ascites. We report a patient who presented with pseudo AKI due to delayed urine leak after prostatectomy.

Case Description: A 53-year-old male with PMH of hypertension, mixed connective tissue disease and prostate cancer was admitted to an outside hospital 6 weeks after prostatectomy due to AKI noted during post op follow up visit. He had abdominal pain for which he was taking naproxen, nausea and oliguria. Labs showed a Cr 6.58 mg/dl (baseline 1.1 mg/dl), proteinuria, hematuria and pyuria. A CT of his abdomen showed fluid in his pelvis and no hydronephrosis. His Cr worsened despite supportive care. Serologic testing was unremarkable and a renal biopsy revealed mild acute tubular injury and glomerulomegaly. His Cr improved to 5 mg/dl with foley catheter placement and he was discharged. He presented to our ED two days later with worsening symptoms. Labs revealed his Cr had worsened to 10.8mg/dl and BUN was 103 mg/dl. He had hyperkalemia, metabolic acidosis, hyponatremia and hyperphosphatemia. A repeat CT of his abdomen revealed fluid in the retropubic space and free fluid in peritoneum concerning for an anastomotic leak. Static cystogram confirmed a leakage from the vesicourethral anastomotic site into the retropubic space. A drain was placed in retropubic space and a foley catheter was maintained. He was discharge with resolution of symptoms, drain and foley catheter in place with Cr of 1.1mg/dl and normal electrolytes.

Discussion: Vesicourethral anastomotic urinary leak is reported in 8.6-13.6% of cases after laparoscopic prostatectomy and most cases present within 8 days after surgery. Patients usually present with symptoms due to urine leak resulting in peritonitis, paralytic ileus and pseudo AKI. Pseudo AKI is a rare condition with biochemical evidence of AKI in the absence of structural kidney damage or injury. It can be seen following genitourinary surgery, blunt abdominal injury or radiation therapy leading to urine ascites. Urine ascites causes reverse auto peritoneal dialysis characterized by flux of small molecules from collected peritoneal urine to blood. Nephrologists should have a high degree of suspicion for pseudo AKI in patients who present with oliguria, ascites and biochemical evidence of AKI following genitourinary surgery.

PO0320

Liraglutide-Induced Hypercalcemia with AKI

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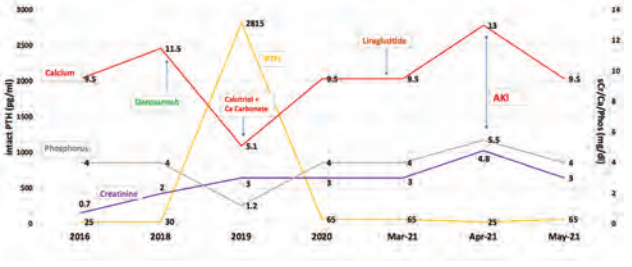
Introduction: Iatrogenic hypercalcemia from Vitamin D analogues and Calcium supplements is well-described. We present a patient who develped AKI and hypercalcemia on stable doses of these agents in CKD after being started on Liraglutide. This diabetic agent is a GLP-1 agonist, used for weight loss and glycemic control. We postulate the decreased gastric and intestinal motility caused by Liraglutide as the cause of increased enteric absorption and bioavailability of CaCO3 + Calcitriol leading to hypercalcemia-induced AKI.

Case Description: A 60 YO man with PMH of DM-2, Obesity and Multiple Myeloma (MM) presented for evaluation of AKI on CKD. He had CKD stage 3b due to MM with a b/l sCr of 3 mg/dl. Two years prior, he developed severe symptomatic hypocalcemia after treatment with Denosumab for osteolytic lesions. He was started on Calcitriol 1 mcg QD and CaCO3 2000 mg TID with stable serum Calcium, phos, iPTH and Cr for the next two years. He presents now with fatiguability, paresthesias and weight loss, one month after being started on Liraglutide by his PCP. Labs: serum Cr 4.3 mg/dl (b/l 3 mg/dl), Ca 13 mg/dl (b/l 9.5 mg/dl), Phos 5.5 mg/dl, iPTH 25 pg/ml. AKI was deemed secondary to hypercalcemia and thus Liraglutide, Calcitriol and CaCO3 were discontinued with resolution over two weeks (Fig 1).

Discussion: Liraglutide improves glycemic control and reduces weight by slowing gastric and intestinal motility inducing early satiety. It modifies the enteric absorption of drugs and can increase the bioavailability of lipophilic drugs such as Calcitriol. Longer contact with gastric acidic pH can potentially render agents more lipophilic with increased absorption. In our case, the temporal relationship between Liraglutide and onset of hypercalcemia, in a patient previously stable on unchanged doses of Calcitriol and CaCO3, suggests increased enteric absorption of calcitriol and calcium induced by the GLP-1 agonist. We suggest close monitoring and potential reduction of Calcitriol and CaCO3 dose prior to starting gastroparetic agents like Liraglutide. Further studies are recommended to better elucidate the pharmacokinetics of Calcitriol and Liraglutide.



PO0321

Recreation with a Concerning Diagnosis

Sobia N. Khan, Heesuck Suh. *Stonybrook University Hospital, Stony Brook, NY.*

Introduction: Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by non-necrotizing/non-caseating granuloma. The diagnosis of sarcoidosis requires stepwise approach to identify organs that may be affected and are amenable to biopsy, exclusion of other causes of granulomatous histopathology with special stains for mycobacteria and fungi, documentation of involvement of at least one additional organ system, and exclusion of other multisystem granulomatous diseases.

Case Description: A 73-year-old male with history of chronic kidney disease stage II serum creatinine 1.4mg/dl, T2DM, hypertension, history of lymphoma presented to the clinic. He was noted to have a black ink tattoo on his shoulder, present for > 40 years. Blood work showed wbc 8.66, H/H 12.8/39.8, platelets 210, BUN/Cr 34/2.86, GFR 21, Na 139, K 3.6, Hco 26, Ca 10.9, P 3.5, Mg 2.2, Hgba1c 6.3%, Ua +protein. Follow up: Further work up for hypercalcemia and acute kidney injury showed Ca 11.2, iPTH 10.2, PTHrP 4.7, 1, 25 vit D 78.2, vit D 41, ACE 84, SPEP/UPEP: no monoclonal gammopathy. CXR negative for hilar lymphadenopathy. Renal ultrasound normal size kidneys with mild echogenicity. Chest CT showed calcified enlarged left lower cervical, supraclavicular, chest wall and axillary lymph nodes and reticular asymmetric mild pleural thickening. He underwent axillary lymph node biopsy which showed granulomatous lymphadenitis, with extensive infiltration by pigment laden macrophages, multiple non-caseating granuloma with foreign body type giant cell, some with intracellular pigment particles staining. Staining was negative for any mycobacterial or fungal organism, melanoma cocktail had negative staining, the immunostains showed increased background due to pigment. The differential included non-infectious granulomatous lymphadenitis and sarcoidosis.

Discussion: Our patient had a tattoo placed > 40 year ago and developed non-caseating granuloma with extensive infiltration by pigment laden granuloma. In an unexplained case of hypercalcemia in the setting of granulomatous histopathologic finding containing tattoo pigment, it is prudent to consider the diagnosis of sarcoidosis. Granulomatous reaction to tattoo pigment histologically can be sarcoidal or foreign body type. These sarcoidal granuloma usually involve the tattooed skin and may represent first manifestation of systemic sarcoidosis.

PO0322

Rifampin-Induced Hemolysis Resulting in Pigment Nephropathy

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Introduction: Rifampin is an antibiotic that is a key component of multidrug regimens used to treat mycobacterial infections. The toxicity profile including hepatotoxicity is relatively well known, however some other complications including hemolysis, is a rare side effect. Pigment nephropathy is an abrupt decline in renal function as a consequence of the toxic action of endogenous heme-containing pigment on the kidney. We present a case of pigment nephropathy in the setting of rifampin-induced hemolysis requiring renal replacement therapy.

Case Description: A 74 year old female with a history of bronchiectasis, cavitary lung lesion due to pulmonary nocardiosis, mycobacterium avium-intracellulare infection (MAI) and atrial fibrillation presented with multi-organ dysfunction and anuria while recently restarting rifampin, azithromycin and ethambutol for the treatment of MAI infection. Key laboratory findings were a serum creatinine of 3.7 mg/dL and BUN 62 up from a baseline creatinine of 0.65 mg/dL with severe thrombocytopenia, platelet count 36 k/μL and hemoglobin of 10.4g/dL. This coupled with liver dysfunction evidenced by INR 1.4, indirect bilirubin 6.2 mg/dL, AST 1311 U/L, ALT 506 U/L, elevated lactate dehydrogenase 2074 U/L, low haptoglobin 16 mg/dL, gave an initial suspected diagnosis of thrombotic microangiopathy (TMA). Peripheral blood smear revealed few schistocytes. Negative ADAMTS13 antibody and a low PLASMIC score guided us not to initiate plasmapharesis. Serological work up including ANA, dsDNA, ANCA were negative, while C3 was low at 76 mg/dL and C4 14 mg/dL. The patient remained anuric and was initiated on hemodialysis. As the platelet count improved, she underwent kidney biopsy showing diffuse acute tubular injury with prominent pigmented casts. Immunofluorescence was negative without any evidence of TMA. After approximately two months of dialysis, renal function recovered back to serum creatinine of 1.14 mg/dL and the patient no longer required hemodialysis.

Discussion: Rifampin induced hemolysis is rare complication but can mimic TMA and cause renal dysfunction due to pigment nephropathy. Nephrologists should be aware of this possible rare complication of rifampin therapy.

PO0323

Paraneoplastic Manifestations of Mantle Cell Lymphoma

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Introduction: Mantle cell lymphoma (MCL) is a rare and aggressive form of Non Hodgkins Lymphoma. Pathological patterns involving extra nodal sites are either the result of lymphoid infiltration or secondary mechanisms such as immune complex deposition triggering paraneoplastic disease, that can be revealing of the underlying pathology.

Case Description: 58-year-old Hispanic male with a history of hypertension, hyperlipidemia presented with nontender, nonpruritic rash from buttocks down that evolved from a petechial scattered rash into a maroon-colored, palpable purpura. He had no associated fever, chills, abdominal symptoms, or weight loss. Labs were notable for WBC 13.3/nL, Hgb 11 g/dL, Platelets 100/nL, Creatinine 2.3mg/dL (Creatinine 1 mg/dL 6/25/2019), AST/ALT 87/70 U/L, ESR 50 mm/hr, CRP 69 mg/L and urinalysis with large blood and 4-10 RBCs, Protein/Creatinine Ratio, Urine 0.34 mg/dL. RUS showed normal size kidneys and 19.5 cm spleen. Patient received 1-gram IV Methylprednisone for presumed IgA nephropathy. Complement levels were low, not consistent with IgA Nephropathy leading to a negative serological workup for infectious disease and secondary glomerulonephritis. Renal biopsy showed immune complex mediated GN with C1q positivity and diffuse foot process effacement. CT scan of abdomen showed splenomegaly with markedly enlarged lymph nodes throughout the abdomen and pelvis. Further outpatient workup was positive for skin biopsy with leukocytoclastic vasculitis. Lymph node biopsy was positive for Ki-67 of 70%, cyclin D1 along with chromosomal analysis positive for t(11:14) confirming mantle cell lymphoma. He was enrolled in a research study which includes Rituxan, bendamustine and high dose cytarabine.

Discussion: Developing a rash led the patient to seek medical attention. Combination of rash, hematuria and abnormal creatinine presumed a diagnosis of IgA nephropathy, however both skin and renal biopsy showed immune complex mediated pathology representing paraneoplastic disease. Further workup revealed splenomegaly and lymphadenopathy (LAD) eventually diagnosing MCL. MCL classically presents with B cell symptoms and LAD, but it is important to recognize that extra-nodal manifestations can unmask and lead to an earlier diagnosis and treatment. Management of MCL also treated his paraneoplastic pathology as seen by improved renal function and no recurrence of rash.

PO0324

Page Kidney Secondary to Ruptured Mycotic Pseudoaneurysm of Renal Artery: An Unusual Complication of Infective Endocarditis

Ebubechukwu Ezeh, Saad Ullah Malik, Zachary S. Higginbotham, John L. Saylor, Ghassan Bandak. *Marshall University Joan C Edwards School of Medicine, Huntington, WV.*

Introduction: Mycotic pseudoaneurysms of renal artery following infective endocarditis are uncommon and their rupture is the most feared complication. This can lead to subcapsular hematoma and development of Page kidney, an uncommon cause of secondary hypertension and renal dysfunction. We present a unique case of ruptured

mycotic pseudoaneurysm of the renal artery that resulted in subcapsular hematoma and Page kidney in an intravenous (IV) drug user.

Case Description: A 36-year-old female IV drug user presented with fever and hemoptysis. She denied history of kidney disease or preceding trauma. Admission blood pressure was 116/61 millimeter of mercury. Initial serum creatinine was 1.6 milligrams per deciliter (mg/dl) and hemoglobin (Hb) was 12 grams per deciliter (g/dl). Renal ultrasound was unremarkable. She was found to have septic emboli on computed tomography (CT) of the chest, and methicillin-resistant Staphylococcus aureus (MRSA) grew in her blood cultures. Patient was diagnosed with infective endocarditis based on Duke's criteria. She was started on IV antibiotics. On the third day of admission, she developed severe right flank pain and hematuria. She had worsening acute kidney injury and was started on hemodialysis. She was persistently hypertensive and progressively anemic. Hb dropped to 6.5 g/dl requiring transfusion of packed red cells. CT abdomen showed a new aneurysm and a large subcapsular hematoma of the right kidney. The bleeding pseudoaneurysm of the superior pole branch of the right renal artery was embolized by interventional radiology. She subsequently improved and no longer required hemodialysis. Plasma renin activity level returned elevated at 12.26 nanograms per milliliter per hour (reference 0.16-5.83).

Discussion: Renal artery aneurysm has a reported incidence of 0.1%. Subcapsular hematoma from rupture of mycotic pseudoaneurysm is a very rare complication of infective endocarditis. Page kidney is a hyperreninemic phenomenon that results from the renal ischemia secondary to external compressive forces from subcapsular hematoma. Elevated renin level and activation of the renin-angiotensin-aldosterone system usually occurs, as in our patient. For this reason, angiotensin converting enzyme inhibitors and relief of external compression are great treatment options in these patients.

PO0325

A Case of AKI with ANCA Vasculitis Associated Retroperitoneal Fibrosis

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Introduction: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) refers to a group of multi-system autoimmune small vessel diseases that can give rise to a broad array of clinical signs and symptoms. ANCA-associated retroperitoneal fibrosis (RPF) is an exceptionally rare condition characterized by fibroinflammatory changes in the retroperitoneal space. Most RPF cases are idiopathic, or can be secondary to other medical conditions, the rarest association is with AAV. We present a case of ANCA-associated RPF in a patient with recurrent acute kidney injury (AKI).

Case Description: A 57-year-old male with a history of reactive arthritis presented to the hospital with acute left-lower quadrant abdominal pain and found to have AKI due to obstruction by a soft tissue nodule on the left pelvic sidewall with mild-moderate hydronephrosis. He underwent left ureteral stent placement and his hydronephrosis resolved. Left iliac lymph node pathology was consistent with RPF. He was started on high-dose prednisone with resolution of his AKI. Steroids were tapered after repeat imaging 6 weeks later showed a decrease in the size of the soft-tissue nodule. He subsequently had a series of repeat admissions to the hospital with fevers, hypotension, shortness of breath, and recurrent AKIs. Each time, he was treated with antibiotics and stress-dose steroids with resolution of his symptoms. He was advised to return to the hospital as his symptoms progressed to include hemoptysis and epistaxis. He was found to have proteinase-3 antibodies (PR-3) consistent with granulomatosis with polyangiitis and was started on rituximab.

Discussion: RPF in association with AAV is an extremely rare condition with very few cases documented in the literature. RPF is an uncommon collagen vascular disease characterized by inflammation of the retroperitoneal space which can produce obstruction notably affecting the abdominal aorta, iliac arteries and ureters. Mostly idiopathic, RPF can be associated with vasculitis, medications, infection, and neoplasms. As highlighted in this case, AAV should be considered with a recently diagnosed RPF and recurrent AKI. A hallmark is improvement of symptoms with steroids. This is important with reference to patient outcomes as delayed treatment, especially when renal disease is present, portends a higher risk of end stage renal disease and early mortality.

PO0326

Runaway Kidneys: First Case of Bilateral Herniated Kidneys in a Ventral Hernia

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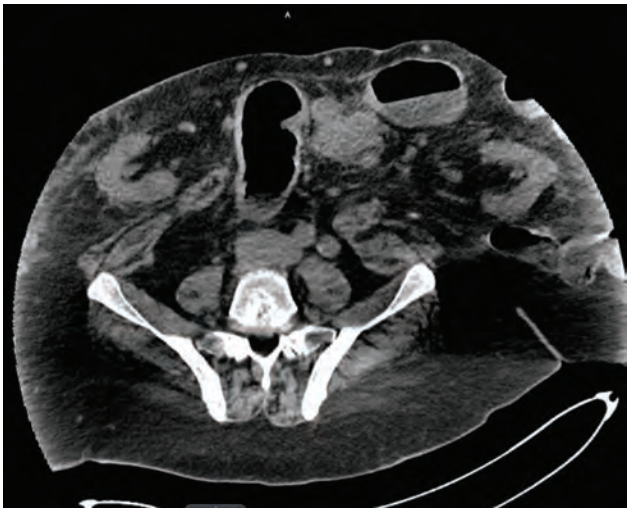
Introduction: Kidney herniation is extremely rare and typically seen in the setting of congenital defects. A handful of case reports have described traumatic thoracic herniation, postoperative renal transplant herniation and one report of postoperative incisional herniation. In this case report, we discuss the first case of bilateral kidney herniation into a ventral abdominal wall hernia.

Case Description: 58-year-old male with a significant history of CKD stage IIIb, hypertension, large abdominal wall hernia, hypothyroidism presented to the Emergency Department with complains of abdominal pain and diarrhea. Vital signs were unremarkable and physical exam was pertinent for morbid obesity (BMI 0kg/m2) and a non-reducible ventral hernia. Labs revealed serum creatinine of 4.77 mg/dL with a prior baseline of 1.9-1.8 mg/dL. CT scan without contrast showed a massive ventral hernia containing pancreas, bilateral kidneys and loops of bowel forming pannus overlying the right anterior pelvic wall. Persistent mild hydronephrosis without a definitive obstructive mass, obstruction might be caused by tethering of the proximal ureter to this large ventral hernia. No improvement in renal function was noted despite fluid resuscitation and Foley catheter placement. Urology was consulted and patient was taken for cystoscopy with bilateral retrograde pyelograms and left diverting single-J ureteral stent insertion. His renal function improved remarkably following relief of obstruction and serum creatinine down trended to 2.87mg/dL at discharge. Patient was scheduled to follow up with nephrology and urology at discharge

Discussion: Kidney herniation is very uncommon and usually, only mobile structures, such as the small intestine and omentum are seen in ventral hernias. We postulate that mechanical forces related to obesity and prior surgeries played a role in the herniation of both kidneys which are normally firmly anchored in the retroperitoneum.



PO0327

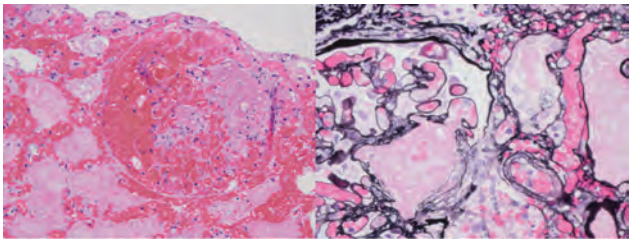
IV Immunoglobulin Triggering Renal Cortical Necrosis

Janame J. Kottey, Niraj K. Yadav, Rama Kethineni, Divya Raghavan, Fuad S. Shihab, Monica P. Revelo Penafiel, Josephine Abraham. *University of Utah Health, Salt Lake City, UT.*

Introduction: Renal cortical necrosis is a rare cause of acute kidney injury mostly seen in infants and young women with obstetric complications accounting for >50% of cases. Intravenous immunoglobulin (IVIG) is used for treatment of various conditions and one of the complications associated with its use is thromboembolism. We report the case of a patient that developed thrombotic microangiopathy with renal cortical necrosis after receiving IVIG.

Case Description: A 50-year-old man with Alport syndrome status post renal transplant in 2008 complicated by nasal Natural Killer T-cell lymphoma in 2017, had cutaneous recurrence in 2020 and was started on treatment with Brentuximab. He subsequently developed Immune Thrombocytopenic Purpura (ITP) and was started on pulse steroids, Rituximab, and IVIG. He was admitted for sudden onset of anuric renal failure after receiving the first dose of IVIG. He was off antimetabolite since diagnosis of NK/T-cell lymphoma in 2008 and Tacrolimus was held after he developed thrombocytopenia raising concern for allograft rejection. The patient was started on dialysis. Evaluation including C3, C4, ANA, anti-GBM antibodies, ANCA, rheumatoid factor, cryoglobulins, HIV, Hepatitis B and C, blood and stool cultures, stool Shiga toxin, echocardiogram, CMV PCR, peripheral smear, BK virus, ADAMTS 13, and DSA were unremarkable. He underwent renal biopsy that showed extensive cortical necrosis and thrombotic microangiopathy. A follow up ultrasound showed no blood flow to the kidney allograft. He did not had renal recovery and was discharged on outpatient dialysis.

Discussion: Thrombosis is a well-known complication of IVIG. IVIG increases blood viscosity and reduced blood flow promoting thrombogenesis. This can manifest as acute coronary syndrome, stroke, or venous thromboembolism. In our patient, it has manifested as thrombotic microangiopathy with cortical necrosis. IVIG, although, a very useful drug in treatment of various medical conditions should be used with caution, ensuring adequate hydration while monitoring baseline viscosity in patients at risk of hyperviscosity, prior to administration.



PO0328

Renal Failure due to Bilateral Renal Artery Stenosis

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Introduction: We present a patient with renal failure and accelerated hypertension while on a chronic, stable dose of an angiotensin-converting enzyme inhibitor (ACEI) due to progression of renal artery stenosis (RAS).

Case Description: A 73 year-old Caucasian male with DM2, HLD, CKD2 was referred for evaluation of resistant HTN. Initial visit, blood pressure (BP) was controlled on stable doses of metoprolol XR 50 mg qd, amlodipine 10 mg qd, hydrochlorothiazide 25 mg qd and lisinopril 40 mg qd. Ultrasound revealed bilateral 11 cm kidneys, left proximal RAS with peak systolic velocities (PSV) of 2.6 m/s, globally elevated resistive indices (RI) >0.83-0.86. Given controlled HTN, stable renal function with baseline Scr range of 1.1-1.2, he was conservatively managed with above medications and statin. On 4 month follow up, BP 160-200/60s, despite stable medication doses and compliance, unexplained elevated Scr 2.1 mg/dL. Given suspicion of RAS progression, renin and aldosterone level were drawn measuring 3000 pg/ml (6 mo prior 1800) and 16 ng/dl (prior 12), respectively. Patient underwent renal artery duplex with noted bilateral RAS: >60% diameter reductions and RI averaging 0.85. ACEI was promptly discontinued and within 48 hours, the patient's Scr improved to 1.5, and he underwent CT-Angiogram (CTA) abdomen to determine if intervention needed. CTA noted bilateral moderate ostial RAS (left 50%, right 30%) due to progression of atherosclerotic calcifications. At follow up, Scr normalized to 1.2, BP controlled on amlodipine 10 mg qd and carvedilol 3.125 mg BID. Given the resolution of uncontrolled resistant HTN, and return to baseline Scr, renal artery stenting was not pursued and the decision remained continued monitoring.

Discussion: ACEI are indicated as effective anti-HTN therapy in unilateral RAS. However, when accelerated hypertension and/or renal failure occurs while on an ACEI in an elevated risk individual with RAS, a high index of suspicion for RAS progression must be entertained and the ACEI promptly discontinued. Individuals at risk for progression of atherosclerotic lesions are elderly individuals, especially those with HLD and DM. Elevated renin levels and Scr, which were rapidly obtainable during our clinic visit, were suggestive of pronounced renal ischemia and prompted quick action of ACEI discontinuation, definitive imaging and overall clinical improvement.

PO0329

The Role of KYNU in Mediating Sex Dimorphism of AKI

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Background: Acute kidney injury (AKI) is a disorder that is associated with high mortality and a high risk for development of chronic kidney disease. It is well documented that female gender is associated with relative resistance to kidney injury, the underlying mechanism is incompletely understood. Mounting evidence suggests that NAD^+ levels are associated with enhanced tolerance of kidney to injury, and exogenous supplement of NAD^+ precursor NMN alleviate AKI. The present study examined NAD^+ synthesis pathways and their association with gender related susceptibility to AKI.

Methods: IRI AKI model was performed on 8 weeks old wild-type C57BL/6J female and male mice, bilateral renal pedicles were clamped for 22 minutes. The animals were euthanized 48 hours after reperfusion. Prepubertal (3 weeks old) wild-type C57BL/6J female or male mice were ovariectomized or castrated respectively and were euthanized after 5 weeks for renal KYNU expression analysis. The metabolites of NAD^+ de novo pathway were examined by HPLC.

Results: Following IRI, female mice had less severe kidney injury, manifested as lower BUN and Cr levels, lower kidney injury marker (NGAL) expression and alleviated tubule damage. Further study revealed renal KYNU, but not other enzymes involved in the NAD^+ synthesis pathways, was 5 fold higher in female mice compared to male at age 8 weeks, despite that it is comparable between female and male mice at age 7 days. Prepubertal oophorectomy in female mice did not significantly decrease renal KYNU expression, in contrast, prepubertal castration of male mice increased renal KYNU levels to that seen in female, demonstrating KYNU is regulated by testosterone other than estrogen. HPLC result showed no difference in the metabolites concentration between male and female mice under physiological condition, however, following IRI, 3-HAA and QA concentration, which are precursors for NAD^+, were significantly upregulated in the female urine but remained unchanged in the male urine, so as QA concentration in the female kidney, suggesting kynurenine pathway is more activated in the female kidney under AKI condition, which may contribute to NAD^+ synthesis and improve AKI.

Conclusions: We propose a KYNU-dependent mechanism, which contributes to the relative renoprotection of female after IRI by regulating renal NAD^+ level. NAD^+ de novo synthesis pathway may be a potential target for IRI-AKI treatment.

Funding: Government Support - Non-U.S.

PO0330

β-Estradiol Protects from Ferroptosis and Explains the Higher Sensitivity of Murine Male vs. Female Kidney Tubules to Acute Tubular Necrosis

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Background: In several preclinical models of acute kidney injury (AKI), male mice are known to exhibit a higher sensitivity compared to females, but mechanistic insights to explain this observation have been lacking over decades. Acute tubular necrosis (ATN) is a common feature of AKI the sensitivity to which might explain this long-standing obstacle.

Methods: Isolated murine kidney tubules were assessed with cell death assays (e.g. LDH release assay).

Results: Here, we demonstrated in isolated murine kidney tubules that spontaneous ATN is a regulated event. While tubules isolated from combined necroptosis- and pyroptosis-deficient mice ($MLKL/GSDMD^{DKO}$) did not show different LDH release levels compared to control, inhibition of ferroptosis by the ferroptosis inhibitor ferrostatin 1 (Fer-1) significantly protected wild type tubules. Importantly, we detected less spontaneous necrosis in female versus male tubules. While female tubules exhibited resistance to LDH release, male tubules were sensitive but could be protected by co-incubation with Fer-1. Tubular sex specific differences could not be explained by potential pro-ferroptotic effects of testosterone but rather by anti-ferroptotic effects of β-estradiol.

Conclusions: In summary, while these data confirm the involvement of ferroptosis in spontaneous tubular necrosis, we identify β-estradiol as a general inhibitor of ferroptosis. This anti-ferroptotic effect explains the difference in sensitivity toward ATN of renal tubules of male and female mice.

Funding: Government Support - Non-U.S.

PO0331

Pharmacological Validation of HDAC8 as a Therapeutic Target for AKI

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Background: Treatment for acute kidney injury (AKI) remains a significant unmet medical need and there are few validated targets on which to base therapeutic interventions and drug discovery programs. Our work has revealed histone deacetylase 8 (HDAC8) as a promising new candidate.

Methods: Known potent, selective HDAC8 inhibitors, as well as negative control compounds within the same scaffold, were evaluated in gentamicin-induced AKI in zebrafish (zfAKI), reperfusion injury AKI (IRI-AKI) in mouse, and in human kidney organoid-derived tubule cells subjected to hypoxia.

Results: Known potent, selective HDAC8 inhibitors such as PCI-34051, tetrahydroisoquinoline hydroxamic acids and an isoindolyl amide were effective in the zf AKI assays, while control compounds (i.e. HDAC8 inactive compounds of the same scaffold) were not effective. Testing of PCI-34051 in the IRI-AKI mouse model showed improvements in kidney function markers (BUN, tGFR) and while there was no significant reduction in renal fibrosis as measured by Sirius red staining, expression of the renal fibrosis markers *Collagen 1a1* and *LoxL2* were reduced. Further evaluation of PCI-34051 and the isoindolyl amide in primary renal epithelial cells from human kidney organoids showed that HDAC8 inhibition is associated with a pronounced suppression of inflammatory cytokine genes, providing one mechanism to explain their *in vivo* efficacy.

Conclusions: Our data supports that pharmacological inhibition of HDAC8 ameliorates AKI injury in multiple *in vivo* models and validates this target as a promising therapeutic lead to treat AKI.

Funding: NIDDK Support

PO0332

Class IIa Histone Deacetylase Inhibition Blunts AKI by Suppressing Apoptosis, Enhancing Autophagy, and Promoting Cellular Proliferation in Mice

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Background: Expression and function of histone deacetylases (HDACs) vary with cell types and insults. Our recent studies have shown that class IIa HDACs contribute to renal fibrosis chronically, but their roles in acute kidney injury (AKI) remain unknown.

Methods: In this study, we examined the effect of TMP269, a potent and selective class IIa HDAC inhibitor on folic acid (FA) and ischemia/reperfusion (I/R) -induced AKI in mice.

Results: Protein levels of four class IIa HDAC isoforms (4, 5, 7, 9) were increased in the kidney of folic acid (FA) and ischemia/reperfusion (I/R)-induced AKI, with HDAC4 being more abundant. Administration of TMP269, a potent and selective class IIa HDAC inhibitor, reduced expression of HDAC4 and increased expression of acetyl-histone H3. This was coincident with improved renal function, reduced tubular injury and less apoptosis, and enhanced tubular cell proliferation. Mechanistical studies showed that

TMP269 treatment inhibited FA or I/R -induced p53 acetylation and phosphorylation, as well as caspase-3 cleavage and Bax expression. In contrast, TMP269 increased expression of Bcl-2, an anti-apoptotic protein and PCNA. TMP269 was also effective in promoting cellular autophagy as indicated by increased expression of Atg7, Beclin-1 and LC3II. Moreover, class IIa HDAC inhibition resulted in the restoration of E-cadherin and upregulation of BMP7 and klotho, two renoprotective proteins.

Conclusions: These results indicated that activation of class IIa HDACs, in particular, HDAC4, contributes to AKI and renal tubular apoptosis, while targeted inhibition of class IIa HDACs protects against AKI through a mechanism associated with reduced apoptosis and enhanced autophagy and cellular regeneration.

Funding: Government Support - Non-U.S.

PO0333

Distinct Spatiotemporal Dynamics of Damaged Proximal Tubular Epithelial Cells After Mild and Severe AKI in Mice

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Background: Clinical and preclinical studies revealed that damage to proximal tubular (PT) epithelial cells after severe acute kidney injury (AKI) is a critical mechanism underlying the development of chronic kidney disease (CKD). Recent advancements of single-cell RNA sequencing (scRNA-seq) approach identified that PT cells adopt heterogeneous molecular states after injury and contribute to maladaptive repair. However, their cell fate after mild versus severe AKI remains poorly understood.

Methods: Single-cell transcriptomics and genetic fate-mapping approaches were used in a mouse model of unilateral ischemia-reperfusion injury (IRI) to investigate PT cell dynamics after short (20 min) and prolonged ischemia (30 min). For scRNA-seq analyses, we analyzed a total of 18,258 cells from the damaged kidneys harvested on 6 hours, and 1, 7, and 21 days after 30 min ischemia and the homeostatic normal kidneys. We used Seurat's integration and label transfer to create the integrated dataset. To infer the dynamic cellular process during injury and repair, we used two computational tools (Monocle 3 and Velocyto).

Results: Our single-cell mouse atlas of maladaptive repair shows that PT cells develop a molecularly distinct, pro-inflammatory state following injury. These cells are characterized by reduced expression of homeostatic genes (ex. *Lrp2*, *Slc34a1*) and enrichment of genes associated with kidney development (ex. *Sox9*, *Cdh6*) and kidney injury (ex. *Vcam1*, *Havcr1*). Gene ontology analysis of these cells revealed high enrichment of pro-inflammatory signaling. Our genetic fate-mapping using a *Sox9IRES-CreERT2; Rosa26-tdTomato* mouse line showed these inflammatory PT cells transiently appear after short ischemia and return to their original state without inducing fibrosis. However, they accumulate and contribute to persistent inflammation after prolonged ischemia.

Conclusions: Our single-cell transcriptomic and genetic fate-mapping approaches identify that the accumulation of inflammatory PT cells after severe injury underlies the maladaptive repair process. Future studies of how this pathologic cell state persists and contributes to inflammation will inform us to develop novel therapeutic approaches for AKI and its transition to CKD.

Funding: NIDDK Support, Private Foundation Support

PO0334

Cisplatin AKI: Localization of Cell State Injury Clusters with Spatial Transcriptomics

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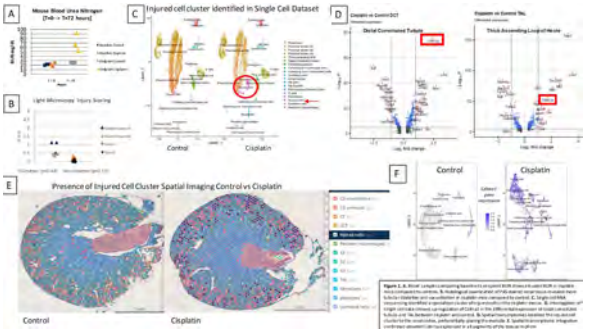
Background: Human acute kidney injury (AKI) is a multifactorial process and severity varies between individuals. The murine cisplatin model is a replicable example of AKI with limited confounding variables. We determined the pathways and injury markers dysregulated across the nephron in cisplatin AKI. We localized relevant human cell state signatures with spatial transcriptomics (ST) to determine which were most prevalent in cisplatin AKI and where these cells reside.

Methods: Six 129S6-SVE mice received vehicle or cisplatin (0.5 mg/g). After 72 hours, mouse kidneys were harvested and preserved for histology, single cell sequencing (scRNAseq), and ST. Gene mapping was completed with Cell Ranger 5.0.1 (scRNAseq) or Space Ranger 1.2.0 (ST). Human scRNAseq data was downloaded from kpmp.org, clustered by cell state (injured, adaptive, degenerative, transitioning, cycling, or reference) and mapped to mouse orthologs in Enembl database. Seurat clustered and integrated scRNAseq data as well as performed spatial mapping. Visualizations were created with R Studio.

Results: Cisplatin mice had increased BUN and tubular atrophy. scRNAseq identified 32 cell clusters, merged across common cell types. Cell cycle genes (*Cdkn1a*) were upregulated across epithelial cell types, but injury markers (*Lcn2* and *Spp1*) were only upregulated in the distal nephron. A novel cluster of dedifferentiated injured cells was identified and defined by cell cycle markers, *Lcn2* and *Spp1*, suggesting a distal nephron origin despite dedifferentiation. *Cdkn1a* was upregulated in ST across all cell types, but the novel injury cluster mapped only to the outer renal cortex. From the 6 identified human cell states, the adaptive epithelial state was found to be upregulated in cisplatin mice.

Conclusions: This study localizes the differential effects of cisplatin across the nephron. It adds support to the human injury cell states defined from scRNAseq of heterogenous human samples, showing their relevance in a well-defined AKI model.



PO0335

Cell Interaction Dynamics in Human AKI Revealed by Single-Cell Transcriptomics

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Background: Single cell transcriptomic maps of human AKI have not been reported, in part due to the difficulty of obtaining tissue. Acute kidney injury (AKI) is characterized by dynamic changes in cellular interactions among epithelia, stroma and inflammatory cells across the acute injury, repair and failed repair spectrums. Single cell transcriptomic technology is ideally suited to unravel the spectrum of cell states and interactions during injury and repair.

Methods: We performed snRNA-seq on 4 human AKI samples (2M and 2F, mean age = 60y, mean sCr = 4.6 mg/dl) and 5 control samples (3M and 2F, mean age = 55.8y, mean sCr = 1.07 mg/dl). Nuclear preparations were processed using 10x Genomics 3′ v3 Chromium kits and sequenced by NovaSeq. Reads were counted with CellRanger and analyzed with Seurat.

Results: After quality control and doublet removal, 62,649 nuclei (18 clusters) were identified in the dataset. GLI1^{high} fibroblasts were enriched in AKI, suggesting hedgehog signaling pathway activation. Among ligands, DHH expression was specifically up-regulated in the ADAMTS6^{high} endothelial subset in AKI, suggesting that AKI-induced endothelial stress may activate fibroblast reprogramming for myofibroblast proliferation. Comprehensive ligand-receptor analysis suggests secreted proteins including TRAIL from injured epithelium signaling to endothelium, driving DHH expression and subsequent myofibroblast proliferation. We define the transcriptomic signature of failed-repair PT in human AKI and show that this is similar to that of primary cultured RPTEC, validating primary RPTEC as a model of failed repair. Indeed, TNFa treatment of RPTEC drove expression of the full complement of failed repair PT marker genes, suggesting a critical role for NFKB activation in human PT injury and repair.

Conclusions: This is the first single cell transcriptomic atlas of human AKI. It reveals a novel PT-endothelium-myofibroblast signaling loop coupling PT injury to endothelial injury and ultimately interstitial fibrosis. This TRAIL and DHH dependent intercellular signaling cascade suggests a molecular mechanism for the AKI to CKD transition.

Funding: NIDDK Support

PO0336

Unraveling Single-Cell Responses in Human AKI

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Background: Acute kidney injury (AKI) is frequently observed in critically ill patients and is associated with a poor prognosis. AKI has recently moved into the focus of interest during the SARS-CoV-2 pandemic as high rates of AKI have been reported in severe COVID-19. We aimed to delineate cell type-specific molecular phenotypes associated with human AKI, including COVID-associated AKI.

Methods: We analyzed human kidney tissues using histology and single-nuclei RNA sequencing. Samples included kidney biopsies obtained within 2 hours post mortem from patients who succumbed to critical illness with and without evidence of AKI. Samples also included tumor-adjacent normal kidney tissues obtained during surgeries. AKI cases included patients with severe courses of COVID-19 (COVID AKI) and patients with other types of critical illness associated with systemic inflammation (Non-COVID AKI). Post-mortem kidney tissues obtained 30 min, 1 hour and 2 hours after death from a brain-dead patient without AKI were analyzed to assess the impact of post-mortem effects.

Results: Single-nuclei sequencing from kidney tissues yielded data of high transcriptional depth, which allowed transcriptome-based identification and de-novo spatial reconstruction of kidney cells. Principal component and differential gene expression analyses indicated that the presence of clinically confirmed AKI was the primary driver of global kidney transcriptomes and that different molecular subtypes of AKI existed. In contrast, the sampling time post-mortem and the presence of COVID-19 had minor effects. Subclustering analyses of different kidney cell types identified subclasses of cells representing injured kidney tubular cells, which were marked by distinct biomarker expression and expression signatures signifying intrinsic responses to inflammation, an induction of epithelial-to-mesenchymal transition, and an upregulation of hitherto unrecognized novel receptor-ligand pairs.

Conclusions: We provide the first cell type-specific molecular atlas of human AKI, revealing unanticipated disease subtypes and cell type-specific injury patterns.

PO0337

Human Kidney Proximal Tubule-on-a-Chip to Model Acute Hypoxic Tubular Injury in AKI

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Background: Acute kidney injury (AKI), with high mortality, is a serious public health issue. Hypoxic injury in proximal tubules (PT) sets the course of ischemic AKI. Microfluidic organ-on-a-chip technology mimics 3D kidney structures in vitro. We asked if AKI-related hypoxic injury may be modelled on a microfluidic 3D PT system comprising human epithelial cells and extracellular matrix (ECM).

Methods: A 2-lane microfluidic device without membrane was set to model 3D PT. Human PT epithelial cells (HK-2) were cultured with K-SFM media against ECM. Hypoxic conditions was designed as 1% O_2, 5% CO_2 and 94% N_2 in humidified multi-gas incubator. Tubular injury was assessed by immunofluorescence (IF) labelling and barrier integrity assay for 48 hours.

Results: Proximal tubules formed successfully at normoxia by phase contrast microscope. Hypoxia increased tubular leakage by 6-fold for 20 kDa (Fig. 1B, p=0.001) and 4-fold for 155 kDa molecules (Fig. 1C, p=0.001) compared to normoxia on 24h. Leakage for 20 kDa molecules remained 2-fold high compared to normoxia on 48h (Fig. 1B, p=0.001). Leakage for 155 kDa molecules restored with similar data as normoxia (Fig. 1C, p=0.268) on 48h. IF data supported impairment of the barrier.

Conclusions: In this study, a novel human kidney PT-on-a-chip was designed and successfully optimized for real time-modelling acute hypoxic tubular injury in AKI. Our human PT-on-a-chip mimics reversible tubule injury of clinical AKI more accurately compared to severe animal tubular damage models and presents a reliable and adjustable platform for testing potential therapeutic interventions. Hacettepe University Research Fund financially supported this work (TSA-2020-18383).

Funding: Government Support - Non-U.S.

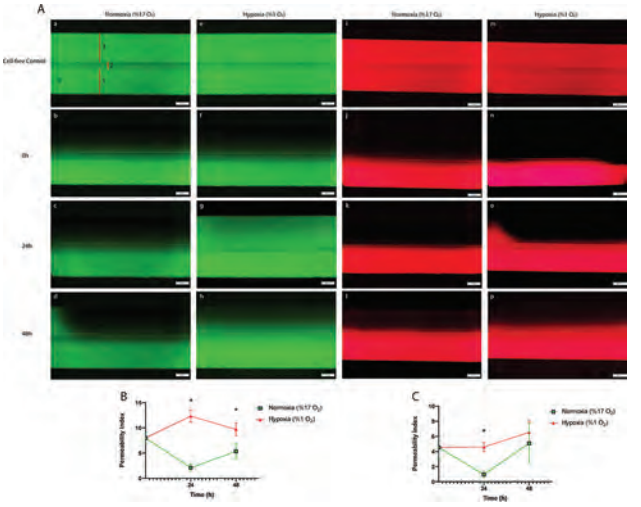

Figure 1. Representative micrographs (**A**) and quantitative analysis (**B, C**) of barrier permeability index assay. 20 kDa-Dextran-FITC (**A**, 1st and 2nd column, **B**) and 155 kDa-Dextran-TRITC (**A,** 3rd and 4th columns, **C**) fluorophore-tagged molecules were utilized.

PO0338

Mechanisms of Nucleophosmin-Mediated Regulated Cell Death During Renal Ischemia

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Background: Nucleophosmin (NPM) is a protein chaperone that potentiates Bax-mediated cell death during ischemic AKI by an unknown mechanism. In contrast, heat shock protein 70 (Hsp70) is a potent anti-apoptotic agent that promotes renal cell survival and preserves organ function. In this study, we characterize for the first time the intracellular events in which NPM and Hsp70 compete to regulate cell survival during ischemic stress.

Methods: Hsp70 wild type (WT) or Hsp70 mutants either restricted to the cytosol (Hsp70 985A) or unable to enter the nucleolar region (Hsp70 M45) were selectively over-expressed in primary murine proximal tubule epithelial cells (PTEC) harvested from Hsp70 null mice. Hsp70 expression, NPM nuclear translocation, NPM de-oligomerization, NPM-Bax complex formation, T95 phosphorylation responsible for NPM translocation, and cell survival were measured.

Results: Equivalent, selective over-expression of the hsp70 proteins significantly improved cell survival after ischemic stress in the following rank order: WT > M45 > 985A (each $P < 0.05$ vs. control). Only Hsp70 members with nuclear access (WT and M45) inhibited T^{95} NPM phosphorylation that mediates NPM translocation and reduced cytosolic NPM accumulation. Neither WT nor the Hsp70 mutants inhibited stress-induced NPM de-oligomerization. In contrast, WT > 985A > M45 Hsp70 significantly improved survival in Hsp70 null PTEC that expressed a cytosol-restricted NPM mutant, interacted with cytosolic NPM, and reduced NPM-Bax complex formation required for mitochondrial injury and cell death. Hsp70 knockout prevented the cytoprotective effect of suppressing NPM in ischemic PTEC and also increased cytosolic NPM accumulation after acute renal ischemia *in vivo*, emphasizing the protective effects of Hsp70 on NPM-mediated renal cell toxicity.

Conclusions: These observations identify key steps that mediate NPM toxicity during ischemia-induced cell death: (**1**) nuclear NPM de-oligomerization, (**2**) NPM translocation into the cytosol and (**3**) cytosolic NPM-Bax complex formation. Hsp70 promotes renal cell survival during ischemic acute kidney injury partly by inhibiting two of these toxic events in distinct cell compartments: nuclear NPM translocation and NPM-Bax interaction in the cytosol. Renal cell survival during ischemic AKI is substantially improved by interfering with events that render NPM toxic.

Funding: NIDDK Support

PO0339

Limonin Protects Against AKI by Targeting ERK Signaling

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Background: Acute kidney injury (AKI) is characterized by tubular cell injury, vascular dysfunction, and inflammation. As a key pathological event, sustained inflammation in AKI plays a critical role in accelerating disease progression. In the clinic, there are no effective therapeutic strategies to prevent AKI by thus far. We previously reported, Limonin, a member of the class of compounds known as furanolactones possesses potent anti-inflammatory effects in multiple auto-immune diseases. Whether Limonin could serve as a candidate to preserve renal function after AKI remains unclear.

Methods: Kidney ischemia-reperfusion injury (IRI) was employed to induce AKI in mice. Limonin was pretreated in mice two days before IRI. A molecular docking study and thermal shift assays were performed to determine the binding capacity between Limonin and key targets. *In vivo* and *in vitro* molecular experimental pathology studies were applied.

Results: After ischemic AKI, pretreatment of Limonin preserved kidney functions, ameliorated tubular injury, and repressed inflammation in the diseased kidneys, compared to the vehicles. In structure, we identified Limonin has active binding sites for 38 significant target proteins, including ERK. A molecular docking study demonstrated a high binding affinity between ERK2 and Limonin, which was confirmed by the temperature- and dose-dependent cellular thermal shift assays. *In vivo*, we further revealed that Limonin activated ERK signaling pathway and then promoted tubular cell proliferation and reduced cell apoptosis after AKI. *In vitro*, blockade of ERK signaling abolished the abilities of Limonin in preventing tubular cell apoptosis under hypoxia conditions.

Conclusions: Our results indicated that Limonin is a novel ERK activator. Its therapeutic effect on murine AKI paved a new avenue for AKI intervention in the clinic.

Funding: Government Support - Non-U.S.

PO0340

Connecting Extracellular Vesicle Transfer RNA to Oxidative Stress in Injured Kidneys

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Background: While urine-based liquid biopsy has recently expanded to the analyses of cell-free extracellular nucleic acid, the potential of transfer RNA (tRNA) encapsulated within extracellular vesicles as a new class of urine biomarkers for kidney injury has not been explored.

Methods: Using rat renal ischemia-reperfusion and tubular cell injury models, we tested if extracellular release of tRNA encapsulated in extracellular vesicles responds to kidney injury and determined the mechanism of tRNA packaging into extracellular vesicles under oxidative stress.

Results: We detected a set of tRNAs present in urine that was packaged inside extracellular vesicles. We then identified extracellular vesicle-loaded tRNAs differentially released after ischemia-reperfusion injury and oxidative stress, in a reproducible manner. Next, we determined post-transcriptional methylation of these tRNA as a response to oxidative stress present in extracellular vesicle tRNAs. Mechanistically, oxidative stress decreases tRNAs loading into intracellular vesicles, mobilizes tRNAs to endosomes destined to extracellular vesicles, suppresses release of extracellular vesicles from the cell surface, and induces Maf1-mediated transcriptional repression of the tRNAs, all of which affect the availability of tRNAs in the cytoplasm.

Conclusions: Our data support that decreased release of non-fragmented tRNAs via extracellular vesicles reflects oxidative stress of kidney tubules, which might be a new source of urine biomarkers for ischemic kidney injury and could lead to rebalance protein translation in response to oxidative stress.

Funding: NIDDK Support

PO0341

Inhibition of miR-155 Ameliorates AKI by Protecting Telomeres and Reducing DNA Damage of Renal Tubular Cells

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Background: Acute kidney injury (AKI) is associated with significant morbidity and mortality, and currently there is no therapy to prevent or treat established AKI. miR-155 is significantly up-regulated in diabetic nephropathy, IgA nephropathy, bilateral renal ischemia-reperfusion injury (IRI) or drug-induced AKI. However, the molecular mechanism of miR-155 in AKI remains to be studied.

Methods: We subjected miR-155$^{-/-}$ mice and wild-type controls, as well as human proximal tubule cells, to cisplatin-induced AKI models. We assessed kidney function and injury with standard techniques and measured telomere by the fluorescence in situ hybridization.

Results: The expression level of miR-155 was upregulated in both cisplatin-induced AKI mice model and cisplatin-treated HK2 cells. Inhibition of miR-155 expression protected cisplatin-induced AKI both in vivo and in vitro. Compared with wild-type mice, miR-155$^{-/-}$ mice had reduced mortality, improved renal function and pathological damage after cisplatin intervention. Moreover, inhibition of miR-155 expression decreased cells apoptosis and suppressed DNA damage. Additionally, we found that miR-155 efficiently regulates TRF1 expression by targeting a partially conserved sequence motif in the TRF1 3′UTR. Inhibition of miR-155 enhanced the expression of TRF1 and reduced the telomere DNA damage induced by cisplatin. In addition, CDK12 had also been identified as a novel target of miR-155. Inhibition of miR-155 increased the expression of CDK12, and reduced DNA damage and maintain genome stability.

Conclusions: We demonstrated that inhibition of miR-155 ameliorates AKI involving the targeting and regulation of TRF1 and CDK12, indicating a novel regulatory mechanism and elucidating a potential target for cisplatin induced AKI treatment.

Funding: Government Support - Non-U.S.

PO0342

Evaluation of Urinary NHE3 in Rats with AKI

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Background: Acute kidney injuries (AKIs), caused by hypovolemia, ischemia-reperfusion, or nephrotoxins, are concerned with high morbidity and mortality. Urinary Na/H exchanger isoform 3 (NHE3) has been demonstrated as a noninvasive marker of acute tubular necrosis. However, the ideal diagnostic biomarker in AKI is still lacking.

Methods: In order to determine the potential role of urinary NHE3 in early diagnosis of AKI, we evaluated the exosome NHE3 in daily urines from rat models of AKIs including low NaCl (0.01%) plus candesartan (1mg/kg/day, IP) for 7 days, ischemia/reperfusion (ischemia for 40min, referfusion for 2h) and cisplatin (20mg/kg for 7 days) in Sprague Dawley rats (male, 2-3 months old, 4-7 rats per group). Urine exosomes were isolated by a series of centrifuges including ultracentrifuges (17k xg, 4°C, 10min;200k xg, 4°C, 1 hr).

Results: NHE3 levels (western blotting) were increased at day 1, which was 1 day before serum creatinine increased in low NaCl/candesartan rats and reperfusion rats (day1) relative to controls. They were also increased in cisplatin rats at day 2 (1 day before serum creatinine increased). Furthermore, NHE3 in original urines from 6 patients diagnosed with AKI (Scr 249.83 ±166.93 umol/L) and 6 volunteers with normal renal function (Scr 68.67±13.20umol/L) were assessed without ultracentrifuge isolation. NHE3 was increased remarkably in AKI patients (333±28, % of controls) compared with volunteers (100±30, %, t-test, $P<0.05$).

Conclusions: Our results in rats and patients suggest that assessment of urine NHE3 may be a potential non-invasive biomarker for early detection of various acute kidney injuries.

Funding: Government Support - Non-U.S.

PO0343

Tubular β-Catenin Ameliorates AKI by Restoring Mitochondrial Biogenesis

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Background: Renal tubular β-catenin signaling plays a protective role in acute kidney injury (AKI), but the underlying mechanisms remain unclear. Mitochondrial dysfunction is responsible for the pathogenesis of AKI. This study aims to investigate the role of β-catenin activation on mitochondrial biogenesis in tubular cells upon AKI and its underlying mechanism.

Methods: Loss- and gain-of-β-catenin function was established in mice with tubular cell-specific β-catenin stabilization (TubCat mice) and knockout (TubCatKO mice). Septic and aseptic AKI was induced by exposure to LPS or ischemia/reperfusion, respectively. Kidney injury was examined by NGAL immunohistochemical staining. Markers of mitochondrial biogenesis were determined by Western blot, real-time quantitative PCR and immunofluorescence staining. Signaling cascade was examined by Western blot.

Results: Compared to the controls, TubCat mice under septic and aseptic AKI had significantly alleviated kidney injury and enhanced mitochondrial biogenesis as indicated by (i) reduction of NGAL positive tubules; (ii) restoration of mitochondrial mass protein TOMM20 and mitochondrial biogenesis molecules PGC-1α and NRF1; (iii) increasing co-localization of PGC-1α and β-catenin in renal tubules and (iv) increasing FOXO3 signaling against septic and aseptic injury. Consistently, kidney injury, and mitochondrial dysfunction were aggravated in TubCatKO mice versus their control littermates.

Conclusions: In both septic and aseptic AKI, tubular β-catenin stabilization restores mitochondrial homeostasis through the FOXO3/PGC-1α signaling pathway. **Funding:** General Research Fund (HKU 17119818), RGC Collaborative Research Fund (Ref: C7018-16G) and Hong Kong Society of Nephrology Research Grant (2019)

PO0344

CB11: Mitochondrial Effects in Renal Proximal Tubular Cells

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Background: Oxidative stress and mitochondrial dysfunction are characteristic of many acute and chronic conditions such as acute kidney injury and chronic kidney disease. Renal proximal tubular cells (RPTC) are mitochondria-dense, dependent on oxidative phosphorylation, and are particularly susceptible to injury. Identifying compounds that induce mitochondrial biogenesis (MB) is of increasing importance for the treatment of renal diseases associated with metabolic dysfunction. We investigated the effects of 1-butyl-3-hydroxy-3-[2-oxo-2-(pyridin-2-yl)ethyl]-1,3-dihydro-2H-indol-2-one, (CB11), on MB, mitochondrial dynamics, antioxidant response, and apoptosis in RPTC using a model of oxidant-induced injury.

Methods: In primary cultures of renal proximal tubular cells, we used uncoupled oxygen consumption rate (FCCP-OCR), transmission electron microscopy, immunoblotting, oxidant-induced injury with tert-butyl hydroperoxide (TBHP), and flow cytometry.

Results: CB11 (0.1 nM) treatment increased FCCP-OCR and mitochondria number after 24h. CB11 exposure decreased expression of fusion protein Mfn1 at 1 and 10 nM concentrations. CB11 had no effect on fusion proteins Mfn2 or OPA1 or phosphorylation of fission protein Drp1 at serine residues S637 or S616. Expression of Nrf2 protein decreased with no effect on Nrf2-regulated antioxidant response proteins (e.g. NQO1, GSTM1, GSR1, GPX2). Following a 24h pretreatment with CB11, TBHP-induced injury at 1h was evaluated. CB11 exposure did not prevent the loss of monolayer confluence at 1h post-injury. However, daily exposure prevented further loss of confluence at 48, 72, and 96h. No significant change in apoptosis, as measured by annexin-V positive cells (AnnV+), was seen in control or CB11 exposed samples 48h post-injury. TBHP-induced injury increased AnnV+, while exposure of CB11 did not attenuate AnnV+.

Conclusions: CB11 represents a new and highly potent inducer of MB with a unique signaling pathway in RPTC. Our data reveal that CB11 pretreatment does not prevent oxidant-induced cell death but acts as a RPTC protectant. Future studies will test this compound in AKI and CKD models.

Funding: Commercial Support - University of Arizona

PO0345

FDA-Approved Drug Lasmiditan Stimulates Mitochondrial Biogenesis and Promotes Recovery of Vasculature and Renal Function After Ischemia-Reperfusion Injury in Mice

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Background: Acute kidney injury (AKI) is induced by multiple mechanisms (e.g. ischemia/reperfusion (I/R), drugs, sepsis) and results in tubular and vascular dysfunction. Mitochondrial dysfunction is a key mediator of injury and recent studies have shown that pharmacological-induced mitochondrial biogenesis (MB) can provide renal recovery. Activation of the 5-HT_{1F} receptor has been demonstrated to induce MB in the mouse kidney and the absence of said receptor results in greater renal injury from I/R, demonstrating the importance of the 5-HT_{1F} receptor in the kidney. The goal of this study was to test the efficacy of the potent, selective, and FDA-approved 5-HT_{1F} receptor agonist lasmiditan in a mouse I/R-induced AKI model.

Methods: Male mice were subjected to I/R-induced AKI. After 24 h, serum creatinine was measured and I/R mice were divided into two groups and dosed with lasmiditan (0.3 mg/kg) or vehicle. Daily dosing was continued until euthanasia at 144 h. Electron microscopy was used to measure mitochondrial number. Serum creatinine was measured. Vascular leakage was determined using Evan's blue dye and tight junction proteins. Mitochondrial proteins and KIM-1 were measured using immunoblot analysis.

Results: Treatment with lasmitidan increased renal cortex mitochondrial number by 33%. Serum creatinine levels were similar between the I/R+vehicle group and I/R+lasmiditan group at 24 h. At 144 h, serum creatinine markedly decreased by 72% and KIM-1 decreased by 50% in I/R+lasmiditan group compared to I/R+vehicle group, respectively. PGC-1α and electron transport chain complexes IV and V were restored in I/R+lasmiditan group. Vascular permeability increased 2.5-fold in the I/R+vehicle group and was restored to control levels in the I/R+lasmiditan group. The tight junction proteins occludin, ZO-1, and Claudin 5 decreased in the I/R+vehicle group and was restored to control levels in the I/R+lasmiditan group.

Conclusions: In this study we demonstrate that FDA approved lasmiditan restores mitochondrial function and renal and vascular function after I/R injury in mice. Lasmiditan could be repurposed for the treatment of AKI in humans.

Funding: Veterans Affairs Support

PO0346

Treprostinil Improves Mitochondrial Dynamics and Reduces Oxidative Stress During Renal Ischemia-Reperfusion Injury in Rats

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Background: Renal ischemia-reperfusion injury (IRI) is a major factor that contributes to acute kidney injury (AKI). Mitochondria enriched in renal proximal tubular cells are particularly susceptible to IRI-induced oxidative stress. Currently, there is no treatment for IRI available. We recently demonstrated the efficacy of treprostinil (Remodulin®), an FDA-approved prostacyclin analog, in reducing AKI during bilateral rat renal IRI. This study investigates the role of treprostinil in improving mitochondrial dynamics and reducing oxidative stress during rat renal IRI.

Methods: Male Sprague Dawley rats were subjected to 45 minutes of bilateral renal ischemia followed by 1-72 hours reperfusion. Placebo or treprostinil (100 ng/kg/min) was administered subcutaneously via an osmotic mini-pump. Blood and kidney tissue were collected for analyses.

Results: Treprostinil significantly reduced renal injury and peak elevated serum creatinine from 24- to 6-hours post-reperfusion compared to placebo-treated animals. PAS staining revealed that treprostinil markedly reduced epithelial cell necrosis and partially attenuated apical brush border loss at 6 hours post-IRI vs. placebo, with near reconstitution of normal histology by 48-hours post-reperfusion. Also, treprostinil restored renal antioxidant levels, including catalase, superoxide dismutase activity, and glutathione content vs. placebo ($p<0.001$). In parallel, treprostinil improved the mRNA expression of *Nqo1* and *Gclc*, that encode NAD(P)H dehydrogenase [quinone] 1 and glutamate-cysteine ligase catalytic subunit (Gclc) to 45% ($p<0.05$) and 52% ($p<0.01$) of sham at 48-hour post-IRI vs. placebo. Treprostinil reduced the renal mitochondrial fission proteins Drp1 and Mff by 61% and 44% relative to placebo ($p<0.001$) and restored the protein expression of mitochondrial fusion marker Sirt3 along with the mRNA expression of *Mfn1, Mfn2,* and *Opa1* to that of sham (vs. placebo, $p<0.0001$).

Conclusions: Treprostinil reduced renal oxidative stress as well as Drp1-mediated mitochondrial fission and upregulated Sirt3-mediated mitochondrial fusion, thereby improving renal mitochondrial dynamics and protecting against renal IRI. These results support the clinical investigation of treprostinil as a viable therapy to reduce renal IRI.

Funding: Other NIH Support - The material presented herein is supported by Institutional Development Award (IDeA) #U54GM115677 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds Brown University Advance-CTR (U54GM115677), and University of Rhode Island Core Lab (P20GM103430).

PO0347

A Mitochondrial Cardiolipin Targeting Peptide Ameliorates Kidney Oxidative Damage

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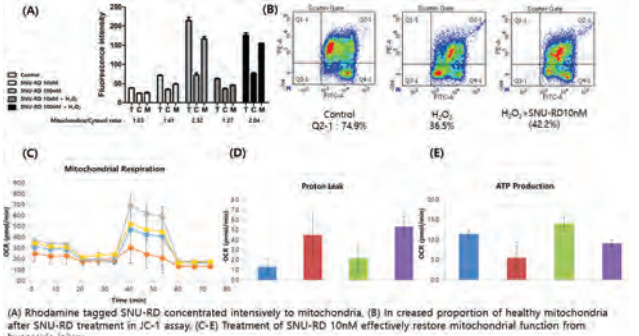
Background: Mitochondria is a major organelle of adenosine triphosphate production and O2 consumption. Also, kidney is mitochondria abundant organ. Many mitochondria-targeting agents were developed, though there is no single agent approved in clinical practice. We investigate renoprotective effect of newly invented mitochondrial cardiolipin targeting peptide, the SNU-RD, in hypoxic condition.

Methods: Based on our experience that dimer formation by bisulfate bond of cell penetrating peptide accelerate cell permeability, we synthesized 15 candidate tetra-peptides which target inner mitochondrial membrane specific phospholipid, the cardiolipin. After cell viability, distribution and mitochondrial functional test, we selected best candidate and tentatively named as SNU-RD. As hypoxic damage, bilateral ischemia-reperfusion injury (IRI) and primary cultured human proximal tubular epithelial cells (hPTECs) with H_2O_2 were chosen. Wild-type mice were divided into four groups: sham, IRI, IRI with low dose or high dose SNU-RD. After SNU-RD treatment with various concentration (10nM, 100nM, 1000nM), high dose H_2O_2 stress was done. Mitochondrial function was tested and mitochondrial oxygen consumption rate (OCR) was measured.

Results: In IRI, serum BUN and creatinine were significantly decreased without SNU-RD dose dependency. Pathologic findings (NGAL and cytochrome C) were improved. Also, mitochondrial anti-oxidative enzyme (NQO-1, SOD-1), ATP6 and IL-10 mRNAs were over-expressed after SNU-RD treatment. Cell viability was increased with dose dependently decrease of early and late apoptosis. IL-1ß, IL-18, p16 and p21 mRNA were dramatically down-regulated. When traced by rhodamine, SNU-RD was intensively distributed to mitochondria then cytoplasm. In JC-1 assay, ratio of healthy mitochondria was increased with SNU-RD. Basal and maximal OCR were most recovered from SNU-RD 10nM.

Conclusions: Mitochondrial cardiolipin targeting peptide, SNU-RD can protect kidney from hypoxic injury by restoring mitochondrial function.



(A) Rhodamine tagged SNU-RD concentrated intensively to mitochondria. (B) In creased proportion of healthy mitochondria after SNU-RD treatment in JC-1 assay. (C-E) Treatment of SNU-RD 10nM effectively restore mitochondrial function from hyperoxic injury

PO0348

Regulation of Mitochondrial Metabolism in T-Regulatory Cells by Programmed Cell Death Protein 1 in AKI

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Background: The T-regulatory cells (Tregs) are important for suppressing inflammation and for resolution of injury during acute kidney injury (AKI). Absence or blocking of programmed cell death 1 (PD-1) mitigates the Treg-mediated protection in AKI. The mechanisms, however remain unknown. Here we test the hypothesis that PD-1 regulates mitochondrial metabolism of Tregs during AKI.

Methods: Bilateral renal ischemia reperfusion injury (IRI) was used to investigate the role of PD-1 function in Tregs. Adoptive transfer of splenic $CD4^+CD25^+$ Tregs isolated either from wild-type (WT) or PD-1-/- Foxp3-GFP mice was performed into recipient mice 1h or 24h prior to IRI. Renal structure and function was assessed by plasma creatinine, *Kim1* and *Ngal* expression, histopathology and flow cytometry. Mitochondrial

metabolism of isolated Tregs was assessed *ex vivo* using Seahorse Metabolic Flux Analyzer and staining with mitochondrial dyes (TMRE and Mito-ROS) for mitochondrial membrane potential and ROS production respectively, as well as by RT-PCR for genes related to mitochondrial dynamics. Scanning Electron microscopy (SEM) was performed on isolated Tregs to image mitochondrial morphology followed by ImageJ™ analyses.

Results: Contrary to the WT, adoptive transfer of PD-1$^{-/-}$ Tregs was unable to protect the recipient mice from IRI-induced AKI. The oxygen consumption rate (OCR), a measure of oxidative phosphorylation, was significantly reduced in PD-1$^{-/-}$ Tregs at baseline and under maximal respiration as compared to WT. PD-1$^{-/-}$ Tregs also had reduced mitochondrial mass, lower mitochondrial membrane potential, and greater mitochondrial ROS production than WT Tregs. Further, the expression of *Pgc1a, Nrf1, Brf2, Tfam, Drp1, Mfn1, Mfn2 and Mff* was also significantly reduced in the PD-1$^{-/-}$ Tregs. Importantly, compared to Tregs from age and sex-matched WT mice and as measured using SEM and ImageJ™, the mitochondria in Tregs from PD-1$^{-/-}$ mice were fewer in number and had lower average pixel area.

Conclusions: The data suggest that PD-1 regulates mitochondrial function and dynamics of Tregs and this is critical for protection from AKI and other inflammatory diseases.

Funding: NIDDK Support

PO0349

Intraflagellar Transport Protein 88 Deficiency in Proximal Tubular Cells Exaggerates Cisplatin-Induced Injury by Suppressing Autophagy

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Background: Primary cilia are widely regarded as specialized sensors in differentiated cells that have been implicated in the regulation of cell proliferation, differentiation, and viability. We previously showed that shortening of primary cilia sensitizes cultured kidney tubular cells to cisplatin-induced apoptosis. IFT88 is an essential component for ciliogenesis and maintenance.

Methods: To study the effect of proximal tubule-specific IFT88 ablation on cisplatin-induced acute kidney injury (AKI), we took advantage of conditional IFT88 knockout mice to study how differently cisplatin affected renal function in knockout mice and age- and sex-matched wild type ones. Furthermore, we used cultured cells to examine whether autophagy was involved.

Results: It was found that more severe AKI occurred in IFT88 knockout mouse than controls. Mechanistically, cisplatin stimulated autophagy in kidney tubular cells as an intrinsic protective mechanism. However, renal autophagy was severely impaired in IFT88 knockout mouse. In cultured HK-2 cells, cisplatin induced more apoptosis when IFT88 was knocked down. Tat-beclin 1 peptide, a specific autophagy activator, could partially prevent IFT88-associated cell death during cisplatin treatment, although cilium length was not improved significantly.

Conclusions: These results indicate that defective autophagy in IFT88-deficient kidney cells and tissues contributes to the exaggerated AKI following cisplatin exposure.

Funding: NIDDK Support, Veterans Affairs Support

PO0350

Urinary UDP-Glucose as a Novel Actionable Biomarker of Dehydration-Induced AKI

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Background: People working in ”extreme” conditions such as sugar cane workers, firefighters, and military personnel are subjected to significant dehydration. Prolonged episodes of dehydration may result in acute kidney Injury (AKI). AKI is associated with inflammation and is usually diagnosed only after the kidneys have gone through significant and often irreversible damage. We showed that the P2Y14 receptor mediates renal inflammation leading to AKI following ischemia-reperfusion-injury. P2Y14 is activated by the danger molecule UDP-glucose (UDP-Glc). Here we hypothesized that UDP-Glc is released by damaged cells throughout the body after dehydration-induced stress. UDP-Glc is filtered by the kidney and concentrated in collecting ducts where it activates P2Y14 in intercalated cells. This would trigger renal inflammation and contribute to dehydration-associated AKI.

Methods: Mice were subjected to water deprivation for 24, 48 and 72 hours. Kidney function was assessed via serum creatinine (SCr), blood urea nitrogen (BUN) and urine albumin. To study proximal tubule (PT) damage, aquaporin 1 (AQP1) localization was analyzed by immunofluorescence (IF). Urinary UDP-Glc concentration was measured by LC-MS, and renal recruitment of immune cells by flow cytometry and IF.

Results: Mice that were subjected to dehydration showed body weight loss. Water deprivation induced elevations in SCr and BUN after 48 and 72 hours, relative to control. Dehydration also promoted albuminuria and the redistribution of AQP1 from the plasma membrane into the PT cell body indicating PT injury. An increase in urinary UDP-Glc concentration, and renal recruitment of macrophages (CD64+F4/80+) were detected at 48 and 72 hours of dehydration. In particular, infiltration of CD11c-positive renal macrophages after dehydration was observed.

Conclusions: This study supports the hypothesis that UDP-Glc, released by damaged cells during severe dehydration, induces the renal recruitment of inflammatory macrophages leading to PT injury. Blocking the UDP-Glc/P2Y14 pathway represents, therefore, a new therapeutic avenue for the attenuation of dehydration-induced renal inflammation and dysfunction. In this context, urinary UDP-Glc is a promising actionable biomarker for dehydration-induced AKI.

Funding: NIDDK Support, Commercial Support - Danone Nutricia Research

PO0351

Role of Collagen Receptors in Radiation-Induced Nephrotoxicity

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Background: Radiation therapy represents a severe late complication for cancer patients and induces radiation nephropathy (RN). Collagen receptors Discoidin domain receptor 1 (DDR1) and integrin α2 are involved in the pathogenesis of renal fibrosis. However, the mechanisms is largely unknown. We hypothesized that radiation therapy (RT)-induced collagen I accumulation in podocytes activates DDR1, integrin α2, and matrix metalloproteinases (MMPs) signaling leading to changes in the laminin and collagen homeostasis in GBM thus inducing RN.

Methods: 10–14-weeks old C57BL/6 male and female mice kidneys received a single dose (SD) 4Gy, 10Gy, and 14Gy or fractionated dose (FD) 6Gyx5 and 2Gyx24 X-irradiation. Kidney function parameters (estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (ACR), serum BUN and creatinine), histopathological changes (determined by H&E, Periodic Acid-Schiff (PAS), Picrosirius red (PSR)), gene expression analysis (by nanostring), ultrastructural changes (by transmission electron microscopy (TEM), were measured at 10- and 20-weeks post-SD and FD.

Results: IHC and nanostring data showed a significant upregulation of Col I, pDDR1, and integrin α2 expression ($p<0.001$) and reduction in integrin α1 ($p<0.001$) in kidney cortices 10 and 20 weeks post-SD and FD. Western blot and gene expression analysis showed that several MMPs expression increased significantly in a dose and time-dependent manner in cultured human podocytes and mouse kidney cortex post-RT. Significant reductions were seen in collagen type IV (Col4A3, Col4A4, Col4A5), laminin α5β2γ1 (LM-521) and a substantial increase in the expression of collagen type I (Col1A1, Col1A2), collagen type IV (Col4A1, Col4A2), laminin α1β1γ1 (LM-111) and laminin α2β1γ1 (LM-211) in radiated mice kidney cortex ($p<0.001$). TEM data demonstrated time and dose-dependent increases in GBM thickness and foot process width ($p<0.001$). Significant increases in fibrosis (PSR), mesangial expansion (PAS), ACR in association with decreased podocyte number and eGFR 20 weeks post SD and FD were observed.

Conclusions: Our data suggest that targeting collagen receptors (DDR1 and integrin α2) with specific small molecule inhibitors and genetic or pharmacological induction of integrin α3 may prevent the RN.

Funding: Other NIH Support - NIH/NCI PQ12 1R01CA227493, and Live Like Bella # 9LA08., Other U.S. Government Support

PO0352

Leucine Metabolism and Ketone Bodies Role in AKI

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Background: Renal ischemia reperfusion (IR) results in injury caused by dynamic process that includes inflammation and extensive cell death. The increase in oxidative stress appears to play a great role in the inflammatory process causing acute kidney injury (AKI) during IR. Oxidative stress activates p53 and promotes cell death. On the other hand, ketones, were shown to decrease oxidative stress and are renal protective under different pathological conditions including AKI. Acetoacetate, one of the major ketone bodies, is a product of leucine catabolism. The means through which ketone bodies could play a protective role still requires further understanding. Computational studies in our lab have uncovered a link between mouse double minute 2 homolog (MDM2), which is a direct inhibitor of p53, and methylcrotonyl-CoA carboxylase 2 (*MCCC2*), which encodes a mitochondrial enzyme essential for leucine and isovaleric acid catabolism.

Methods: To explore amino acid metabolism and ketone bodies role in AKI we analyzed gene expressions in kidney cortex of mice that have undergone 35 minutes of renal ischemia followed by 24h of reperfusion. Moreover, to further investigate a connection between MDM2 and MCCC2, we knocked-down MDM2 in human kidney 2 (HK2) cells using small interfering RNA (siRNA) transfection at 2 concentrations (100nM and 200nM). Cells were harvested 48 hours post-transfection for mRNA and protein analysis.

Results: Renal ischemia- reperfusion increased levels of p53 and HIF1-alpha consistently with previous studies. Intriguingly, we also got significant decrease in MCCC2 mRNA (n=6) in IR-mice compared to sham operated mice (n=5). Preliminary data from MDM2 knock-down HK2 cells also show p53 upregulation, increased cell death and MCCC2 downregulation. These results are observed both at the mRNA and protein levels at 200nM MDM2 siRNA.

Conclusions: Though preliminary, our data show a consistent decrease in MCCC2 expression at the mRNA levels under AKI provoked by IR. This novel finding could be a steppingstone towards deciphering important pathways in AKI that involve oxidative stress related cell death and dysregulated amino acid. metabolism.

Funding: Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002647 and Internal funding

PO0353

Targeting Polycomb Repressive Complex 2 Protects Against Cisplatin-Induced AKI in Mice

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Background: Our previous studies have shown that blocking EZH2 (Enhancer of Zeste Homolog 2), a catalyzing subunit of polycomb repressive complex 2 (PRC2) with histone methyltransferase activity, protects against acute kidney injury (AKI). The role and mechanism of the entire PRC2 in AKI remain undefined. In this study, we investigated the involvement of PRC2 in the pathogenesis of AKI following cisplatin exposure.

Methods: A potent and selective PRC2 inhibitor EED226 was used to evaluate the effect of loss of PRC2 catalytic activity on renal function and tubular cell injury as well as activation of key apoptotic signaling pathways and expression of renoprotective proteins in a murine model of cisplatin-induced AKI.

Results: Administration of EED226 improved renal function, attenuated renal pathological changes, and reduced renal tubule injury and apoptosis in a murine model of cisplatin-induced AKI. In cultured renal epithelial cells, treatment with either EED226 or EED siRNA also reduced apoptosis. Mechanistically, EED226 treatment inhibited cisplatin-induced phosphorylation of p53 and fox3a, two transcriptional factors associated with apoptosis, and prevented downregulation of expression of Sirt3 and PGC-1α, two proteins that contribute to mitochondrial protection. Moreover, EED226 also enhanced renal tubular cell proliferation and suppressed inflammatory responses and phosphorylation of STAT3 and NF-κB, two transcriptional factors associated with inflammation.

Conclusions: These results indicate that targeted inhibition of PRC2 can improve renal function and promote the survival and proliferation of renal tubular cells through mechanisms associated with inhibition of p53 and fox3a signaling pathways and preserved expression of Sirt3 and PGC-1α.

Funding: Government Support - Non-U.S.

PO0354

Kidney Protection by Caloric Restriction Depends on De Novo NAD+ Synthesis Activation

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Background: In clinical practice, targeted measures for the treatment of acute kidney injury (AKI) are lacking. In mouse models, AKI by ischemia-reperfusion injury (IRI) can be reduced effectively through preconditioning protocols using hypoxia (HP) or caloric restriction (CR). In previous transcriptome analyses of murine kidneys after HP or CR, we identified *Kynu* as a common downstream target. The kynureninase encoded by *Kynu* is one of the key enzymes in tryptophan metabolism and the aim of this work was to further characterize the role of KYNU in the protection of AKI.

Methods: CRISPR-cas9 based non-homologous end joining (NHEJ) resulted in a KYNU-deficiency in C57Bl6 mice. This was followed by basal (e.g. biometry, kidney function) and special (e.g. kidney function 24h after renal IRI with or without HP/CR) phenotyping of the KYNU-deficient ($KYNU^{null}$) mice in comparison to wildtype littermates ($KYNU^{wt}$). The changes in the murine transcriptome, proteome and tryptophan metabolism mediated by HP and CR were then investigated before and after renal IRI. Finally, confirmatory analyses of the CR-mediated changes in the tryptophan metabolism of human blood samples were carried out.

Results: NHEJ resulted in a nonsense mutation in *Kynu* exon 2 and various protein analyses (e.g. Western blot and immunohistochemistry) confirmed the KYNU-deficiency. In the basal phenotyping and 24 h after IRI, $KYNU^{null}$ mice showed no differences from $KYNU^{wt}$ mice. However, the protection mediated by HP was no longer detectable in $KYNU^{null}$ mice and after CR the $KYNU^{null}$ mice showed significantly worse AKI than the $KYNU^{wt}$ littermates. Analyses of the transcriptome, proteome and tryptophan metabolism showed that KYNU is necessary for CR-mediated maintenance of nicotinamide adenine dinucleotide levels (NAD+) by inducing *de novo* NAD+ synthesis. The changes in *de novo* NAD+ synthesis identified in murine blood and induced by CR can also be recapitulated in human blood samples.

Conclusions: The CR-mediated induction of *Kynu* results from an increased activity of the *de novo* branch of NAD+ synthesis, which can also be recapitulated in humans. This finding offers new options for targeted therapeutic measures for the treatment of AKI.

PO0355

De Novo NAD+ Biosynthesis May Promote AKI Resistance

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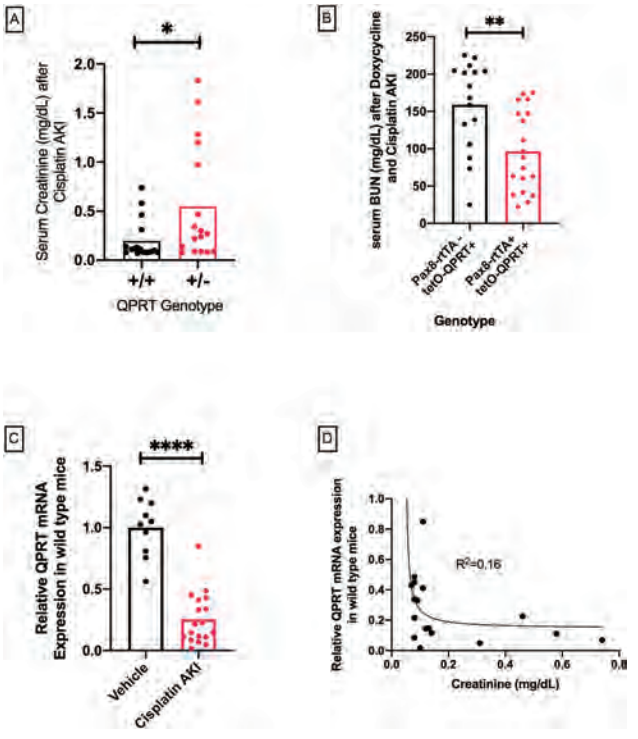
Background: Acute kidney injury (AKI) is a wide-spread, costly condition with no treatment. Renal energy metabolism impairment is a key feature of AKI. Nicotinamide adenine dinucleotide (NAD+) plays a critical role in maintaining ATP and regulating energy metabolism. It is produced from three pathways: dietary tryptophan, niacin, and NAD+ recycling. Ischemic AKI suppresses de novo NAD+ biosynthesis from tryptophan, including the bottleneck enzyme, quinolinate phosphoribosyl transferase (QPRT). QPRT +/- mice have worse AKI after ischemia-reperfusion (IRI). It is unknown if these disturbances are specific to ischemia, whether QPRT suppression contributes to AKI, or if restoration of this minor NAD+ pathway may be sufficient to improve AKI.

Methods: Nephron-specific conditional QPRT over-expressing mice were created (Pax8-rtTA, tetO-QPRT, iNephQPRT). Cisplatin was administered to induce AKI. Parallel AKI was induced in QPRT +/- and QPRT +/+ mice. QPRT expression was measured via qPCR. AKI severity was assessed with serum biochemistries and histology.

Results: Toxic AKI suppressed QPRT mRNA proportionally to AKI severity (Fig C,D). QPRT +/- mice were more susceptible to toxic AKI (Fig A). Conversely, iNephQPRT mice exhibited protection against AKI (Fig B).

Conclusions: QPRT suppression is necessary for severe nephrotoxic injury, and renal tubular QPRT augmentation is sufficient to ameliorate injury. Given that de novo NAD+ synthesis is considered a minor contributor to steady-state NAD+ balance, these results provide striking evidence of this pathway's importance to renal health during acute stress. Further, these findings implicate de novo NAD+ biosynthesis suppression as a pathogenic event in a mechanistically distinct context compared to IRI. Elucidating the regulation of QPRT and NAD+ homeostasis may be critical to understanding AKI physiology and developing novel therapies.

Funding: NIDDK Support, Other NIH Support - K12-HD000850, R01 DK095072, R01 AG027002



PO0356

Lack of Gb3 Elevated Renal Tubular Injury in a Mouse Model of Aristolochic Acid Nephropathy

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Background: Globotriaosylceramide (Gb3) is a glycosphingolipid serving as the receptor for Shiga toxin (Stx) and is responsible for mediating binding of Stx onto kidney tissues. However, the normal physiological function of Gb3 in kidney remains unknown. Under normal circumstances, Gb3-knockout (KO) mice (A4GALT (α-1, 4-galactosyltransferase) knockout) showed no obvious physical and chemical abnormalities. Gb3 is known to be mainly distributed in proximal renal tubule and collecting duct epithelial cells in C57 mouse strain, and aristolochic acid (AA), which has nephrotoxic properties, can cause the necrosis in proximal renal tubule epithelial cells. Here we examined whether Gb3 plays a role in AA-induced kidney damage and repair by comparing renal function and pathological changes of wild type (WT) versus A4GALT KO mice after AA challenge.

Methods: WT and A4GALT KO C57 mice were intraperitoneally injected with AA 5mg/kg/d for a total of 8 days. Mice general status and body weight were monitored. The urine, blood, kidney and bladder tissues of the mice were collected on the 9th day to determine the function and pathological changes.

Results: Compared with WT C57 mice, A4GALT KO mice were more sensitive to AA. From day 5 of administration, A4GALT KO mice began to show significant weight loss. On day 9, More severe renal tubular injury pathological changes, significantly increased urine leukocytes and ketones were detected in A4GALT KO mice. The proliferation of bladder transitional epithelial cells was significantly increased in AA treated WT and A4GALT KO C57 mice, accompanied with fibrin deposition, vascular dilatation and a small amount of inflammatory cell infiltration in the bladder compared with that in the untreated group. There was no significant difference in bladder changes between WT and A4GALT KO groups after AA administration.

Conclusions: Our findings uncovered that Gb3 is protective in AA-mediated renal tubular necrosis and its presence reduces kidney injury. We will further explore its specific mechanism in the following study.

Funding: Other NIH Support - Borroughs Wellcome Fund

PO0357

The Effect of Ischemia-Reperfusion Injury on Nuclear-Reduced Glutathione Levels in Kidneys from Old Female Lewis Rats

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Background: The purpose of the study was to determne the effect of ischemia/reperfusion injury (IRI) on nuclear reduced glutathione (GSH) levels in kidneys from old rats. GSH is the major antioxidant inside cells, and a decrease in GSH levels would contribute to the damage caused by free radicals that are elevated in IRI. There is limited information on the effect of IRI on nuclear GSH levels.

Methods: Anesthetized old female Lewis rats (22 months of age) were used in the study. The left and right renal pedicles was clamped for 60 min, followed by 60 min of reperfusion in the Experimental Group (n=5). The kidneys were then harvested, separated into cortex and medulla, and homogenized. Kidneys in the Control Group (n=5) were not subjected to IRI before being harvested. The nuclear fractions were isolated using differential centrifugation, and GSH levels were measured using a spectrophotmetric assay. The water contents of the cortex and medulla were determined to allow GSH levels to be expressed as nmol/ g kidney dry weight. A Student's T test was used to compare the groups, and statistical significance was determined at $p < 0.05$. All data shown as X ± SEM.

Results: Nuclear GSH levels were significantly decreased in both the kidney cortex and medulla of the Experimental Group when compared to the Control Group. Nuclear GSH levels in the cortex decreased by **28%**, with nuclear GSH being **535 ± 56 nmol/g kidney dry wt** in the Control Group, and decreased to **385 ± 23 nmol/g kidney dry wt** in the Experimental Group exposed to IRI. Nuclear GSH levels in the medulla decreased by **54%**, with nuclear GSH being **676 ± 72 nmol/g kidney dry wt** in the Control Group, and decreased to **309 ± 29 nmol/g kidney dry wt** in the Experimental Group exposed to IRI.

Conclusions: After 60 min of ischemia, nuclear GSH levels in rat kidney cortex and medulla did not return to normal levels after 60 min of reperfusion. The results suggests that the nucleus is experiencing major oxidative stress and damage caused by free radicals in IRI, and this may be contributing to the renal dysfunction seen in IRI.

PO0358

Metabolomics Reveals the Efficacy of Limonin on Mitigating Cisplatin-Induced AKI

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Background: In the clinic, acute kidney injury (AKI) is one of the most severe cisplatin side effects, limiting its use in cancer therapy. Our previous study demonstrated that Limonin, a triterpenoid compound extracted from citrus, alleviated cisplatin-induced AKI. However, the involved mechanisms remain largely unknown. In this study, we elucidated how Limonin mitigates cisplatin-induced AKI from a new perspective, metabolomics.

Methods: A total of 30 mice were divided into three groups: Sham, Cisplatin + vehicle, and Cisplatin + Limonin. Limonin was administrated once daily *via* oral gavage started 3 days before cisplatin injection. At 72 h after cisplatin injection, kidney tissues were collected for metabolomics. Metabolomics was performed using Trace 1310 Gas Chromatograph equipped with an AS 1310 autosampler connected to a TSQ 8000 triple quadrupole mass spectrometer.

Results: After AKI, Limonin significantly preserved serum creatinine and blood urea nitrogen levels and ameliorated kidney tubular injury, compared with vehicles. Kidney samples were then subjected to metabolomics. A total of 302 metabolites were detected. The principal component analysis indicated that these metabolites could be well separated, reflecting the changes of metabolite distribution after treatment of Limonin. Multivariate statistical analysis further identified 34 endogenous differentially expressed metabolites within three groups. Intriguingly, phenylalanine, tyrosine and tryptophan biosynthesis, phenylalanine metabolism, and linoleic acid metabolism were the top disturbed metabolic pathways amid the AKI repair process. These metabolic pathways are tightly correlated with oxidative stress, inflammatory response, and energy metabolism. Specifically, Limonin reduced Linoleic acid content, a major metabolite in the linoleic acid metabolism pathway in the AKI kidneys. Downregulation of Linoleic acid subsequently inhibited the synthesis of arachidonic acid. It ultimately influenced the abundance of metabolites in the tricarboxylic acid cycle to exhibit its protective role of Limonin in mitigating AKI.

Conclusions: Our data suggested that Limonin mitigates cisplatin-induced AKI through alternating multiple metabolic pathways.

Funding: Government Support - Non-U.S.

PO0359

Role and Regulatory Mechanism of Adropin in AKI by Regulating PDK4

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Background: Oxidative stress and inflammation are the important biological mechanisms of the development of ischemic Acute kidney injury (AKI). Pyruvate Dehydrogenase Kinase 4 (PDK4) is a key enzyme in the process of glucose oxidation, which can inhibit glucose oxidation. Adropin, a secreted protein encoded by Energy Homeostasis Associated (ENHO) gene, is involved in the pathogenesis and pathological process of metabolic and inflammatory diseases and other diseases, can inhibit oxidative stress and inflammation, but its mechanism is unclear in AKI.

Methods: *In vitro*, HK2 cells were incubated with rotenone to mimicked Ischemia Reperfusion Injury (mIRI) and treated with Adropin, the changes of mitochondrial membrane potential, indicators of autophagy, antioxidant protein, ROS levels and PKD4 were detected. *In vivo*, we established AKI model with IRI, and Adropin was given intravenously to detect the changes of renal injury indexes, antioxidant protein (SOD2), Adropin and PKD4 in mice.

Results: 1. Adropin up-regulated the antioxidant enzyme SOD2 and decreased the ROS level in HK-2 cells with mimicked Ischemia Reperfusion Injury. 2. The expression of PDK4 was significantly up-regulated and SOD2 was down-regulated in AKI mice induced by IRI. With the treatment of Adropin, the expression of SOD2 was up-regulated, and renal injury was alleviated.

Conclusions: Adropin can reduce the production of ROS by down-regulating the expression of PDK4 and up-regulating SOD2, thus alleviating renal injury in AKI.

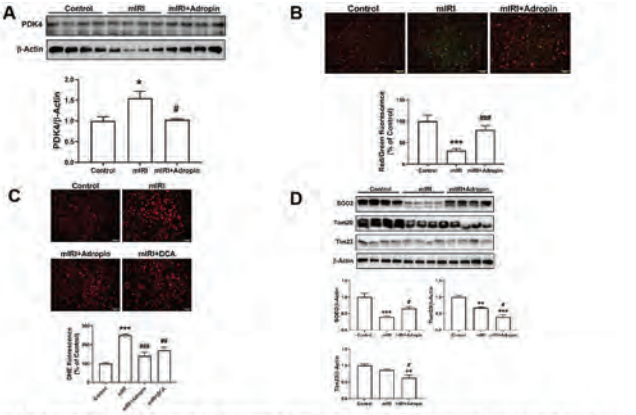

Fig.1 The method of ATP depletion by incubating a sugar-free medium containing rotenone (100 mol/L) in HK-2 cells to MIRI in vitro. The expression of PDK4, mitochondrial ROS, membrane potential, indicators of autophagy and SOD2 in HK2 cells with the treatment of Adropin were detected.

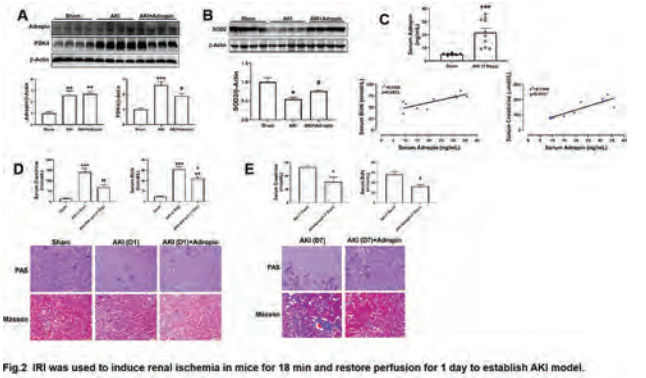

Fig.2 IRI was used to induce renal ischemia in mice for 18 min and restore perfusion for 1 day to establish AKI model. The expression of PKD4, SOD2 and renal injury indexes and changes after intravenous administration of adropin.

PO0360

Targeting Myeloid Ferritin Heavy Chain (FtH) in Rhabdomyolysis-Induced AKI

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Background: Acute kidney injury (AKI) is defined as an abrupt decrease in kidney function and significantly impacts mortality. During rhabdomyolysis, muscle injury leads to release of myoglobin, causing an increased heme/iron delivery to the kidney, leading to AKI. Iron exacerbates oxidative stress and causes cell death. Kidneys respond to increased iron by inducing ferritin heavy chain (FtH) expression. FtH is a ferroxidase

that converts ferrous iron into ferric form. Distinct myeloid populations promote injury and depletion of macrophages protect against rhabdomyolysis. Myeloid cells express high levels of FtH and mediate iron recycling. Therefore, we tested the hypothesis that myeloid FtH confers protection against rhabdomyolysis-induced AKI.

Methods: To induce rhabdomyolysis, female mice (10-12 weeks) deficient in myeloid FtH ($FtH^{Lysm-/-}$) and floxed controls ($FtH^{fl/fl}$) were deprived of water for 16 h and administered 50% glycerol via intramuscular injection into hindlimbs (7.5 or 11 ml/kg body weight). Mice were harvested at 1-, 3-, or 7-days post-glycerol. Kidney function and injury were evaluated by serum creatinine, and kidney injury marker 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) expression, respectively. Kidneys were analyzed for markers of cell injury/death (KIM-1, calcium-binding protein A8 (S100A8)), cleaved caspase 3 (CC3) and TUNEL positivity and fibrosis.

Results: Rhabdomyolysis led to a significant loss in kidney function and an increase in kidney injury (NGAL and KIM-1) in all groups of mice. However, at 7 days, while these markers returned to baseline in $FtH^{Lysm-/-}$ mice, there was a persistent tripling of creatinine and elevated KIM-1 levels only in $FtH^{fl/fl}$ mice. This was associated with increased activation of JNK, and markers of cell death. Additionally, $FtH^{fl/fl}$ kidneys expressed higher levels of aSMA and collagen when compared to $FtH^{Lysm-/-}$ kidneys. This was associated with increased expression of TGFb and Gal-3, which mediate myofibroblast activation and promote fibrosis.

Conclusions: Our findings demonstrate that while myeloid FtH deletion does not impact acute injury following rhabdomyolysis, it mitigates injury progression and promotes recovery. Current studies are aimed at using single cell RNA sequencing approaches to identify key pathways that are activated during the resolution phase following rhabdomyolysis.

Funding: NIDDK Support

PO0361

Nicotinamide Retains Klotho Expression and Ameliorates Rhabdomyolysis-Induced AKI

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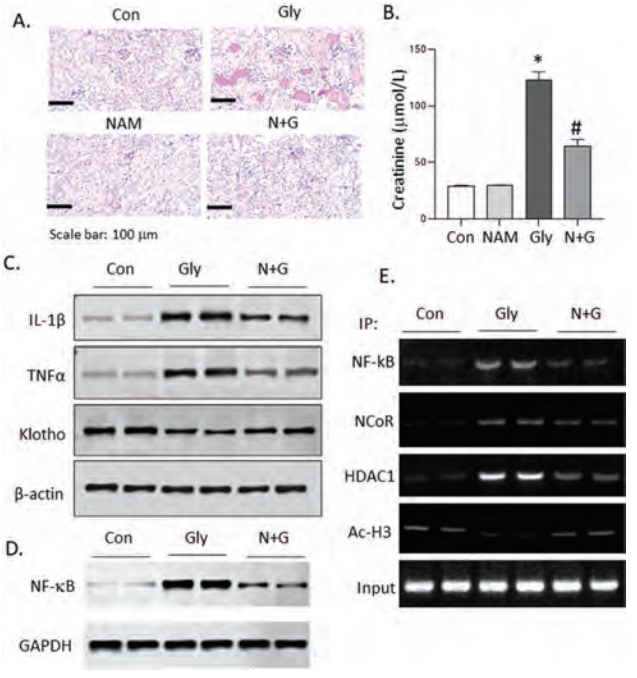
Background: Acute kidney injury is a severe complication of rhabdomyolysis. Inflammation plays a critical role in the pathogenesis of rhabdomyolysis-induced AKI. Nicotinamide, a form of vitamin B3 and a precursor of nicotinamide adenine dinucleotide, has been shown potent anti-inflammation effects. Klotho is a tubular highly expressed renoprotective protein. Therefore, we explored the effect of nicotinamide on rhabdomyolysis-induced AKI and the underlying mechanisms.

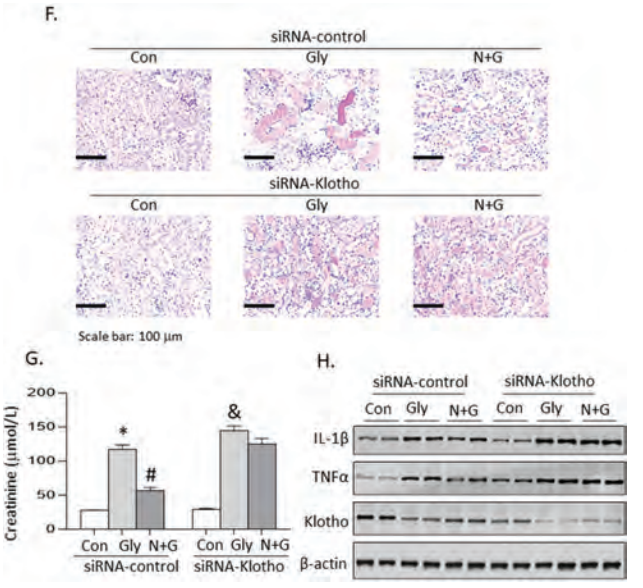
Methods: We used glycerol-induced rhabdomyolysis mice model to observe the effect of nicotinamide on kidney injury. Western blot, chromatin immunoprecipitation and small interfering RNA were used to evaluate the role of Klotho in nicotinamide-related renoprotection.

Results: The results showed that nicotinamide attenuated kidney injury in rhabdomyolysis. Moreover, nicotinamide effectively blocked the recruitment of NF-kB, NCoR and HDAC1 to the promoter of Klotho and preserved Klotho expression. More importantly, renoprotection effect of nicotinamide was abrogated when Klotho was knockdown by small interfering RNA.

Conclusions: Our study demonstrates that Klotho preservation is essential for the renoprotection effect of nicotinamide and provides a new preventive strategy for rhabdomyolysis-induced AKI.

Funding: Government Support - Non-U.S.





PO0362

Defective Clearance of Nucleic Acids Exacerbates AKI

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Background: Extracellular nuclear DNA and RNA released from dying cells can act as damage associated molecular pattern (DAMP) to trigger inflammatory pathology during acute kidney injury (AKI). Cell-free or cytoplasmic DNA can activate immune cells through the interferon stimulatory DNA (ISD) pathway to contribute to tissue damage. We aimed to understand immune dysregulation due to defective DNA clearance in the setting of murine AKI models. To study direct effect of defective DNA clearance in AKI, we utilized Three prime repair exonuclease (TREX1) deficient mice.

Methods: C57BL/6J (B6) mice or bone marrow derived macrophages (BMDM) were treated with poly I:C (pIC) to mimic elevated nucleic acid DAMPs. Bilateral ischemic reperfusion injury (IRI) or treatment of TREX1 deficient (TREX1 KO and TREX1 D18N) and STING KO mice with cisplatin (Csp), which causes DNA damage-induced AKI, was employed. Renal function was assayed using plasma creatinine (PCr) and blood urea nitrogen (BUN) levels. Levels of proinflammatory cytokines (IFNg, TNFa), renal injury markers (*Kim1* and *Ngal)* and pro-inflammatory genes (*Il1b, Mx1, Nos2, Ifi44, Tnfa* and *Il6)* were measured by Flow cytometry, ELISA and RT-PCR. H&E-stained kidney sections were used to assess renal injury.

Results: Treatments of wildtype (WT) B6 mice with pIC upregulated proinflammatory cytokines leading to a Th1 predominance, indicative of excessive inflammatory predisposition. Csp and IRI induced significantly higher injury and dysfunction in TREX1 deficient (TREX1 KO and TREX1 D18N) mice. Kidney injury markers *Kim1* and *Ngal* were also significantly elevated along with elevated proinflammatory cytokines. The TREX1 D18N mice subjected to IRI also exhibited upregulated recently activated ($CD4^{+}CD69^{hi}$) and elevated T effector memory ($CD4^{+}CD44^{+}CD62L^{lo}$) phenotype confirming immune dysregulation. CD4 T cells in TREX1 D18N mice also had reduced levels of the anti-inflammatory cytokine IL-10. Interestingly, STING KO and TREX1 D18N-STING double KO mice also had exacerbated injury levels indicating the role of uncleared DNA and the cGAS-STING DNA sensor pathway in AKI as a result of TREX1 deficiency.

Conclusions: The study presents evidence of the role of TREX1 and uncleared DNA to cause immune dysregulation in AKI and supports employing approaches that can target DNA scavenging to counteract the burden of AKI.

Funding: NIDDK Support, Other NIH Support - National Institute of Allergy and Infectious Diseases

PO0363

Heme Oxygenase 1 Is a Key Player in Arsenical-Induced AKI

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Background: Arsenicals, such as Lewisite, are a class of warfare vesicants that cause immediate and painful blistering of the skin and mucous membranes upon contact. Systemic absorption of arsenicals results in "Lewisite shock," which is characterized by hypovolemia due to capillary damage, and multi-organ dysfunction. There is an ongoing risk of exposure from arsenical weaponization, but accidental exposures from underground storage of these compounds in several countries including the US, Italy, Russia, and Japan also pose a risk. Molecular mechanisms of arsenical-induced injury

involve oxidative and endoplasmic reticulum (ER) stress, inflammation, and cell death. We have previously reported that a single cutaneous exposure to arsencials causes acute kidney injury (AKI) in mice as evidenced by increased serum and urinary biomarkers of AKI. Intrarenal heme oxygenase-1 (HO-1), a protective anti-oxidant enzyme, is also upregulated as a response to injury in addition to ATF4 and CHOP, molecules involved in regulation of ER stress and cell death.

Methods: To interrogate the precise role of HO-1 in arsenical-induced AKI, we exposed HO-1 knockout mice (HO-1$^{-/-}$) and wild-type controls to phenylarsine oxide (PAO), an analog of Lewisite that is commonly used due to the restricted use of this vesicant. Employing *in vitro* techniques, we further tested the efficacy of a novel small molecule inducer of HO-1, SR-37618 after PAO treatment.

Results: Our data show that HO-1 deficiency results in worse kidney damage post-PAO exposure, suggesting it is a targetable enzyme for intervention. Utilizing a novel small molecule inducer of HO-1 created in collaboration with Southern Research, we demonstrate that 1 hour pre-treatment with SR-37618 diminishes PAO-induced ATF4 and CHOP expression in HEK-293 cells.

Conclusions: While further studies to assess the efficacy of SR-37618 in mouse models are ongoing, the data presented here provide evidence that HO-1 induction by SR-37618 is protective against arsenical-induced AKI. Moreover, small molecule inducers of HO-1 could potentially serve as a novel therapeutic for intervention in other forms of AKI.

Funding: NIDDK Support, Other NIH Support - National Institute of Environmental Health Sciences U54ES030246

PO0364

Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Acute Proximal Tubule Epithelial Cell Injury and Associated Renal Hemodynamic Responses

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Background: Renal proximal tubule epithelial cells (RPTEC) are vulnerable to drug-induced toxicities which often result in acute kidney injury (AKI). Drug toxic effects range from mild sub-lethal RPTEC injuries to cellular death via multiple cellular damage mechanisms. At the systems level, decline in glomerular filtration rate (GFR) is a common manifestation of AKI. The complexity of pathophysiological responses (cellular, neurohormonal, hemodynamic) that lead to impaired filtration pose a challenge for reliable prediction of AKI. QST modeling is a promising method for translating cellular-level renal damage to clinical manifestations of AKI.

Methods: We developed RENAsym, a QST model of drug-induced AKI that includes key cellular injury mechanisms and renal hemodynamic responses. At the cellular level, RENAsym represents RPTEC life cycle, bioenergetics, and immune responses to renal toxicity. *In vitro* assays were used to parameterize key cellular injury mechanisms. At the systems level, RENAsym model represents renal function and feedback mechanisms including tubuloglomerular feedback (TGF) and renin-angiotensin-aldosterone systems (RAAS). RENAsym was employed to characterize the renal hemodynamic responses of drug induced RPTEC injury in humans treated with cisplatin.

Results: At the cellular level, urinary biomarkers such as KIM-1 and αGST were used to represent cellular injury and death following cisplatin exposure. RENAsym was able to capture the elevations in KIM-1 and αGST. The model also captured GFR decline and demonstrated that it occurs due to 1) increased Bowman's pressure, 2) reduced intraglomerular pressure caused by vascular effects due to RAAS activation and TGF mechanisms, and 3) lower renal perfusion pressure from excess sodium and water excretion. The model quantitatively relates cellular injury and biomarker changes with renal hemodynamic responses.

Conclusions: RENAsym represents kidney function at cellular and organ levels in healthy and pathologic states caused by toxic drug effects. By describing drug induced cellular injury and subsequent hemodynamic changes it can predict clinical responses during AKI.

Funding: NIDDK Support

PO0365

Elastin-Like Polypeptide Vascular Endothelial Growth Factor (ELP-VEGF) Improves Renal Function and Decreases Inflammation Following Ischemia-Reperfusion Injury in Mice

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Background: Acute Kidney Injury (AKI) represents a significant clinical concern and significant risk factor for the development of chronic kidney disease (CKD). AKI is associated with impaired renal function, increased inflammation and microvascular congestion, damage and loss. A fusion protein between the elastin-like polypeptide biopolymer and human VEGF-A_{121} (ELP-VEGF) efficiently targets the renal vasculature and promotes vascular protection and angiogenesis, while potentially altering inflammatory processes. However, it is unknown if ELP-VEGF administration following ischemia-reperfusion mitigates injury, facilitates vascular protection and hastens repair.

Methods: Male C57BL/6 mice were subjected to unilateral ischemia (I/R) for 25 minutes. Post-ischemic animals were treated daily with either vehicle or ELP-VEGF (10ug/kg bw; i.p) at reperfusion, and every 24 hours for 7 days. Serum creatine (sCre) and BUN were collected 24 hours and 7 days following ischemia to assess renal function. At day 7, kidneys were harvested for analysis of infiltration of inflammatory cells by FACS and measurement of peritubular capillary density by immunofluorescent staining.

Results: Increases in BUN following unilateral I/R were significantly attenuated in the ELP-VEGF treated group compared with vehicle at both 24 hours (66% vs. 15%) and 7 days (49% vs. 19%) following ischemia ($p<0.05$). I/R significantly reduced the number of CD31+ endothelial cells in the injured kidney of the vehicle-treated mice compared with sham ($p<0.05$), and ELP-VEGF attenuated that reduction. ELP-VEGF also attenuated the pro-inflammatory response following I/R, with significant reductions in total number of infiltrating mononuclear cells ($p<0.05$). In ELP-VEGF treated mice, there was a significant reduction in Th17 cells (CD4+IL17+; 408236 vs. 182277 cells/g kidney: CD8+IL17+; 484483 vs. 99391 cells/g kidney), DC/Macrophages (12404078 vs 4764147 cells/g kidney) and B cells (16201335 vs. 7641714 cells/g kidney) compared with vehicle treated rats ($p<0.05$).

Conclusions: ELP-VEGF represents a novel reno-protective therapeutic compound related to its anti-inflammatory and renovascular protective effects.

Funding: NIDDK Support

PO0366

Inhibition of PFKFB3 Alleviates Cisplatin-Induced AKI

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Background: Metabolism and its reprogramming may have influence on acute kidney injury (AKI) and subsequent kidney repair. 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) is an important rate-limiting enzyme in glycolysis. Recently, PFKFB3 has gained substantial interest as an attractive target for cancers and pulmonary hypertension therapy. However, the role of PFKFB3 in AKI remains poorly understood.

Methods: To investigate the role of PFKFB3 in cisplatin nephrotoxic AKI, we established stable PFKFB3 knockdown rat renal tubular cell lines (RPTC) and generated the kidney proximal tubule-specific PFKFB3 knock-out mice by crossing PFKFB3-floxed mice with PEPCK-CRE mice. PFKFB3-knockdown and wild-type RPTC cells were treated with 20μM cisplatin for 24h *in vitro*, while PFKFB3 knock-out or wild type male mice of 8-10 weeks were intraperitoneally injected with 30 mg/kg of cisplatin *in vivo*.

Results: PFKFB3 was up-regulated in cisplatin-induced AKI models both *in vitro* and *in vivo*. In the mouse model, deficiency of PFKFB3 reduced cisplatin-induced kidney injury and improved renal functions. Moreover, genetic and pharmacological inhibition of PFKFB3 in RPTC cells suppressed cisplatin-induced apoptosis. In addition, phosphorylated Erk1/2, phosphorylated p38 and phosphorylated NF-κB were decreased in PFKFB3 knockdown RPTC cells compared to the vector group.

Conclusions: These results indicate that PFKFB3 is a key mediator of renal tubular injury in cisplatin-induced AKI and may be an effective therapeutic target for alleviating cisplatin nephrotoxicity in chemotherapy.

Funding: NIDDK Support, Veterans Affairs Support

PO0367

Cilastatin Inhibits Renal Myoglobin Endocytosis and AKI Following Rhabdomyolysis

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Background: Muscle-derived myoglobin, a renal toxin, causes rhabdomyolysis-induced acute kidney injury (AKI) via megalin-mediated endocytosis into proximal tubule cells (PTs). Endocytosis kinetics and inhibition are poorly understood. We characterized myoglobin uptake *in vivo*, hypothesizing cilastatin, a putative megalin inhibitor, would prevent endocytosis akin to megalin knockouts.

Methods: Procedures in wild-type (WT) male C57BL/6 mice and inducible, PT-specific megalin-deleted mice (iMegKO) were approved by OHSU or PVAMC IACUC. FITC-myoglobin (FMb) and cilastatin (200 mg/kg) were injected retroorbitally. Experimental rhabdomyolysis (ER) was induced via intramuscular injection of 50% glycerol (8 mL/kg). Glomerular filtration rate (GFR) was measured 24h later, and immunofluorescence and single-cell RNASeq were performed on renal tissue.

Results: FMb was observed in PTs 15 min post-injection in control mice; in iMegKO mice, FMb puncta were nearly absent ($p<0.0001$). FMb puncta were reduced in cilastatin-treated WTs without ER vs vehicle controls ($p=0.0012$). iMegKO prevented AKI following ER, with 24h GFR 5x control ($p<0.001$). Cilastatin injection did not affect GFR in iMegKO ($p=0.89$), but had a significant effect on ER-induced AKI in wild-type mice: GFR was 8x vehicle ($p=0.03$) while PT uptake of endogenous myoglobin decreased ($p<0.05$). A composite score of endocytosis related genes (endoscore) showed significant alterations (Figure 1).

Conclusions: Megalin interference prevents ER-induced AKI by reducing myoglobin endocytosis; cilastatin recapitulates the effect in a megalin-inhibitory fashion. Alteration of endocytosis-related genes confirms this process is critical in rhabdomyolysis, and may suggest additional therapeutic targets. Future studies will also include cilastatin delivery timing, dosage, and formulation.

Funding: NIDDK Support, Veterans Affairs Support, Other U.S. Government Support

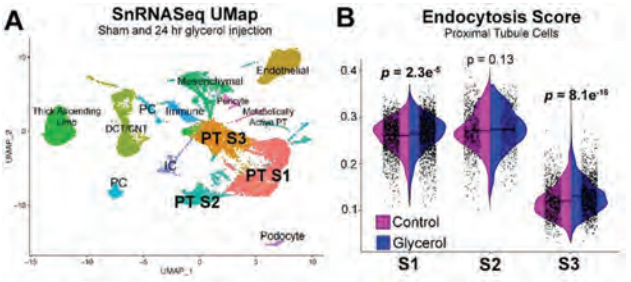

Figure 1. Kidney SnRNASeq after RIAKI. A) Umap clustering of cells isolated from whole kidney tissue 24 hrs after glycerol or vehicle injection (n=2 kidneys and approximately 10,000 cells per group). Data generated in Seurat V4 using Rstudio. PT = proximal tubule, PC = principal cells of the collecting duct, IC = intercalated cells of the collecting duct. DCT = distal convoluted tubule. B) Split violin plots of different PT segments depicting "endocytosis score", generated by calculating average expression of 657 genes in gene ontology term "endocytosis" (GO:0006897). Line = median endocytosis score of all cells within group. P values generated from student's t-test.

PO0368

PKM2-Specific Deletion in Myeloid Cells Ameliorates Renal Impairment by Alleviating Metabolic Changes in CaOx-Induced AKI

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Background: Macrophages are plastic cells and can polarize towards pro- or anti-inflammatory phenotype. PKM2 catalyzes the last step of glycolysis, which is a crucial metabolic pathway for activation of macrophages. We investigated whether deletion of PKM2 in myeloid cells would interfere with renal metabolism and exert protection in calcium oxalate (CaOx) crystal-induced acute kidney disease (AKI).

Methods: Myeloid-specific PKM2-knockout mice ($PKM2^{fl/fl}$;LysM-Cre^{+}) and their Cre-negative littermates ($PKM2^{fl/fl}$) underwent AKI by a single i.p. injection of NaOx (100mg/kg) and 3% NaOx in drinking water for 24hr before sacrifice. Expression of PKM2 in bone marrow-derived macrophages was assessed by FACS. Serum creatinine, blood urea, renal CaOx crystal deposition (Pizzolato staining), IL-6, NGAL, KIM-1, HK2, CPT1a and CPT2 mRNA expression (quantitative PCR), macrophage number/phenotype (FACS), and lactate levels were all measured.

Results: In $PKM2^{fl/fl}$, intrarenal CaOx deposition impaired renal function, as well as increased the expression of IL-6, NGAL, KIM-1 and HK2 and the levels of lactate in kidneys compared to healthy controls ($p<0.05$). Renal expression of CPT1a and CPT2 did not differ among groups. $PKM2^{fl/fl}$;LysM-Cre^{+} exhibited similar deposition of crystals but less impairment of renal function, inflammation/injury and renal lactate content ($p<0.05$). The number of F4/80+CD11b+ cells in kidneys were similarly elevated by CaOx in both $PKM2^{fl/fl}$ and $PKM2^{fl/fl}$;LysM-Cre^{+}, while pro-inflammatory macrophages (Ly6C+CD206-) were significantly reduced in PKM2;LysM-Cre^{+} mice ($p<0.01$).

Conclusions: Pro-inflammatory macrophages rely mainly on glycolysis in oxalate induced-AKI. Deletion of PKM2 in myeloid cells partially prevents renal metabolic changes and inflammation/injury. FAPESP (2019/02893-9 and 2017/05264-7), CNPq and CAPES (Financial Code 001).

Funding: Government Support - Non-U.S.

PO0369

Tubular MPC1 Deletion Protects from Glycerol-Induced Kidney Injury

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Background: Pyruvate fuels mitochondrial oxidation, scavenges H_2O_2, and regulates the glutathione and thioredoxin dependent antioxidant systems. Acute kidney injury (AKI) results in damaging oxidative stress and metabolic disruptions that are lessened upon pyruvate treatment. The specific mechanism by which pyruvate protects against AKI is unknown. We hypothesize that the Mitochondrial Pyruvate Carrier 1 (MPC1), which controls the cellular fate of pyruvate, plays a central role in AKI and injury recovery.

Methods: MPC1 was disrupted in tubular epithelial cells by generating $Pax8^{Cre+/-}Mpc1^{f/f}$ (Tub-MPC1-KO) mice and was tested against $Mpc1^{f/f}$ (Tub-MPC1-WT) littermates. 13C-tracer and steady state metabolomics were performed in 4 hour-fasted mice. Rhabdomyolysis-induced AKI was initiated by injecting 10 ml/kg of 50% glycerol into the hind limb of Tub-MPC1-WT vs Tub-MPC1-KO mice and we evaluated toxicity and kidney function prospectively.

Results: 13C enrichment into TCA cycle intermediates demonstrated decreased glucose-driven PDH- and PC-dependent pyruvate metabolism in Tub-MPC-KO mice. At steady state, this fueled adaptations in carbohydrate, fatty acid, and amino acid metabolism. Interestingly, pathway analysis identified glutathione metabolism as significantly altered in Tub-MPC1-KO. Glutathione biosynthetic precursors were decreased and NADPH/NADP was increased in Tub-MPC1-KO kidney. This implies that the renal redox environment was potentially primed to be better able to respond to renal oxidative stress. To test this idea, rhabdomyolysis-induced AKI was initiated by injecting Tub-MPC1-WT and Tub-MPC1-KO mice intramuscularly with glycerol. Following AKI, Tub-MPC1-KO mice lost less weight and had significantly decreased serum cystatin C and BUN compared to Tub-MPC1-WT mice.

Conclusions: *In vivo* disruption of tubular MPC1 results in metabolic changes that favor a reduced cellular environment and protects from glycerol induced AKI.

Funding: NIDDK Support, Other NIH Support - NICHD K12 HD027748

PO0370

Ginsenoside Rg3 Attenuates Ischemia Reperfusion-Induced Renal Injury in Mice via Induction of Autophagy Flux

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Background: Ginsenoside Rg3 (Rg3) has been shown as protective effects via various mechanism. However, the reno-protective effect and the role of autophagy are not clearly evaluated. This study investigate Rg3 induces autophagy flux and reduces renal cell death in renal ischemia reperfusion injury (IRI).

Methods: C57Bl/6 mice were divided into the following groups: sham; Rg3 treated sham; saline treated IRI mice; Rg3 treated IRI mice. Kidneys and blood were collected 24h after operation of mice (sham and IR operation). Renal function, kidney histology, and the protein expression of autophagy signals were evaluated.

Results: In IRI mice, the levels of BUN and s-Cr were increased, compared to sham. The Rg3 treatment decreased the BUN and s-Cr in IRI mice. In addition, Rg3 treatment decreased the renal injury score including the renal tubular cell detachment and necrosis in IRI mice. Rg3 treated IRI mice showed significantly less oxidative stress and autophagy impairment, greater amounts of LC3 and Beclin-1, lower amounts of p62, and higher levels of renal ATP6E compared to saline treated IRI mice. Rg3 treatment also increased phosphorylation of AMPK in IRI mice kidney.

Conclusions: Rg3 has renoprotection against renal IR injury via enhancement of autophagy flux.

PO0371

A Novel Immunomodulatory Peptide Suppresses Inflammatory Macrophages and Mitigates AKI

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Background: Monocytes/macrophages are known to play a critical role in the pathogenesis and progression of acute kidney injury (AKI), as large numbers of monocytes are recruited to the kidney and differentiate into pro-inflammatory macrophages (M1 phenotype) after injury. Although targeting macrophages has emerged as a promising therapeutic strategy for AKI, the effective treatment is still limited. We previously identified a novel peptide, the MPS peptide, which targets the signaling molecule myristoylated alanine-rich C-kinase substrate (MARCKS), a central inducer of M1 macrophages. In this study, we have employed this novel peptide to determine if MARCKS inhibition reduces kidney injury.

Methods: High-dimensional single-cell mass spectrometry was used to reveal immune profiling in an AKI mouse model. Both commercial macrophage cell lines and primary macrophages isolated from peripheral blood mononuclear cells were utilized in this study for gene expression analysis. In vitro and in vivo inflammatory activities of the MPS peptide were confirmed by Western blots, real-time reverse transcription-polymerase chain reaction (RT-qPCR), flow cytometry, ELISA cytokine assays, and immunohistochemistry.

Results: Analysis of the single-cell RNA sequencing data has identified that the immune microenvironment of injured kidneys is associated with the expansion of monocytes/macrophages, particularly M1 macrophages. We next show that an elevated abundance of phospho-MARCKS in macrophages upon cisplatin treatment and this increase occurred in parallel with an increase of M1 markers as well as upregulation of inflammatory cytokines and markers of nephrotoxicity in cisplatin-exposed kidneys. Mechanistically, we demonstrate that MPS peptide had an inhibitory effect on cisplatin-induced phospho-MARCKS, p65 phosphorylation, and NF-κB activation in macrophages. Targeting of MARCKS phosphorylation using MPS peptide not only downregulated kidney-infiltrating M1 macrophages but also suppressed levels of serum creatinine and blood urea nitrogen in mice exposed to cisplatin.

Conclusions: Our results suggest that MARCKS phosphorylation is a novel NF-kB activator in pro-inflammatory macrophages and also presents a proof of concept for the use of MPS peptide as a renal protection agent for AKI.

Funding: Other U.S. Government Support

PO0372

Renal NG2-Expressing Cells Have Phagocytic Activity and Facilitate Renal Recovery After Ischemic Injury

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Background: Pericytes play an important role in the recovery process after ischemic injury of many tissues. Brain pericytes in the peri-infarct area express macrophage markers in response to injury stimuli and are involved in neovascularization. In the kidney, nerve/glial antigen 2 $(NG2)^+$ pericytes have been found to accumulate after renal injury. However, the role of accumulated $NG2^+$ cells in injured kidneys remains unknown.

Methods: A reversible ischemic reperfusion model, we found that renal $NG2^+$ cells were increased in injured kidneys and expressed macrophage markers (CD11b or F4/80) on day 3 after reperfusion.

Results: Isolated $NG2^+$ cells from ischemia/reperfusion (I/R) kidneys also had phagocytic activity and expressed anti-inflammatory cytokine genes, including mannose receptor and IL-10. These macrophage-like $NG2^+$ cells did not likely differentiate into myofibroblasts because they did not increase α-SMA expression. Intravenous transfusion of renal $NG2^+$ cells isolated from donor mice on day 3 after reperfusion into recipient mice on day 1 after I/R surgery revealed that $NG2^+$ cell-injected mice had lower plasma blood urea nitrogen, reduced KIM-1 mRNA expression, ameliorated renal damage, and reduced cellular debris accumulation than PBS-injected mice on day 5 after reperfusion.

Conclusions: In conclusion, these data suggest that renal $NG2^+$ cells have an M2 macrophage-like ability and play a novel role in facilitating the recovery process after renal I/R injury.

Funding: Government Support - Non-U.S.

PO0373

The Role of Renal Hmgcs2 in Fasting and Bacterial Inflammation

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Background: The purpose of inflammatory anorexia during states of acute illness, such as sepsis, remains incompletely understood. We have found that glucose supplementation during bacterial sepsis suppresses ketogenesis and increases mortality, suggesting a potential protective effect of fasting metabolism. Gene expression analysis of the liver and kidney during fasting and after lipopolysaccharide (LPS) challenge, to model sterile bacterial inflammation, revealed that *Hmgcs2*, the rate-limiting enzyme of ketogenesis, is suppressed in the liver while upregulated in the kidney during LPS sepsis. This expression pattern differs from fasting, during which *Hmgcs2* is induced in both the kidney and liver. The significance of renal *Hmgcs2* upregulation during bacterial inflammation is unclear.

Methods: Liver-specific *Hmgcs2* knockout mice *(Alb-CreERT2; Hmgcs2fl/fl*), kidney-specific knockout mice (*Six2-Cre*; *Hmgcs2*$^{fl/fl}$), *Ppara*$^{-/-}$, and wild-type C57BL/6J mice were fed *ad libitum*, fasted or injected i.p. with 10 mg/kg LPS. Plasma was analyzed for lipids and ketones. Livers and kidneys were harvested for RNA and protein analysis.

Results: In wild-type mice, circulating ketones increase during fasting and LPS sepsis. While not expressed in the fed state, HMGCS2 protein is induced in the proximal tubules in a PPARa-dependent manner during both fasting and LPS sepsis. Liver-specific *Hmgcs2* deletion results in a significant attenuation of circulating ketones during fasting and LPS sepsis, while kidney-specific *Hmgcs2* deletion has no effect. Preliminary data show that the loss of *Hmgcs2* in the kidney results in an increase in KIM1 protein, a marker indicative of kidney injury, up to 48 hours after LPS injection.

Conclusions: It is well-established that the liver is the main source of circulating ketones. Our data support this notion and demonstrate that although fasting and LPS sepsis induce an upregulation of renal HMGCS2, the expression of this enzyme in the kidney does not appear to contribute to circulating ketones. Our data suggest that while renal HMGCS2 does not produce systemic ketones, it may be important for mitigating kidney injury during LPS sepsis.

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

PO0374

Head-to-Head Comparison of Two SGLT-2 Inhibitors on AKI Outcomes in a Rat Ischemia-Reperfusion Model

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Background: The CREDENCE trial testing canagliflozin and the EMPA-REG OUTCOME trial testing empagliflozin suggest different effects on acute kidney injury (AKI). Since the diagnosis of AKI was made in these studies usually based on changes of serum creatinine (sCr) although changes of sCr may reflect the mode of action of SGLT-2 inhibitors.

Methods: We analyzed both drugs in a rat AKI model (ischemia-reperfusion injury (IRI) model) focusing on established morphological and biochemical AKI markers. Four groups were analyzed: sham, IRI+placebo, IRI+canagliflozin, IRI+empagliflozin.

Results: Urinary glucose excretion was comparable in both treatment groups indicating comparable SGLT-2 inhibition. Comparing GFR surrogate markers after IRI (sCr and BUN). At all investigated time points after IRI, sCr and BUN were higher in the IRI+canagliflozin group than placebo-treated rats, whereas the empagliflozin group did not differ from the placebo group. IRI led to tubular dilatation and necrosis. Empagliflozin was able to reduce that finding whereas canagliflozin had no effect. Renal expression of KIM-1 increased after IRI and empagliflozin but not canagliflozin normalized KIM-1 expression (Figure). IRI reduced urinary microRNA-26a excretion. Empagliflozin but not canagliflozin was able to restore normal levels of urinary miR-26a.

Conclusions: In conclusion, our study confirmed the observations made in the CREDENCE and the EMPA-REG OUTCOME trials. The empagliflozin effects on KIM-1 and miR-26a might indicate beneficial regulation of inflammation and innate immune response. Our data should stimulate clinical studies analyzing whether empagliflozin is a preferable SGLT-2 inhibitor in patients at high AKI risk.

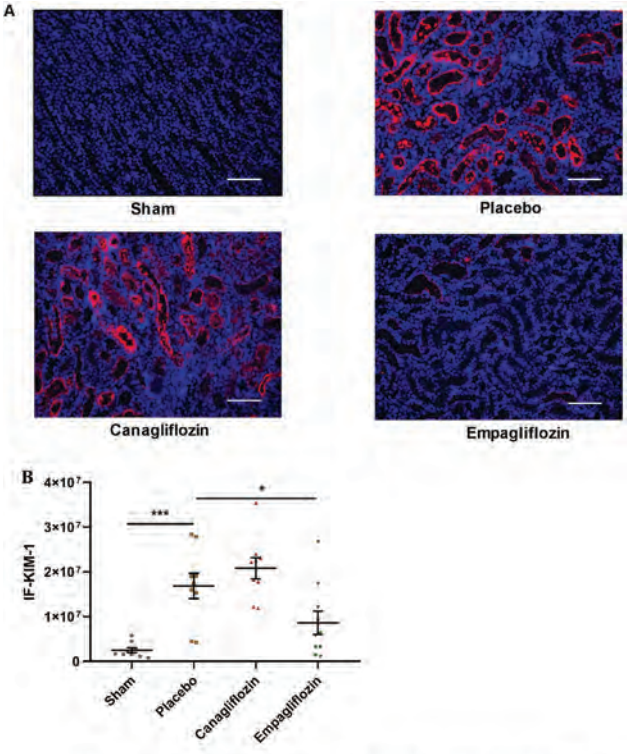

Figure 1. KIM-1 expression in kidney tissue. (A) Representative microphotographs from kidney sections of each treatment group. (B) KIM-1 expression in kidney tissue, n-values: sham (n = 9), placebo (n = 9), canagliflozin (n = 9), empagliflozin (n = 10). Values shown are means ± SEM. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001, significantly different as indicated; one-way ANOVA followed by least square method post-hoc test. Scale bars = 100 µm.

PO0375

Modeling Sepsis in Human Kidney Organoids: Cell-Free Hemoglobin-Induced Cytotoxicity Is Attenuated by Ascorbate or Acetaminophen

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Background: Sepsis-associated acute kidney injury (AKI) is associated with high morbidity and mortality. Cell-free hemoglobin (CFH) is released into the circulation of patients with severe sepsis and higher levels are independently associated with mortality. CFH is toxic to HK-2 cells, suggesting that CFH can directly injure the renal tubular epithelium. Treatment with ascorbate (Vitamin C) or acetaminophen provides protection from CFH-induced toxicity in endothelial cells. Therefore, we sought to generate a model of sepsis-induced AKI in human kidney organoids in which to study CFH-targeted AKI treatments.

Methods: We cultured human kidney organoids from fibroblast-derived human induced pluripotent stem cells (hiPSCs) by the Takasato protocol, with optimization. We then treated mature human kidney organoids with CFH (1 mg/ml) for 48 hours and evaluated cell toxicity, viability, reactive oxygen species (ROS), and mitochondrial fragmentation. To study the protective effects, CFH-exposed organoids were co-treated with ascorbate (200 uM) or acetaminophen (1000 uM) for 48 hours.

Results: The kidney organoids expressed the expected kidney cell type markers ECAD (distal tubule), GATA3 (collecting duct), LTL (proximal tubule) and NEPHRIN (Glomeruli) at Day 21 (n=3). CFH treatment resulted in ROS production in 80% of cells within organoids compared to 5% in control group (n=3). Analysis by Lactate Dehydrogenase showed CFH treatment increased toxicity by 30% in organoids and and analysis by MTT (tetrazolium dye) assays showed reduced viability [by 70% within

organoids compared to control group (n=3)($p<.005$). LDH assay also revealed that the addition of ascorbate or acetaminophen attenuated the impact of CFH on organoids by decreasing the toxicity by ~23% within the organoids (p value<.0001).

Conclusions: Human kidney organoids can be used to model sepsis-induced AKI. CFH treatment induced toxicity and reduced viability of the human kidney organoids. Both ascorbate and acetaminophen had protective effects on CFH-induced organoid injury.

Funding: Private Foundation Support

PO0376

Pulsed Ultrasound Reduces Oxidative Stress-Induced Disruption of Epithelial Barrier in Sepsis-AKI

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Background: Oxidative stress disrupts epithelial junctions leading to increased paracellular permeability and kidney dysfunction. We previously showed that pulsed ultrasound (pUS) reduced inflammation and kidney injury. We hypothesized that pUS mitigates renal injury by maintaining epithelial tight junctions. Here, we utilized lipopolysaccharide (LPS) induced sepsis to create acute kidney injury (S-AKI) in a mouse model and RAW 264.7 cells to investigate the effects of pUS on the epithelial tight junction barrier and renal macrophages.

Methods: C57/BL/6 mice received pUS 24 hrs before LPS treatment. The parameters of pUS therapy followed the protocol previously published by us (PMID: 23907510). Following pUS treatment, mice received a single injection of LPS (5 mg/kg, ip). Animals were euthanized at increasing time intervals for measurement of mRNA expression and kidney imaging. Kidney histopathological changes were observed by using PAS staining. Co-staining with TUNEL and cleaved caspase-3 was used to assess kidney injury. For in-vitro assays, RAW cells were seeded onto 4-well plates and incubated for 24 hrs at a density of 5×10^5 per well. Cells were treated with LPS (100 ng/mL) in serum-free DMEM for 2 hrs.

Results: LPS induced kidney injury and apoptosis, as observed by PAS and TUNEL staining, was attenuated by pUS. Co-staining with PSD95 (postsynaptic scaffolding density protein 95) and ZO-1 (zonula occludens-1) showed both were expressed in kidney. LPS also induced a significant loss of PSD95 accompanied by a reduced mRNA expression of nuclear factor erythroid 2-related factor 2 (NRF2) and activated macrophages. The structural changes, extent of loss of PSD95 and NRF2, as well as macrophage infiltrate were all partially reversed by prior pUS treatment. In cultured RAW cells, pUS upregulated the expression of NRF2 and heme oxygenase-1 (HO-1), and attenuated CD68-positive macrophage signals.

Conclusions: pUS protected kidneys from LPS-induced S-AKI by preserving antioxidant NRF2 expression and attenuating oxidative stress-induced disruption of epithelial tight junctions.

Funding: NIDDK Support

PO0377

Hypertensive Diabetic Kidney Disease Increases the Severity of Experimental AKI

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Background: Patients with diabetic kidney disease (DKD) are at increased risk of severe AKI and adverse outcomes. Since DKD may alter cellular and therapeutic responses in AKI, there is a need to establish a model to evaluate the mechanisms and therapeutics of AKI in the context of DKD. These studies address this deficiency by characterizing AKI in transgenic mice with renin-induced hypertension and progressive DKD.

Methods: Hypertensive male transgenic TThRen (TR+) mice, which over-express renin in the liver, were treated +/- streptozotocin to induce diabetes (DM). Tail cuff BP; urinary albumin/creatine ratio (ACR); BUN; and transdermal GFR (tGFR) were measured from 11-31 wks in DM and non-diabetic (ND) cohorts. After optimizing renal pedicle clamp times in DM (19 mins) vs. ND mice (24 mins) to induce similar injury after ischemia-reperfusion AKI (IR-AKI), mice underwent bilateral IR-AKI at 32 wks, followed by serial BP, BUN, ACR and tGFR measurements over 8 wks.

Results: ND and DM TR+ mice had increased albuminuria (31wk ACR, mg/mg: ND TR - vs. +, 17.7 (2.0) vs. 498.2 (325.2), $p<0.0001$; DM TR – vs. +, 136.7 (50.3) vs. 1028 (420.3) $p<0.01$), with no significant difference between DM and ND TR+ mice. BP was elevated in TR+ mice, with no difference between DM and ND mice, but there was a decrease in tGFR in DM TR+ vs. ND TR+ over time (2 way ANOVA, $p<0.05$). After IR-AKI, DM TR+ mice had more severe injury than DM TR- mice (e.g.: day1 BUN, mg/dl: DM TR- vs. +, 56.7 (8.6) vs. 95.1 (11.8), $p<0.01$), but there was no difference in severity of injury in ND TR- and + mice. This was associated with a progressive increase in albuminuria, but after 14 days, no difference in tGFR in DM TR- vs. + mice, and no change in albuminuria or tGFR in ND TR- vs. + mice up to 8 weeks after IR-AKI.

Conclusions: Hypertensive DM and ND mice develop albuminuria, but only hypertensive DM mice develop reduced tGFR consistent with progressive DKD. After optimizing renal pedicle clamp times to induce similar injury, only hypertensive DM mice had increased injury and progressive nephropathy after IR-AKI, as determined by increased albuminuria, compared with non-hypertensive DM and both hypertensive and non-hypertensive ND controls. This model mimics human disease as there is increased injury and progressive DKD after IR-AKI mice with pre-existing DKD.

Funding: Other U.S. Government Support

PO0378

Kidney-Specific Intestinal Alkaline Phosphatase (IAP) in Transgenic Mice Protects Lipopolysaccharide (LPS)-Induced Inflammation and Renal Failure

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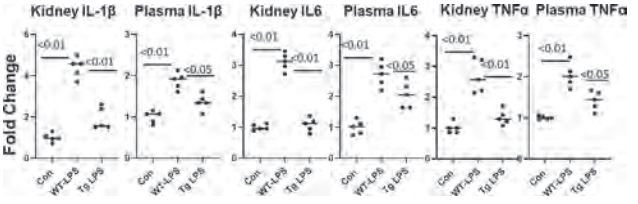
Background: LPS is a major player in septic AKI. However, LPS can be dephosphorylated to an inactive form by IAP. We generated kidney specific IAP transgenic mice (Tg) mice to test whether the targeted increase in IAP can decrease inflammation and improve renal function.

Methods: Tg mice were developed in C57Bl6 background using human chimeric IAP under the control of villin promoter making them kidney specific albeit some expression was also observed in the intestine. The 3′ prime end of the transgenic codon had a cmyc tag to distinguish human IAP from resident mouse IAP. Tg and non-transgenic littermates (Wild type, WT) were given 10 mg/kg LPS. Wild type control (Con) received saline. Renal function tests, plasma BUN creatinine, proteinuria, and albuminuria were performed. Plasma, Kidney, and liver were harvested after 12 hours for western blots and ELISA. Electron microscopy (EM) was done to evaluate podocytes.

Results: Serum creatinine and BUN were 2.5 and 3 fold higher in WT compared to Con ($p<0.01$), the increases were attenuated in Tg ($p<0.05$). In WT proteinuria and albuminuria were 3 and 5 fold higher than Con ($p<0.05$) these were attenuated in Tg ($p<0.05$). Cytokines (IL-1β, IL-6, and TNFα) in the liver, kidney, and plasma of WT after LPS injection was 2 to 4-fold higher than Con. However, in the liver of Tg+LPS, only TNFα was significantly reduced. Plasma and kidney cytokines of Tg+LPS were significantly lower than WT+LPS (Fig). The reduction of cytokines in the kidney of Tg+LPS was more profound than the plasma of TG+LPS. Podocyte effacement in Tg mice was less severe than WT. We could detect cmyc in plasma and kidney in Tg mice.

Conclusions: This study shows targeted increase of IAP in the kidney can abate LPS mediated deterioration of renal function, inflammation, and podocyte effacement. IAP has been shown to be released after LPS administration perhaps as a protective mechanism. An increase in plasma cmyc after LPS injection indicate that human IAP could have been secreted in the blood from the kidney or intestine. This may have decreased the inflammatory burden in the plasma.



Fold changes in cytokines

PO0379

Pretreatment with Low-Dose Lipopolysaccharide Attenuates Ischemia Reperfusion-Induced Vascular Congestion Through Vasoconstriction of the Outer Medulla During Reperfusion

Sarah C. Ray, Paul O'Connor. *Augusta University, Augusta, GA.*

Background: Vascular congestion in the renal outer medulla (OM) is common in acute tubular necrosis caused by ischemia and has been shown to promote tubular injury. Evidence from our laboratory suggests that vascular congestion originates in the renal venous vessels during ischemia and backfills the outer-medullary circulation with red blood cells (RBCs) during the reperfusion phase. We have previously reported that pretreatment with low dose lipopolysaccharide (LPS) attenuates ischemia reperfusion (IR) induced vascular congestion, however the mechanisms mediating this effect remain unknown. In the current study, we hypothesized that pretreatment with LPS prevents vascular congestion by limiting early reperfusion of the OM capillaries following ischemia.

Methods: To test this hypothesis, male WKY rats (12wks) were pretreated (i.p) with 1mg/kg LPS (n=6) or saline control (n=7) daily for 3 days. Rats were then anesthetized, and Transonic Laser Doppler probes were inserted in the cortex and OM. Regional kidney blood flow was then measured over 10 minutes of baseline, 45 minutes of renal artery clamping and 30 minutes of reperfusion.

Results: There were no differences in baseline blood flow between rats pretreated with low dose LPS or control ($p_{treat}=0.51$). The return of blood flow to the cortex was gradual ($p_{time}<0.0001$), reaching a plateau following 10 minutes of reperfusion in both groups ($p_{treat}=0.98$). The return of blood flow to the OM, however, rapidly returned to baseline levels within 1 minute of reperfusion only in control animals (1 min: 0 to 0.43AU). In contrast, OM blood flow returned slowly in LPS treated rats (1 min: 0 to -0.08AU) and did not return to baseline levels during the 30-minute reperfusion period ($p_{interaction}=0.01$).

Conclusions: Our data indicate that LPS pre-treatment, paradoxically, slows the early reperfusion of the renal OM through regional vasoconstriction. We speculate this effect attenuates medullary congestion by allowing RBCs in the shared venous circulation to clear. These findings support the hypothesis that backfilling of the renal medullary circulation before cortical reperfusion is restored, is responsible for the development of vascular congestion. New therapeutics focused on renal hemodynamics after ischemia may prevent much of the injury associated with acute kidney injury.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO0380

Dexamethasone Attenuates Kidney Ischemia Reperfusion Injury in SD Rats by Mediating M1 Macrophage Cytokine Production

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Background: Published evidence suggests a beneficial effect of adjunctive corticosteroid therapy on time of withdrawal from ventilation and time in ICU, as well as a faster reversal of septic shock. Studies in rodent models of acute kidney injury (AKI) have demonstrated a protective role of dexamethasone (Dexa), however its mechanism in attenuation of AKI is not clearly understood. Because M1 macrophages play role in the early stage of sepsis and ischemic kidney injury by producing proinflamatory cytokines contributing to AKI progression, we investigated the effect of Dexa during AKI on M1 polarized macrophages and kidney tubular epithelial cells.

Methods: Bilateral kidney Ischemia Reperfusion (IR) (30 minutes) was performed in 20 male SD rats (n=10/group). Dexa (3mg/kg) was injected IP 30 min before IR. Plasma creatinine, BUN and transcutaneous glomerular filtration rate (tGFR) were evaluated as readout for kidney function. Plasma cytokines were measured at 4 and 24h after IR using a Luminex Multiplex Assay. The human monocytic cell line THP1 was differentiated for 72h after a 4h pulse of 20 ng/mL PMA and then polarized to M1 phenotype in the presence or absence of Dexa. Macrophage-conditioned keratinocyte media was then collected and transferred to HK-2 cells (a human kidney tubular epithelial line) in a hypoxic chamber (0.2% O2) for 48 hrs. Apoptosis of HK-2 cells was evaluated by determining Casp3/7 activity.

Results: Pretreatment of rats with Dexa reduced plasma creatinine (2 vs 1 mg/dL), BUN (121 vs 96 mg/dL) and increased tGFR (0.5 vs 0.8 mL/min) at 24h post IR. Plasma cytokines known to be produced by M1 macrophages such as IL-1β and keratinocyte-derived chemokine (KC) were significantly reduced at 4h while MCP-1 was reduced 4 and 24h after IR. HK-2 cells treated with conditioned media obtained from M1 macrophages in the presence of Dexa and hypoxic conditions showed reduced casp3/7 activity.

Conclusions: Our data demonstrate that Dexa has a renoprotective effect in SD rat with IR-induced AKI. The observed beneficial effect of Dexa seems to involve an indirect anti-apoptotic effect on tubular epithelial cells and potentially a reduction of cytokine production by M1 macrophages.

PO0381

IL-33/ST2 Alarmin Signaling Axis in Myeloid Cells Regulates Kidney Injury

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Background: Macrophages are a heterogeneous class of cells that play a vital role in inflammation, repair and fibrosis post-injury; however, their role in early and late phases of injury is not well understood. IL-33 is a nuclear-localized alarmin cytokine that is released upon tissue damage and signals through IL-1 receptor-like 1 (IL1RL1 or ST2). ST2 is expressed in a variety of cells, including myeloid cells. The role of IL-33/ST2 in regulation of macrophages in ischemia reperfusion injury (IRI) is unclear. Here, we studied the role of $ST2^{+}$ macrophages using acute and chronic IRI models.

Methods: For myeloid cell-specific deletion of ST2, $ST2^{fl/fl}$ mice were crossed with LysM-Cre mice. Bilateral IRI (26min renal pedicle clamping and 24 hours reperfusion) was used to model acute kidney injury (AKI). Unilateral IRI (24min) was used for chronic injury studies. Contralateral nephrectomy was performed on day-13 post-IRI and the mice were euthanized 24hrs later for analyses. The structure and function of kidneys were probed using flow cytometry, histology, immunohistochemistry, quantitative gene expression, and biochemical analyses. The *in vitro* analyses were performed using peritoneal and bone-marrow-derived macrophages.

Results: Although global ST2 deficiency in mice showed reduced renal injury, it is challenging to ascertain the contribution of different cells involved in the inflammation and fibrosis process. Preliminary metanalysis of single cell RNA seq data indicated high expression of ST2 on renal macrophages. Therefore, we performed acute and chronic IRI studies on myeloid-cell specific deletion of ST2. Interestingly, loss of ST2 on myeloid cells also resulted in attenuation of acute renal injury. In vitro, efferocytosis assays on both peritoneal and bone-marrow derived macrophages demonstrated that loss of ST2 on macrophages resulted in a decrease in functional phagocytosis of apoptotic cells. Intriguingly, results from the chronic injury model showed that the absence of myeloid-ST2 resulted in exacerbated injury and fibrosis and a significant reduction in the immunoregulatory cells and cytokines.

Conclusions: The data suggest that ST2 signaling in macrophages is essential not only for the regulation of inflammation early on after injury but is also critical for immune-mediated resolution of injury in later stages.

Funding: NIDDK Support

PO0382

Curcumin Protects Lipopolysaccharide (LPS)-Induced AKI in Cirrhotic Mice

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Background: Cirrhotic patients frequently develop AKI in a variety of settings one of which is spontaneous bacterial peritonitis (SBP). Alteration in intestinal permeability associated with cirrhosis leads to leakage of inflammatory materials from the gut to circulation, aggravating AKI. Using our published model of AKI with cirrhosis and LPS injection mimicking SBP we show that curcumin improves hepatic and renal function by ameliorating alteration in intestinal permeability.

Methods: 12 weeks biweekly oral gavage (1ml/kg) of carbon tetrachloride (CCl4) in mice induced cirrhosis. AKI was precipitated by injecting 2 mg/kg IP LPS one day before culling. The dose of LPS, chosen after careful titration, precipitated AKI only in cirrhotic mice. Animals were divided into four groups control (CO), CCl4, CCl4+LPS (CCl4+L), CCl4+LPS+Curcumin (CCl4+L+CU). CCl4+L+CU received 100 mg/kg CU for 12 weeks. FITC-dextran was administered a day before culling orally and blood levels assessed to determine intestinal permeability. Blood, urine, liver, and kidney were harvested to measure various parameters.

Results: BUN and creatinine of CCl4 and CCl4+L were significantly higher than CO however, a significant decrease of urinary sodium (50±8%, $p<0.01$) and urine output (70±9%; $p<0.01$) was seen only in the CCl4+L group. Liver injury markers SGOT and SGPT were significantly high in CCl4 and were even higher in CCl4+L. CU treatment (CCl4+L+CU) significantly improved all the liver and renal functions. Inflammasome markers NFkB, caspase 1, and IL-1β in the liver and kidney of CCl4 were significantly higher than the control which was further augmented in the CCl4+L group. There was a significantly increased absorption of FITC-dextran and decreased expression of tight junction proteins ZO 1 and claudin in the jejunum and ileum of CCl4 and CCl4+L cohorts suggesting increased intestinal barrier permeability. Curcumin treated, CCl4+L+CU group had decreased expression of inflammasome markers, decreased absorption of FITC-dextran, and increased expression of intestinal tight junction proteins.

Conclusions: Although curcumin has a significant anti-inflammatory property its systemic anti-inflammatory effect is limited by its poor bioavailability. We posit that curcumin by mitigating intestinal permeability reduces inflammatory burden in the circulation which helps in preserving liver and kidney function.

PO0383

Identification of Hub Genes and Pathways of Ischemia-Reperfusion Injury and AKI by a Bioinformatics Method

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Background: Ischemia/reperfusion injury (IRI) is the most common cause of acute kidney injury (AKI). However, mechanisms underlying the rapid loss in kidney function and tissue injury are not fully elucidated. We aimed to explore the potential crucial genes and pathways involved in the pathogenesis of IRI/AKI by the bioinformatics method.

Methods: We extracted two gene expression profiles (GSE87024 and GSE34351) from the GEO database of wild-type mice and the early onset of the IRI-AKI. Differentially expressed genes (DEGs) were identified from the two expression profiles, enriched with its gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of the DEGs. Then we applied Gene set enrichment analysis (GSEA) methods to detect the potential crucial gene sets, the string network to identify PPI, and Cytoscape with plug-ins to find the hub genes and modules. We also used the robust rank aggregation (RRA) to the combined DEGs of the two datasets and analyzed the target genes for miRNA/TF, drug-gene interaction networks to find the potential therapeutic targets.

Results: We extracted a total of 239 and 384 DEGs in GSE87024 and GSE34351 separately, with the 73 same DEGs. GO and KEGG enrichment analysis of the DEGs and GSEA revealed that the significant pathways involve MAPK signaling pathway, IL-17 signaling pathway, and TNF signaling pathway. RRA analysis detected a total of 27 common DEGs. We identified JUN, ATF3, FOS, EGR1, HMOX1, DDIT3, JUNB, NFKBIZ, PPP1R15A, CXCL1, ATF4, and HSPA1B as hub genes. A total of 23 miRNAs interacted with the target genes and interact with curcumin, staurosporine, and deferoxamine by the drug-gene interaction networks analysis.

Conclusions: Our study focused on the early IRI-AKI by firstly adopted RRA analysis to combine DEGs in different datasets, identified hub genes and pathways. We further detected the potential therapeutic targets of the IRI-AKI such as curcumin and staurosporine.

PO0384

Resident Macrophages Limit IL-6 generation to Protect Against Septic AKI

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Background: The most common cause of acute kidney injury (AKI) in critically ill patients is sepsis. There are currently no treatments for septic AKI. Intra-renal macrophages include both tissue-resident ($CD11b^{mid}$, $F480^{hi}$) and infiltrating ($CD11b^{hi}$, $F480^{lo}$) populations. The role of resident and infiltrative macrophages in septic AKI pathogenesis remains unclear. As resident macrophages are reported to contribute to tissue repair following injury, we hypothesized that selective depletion of resident macrophages would worsen septic AKI.

Methods: Resident macrophages were selectively depleted via diphtheria toxin injection in *CD11cCre(+)/CX3CR1$^{dtr/wt}$* (RM KO mice) compared to *CD11cCre(-)/CX3CR1$^{dtr/wt}$* (RM WT) mice. RM WT and RM KO mice were subjected to sham or cecal ligation and puncture (CLP) sepsis. Kidney injury was assessed by serum creatinine and histologic injury scoring. Cytokine mRNA and protein levels in the serum and kidney were measured by RT-PCR and ELISA. Fluorescent cell-sorting and single cell RNA sequencing were used to profile gene expression following CLP in various intra-renal cell lineages.

Results: After CLP, resident macrophages expressed high levels of anti-inflammatory genes including interleukin 1 receptor antagonist (IL1rn), known to suppress IL6 generation. Compared to RM WT mice, RM KO mice displayed worsened septic AKI at 24 hours as measured by serum creatinine (0.17 +/- 0.08 vs 0.41 +/- 0.17 mg/dl, p<0.001-Fig. 1) and histologic injury (median injury score 0 vs 1, p=0.02). Furthermore, RM KO mice elaborated higher circulating and kidney IL-6 levels. In turn, anti-IL6 therapy ameliorated septic AKI in RM KO mice (Fig. 1).

Conclusions: Resident macrophages protect against septic AKI by limiting IL6 generation. Production of anti-inflammatory IL1rn by resident macrophages may limit tissue damage by constraining IL-6 generation in the septic kidney.

Funding: NIDDK Support, Other NIH Support - K08 GM132689 to JRP, Veterans Affairs Support

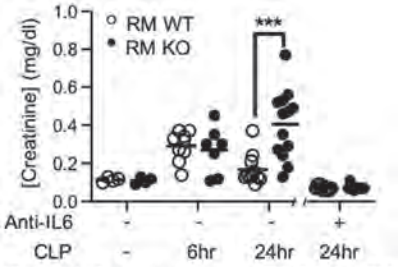

Figure 1: Serum creatinine in RM WT and RM KO mice after CLP sepsis (***p<0.001)

PO0385

Untargeted Lipidomics Reveals the Potential Mechanism of Ferroptosis in HK-2 Cells Treated with Iohexol

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Background: The purpose of this study was to explore significantly different lipid markers that may be involved in the potential mechanism of ferroptosis in CIN.

Methods: Lipids were extracted from HK-2 cells (HK2-NC group), HK-2 cells treated with 100mg I/ml iohexol for 6 hours (HK2-I6 group) and HK-2 cells co-treated with iohexol and Ferrostatin-1(a potent and selective inhibitor of ferroptosis, Fer-1) (HK2-I6+FeI group) according to MTBE method. An Untargeted Relative uantitative lipidomics based on ultra-high performance liquid chromatography-Orbitrap mass spectrometry was used, combined with the lipids Search software (Thermo Scientific).

Results: In our study, the Principal Component Analysis(PCA) and orthogonal partial least squares analysis(OPLS-DA) models were performed to explore the difference in lipid metabolites between the four groups. Both the PCA score plot and the OPLS-DA model revealed lipid differences, with a clear separation of metabolites between the HK2-I6 and HK2-NC groups, HK2-I6+FeI and HK2-I6 groups. The heat map result showed 132 lipid variations of HK2-I6 group compared to the HK2-NC group, and 170 lipid variations of HK2-I6+FeI group compared to the HK2-I6 group. Among the varied lipid species (HK2-I6 group vs. HK2-NC group), 35 out of 42 PC, 8 out of 10 PS, two out of three SM, and all the 6 LPC increased with statistical significance, while 38 out 39 TG, 16 out of 17 PE, and all the 9 Cer, 2 CerG2, 1 GM, 1 LPI, 2 PG decreased significantly. Among the varied lipid species (HK2-I6+FeI group vs. HK2-I6 group), 35 out of 36 PE, 19 out of 36 PC, 3 out of 5 PS, and all the 50 TG, 15 SM, 5 PI, 5 PG, 6 Cer, 2 CerG1, 2 CerG2, 2 CerG3, 2 LPE increased with statistical significance. According to multivariate statistical analysis, PC(20:3/22:6), LPC(18:0), and PC(44:10), etc. were clearly increased in HK2-I6 group, while these lipid species were significantly decreased after Fer-1 treatment. Cer(d18:1/18:0), Cer(d18:2/24:1), and TG(18:0/18:1/22:2), etc. were clearly decreased in HK2-I6 group, while these lipid species were significantly increased after Fer-1 treatment.

Conclusions: This study revealed that increased PC, decreased PE and TG may involved in the potential mechanism of ferroptosis in the HK-2 cells treated with iohexol.

PO0386

CRISPR-Induced Knockout of Ubiquitin Ligase Cullin 3 in Human Proximal Tubule Cells

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Background: We have shown earlier that kidney-specific deletion of Cullin 3 (Cul3) causes proximal tubule injury and fibrosis, but the mechanism is still unclear. Cul3 is essential for the ubiquitination and thus degradation of many critical proteins in several organs. This study aims to generate a Cul3-deficient human proximal tubule cell line using the CRISPR-Cas9 system. This model will allow us to understand the mechanistic role of Cul3 in the human proximal tubule.

Methods: $CD10^+$ proximal tubule cells were isolated by cell sorting from healthy human kidney cortex of a nephrectomy specimen. The primary proximal tubule cells were cultivated and then immortalized using SV40LT and HTERT. Using different CRISPR/Cas9 approaches, Cul3 knockout clones were aimed to achieve. The most successful approach is depicted in the results section.

Results: The Cul3-specific guide RNA was cloned into pL-CRISPR.EFS.GFP using BsmBI restriction digestion. Lentiviral particles were produced by transient co-transfection of HEK293T cells with lentiviral transfer plasmid, packaging plasmid psPAX2 and VSVG packaging plasmid pMD2. G using TransIT-LT. Viral supernatants were collected 48–72 h after transfection, clarified by centrifugation, supplemented with 10% FCS and polybrene and sterile filtered. Cell transduction was performed by incubating the $CD10^+$ cells with viral supernatants. eGFP-expressing cells were single-cell sorted into 96-well plates. Expanded colonies were assessed for mutations with mismatch detection assay: gDNA spanning the CRISPR target site was PCR amplified and analyzed by T7EI digest. To determine specific mutation events on both alleles within the clones grown, the PCR product was subcloned into the pCR 4Blunt-TOPO vector. Minimum 6 colonies per CRISPR-clone were grown and sent for sanger sequencing. Results from qPCR and western blot confirmed Cul3 knockout. The clones were sent out for bulk RNA sequencing to reveal differentially regulated genes upon Cul3 deletion.

Conclusions: Cul3 is a major upstream player in different cell signaling pathways. This study will show the role of Cul3 in the proximal tubule of human kidney.

Funding: Government Support - Non-U.S.

PO0387

Role of Megalin and Sex in AKI-CKD Transition due to Cardiorenal Syndrome Type 1

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Background: Cardiorenal syndrome type 1 (CRS-1) is acute kidney injury (AKI) due to rapid worsening of cardiac function. The megalin-mediated endocytic system is an important component of renal function which may influence AKI and which likely influences development of chronic kidney injury (CKD). As part of investigating AKI-CKD transition after CRS-1, we tested whether megalin deletion affects the severity of CRS-1 and consequential CKD.

Methods: Male and female proximal tubule-specific inducible megalin deletion mice (iMegKO, LRP2 fl/fl NDRG1-CreERT2) received tamoxifen (150 mg/kg) for 5 days, 16 days before cardiac arrest and cardiopulmonary resuscitation (CA/CPR). 24 hours after CA/CPR, glomerular filtration rate (GFR), cystatin c, KIM-1 were measured and urine proteins were characterized. Immunofluorescence and immunoblotting were performed to quantify acute and chronic renal injury, fibrosis, and megalin expression.

Results: Tamoxifen only induced deletion of megalin in cre+ mice. Urine protein and urine albumin were increased by proximal tubule-specific megalin deletion, primarily low-molecular weight proteins. Specific megalin ligands including RBP-4 were elevated in the urine. At baseline, GFR of iMegKO mice was higher than control mice (p<0.001 by student's t-test, n=11-12/group). CA/CPR variables, including time to resuscitation and epinephrine dose were not different between groups (p>0.05 by one-way Anova, n=9-13/group). Body weight-corrected urine volume at 24 hours after CA/CPR or 49 days after CA/CPR were not different between iMegKO mice and cre- littermate control mice, both in male and female groups (p>0.05 by one-way Anova; for 24h analysis, n=5-9/group, for 49day analysis, n=2-3/group). GFR at 24 hours and 49 days after CA/CPR was not different in iMegKO mice compared with littermate control mice (p>0.05 by one-way Anova; for 24h analysis, n=5-6/group, for 49day analysis, n=2/group). In female, iMegKO didn't mediate GFR at 24 hours or 49 days after CA/CPR (p>0.05 by one-way Anova; for 24h analysis, n=2-3/group, for 49day analysis, n=3/group).

Conclusions: iMegKO causes low molecular weight proteinuria, of specific megalin ligands. GFR of iMegKO and control is different at baseline, but not different by 24h or 49days after CA/CPR in male and female.

Funding: Veterans Affairs Support

PO0388

Spatially Resolved Transcriptomics Reveal Temporal Dynamics of Gene Expression Changes in a Model of Female AKI

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Background: Preclinical studies of acute kidney injury (AKI) have focused on male rodents leaving a substantial gap in our understanding of AKI in females. Single cell transcriptomic studies are remarkably powerful, but the loss of positional information with tissue dissociation handicaps our interpretation. Therefore, we applied the 10X Genomics spatial transcriptomic solution, Visium, to investigate interactions between cell types in their physiological orientation during injury.

Methods: We performed bilateral ischemia reperfusion injury (Bi-IRI) on female C57BL/6J mice. Kidneys were collected at acute and late injury timepoints. The efficacy of IRI cross-clamp was validated by transdermal GFR measurements using FITC-sinistrin. Sequencing libraries were created from flash frozen kidney tissues, sequenced by NovaSeq, and integrated with corresponding images using SpaceRanger.

Results: New analytic pipelines SPOTlight and Giotto, enriched with gene expression data from our previously published single cell RNA transcriptomic atlas of mouse injury, significantly enhanced the visualization and resolution of spatial data in our female Bi-IRI model. Spatial libraries detected 16,856 unique genes across all injury timepoints. Integration with scRNAseq increased resolution of specific underrepresented cell types, such as macrophages, T cells, and fibroblasts. Key visualization tools demonstrated changes in the temporal and spatial expression of differentiation markers, including Krt20 and Vim, after injury. Spatial interaction analyses of macrophages and T cell related genes, such as Lyn and Tmem30b, revealed dynamic cell type interaction changes in addition to specific interactions with a proinflammatory and pro-fibrotic proximal tubule injury-induced cell state. We prioritized cell-cell interactions based on physical proximity and validated these results by immunofluorescence. We curated an online data visualization tool to provide broad access of this dataset to the community.

Conclusions: We present the first comprehensive spatial transcriptomic atlas for a female mouse model of AKI along a time course after ischemic injury. We leveraged this spatial transcriptomic dataset to investigate cell type interaction changes, revealing previously unknown cellular dynamics of macrophages and T cells in the proximal tubule.

Funding: NIDDK Support

PO0389

Single-Cell Sequencing of Immune Cells in AKI and Renal Fibrosis

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Background: Immune responses help determine outcome following acute kidney injury (AKI) and Chronic Kidney Disease (CKD) progression. Single Cell RNA Sequencing (scRNAseq) provides an unparalleled opportunity to uncover heterogeneity and provide new mechanistic understanding in AKI-CKD. We have performed scRNAseq of immune cells at specific timepoints mimicking human disease pathology in models of AKI and renal fibrosis.

Methods: Kidneys were harvested from three mice at each time point (*Figure 1*) mimicking disease states in AKI/CKD. Using a cell sorting strategy, CD45+ cells were isolated from whole kidneys and libraries were prepared on the 10X Genomics platform. ScRNASeq was performed using the Illumina NextSeq 550 System. We conducted Genome mapping using Cellranger and zUMIs and downstream expression analysis was carried out using R and Seurat.

Results: 21,734 CD45+ve Cells were sequenced in total. Analysis of gene expression profiles delineated transcriptomic profiles in distinct sub-clusters of immune cells across disease states. Comparison of these demonstrated dynamic changes in immune cell compositions, recruitment and patterns of gene expression, in line with an immune response, to AKI, recovery and fibrosis. Heterogenous clustes of macrophages were seen in disease states, revealing an inverse pattern of gene expression when comparing AKI-recovery and AKI-fibrosis.

Conclusions: ScRNASeq has enabled unbiased profiling of gene expression in disease states important in AKI-CKD. We have identified a novel mechanistic target which we are currently pursuing in knock-out gene experiments that impact macrophage phenotype, that we hypothesise, impacts recovery. This presents an exciting opportunity to study the mechanism of renal fibrosis following AKI.

Funding: Private Foundation Support

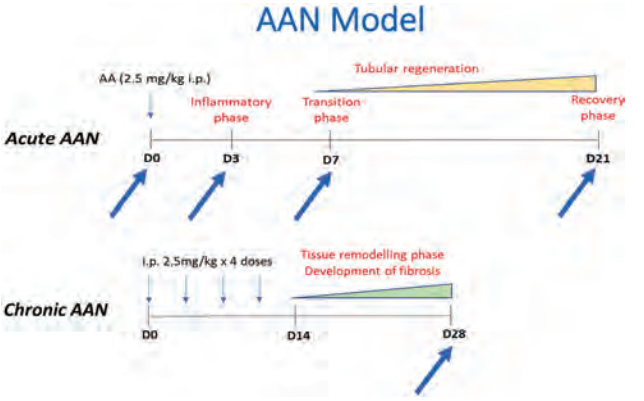

Figure 1: A schematic diagram of aristolochic acid nephropathy (AAN). Acute AAN represents AKI and chronic AAN represents CKD. Blue arrows represent time points at which kidneys were harvested and scRNASeq of CD45+ immune cells performed.

PO0390

An Improved Protocol for the Isolation and Monoculture of Primary Murine Renal Peritubular Endothelial Cells to Enhance Long-Term Phenotypic Retention

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Background: Acute kidney injury (AKI) is often followed by a persistent reduction in mitochondrial function, microvasculature (MV) dysfunction/rarefication, and tubular injury/necrosis. While the functional restoration of the renal MV is crucial, the mechanisms by which MV angiogenesis improves renal recovery remain understudied. Unfortunately, primary cultures of renal microvascular endothelial cells (RMEC) exhibit variability in purity and outgrowth, and undergo phenotypic losses in monocultures. Thus, we focused on refining the isolation and phenotypic retention of monocultured mouse renal peritubular endothelial cells (MRPEC).

Methods: MRPEC were initially isolated using the method of Zhao et al (2014). MRPEC were then subjected to a second round of CD146+ magnetic bead purification. Twice purified MRPEC (TP-MRPEC) were seeded in cloning cylinders within 35mm culture dishes precoated with fibronectin or gelatin, and incubated overnight at 37°C with 5% CO2 in ScienceCell™ EC media. Cloning cylinders were removed the next day, and media was changed every 24h. After 48h, cells were placed onto a circular rotor in a 37°C incubator. After 10 days, purity and phenotype were assessed by flow cytometry analysis using a CD146-PE+ antibody (Biolegend™) and confirmed by immunofluorescent (IF) staining of endothelial markers VE-Cadherin and CD31.

Results: Brightfield micrographs revealed that TP-MRPEC seeded in cloning cylinders increased seeding density, promoted faster outgrowth, and preserved MRPEC morphology. MRPEC seeded onto fibronectin exhibited faster outgrowth; however, MRPEC seeded onto gelatin reduced morphological variability. MRPEC placed onto a circular rotor set to ~45rpm enhanced endothelial cell polarization and paracrine signaling. Flow cytometry analysis revealed that standard MRPEC had an average PE+ purity of ~76% compared to the IgG isotype and unstained controls. Conversely, TP-MRPEC average purity was ~93% (N=5, T(x)=829.09). Immunofluorescence staining confirmed high levels of CD-31 and VE-Cadherin 10 days after isolation (EVOS-M500).

Conclusions: In conclusion, we have developed a modified MRPEC isolation and cell monoculture protocol that enhances the uniformity, purity, and long-term phenotypic retention of primary MRPEC monocultures.

Funding: Veterans Affairs Support

PO0391

Modeling Kidney Injury and Repair in Kidney Organoids Reveals an Intrinsic Repair Mechanism

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Background: Kidneys have the capacity for intrinsic repair, preserving kidney architecture with return to a basal state following tubular injury. When injury is overwhelming or repetitive, that capacity is exceeded and incomplete repair results in scar tissue replacing normal kidney parenchyma. Loss of nephrons correlates with reduced kidney function, which defines chronic kidney disease (CKD) and confers significant morbidity and mortality to the worldwide population. Despite the identification of pathways involved in intrinsic repair, limited treatments for CKD exist, in part due to the limited throughput and predictivity of animal studies.

Methods: hPSC-derived kidney organoids were subject to repeated cisplatin injury twice weekly from differentiation days 49 to 63. Samples were harvested following each injury for immunostaining and qPCR to determine transition from intrinsic to incomplete repair. Single nuclear sequencing (snRNAseq) of pooled samples of control, intrinsic repair, and incomplete repair were compared to similar data sets of mouse UUO and IRI, and human rejecting kidney transplant. Transcriptomic results were validated with fibrotic human kidney biopsy samples by immunostaining. Targeted drug screening was conducted in kidney organoids to promote intrinsic repair for the identification of novel therapeutic candidates.

Results: snRNA-seq from kidney organoids identified 159 differentially expressed genes and 29 altered signal pathways during intrinsic repair. Tubular atrophy and the induction of scar-forming myofibroblasts correlates with reduced expression of homology-directed repair genes in injured tubular cells, a finding supported by single cellular transcriptomics in models of obstructive, hemodynamic, and immune-mediated kidney injury, as well as biopsy samples of patients with fibrotic kidney disease. We identified FANCD2/RAD51-mediated repair as a critical determinant governing the transition between intrinsic and incomplete repair and identified a novel therapeutic target for the prevention of CKD onset and progression following AKI.

Conclusions: Our findings demonstrate the utility of kidney organoids in determining novel pathologic pathways, conducting mechanistic studies of human kidney disease and identifying druggable targets through translational studies.

Funding: NIDDK Support, Other NIH Support - NIH DP2EB029388 award, NIH U01EB028899, NCATS UCLA CTSI KL2, Private Foundation Support

PO0392

Acetylcholine Receptor Agonist Reduces Acute Lung Injury After Renal Ischemia-Reperfusion Injury by Acting on Splenic Macrophages

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Background: Acute kidney injury (AKI) has been reported to contribute to development of acute lung injury (ALI) via proinflammatory response. Although the inflammation caused by AKI directly might affect the lungs, this inflammation has been exacerbated by splenectomy. Macrophages with α7 nicotinic acetylcholine receptor(α7nAChR), which play a central role in the cholinergic anti-inflammatory pathway (CAP), are abundant in the lung and spleen. We hypothesized that CAP could reduce ALI after AKI. The objectives of this study were to determine 1) whether AChR agonist could reduce ALI after AKI, and 2) which macrophages in the lung or spleen, could contribute to the improvement of ALI by AChR agonist.

Methods: AKI was induced in C57BL/6 male mice by unilateral ischemia-reperfusion injury (IRI) with contralateral nephrectomy. The α7nAChR selective agonist, GTS-21 was administered in three experimental settings: 1) splenectomy, 2) splenic macrophage deletion via intravenous administration of clodronate liposomes, 3) alveolar macrophage deletion via intratracheal administration of clodronate liposomes. The lung neutrophil infiltration and evans blue dye (EBD) leakage were assessed as lung injuries.

Results: GTS-21 significantly reduced lung neutrophil infiltration (23.04±3.30 vs 11.69±2.38/HPF, p<0.0001) and EBD vascular leakage (13.54±5.32 vs 8.04±3.25μg/g lung tissue, p<0.01) after renal IRI. In splenectomized mice, GTS-21 did not reduce lung injuries after renal IRI. (neutrophil infiltration: 46.39±16.65 vs 37.54±12.91/HPF, p=ns, EBD vascular leakage: 23.30±8.88 vs 22.18±10.41μg/g lung tissue p=ns). In mice depleted of splenic macrophages, GTS-21 did not reduced lung injuries after renal IRI(neutrophile infiltration: 37.03±10.54 vs 34.36±11.61/HPF, p=ns, EBD vascular leakage: 34.78±20.55 vs 49.92±39.83μg/g lung tissue, p=ns). In mice depleted of alveolar macrophages, GTS-21 significantly reduced lung injuries after IRI (neutrophil infiltration: 21.00±7.52 vs 12.93±3.64/HPF, p<0.05, EBD vascular leakage: 13.86±4.59 vs 9.74±2.25μg/g lung tissue, p<0.05).

Conclusions: AChR agonist reduces acute lung injury after renal IRI by acting on splenic macrophages.

PO0393

Macrophage Heterogeneity in Progression and Regression Phages of Cisplatin-Induced AKI Mice Model: A Single-Cell RNA Sequencing Study

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Background: Immune cells, especially innate immune cells, play an important role in the pathogenesis of AKI. However heterogeneous of macrophage (M) and its dynamic change during progression and regression of cisplatin induced AKI (cis-AKI) remain uncertain.

Methods: 8-week-old male C57BL/6 mice were randomly divided into sham, cis3d and cis7d groups (Fig.1A). Single-cell analysis were conducted based on 10×Chromium platform. Differentially expressed genes were analysed.

Results: 36 cell clusters were identified and integrated into 11 cell types according to cell-specific markers in murine kidneys (Fig.1B). 4 clusters were identified as macrophage (Fig.1C). Cluster 4 ($Cx3cr1^+$M) was defined as embryonic derived renal resident macrophage (EMRM) for its high expression of F4/80, Cd74, Cx3cr1 (Fig.1D). Cluster 15 ($Itgam^+$M) was defined as recruit M due to its high expression of Itgam (Fig.1D). Cluster 26 ($Cd74^+$M) was defined as bone marrow derived resident macrophage according to its high expression of Cd74 (Fig.1D). Cluster 30 ($Cx3cr1^+Mki67^+$M) was the proliferation subset of EMRM (Fig.1D). The proportion of $Itgam^+$MΦ was increased in the injury stage, and restored in repair stage (Fig.1E). Resident-M ($Cx3cr1^+$M, $Cd74^+$M and $Cx3cr1^+Mki67^+$M) slightly decreased in injury period and recovered in the repair period (Fig.1E). KEGG analysis showed $Itgam^+$M mainly enriched in apoptosis and damage-related pathway, while $Cx3cr1^+$M and $Cd74^+$ enriched in phagocytosis and antigen presentation pathway (Fig.1F).

Conclusions: A total of 4 clusters were classified as M, while recruit-M and resident-M shown opposite dynamic trends in the injury and repair stages. KEGG analysis demonstrated that recruit-M may dominant injury phage while resident-M contribute to regression phages in cis-AKI.

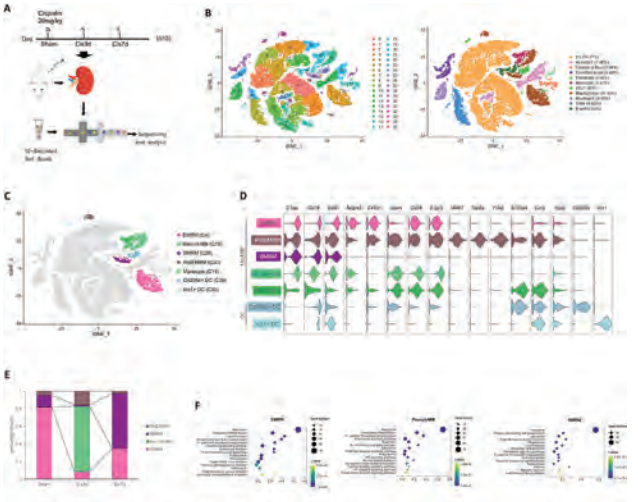

Figure 1. (A) Schematic diagram of current single-cell RNA sequencing study. 8-week-old male C57BL/6 mice underwent 20mg/kg cisplatin intraperitoneal injection and were harvest 3 days later (cis3d) or 7 days later (cid7d). Sham group underwent same amount of saline intraperitoneal injection and harvest 3 days later. (B) scRNA-seq analysis identifies discrete renal cell types in AKI and sham operated mice. tSNE plots of cell cluster(left) and cell types(right) of 36,735 cells from libraries pooled from mice of sham (n=3), cis3d (n=2) and cis7d (n=3) groups were shown. (C) tSNE plot of pooled myeloid cells annotated by cell type. (D) Violin plots showing the expression levels of selected marker genes in each cluster. (E) Relative proportions of each cells clusters of mono-macrophage at each time point. (F) KEGG pathway analysis showing the top 15 riched pathways of DEGs in EMRM (left), recruit-M? (middle), BMRM (right). PT, proximal tubule; ALH, ascending loop of Henle; DCT, distal convoluted tubule; CD-PC, collecting duct principal cell; CD-IC, collecting duct intercalated cell; NK, natural killer cell; DC, dendritic cell.

PO0394

T Cell Metabolic Reprogramming and Effect of Glutamine Blockade in Ischemic AKI

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Background: T cells play an important role in the pathogenesis of AKI. Metabolic programming of T cells regulates T cell function, is a rapidly emerging field, and has not been studied in detail during AKI. We aimed to elucidate dynamics of T cell metabolism as well as the effect of blocking glutaminolysis on ischemic AKI.

Methods: We induced ischemic AKI with 30 min ischemia followed by reperfusion in C57B6 mice and harvested kidneys and spleens at multiple early time points including during ischemia. Human nonischemic and ischemic kidney tissue was obtained from nephrectomy cases. T cells were isolated and analyzed by a flow cytometry-based immune-metabolic assay with interrogating metabolic programs. The data was evaluated by computational multidimensional analyses with machine learning. The glutamine antagonist JHU083, which targets T cell metabolism, was injected intraperitoneally and effects on AKI were evaluated.

Results: Unbiased high-dimensional analyses identified a distinct T cell subset with reduced expression of mitochondrial VDAC1 and phospho-S6 ribosomal protein (pS6) in postischemic kidneys. H3K27Me3 expression, regulated by TCA cycle, drove the segregation of ischemic kidney T cells from those of nonischemic kidneys in both humans and mice. Splenic T cells from post-AKI mice showed higher expression of GLUT1, hexokinase II (HKII), and CPT1α, indicating upregulation of glycolysis and fatty acid oxidation. Blocking glutamine uptake by JHU083 treatment attenuated renal injury at 24h (plasma creatinine 1.7±0.8 vs 1.0±0.5 mg/dL, *P*=.03) and enhanced expression of pS6 (normalized MFI 0.38±0.07 vs 0.47±0.06, *P*<.01) and HKII (0.31±0.04 vs 0.41±0.05, *P*<.01), compared to vehicle-treated mice. Activation and proliferation were reduced in CD4 (CD44, 67±5 vs 56±6%, *P*<.01; Ki67, 59±9 vs 51±6%, *P*=.03) and CD8 T cells (CD44, 61±11 vs 41±11%, *P*<.01; CD69, 25±7 vs 18±4%, *P*=.02; Ki67, 61±13 vs 48±12%, *P*=.04) but increased in double-negative T cells (CD44, 94±2 vs 96±1%, *P*=.04; CD69, 61±8 vs 72±7%, *P*<.01; Ki67, 79±9% vs 91±3%, *P*<.01) from post-AKI kidneys of the JHU083-treated group.

Conclusions: T cells undergo distinct metabolic reprogramming during ischemic AKI. Reconstitution of metabolism by targeting the T cell glutamine pathway could be a promising therapeutic approach for AKI.

Funding: NIDDK Support

PO0395

IRF8-Dependent Type I Conventional Dendritic Cells (cDC1s) Control Post-Ischemic Inflammation and Mildly Protect Against Post-Ischemic AKI and Disease

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Background: Post-ischemic acute kidney injury and disease (AKI/AKD) involve acute tubular necrosis and irreversible nephron loss. Mononuclear phagocytes including conventional dendritic cells (cDCs) are present during different phases of injury and repair, but the functional contribution of this subset remains controversial. Transcription factor interferon regulatory factor 8 (IRF8) is required for the development of type I conventional dendritic cells (cDC1s) lineage and helps to define distinct cDC1 subsets.

Methods: Unilateral ischemia reperfusion injury (IRI) was induced in mice by 25 mins' kidney pedicle clamping. Organ harvest was taken from healthy state, day 1 (IRI-1D) and day 7 (IRI-7D) after IRI. Time point D0 represents healthy state.

Results: We identified one distinct subset among mononuclear phagocyte subsets according to the expression patterns of CD11b and CD11c in healthy kidney and lymphoid organs, of which IRF8 was significantly expressed in the $CD11b^{low}CD11c^{high}$ subset that mainly comprised cDC1s. Next, we applied a *Irf8*-deficient mouse line (*Irf8*$^{fl/fl}$*Clec9a*^{cre} mice) to specifically target *Clec9a*-expressing cDC1s *in vivo*. During post-ischemic AKI/AKD, these mice lacked cDC1s in the kidney without affecting cDC2s. The absence of cDC1s mildly aggravated the loss of living primary tubule and decline of kidney function, which was associated with decreased anti-inflammatory Tregs-related immune responses, but increased T helper type 1 (T_{H1})-related and pro-inflammatory cytokines, infiltrating neutrophils and acute tubular cell death, while we also observed a reduced number of cytotoxic $CD8^+$ T cells in the kidney when cDC1s were absent.

Conclusions: Together, our data show that IRF8 is indispensable for kidney cDC1s. Kidney cDC1s mildly protect against post-ischemic AKI/AKD, probably via suppressing tissue inflammation and damage, which implies an immunoregulatory role for cDC1s.

PO0396

Myeloid Heparin-Binding Epidermal Growth Factor-Like Growth Factor (HB-EGF) Protects Against Ischemic AKI

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Background: Epidermal growth factor receptor (EGFR) activation plays an important role to mediate recovery of epithelial integrity following ischemic acute kidney injury (AKI) and subsequent development of interstitial fibrosis when recovery is incomplete. EGFR can be activated by a family of ligands. The ligand responsible for EGFR activation after AKI has not been previously identified. In response to various stimuli, EGFR can be transactivated by its ligand, HB-EGF. The present study examined the potential role of myeloid HB-EGF in recovery from ischemic AKI and subsequent development of fibrosis.

Methods: Wild type (WT, HB-EGF$^{f/f}$) or LysM-Cre; HB-EGF$^{f/f}$ (myeloid HB-EGF$^{-/-}$) mice (male, 8 weeks old, C57BL/J background) were uninephrectomized, immediately followed by unilateral ischemia-reperfusion with renal pedicle clamping for 31.5 min. Mice were sacrificed at different time points after ischemic AKI. Renal myeloid cells were isolated with a mixture of CD11b and CD11c microbeads.

Results: Compared to WT mice, LysM-Cre; HB-EGF$^{f/f}$ mice had delayed functional recovery after ischemic AKI. At 28 days after AKI, myeloid HB-EGF-/- mice had more severe persistent kidney damage, indicated by higher KIM-1 mRNA and protein levels. Myeloid HB-EGF-/- mice also had more renal immune cell infiltration, including macrophages, neutrophils, and lymphocytes. The myeloid HB-EGF-/- mice exhibited more renal fibrosis, as indicated by quantitative Sirius red and Masson's Trichrome staining and increased mRNA and protein levels of profibrotic and fibrotic components including α-SMA, collagen I, collagen IV, IL-11, fibronectin, and PDGFRβ. The myeloid HB-EGF-/- mice also had increased renal ER stress as indicated by increased CHOP. In renal myeloid cells from WT mice, HB-EGF mRNA levels were increased by 10 fold at 2 h after ischemic AKI. Immunofluorescent staining demonstrated increased HB-EGF expression in myeloid cells and increased phosphor-EGFR in the proximal tubule epithelial cells.

Conclusions: Early HB-EGF upregulation in myeloid cells in response to ischemic injury may promote functional and structural recovery after ischemic AKI, possibly due to stimulation of epithelial cell proliferation via EGFR activation.

Funding: NIDDK Support, Veterans Affairs Support

PO0397

circBNC2 Inhibits Renal Fibrosis Through Regulating G2/M Cell Cycle Transition

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Background: Emerging evidence indicates that AKI is a causative factor for subsequent development of chronic kidney disease (CKD). G2/M cell cycle arrest of TECs promotes AKI to CKD progression, but the regulation of G2/M cell cycle arrest of TECs is largely unclear. Circular RNAs (circRNAs), a class of noncoding RNA, are recently found to be dysregulated in tubular epithelial cells (TECs) during renal ischemia/reperfusion (I/R) injury. However, the effects and underlying mechanisms of circRNAs in the progression of renal fibrosis are largely unrevealed.

Methods: Mild-AKI (20 min- IRI) and severe-AKI (40 min-IRI) were performed in C57BL/6 mice. The expression of circRNA were analyzed in the freshly isolated tubules from these mice by RNA-seq. One of the dysregulated circRNA, circBNC2 were identified and analyzed by Northern blot, FISH and real-time qPCR in HK2 cells, mouse primary TECs and in mouse kidney. HK-2 cells were exposed to hypoxia as *in vitro* model. To study the function of circBNC2, we used the CRISPR-Cas9 genome editing system to specifically knocked out circBNC2 in HK2, while circBNC2 was overexpression by plasmid. To study the function of circBNC2 *in vivo*, we applied adeno-associated virus (AAV)-based circBNC2 overexpression in C57BL/6 mice 3 weeks before performing IRI model. G2/M cell cycle arrest and pro-fibrotic cytokine expression were evaluated in HK2 and primary TECs. Renal fibrosis was evaluated in mouse kidney sections.

Results: The un-biased sequencing showed significant down-regulation of circBNC2 in TECs from severe-IRI mice, as compared to the TECs from mild-IRI mice and control mice. Knockout circBNC2 in HK2 and primary TECs led to G2/M cell cycle arrest and pro-fibrotic cytokines expression. While overexpression of circBNC2 decreased hypoxia-induced G2/M cell cycle arrest of TECs. Preventative overexpression of circBNC2 *in vivo* ameliorated 40 min-IRI induced renal fibrosis.

Conclusions: Our results showed that circBNC2 regulated G2/M cell cycle transition of TECs and might be served as a therapeutic target for AKI-progressed CKD.

Funding: Government Support - Non-U.S.

PO0398

Ischemia Reperfusion Activation of Kidney HDAC1 Results in Interstitial Fibrosis

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Background: Following a kidney ischemic event the chromatin remodeling enzyme, histone deacetylase-1 (HDAC1), is activated in many cell types of the kidney including fibroblasts/pericytes. Pharmacological inhibition of HDACs can attenuate ischemia-reperfusion-injury (IRI) mediated interstitial fibrosis. In this study, we tested the hypothesis that fibroblast/pericyte HDAC1 activation promotes interstitial fibrosis.

Methods: Tamoxifen inducible, fibroblast/pericyte HDAC1 knockout (KO) mice (HDAC1$^{Fl/Fl}$; Col1a2-CreEr) and littermate controls (HDAC1$^{Fl/Fl}$) were used. Male and female mice (8-10 wks of age) were given tamoxifen i.p. and IRI or sham surgery was performed after a 2-week tamoxifen washout period. A mild, 18 min, bilateral, warm IRI model was used and samples collected over 4 weeks. Additional groups of mice underwent unilateral ureteral obstruction (UUO) for 48 h. In vitro experiments with kidney fibroblast cells (NRK49F) overexpressing HDAC1 were used for RNA-sequencing studies.

Results: HDAC1 KO was confirmed in myofibroblast cells by co-immunolocalization of HDAC1 and platelet-derived growth factor receptor beta or a-smooth muscle actin (α-sma) in the kidneys of IRI mice. 24 h post ischemia there was a tripling of plasma creatinine (PCr) in all IRI mice, regardless of sex or genotype. 2- and 4-weeks after IRI, PCr were similar to sham values for all mice. However, the male control IRI mice had significant interstitial fibrosis but this was attenuated in the KO male IRI mice. The female mice, regardless of genotype, had very mild kidney damage and interstitial fibrosis at 4 weeks. The UUO male KO mice had reduced α-sma abundance compared to control male mice. Transcriptomes of NRK49F cells overexpressing HDAC1 had 15 genes upregulated (0.1% of the genes sequenced) and 64 genes downregulated (0.5%). Upregulated genes included *C3, Bmp6, Cxcl12, and Fzd1*. Downregulated genes included *Ccl4, Ifnb1*. Gene Ontology analysis determined significant enrichment in the regulation of Wnt signaling and innate immune response activating signal transduction.

Conclusions: For male mice, fibroblast/pericyte HDAC1 activation leads to pro-fibrotic programming of the myofibroblast and interstitial fibrosis. Future studies will determine the specific epigenetic pathways that may be significantly changed by HDAC1 activation leading to maladaptive interstitial fibrosis.

Funding: NIDDK Support

PO0399

Endothelial and Not Proximal Tubule Epithelial Pannexin 1 Plays a Critical Role in Fibrosis Progression After AKI

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Background: Activation of pannexin-1 (Panx1) channels during acute kidney injury (AKI) and Panx1-mediated release of tissue messengers facilitates the recruitment and activation of immune cells to the site of injury. Lack of *Panx1* in the proximal tubules (PT) or in the endothelial cells (EC) significantly reduces AKI. Metabolites released from Panx1 affect a number of biological processes that regulate inflammation and cellular metabolism. Thus, we investigated the role of PT or EC Panx1 during AKI to chronic kidney disease (AKI-CKD) transition by inducing deletion of Panx1 from PT or EC before or after an established AKI.

Methods: AKI was induced by unilateral ischemia-reperfusion injury (IRI), folic acid, or bilateral IRI. Cell-type specific deletion of Panx1 was achieved by injecting tamoxifen before or after AKI to Panx1 floxed (*Panx1*$^{fl/fl}$) animals expressing either PT (*SLC34a1*^{GCE}) (provided by B. Humphreys, Washington University) or EC (*Cdh5*^{CreER}) specific inducible Cre-recombinase to generate either PT (*SLC34a1*^{GCE}*Panx1*$^{-/-}$) or EC

(*Cdh5^{CreER}Panx1$^{-/-}$*) specific Panx1 knockout animals. Kidneys were analyzed for extent of fibrosis by measuring mRNA expression of fibrotic markers and Masson's trichrome staining and for immune cell infiltration by flow cytometry.

Results: Deletion of Panx1 before AKI globally, in PT, or in EC attenuated renal fibrosis. Deletion of *Panx1* after AKI did not alter the extent of fibrosis in *SLC34a1^{GCE}Panx1$^{-/-}$* animals compared to *SLC34a1$^{+/+}$Panx$^{fl/fl}$* controls that received tamoxifen, however, deletion of *Panx1* after AKI significantly increased fibrosis in *Cdh5^{CreER}Panx1$^{-/-}$*compared to *Cdh5^{CreER}Panx1$^{fl/fl}$* controls. Tamoxifen itself did not alter the extent of fibrosis. Flow cytometry revealed robust immune cells recruitment including neutrophils, macrophages, dendritic cells, and T-cells in injured kidneys post-AKI. While there was no significant difference in other immune cell proportions at day 3 and day 7 post AKI, *Cdh5^{CreER}Panx1$^{-/-}$* animals had a significantly higher CD103-positive dendritic cell population at day 10 post AKI.

Conclusions: Our data show that while Panx1 from PT or EC play crucial role during AKI, Panx1 from EC is vital for limiting extent of fibrosis during AKI-CKD potentially by releasing metabolites that regulate immune cell function and fibrosis/repair.

Funding: NIDDK Support, Private Foundation Support

PO0400

Apoptotic Exosome-Like Vesicles Aggravate Inflammation and Renal Injury After Ischemia-Reperfusion

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Background: Ischemia-reperfusion injury (IRI) is a common cause of acute kidney injury (AKI) and chronic kidney disease (CKD). Mounting evidence suggests that damage to microvascular peritubular capillaries (PTC) is a critical determinant of CKD transition after IRI. We previously identified anti-LG3/perlecan autoantibodies in patients with CKD, as a negative prognostic factor for long-term renal function after AKI. We also showed that a new class of extracellular vesicles produced by apoptotic endothelial cells (ApoExo), characterized by the LG3 autoantigen, active 20S proteasome and a specific pattern of immunogenic RNAs, can prompt the production of anti-LG3. Here, we test the hypothesis that ApoExo drive renal inflammation after renal IRI leading to anti-LG3 production, defective microvascular repair and loss of renal function.

Methods: ApoExo were purified by sequential ultracentrifugation from serum-free media conditioned by apoptotic murine endothelial cells. Renal IRI in mice was performed with renal artery clamping for 30 minutes and contralateral nephrectomy. ApoExo were injected twice every other day before IRI and thereafter up to eight injections, and end-points were assessed at day 21 post-IRI. Interstitial inflammation was assessed with immunohistochemistry for CD3 and IL-17A. PTC rarefaction, complement activation and myofibroblasts accumulation were monitored by immunohistochemistry for MECA-32, C4d and α-SMA. Circulating anti-LG3 levels were measured by ELISA.

Results: ApoExo injection enhanced tubular damage and interstitial inflammation with increased CD3$^+$ lymphocytes infiltration and IL-17A staining (p=0.004 and p=0.002, respectively). PTC rarefaction, C4d deposition and interstitial accumulation of α-SMA$^+$ cells were also increased in ApoExo treated mice (p=0.01, p=0.009 and p=0.04, respectively) as were anti-LG3, which correlated strongly and positively with PTC-C4d deposition and myofibroblasts accumulation (r=0.86, p=0.007 and r=0.75, p=0.03, respectively).

Conclusions: Collectively, these results identify ApoExo as novel regulators of inflammation after renal IRI, driving anti-LG3 formation, complement activation and fibrosis. These results suggest that autoimmune pathways triggered by ApoExo can contribute to microvascular rarefaction and renal fibrosis.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO0401

The Brain-Gut-Kidney Axis in the Development of Cognitive Dysfunction Following AKI

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Background: Although epidemiological studies suggest that long-term survivors of dialysis requiring AKI show increased prevalence of dementia, its underlying mechanisms remain uncertain. Based on recent data showing kidney-gut crosstalk mediated by immune modulation in acute kidney injury (AKI), we hypothesized that gut dysbiosis and aberrant gut immune response might contribute to the cognitive dysfunction following AKI.

Methods: Thirty min ischemia/reperfusion injury (IRI) was performed in C57/BL6 mice, cognitive dysfunction, histological damage including blood-brain barrier (BBB) disruption and inflammation, gut microbiome and immune cell activation were determined at 6 months after IRI.

Results: Glomerular filtration rate showed complete recovery of renal function at 6 months after IRI. However, in the open field behavior test, IRI mice traveled shorter distance and walked more slowly compared to sham, suggesting the development of cognitive dysfunction long after kidney IRI. Evans blue dye extravasation showed disrupted BBB and the number of microglial cells, amyloid-beta deposits increased in the brain in IRI mice. Principal coordinate analysis of gut microbiome in IRI was clearly distinguished from that of sham. Despite no difference in alpha-diversity, relative increase of abundance of bacterial families of Saccahrimonas, Erysipelotrichaceae, Bacteroidaceae, Lactobacillaceae while decrease of Lachnospiraceae and Prevotellaceae were the hallmark of dysbiosis. Flow cytometry of gut immune cells showed a significantly increased percentage of IL-17A+CD4+ cells in small intestine, whereas percent CD25+CD4+ Tregs decreased significantly in colon, showing the gut immunity moving toward inflammation long after AKI.

Conclusions: This is the first animal study that showed the development of structural brain injury and cognitive dysfunction long after AKI. Given that the important role of dysbiosis in various neurologic diseases, presence of dysbiosis and gut inflammation at 6months after IRI might contribute to the development of long-term neurologic sequelae of AKI. Targeting the gut might be a novel therapeutic target for prevention of long-term adverse outcomes in AKI patients.

PO0402

Probiotics Supplementation Protects the Transition from AKI to CKD in Aged Mice via the Kidney-Gut Axis

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Background: Several epidemiological studies have reported that acute kidney injury (AKI) is more frequent in the elderly and they often progress to chronic kidney disease (CKD). Chronic inflammation has recently been reported as an important mechanism mediating CKD progression after AKI in the elderly. This study investigated how kidney and intestinal crosstalk is involved in exacerbation of inflammation in AKI and whether microbial targeted therapy could modulate the transition from AKI to CKD in aged mice.

Methods: In young and aged C57BL/6 mice, 25min bilateral ischemia reperfusion injury (IRI) was applied, and then colon inflammation, histological changes and intestinal barrier integrity were compared for 28 days post-IRI. To determine the role of the microbiome on kidney-gut crosstalk, we analyzed microbiome from feces in young and aged mice and examined the effects of probiotics supplementation.

Results: M1 predominant inflammation was observed in the kidneys of aged mice compared to young mice for 28 days after IRI. Interestingly, this intrarenal inflammatory milieu in aged mice was similarly observed in the colon on day3 post IRI. The increased inflammatory cytokines in the colon were accompanied by an increase in TUNEL-positive apoptotic colon epithelial cells, resulting in increased intestinal permeability in aged mice for 28 days. The AKI-induced "leaky gut" also showed a strong positive correlation with high TNF-α expression in mesenteric lymph nodes. Microbiome analysis revealed changes in Lactobacillus and Bifidobacterium in aged mice at the genus level. To clarify the role of the microbiota, probiotics were administered for 2 months during the AKI recovery period. We observed that administration of Bifidobacterium (B. longum + B. bifidum) altered intestinal Th17/Treg balance and improved kidney inflammation, but not intestinal leakage. They finally resulted in improvements in GFR and kidney fibrosis, suggesting that kidney-gut crosstalk in aged mice makes an important contribution to AKI to CKD transition.

Conclusions: Our study suggests that exacerbation of chronic inflammation through the kidney-gut axis is an important mediating mechanism of the transition from AKI to CKD in the elderly. Therefore, strategies to modulate the microbiota are considered promising to improve outcomes in elderly AKI.

Funding: Government Support - Non-U.S.

PO0403

The Proteomic Landscape of Liver After AKI

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Background: Acute kidney injury (AKI) was traditionally viewed as an 'innocent bystander' in various critical illnesses that reflected disease severity in the clinic. Emerging evidence suggests that AKI is an independent protagonist that may cause acute diseases in other organs such as the liver. Thus far, the mechanisms of hepatic dysfunction in patients with AKI have not been well described. We have previously characterized the kidney proteome changes after septic AKI. Here, we further described the proteomic landscape of the liver and assessed the reno-hepatic communications after septic AKI.

Methods: Cecal ligation and puncture procedure was employed to construct the sepsis-induced AKI model. A high-resolution accurate mass-based quantitative proteomics approach was applied.

Results: After septic AKI, alanine aminotransferase (ALT) levels were markedly induced in serum at day 2, while it then dropped, approaching the baseline at day 7, reflecting the process of liver damage and repair. PAS staining exhibited a consistent trend in liver morphological changes. To understand the molecular mechanisms in AKI-caused liver injury, we examined the global proteome and phosphoproteome of the liver on day 2 and day 7 after AKI using a recently developed ultrafast and economic filter-based sample processing approach. We collectively quantified a total of 1,673 proteins and 1,219 phosphosites in the liver. The principal component analyses indicated that the liver's completely distinct protein expression patterns between day 2 and day 7 after AKI. The network analyses revealed that oxidation-reduction and metabolic processes are the top changed pathways in liver injury and repair. In the meantime, we identified a wide range of differential proteins in the liver after AKI, including Cyp7b1, cyp1a2, Hemopexin, Acss2, Orm1, Steap 4, and Haptoglobin. These proteins were further validated by western blot and immunostaining. Of particular interest, Steap4, a member of the six transmembrane epithelial antigen of the prostate, was significantly upregulated in the liver but not in the kidney upon septic AKI, suggesting a tissue-specific inflammatory response.

Conclusions: Our results implied that describing the liver's proteomic landscape after AKI would help understand reno-hepatic crosstalk, and Steap4 may serve as a potential candidate to monitor AKI-caused liver injury in the clinic.

Funding: NIDDK Support

PO0404

COX-2-EP4-MafB Axis Protects Against Renal Fibrosis in Mice with Renal Ischemic Injury

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Background: The mammalian kidney is easily injured by ischemic or toxic insults but can often recover functional and structural integrity. Innate immunity is involved in both the injury and recovery processes, and its maladaptive response causes delayed recovery and development of kidney fibrosis. Cyclooxygenase 2 (COX-2) plays an essential role in antiinflammatory and tissue-reparative M2 polarization of macrophages, the major renal myeloid cells. Renal macrophage COX-2 increases after ischemic acute kidney injury (AKI). The current study investigated the role of renal macrophage COX-2 in ischemic AKI and subsequent development of fibrosis.

Methods: We developed myeloid COX-2-/- mice (CD11b-Cre; COX-2$^{f/f}$), myeloid EP4-/- mice (CD11b-Cre; EP4$^{f/f}$), and myeloid MafB-/- mice (LysM-Cre; MafB-/-). The animals were uninephrectomized, immediately followed by unilateral ischemia-reperfusion with renal pedicle clamping for 32 min.

Results: Following ischemic AKI, COX-2 was selectively increased in renal macrophages as indicated by colocalization with CD68, and myeloid COX-2-/- mice exhibited delayed renal recovery and increased tubulointerstitial fibrosis, in association with augmented proinflammatory cytokines in isolated renal macrophages. In bone marrow derived monocytes, PGE2 is the major COX-2-mediated arachidonic acid metabolites and acts primarily via EP4 receptors. Myeloid EP4-/- mice mimicked the effects seen with myeloid COX-2-/- mice in response to ischemic AKI. We found that myeloid EP4 activation induced expression of MafB, a master transcription factor, to upregulate antiinflammatory genes and suppress proinflammatory genes in macrophages. Selective myeloid MafB deletion recapitulated the effects seen with myeloid COX-2 or EP4 deletion, with delayed recovery and increased kidney fibrosis. Mice with myeloid deletion of COX-2, EP4, or MafB had similar impairment of renal macrophage efferocytosis.

Conclusions: These studies show that COX-2/EP4-dependent MafB expression mediates renal macrophage antiinflammatory and pro-resolving polarization and identify a previously unknown mechanism by which myeloid COX-2 inhibition exacerbates acute and chronic kidney injury, a finding that is relevant to understanding detrimental effects of NSAIDs in the setting of renal dysfunction.

Funding: NIDDK Support

PO0405

Subcutaneous Adipose Stromal Cell-Derived Secretome Improves Renal Function and Inflammation in Established AKI

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Background: Previous studies demonstrated that human adipose derived stromal cells (ASC) attenuated the development of acute kidney injury (AKI) and preserved vascular density, when administered in the suprarenal aorta immediately following ischemia reperfusion (IRI). Recently, stem cell derived secretome, has received attention for the potential treatment of renal disease. We hypothesized that cell-free, concentrated fraction of ASC-derived secretome would improve renal function in a well-established rat model of AKI.

Methods: Male Sprague Dawley rats underwent bilateral IRI-40 min to induce AKI. 24 hours later, renal function was evaluated (serum creatinine; SCre) and rats were randomized into vehicle or secretome-treated groups. Rats received subcutaneous (SQ) injection either secretome (2 mg/kg in 1 ml) or saline (1 ml) on day 1 and day 3 post IRI. After 5 days of IRI, kidneys were collected for further analysis.

Results: At 24 h post IRI, SCre levels were 3.3±0.2 mg/dl in vehicle treated rats and 3.1±0.1 mg/dl in secretome treated rats (P=0.31). SCre level significantly (P=0.03) decreased in secretome treated ratscompared to the vehicle treated rats across 5 days study period. After 24 h administration of first secretome injection, there was a significant reduction of SCre level (27.8%, P>0.001) in secretome treated rats compared to their baseline. There was a significant increase of infiltration of dendritic/macrophage cells following IRI which was significantly reduced in secretome group (IRI; 1.2 X10^6 vs. secretome; 5.0 X10^5 cells/g kidney; p<0.05). Additionally, there was a significant reduction of TH-17 cells (CD4+IL-17+) following secretome treatment compared to vehicle group (secretome: 2.0 X10^4 vs. IRI: 4.6 X10^4 cells/g kidney; p<0.05). Kidney tissue stained with periodic acid-Schiff reagent shown secretome treatment improved the degree of tubular damage following IRI.

Conclusions: These data indicate that SQ injection of secretome following established AKI hastens recovery of renal function and reduces infiltration of renal inflammatory cells. Thus, secretome might represent a useful option to treat AKI.

Funding: NIDDK Support

PO0406

The Role of Disrupted Iron Metabolism in AKI: Targeting Iron Trafficking via the Hepcidin-Ferroportin Axis in Renal Proximal Tubules

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Background: Acute Kidney injury (AKI) and iron-related disorders remain major clinical challenges associated with significant morbidity and mortality. Ferroportin (FPN) is an iron exporter, identified as a modulator of iron balance. Hepcidin binds to FPN, causing its internalization and degradation. Though FPN and Hepcidin are expressed in proximal tubule cells (PTCs) of the mouse kidney, their role in the pathogenesis of AKI is unclear. Through this work, we hope to determine if modulation of iron homeostasis by selective depletion of hepcidin or FPN in PTCs alters the response to AKI.

Methods: We generated PTCs-specific Hepcidin1 and Ferroportin (FPN) knockout (KO) by selectively expressing Cre in PTCs and confirmation with a red-green reporter (mT/mG; Pepck-cre) allele. We subjected these mice to either the Folic Acid induced injury model or the ischemia-reperfusion injury models of AKI. Serum samples were collected at 2, 7, 14, 21, and 28 days after injury and BUN, creatinine, iron, and ferritin level were measured. Kidney tissues were collected at each time point for histology, iron deposition, immunohistochemistry, RNA isolation, and immunoblot analysis.

Results: Conditional KO mice were generated and deletion of Hepcidin1 and FPN specifically in PTCs was confirmed at the DNA and protein levels. Mutant young adult mice showed no gross morphology phenotype. However, both mutant strains developed pronounced iron deposition in PTCs measured with DAB-enhanced Perls stain for iron which further increased following injury. After AKI, mutant mice failed to recover and regenerate damaged tubules leading worsening interstitial fibrosis, necrosis, and ferroptosis compared with wild type mice of the same genetic background. Markers of fibrosis, ferroptosis, and levels of ferritin will be quantified in serum and kidney tissue.

Conclusions: Our preliminary data indicate that disrupting iron trafficking in PTCs by manipulating the expression of FPN and hepcidin increases AKI severity and impairs recovery. These findings may offer new insights into the role of iron metabolism in AKI and illuminate new therapeutic strategies for progressive kidney disease and other syndromes of iron overload.

PO0407

Noncanonical Wnt5a/CD146 Signaling Drives Renal Fibrosis by Activating Transcriptional Factor Snail in AKI

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Background: Acute kidney injury (AKI) with severe and persistent kidney cell injury will more likely progress to permanent damage, progressive fibrosis and chronic kidney disease (CKD). However, the exact cellular and molecular mechanisms mediating the progression of AKI to CKD remain incompletely understood. We recently reported that Wnt5a promotes renal tubular inflammation in diabetic nephropathy by binding to CD146 through noncanonical Wnt signaling. Snail, which expressed in the precursors of the renal epithelial cells, can induce partial epithelial-to-mesenchymal transition and drive renal fibrosis in mice. Here, we investigated whether modulation of Wnt5a expression during AKI would contribute to the progression to CKD.

Methods: To examine whether Wnt5a mediated CD146/JNK pathway was involved in AKI, we determined the expression of Wnt5a and CD146 in the kidneys of AKI patients. Wnt5a knockdown mice underwent either unilateral ureteral obstruction (UUO) or ischemia reperfusion injury (IRI) was established to assess whether the loss of Wnt5a attenuated renal injury. *In vitro*, HK-2 proximal tubule cells were subjected to oxygen glucose deprivation (OGD) to mimic the ischemia-reperfusion injury. More over, HK-2 cells were transfected a wnt5a small interfering RNA (siRNA) to reduce the expression of Wnt5a to further confirm the role of Wnt5a/CD146 signaling in the kidney injury.

Results: Increased expression of Wnt5a and CD146 were found in the kidney sections of patients with AKI, which was associated with the severity of kidney injury and the progression to CKD. In an Wnt5a-knockdown mouse model subjected to UUO or IRI, Wnt5a ablation significantly ameliorated kidney cell injury and renal fibrosis development. Mechanistically, Wnt5a promoted the phosphorylation of JNK and the activation of snail in UUO and IRI models. Silencing Wnt5a with small interfering RNA (siRNA) attenuated the activation Wnt5a/CD146 signaling and the expression of snail in HK-2 cells with oxygen glucose deprivation (OGD).

Conclusions: Together, our data suggest that noncanonical Wnt5a/CD146 signaling may be an important determinant in the severity of AKI. Through the activation of snail, it drives the renal fibrosis and promotes the progression to CKD.

Funding: Government Support - Non-U.S.

PO0408

Hyperactivation of CDK5 Promotes Proximal Tubule Cell Dedifferentiation and Interstitial Fibrosis in CKD

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Background: Chronic kidney disease (CKD) effects ~15% of the world's population. Recently, we demonstrated that Cyclin G1 (CG1) regulates proximal tubule cells (PTCs) G2/M arrest and promotes fibrosis. CG1 is known to act through Cyclin dependent kinase 5 (CDK5), which regulates cell cycle exit and homeostasis in differentiated cells. Under

normal conditions, CDK5 activity is kept in check by p35; however, during cellular stress p35 is cleaved to p25, leading to hyperactivation of CDK5, a leading driver of many neurodegenerative diseases. The aim of the current study is to determine if CG1 induced hyperactivation of CDK5 plays a pathological role in PTCs dedifferentiation and profibrotic signaling.

Methods: A novel CDK5/p25 inhibitor, Glixx, was utilized to inhibit hyperactivation of CDK5. Protocol 1; Aristolochic acid nephropathy (AAN) and low-dose cisplatin model were conducted as AKI-to-CKD model by repeated doses of AA and cisplatin in 8 to 12-week-old male wild-type (WT) and CG1 globally knockout mice (CG1KO). Protocol 2; To investigate the effect of CDK5 hyperactivation, unilateral ureter obstruction (UUO) was conducted with administration of Glixx. Protocol 3; CDK5 was overexpressed in cultured PTCs. Protocol 4; Primary PTCs of WT and CG1KO mice were co-incubated with AA in the presence or absence of Glixx or roscovitine, a selective CDK inhibitor.

Results: AAN and low-dose cisplatin induce phosphorylation and activation of CDK5 in wild-type but not CG1KO kidneys. Expression and cleavage of p35 to p25 is also reduced in CG1KO PTCs compared to wild-type. Inhibition of CDK5 or CDK5/p25 interaction (hyperactivation) prevents dedifferentiation and profibrotic cytokine secretion in AA treated primary PTCs. Overexpression of either CG1 or CDK5 induces upregulation of dedifferentiation and profibrotic markers, which can be reversed through inhibition of CDK5. In vivo, inhibition of CDK5/p25 binding reduces fibrosis and prevents PTC dedifferentiation following UUO.

Conclusions: CG1 expression induces hyperactivation of CDK5 in PTCs. Inhibition of CDK5 or CDK5/p25 binding prevent CG1 induced dedifferentiation, profibrotic cytokine secretion and fibrosis. Targeting the CG1/CDK5 pathway is a potential therapeutic target for inhibiting AKI-to-CKD transition.

PO0409

Clearance of Chronic Senescent Tubular Cells by ABT263 After Ischemic AKI Halts the Progression of Established Fibrosis and Restores Tubular Regeneration

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Background: Emerging studies from aging models demonstrate that increased senescent cell load causes kidney dysfunction and removal of senescent cells by senotherapeutics may rejuvenate aged kidneys for renoprotection. Senescent cells also accumulate in the kidney during maladaptive repair after AKI. However, the pathological role of cellular senescence in post-injury kidney and the therapeutic significance of targeting senescence to treat fibrosis during AKI to CKD transition remain less understood.

Methods: To induce post-ischemic kidney fibrosis, 10 to 12-week-old C57/BL6 mice underwent 30-minute unilateral or 22-minute bilateral renal ischemia followed by reperfusion for 2 weeks. The mice were then treated with either vehicle or ABT263 at 50 mg/kg/day, daily i.p. injection, 5 days/week for 2 weeks. One week after the completion of ABT263 treatment, the morphology and function of the fibrotic kidneys were examined.

Results: Following ischemic AKI, senescent cells accumulated in renal tubules, as indicated by upregulation of p16 and SASP factors, increased tubular staining of SA-β-gal, and induction of γ-H2AX nuclear foci. This injury-induced tubular senescent phenotype was accompanied by persistent interstitial fibrosis. Compared with vehicle treatment, ABT263 significantly eliminated senescent tubular cells and partially suppressed the progression of post-ischemic kidney fibrosis. Along with fibrosis resolution, ABT263 also reduced the infiltration of macrophages in interstitial tissues and attenuated the chronic expression of KIM-1 in injured proximal tubules, therefore creating a pro-regenerative environment for tubular repair. As a result, the number of Ki67-positive tubular cells was promoted and tubular expression of LTL was restored to some extent as well, indicating increased tubular proliferation and redifferentiation. Consistent with the morphological findings, renal function, as assessed by BUN, serum creatinine and eGFR, was also improved in mice treated with ABT-263.

Conclusions: These results support the pathological role of tubular injury-induced accumulation of senescent cells in fibrotic repair after AKI. Targeting these chronic senescent cells by senolytic drugs may represent a therapeutic strategy to reverse maladaptive tubular repair and to halt AKI to CKD progression.

Funding: NIDDK Support, Veterans Affairs Support

PO0410

Defects in KIM-1-Mediated Phagocytosis Do Not Predispose to AKI in Humans

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Background: Phagocytosis of dying cells is critical for homeostasis and tissue repair. During renal injury, upregulation of kidney injury molecule-1 (KIM-1) transforms kidney epithelial cells into phagocytes which engulf apoptotic and necrotic cells. A mutation that impairs KIM-1 phagocytic function (mucin domain deletion) resulted in worse kidney dysfunction after ischemia-reperfusion-injury (IRI) in mice, but this has not been studied in humans.

Methods: We expressed three common mucin domain nonsynonymous variants (rs12522248, rs45439103, rs6149307) of the human KIM-1 gene (*HAVCR1*) in human kidney cells. To test if impaired KIM-1-mediated phagocytosis predisposes to kidney dysfunction after IRI, we genotyped 627 consecutive kidney donors and assessed risk of delayed graft function in recipients.

Results: Cells expressing these variants exhibited markedly reduced phagocytosis of apoptotic and necrotic cells, compared to cells expressing *wild type* KIM-1; rs6149307 showed the most severe defects (<5% phagocytosis vs. *wild type*). Surprisingly, the risk of delayed graft function in recipients of donor kidneys homozygous for rs6149307 was not significantly increased compared to recipients of donor kidneys with one or no copies (adjusted relative risk 1.0 [0.7-1.3]). Analysis of rs12522248 and rs45439103 yielded similar resutls.

Conclusions: Contrary to murine models, these results suggest severe defects in KIM-1-mediated phagocytosis do not predispose to acute kidney dysfunction after IRI in humans.

Funding: Government Support - Non-U.S.

PO0411

Mechanistic Modeling of Kidney-Injury Molecule 1 (KIM-1) as a Biomarker for Cisplatin-Induced AKI

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Background: Kidney Injury Molecule 1 (KIM-1) is a specific and sensitive biomarker for drug-induced acute kidney injury (AKI) prediction. Cisplatin-induced injury of the renal proximal tubular epithelial cells (RPTEC) has been characterized using KIM-1 in both *in vivo* and *in vitro* studies. Despite growing interest in clinical use of KIM-1 as a key biomarker for AKI diagnosis, a mechanistic model of KIM-1 that accurately predicts the kinetics of KIM-1 is still lacking. We developed a mechanistic model of KIM-1 as part of a quantitative systems toxicology (QST) model to predict urinary KIM-1 in rats treated with cisplatin.

Methods: We developed a mechanistic model of KIM-1 within the framework of RENAsym, a QST model of drug-induced AKI that incorporates key cellular injury mechanisms and renal hemodynamics. The KIM-1 model represents the early shedding of KIM-1 arising from the loss of brush borders during sub-lethal injury of RPTEC followed by the marked expression of KIM-1 in dedifferentiated cells in regenerating proximal tubules (Ichimura et al. 1998). The model is integrated with the RENAsym to capture RPTEC injury and regeneration following toxic renal injury.

Results: RENAsym was used to simulate the response of urinary KIM-1 in rats treated with cisplatin. The model parameters were fitted to data from rats treated with 2.5 mg/kg cisplatin (Gebremichael et al. 2017). The magnitude and time profile of KIM-1 were captured by the model. The KIM-1 model was also analyzed using data obtained from rats treated with single doses of 1 and 5mg/kg of cisplatin, and it can recapitulate the dose-dependent responses of urinary Kim-1.

Conclusions: Mechanistic model of KIM-1 was developed to quantitatively predicted cisplatin-induced AKI. The model recapitulated the urinary KIM-1 data obtained from rats treated with cisplatin. Human data will be used in the future for model validation.

Funding: NIDDK Support

PO0412

The Role and Mechanism of DcR2-Positive Failed Repair Cells in AKI

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Background: Acute kidney injury (AKI) is a common clinical emergency and critical illness. The regeneration and repair of renal tubular cells determine the prognosis of AKI. Our previous study found that decoy receptor 2 DcR2, a senescent marker, was specifically expressed renal tubules and did not have the ability to proliferate in AKI, suggesting DcR2 may be associated with repair of tubular cells. This study aims to investigate the role and mechanism of DcR2-positive tubular cells in AKI.

Methods: The DcR2-GFP lineage trace mice, KSP-creDcR2f/f and GGT1-creDcR2f/f mice and Ischemia-Reperfusion (I/R) Injury models were constructed. Confocal analysis the co-expression of DcR-GFP and proximal tubular markers(AQP1, Villin), distal markers (AQP2), failed repair markers (Vcam1, Dcdc2), proliferative markers (Ki-67, Edu, PCNA), Kim1, differentiated markers (pax2, sox9, six2), senescent markers (P16, P21, SA-β-gal) and fibrotic markers (a-SMA, collagen I, Fibronectin). And wild type (WT) mice and DcR2 CKO mice were used to compar the degree of renal tissue, functional damage and tubular repair after I/R injury. Furthermore, quantitative proteomics analyzed the downstream molecules of DcR2 in renal tissues from WT-AKI and CKO-AKI, and validated studied were done.

Results: The DcR2-GFP were mainly expressed proximal tubular cells in AKI. DcR2-GFP positive cells were co-expressed failed repair markers, senescent markers and co-localization with fibrotic markers. And DcR2-GFP positive cells were not expressed Kim1, proliferative and differentiated markers. The levels of Scr, BUN and renal injury scores were significantly lower in GGT1-creDcR2f/f -AKI than that of WT-AKI. Meanwhile, the area of renal fibrosis and fibrotic markers expression was decreased. However, the above phenomenon of KSP-creDcR2f/f–AKI were not obviously improved. Additionally, quantitative proteomics and validated studies showed HMGCS2, a key enzyme for Ketone Synthesis, was increased in GGT1-creDcR2f/f mice compared with WT. And the levels of urinary and serum β-hydroxybutyrate were higher in GGT1-creDcR2f/f mice.

Conclusions: DcR2-positive tubules were failed-repair cells in AKI. And DcR2 promotes failed repair of tubular cells through regulating the expression of HMGCS2 then affects the metabolism of β-hydroxybutyrate, suggesting that DcR2 may be a potential intervention target during the progression of AKI.

Funding: Government Support - Non-U.S.

PO0413

Mini-Pulse and Fast-Tapering Corticosteroids in Acute Tubulointerstitial Nephritis Related to Immune Checkpoint Inhibitors: Testing a Treatment Scheme

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Background: Acute tubulointerstitial nephritis (ATIN) is the most common lesion seen on kidney biopsy related to immune check-point inhibitors (ICI) in oncological patients. Clinical and laboratory features as well as risk factors are well known, albeit non-specific in predicting the underlying renal lesion. Corticosteroid-based therapy has proven to be effective, however, the optimal duration of treatment has not yet been established.

Methods: We conducted a retrospective single-center study to evaluate a treatment scheme with low-dose corticosteroids in patients diagnosed with ICI-related ATIN between 2017-2021. Extrapolating our treatment scheme for acute interstitial nephritis, we administer pulses of methylprednisolone (2 mg/kg/day for 3 consecutive days) followed by prednisone 1mg/kg/day with rapid-tapering until total withdrawal 2 months after treatment onset. The main outcome was to assess renal response during follow-up.

Results: We included a total of 8 patients (87.5% males) with a median age of 66.5 years and diagnosis of metastatic disease in all cases. Three patients had urothelial cancer, two had renal cell carcinoma and lung cancer, and one had hepatocellular carcinoma. Monotherapy as first- or second-line treatment with PDL-1 and PD-1 inhibitors was employed in 62.5 and 37.5% of the cases, respectively. Baseline serum creatinine (SCr) was 1.1 mg/dl(0.82-1.5), three patients had chronic kidney disease and six patients were on treatment with proton pump inhibitors. Acute kidney injury presented 13.5 weeks after starting ICI therapy. The median highest SCr was 3.2 mg/dl(2.5-5) and one patient required acute dialysis. Urinalysis alterations were present in all patients (proteinuria in 50%, hematuria in 75%, and sterile pyuria in 87.5%). Complete renal response was observed in all cases, except for one patient who showed a partial response. ICI rechallenge was not applied to any patient and no ATIN recurrences were documented after corticosteroids discontinuation. Two patients died due to oncologic disease progression. Median follow-up was 12.5 months(2.5-27.5).

Conclusions: Our treatment scheme with fast-tapering corticosteroids was effective for inducing renal response in ICI-related ATIN, without evidence of relapses.

PO0414

Contralateral Nephrectomy Stimulates Proliferation of Renal Epithelial Progenitor Cells After Unilateral Ischemia

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Background: Acute kidney injury is a global health concern and important risk factor for the development of chronic kidney disease. Crucial for successful renal recovery after AKI is the proliferation of surviving tubular epithelial cells. We established a murine model in which functional and histological recovery of a kidney, injured by ischemia, is enhanced by removal of the contralateral kidney, i.e. nephrectomy-induced recovery. The epithelial reparative response in this unique model has not been investigated, yet can provide new insights in the inherent regenerative potential of the renal epithelium.

Methods: AKI was induced in two different mice strains by left unilateral ischemia/reperfusion (UIRI) after which either right nephrectomy (Nx) or no Nx was performed on day 3. In $R26R^{tdTomato}$ mice kidney-to-body-weight ratio, renal function (serum creatinine) and fibrosis (Sirius Red histology) were measured at week 6. Additionally, renal tissue of PAX2/Confetti mice was processed to study clonal expansion by lineage pattern analysis of $PAX2^+$ renal epithelial progenitor cells at day 28.

Results: When no Nx was performed after UIRI, a significant decrease in left kidney-to-body weight ratio along with increased fibrosis and functional loss were observed in the injured kidney at week 6 compared to controls. However, when Nx was performed, renal function and mass were preserved. During spontaneous repair after UIRI (i.e. without Nx) clonal analysis in PAX2/Confetti mice revealed a significant increase in clone size frequency from mainly monoclonal $PAX2^+$ progenitor cells in controls to an increased number of multicellular clones. When Nx was performed after UIRI, this clonal expansion was further significantly stimulated. Likewise, the percentage of PAX2+ cells stimulated to divide (i.e. clonogenicity) was significantly higher when Nx was performed after UIRI (42%) as compared to when no Nx was performed (28%).

Conclusions: Nx overcomes loss of renal mass and function after UIRI. This enhanced recovery is at least established by increased clonogenicity and enhanced clonal expansion of renal progenitor cells that surpasses that of spontaneous repair after UIRI. Getting insight in the signaling mechanisms by which nephrectomy achieves this response may open new therapeutic research avenues.

PO0415

Long Noncoding RNA Neat1 Promotes Tubular Epithelial Cells Apoptosis to Facilitate the Progression of AKI to CKD

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Background: The severity and frequency of acute kidney injury (AKI) determine if the injury leads to chronic kidney disease (CKD). A growing number of research shows that the injury of tubular epithelial cells (TECs) is the driving force during chronic progression of AKI. However, there are limited knowledge about the role of lncRNAs in the progression of AKI.

Methods: To screen out the candidate lncRNA in the progression of AKI to CKD, 8-week old C57BL/6 mice were subjected to mild-AKI (20 min-ischemic reperfusion injury) and severe-AKI (40 min- ischemic reperfusion injury). RNA-sequencing was performed with the isolated tubules from mild- or severe- AKI mouse. The expression of a candidate lncRNA Neat1 was evaluated by FISH, Northern blot and real-time qRT-PCR in HK2 cells and mouse kidney tissues. To study the biological function of Neat1 *in vitro*, CRISPR-Cas9 was used to knock out Neat1, while Neat1 was ectopic overexpressed by lentivirus. HK2 cells were cultured in anoxic environment as the *in vitro* model to study the function of Neat1. RNA pull down was performed to screen out the microRNAs that bound to Neat1. Knocking down Neat1 *in vivo* was performed by injecting Adeno-associated virus serotype 9 (AAV9) particles carrying siRNA targeting Neat1. Flow cytometer was used to calculate the apoptotic cells under each treatment. TUNEL was applied to evaluated the apoptotic TECs in kidney sections.

Results: The expression of Neat1 was upregulated in the tubules from severe AKI mouse, as compared to mild AKI mouse. Knocking out Neat1 inhibited hypoxia-induced HK2 cells apoptosis while overexpression of Neat1 enhanced the apoptosis of HK2 cells *in vitro*. Furthermore, knockdown of Neat1 *in vivo* reduced the apoptosis of TECs and improved the kidney functions of IRI mice.

Conclusions: Our results showed that LncRNA neat1 regulated apoptosis of TECs and might be served as a therapeutic target to ameliorate AKI.

Funding: Government Support - Non-U.S.

PO0416

Effects of Proton Pump Inhibitors (PPIs) on Renal Vascular Reactivity in Cirrhotic Rats

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Background: Hepatorenal syndrome is, a lethal complication of cirrhosis, defined as renal hypoperfusion resulting from intense renal vasoconstriction. Vascular dysregulation such as ET-1 and nitric oxide (NO) might be the contributing factor. Proton pump inhibitors (PPIs) are widely used for peptic ulcer. Although generally safe, recent studies reported that PPIs decreased NO production, leading to reduction of arterial relaxation. The prevalence of gastric ulcer in cirrhotic patients is higher than healthy controls. The impact of PPIs on renal vascular responsiveness in cirrhosis is worth to be studied.

Methods: Liver cirrhosis was induced in S-D rats by common bile duct ligation (CBDL). Sham-operated (SHAM) rats were surgical controls. On the 29th day after surgery, in-situ renal perfusion was performed. In acute treatment study, rats were randomized to receive Krebs solution or Esomeprazole (30 mM) incubation for 1h before renal perfusion. In chronic treatment study, rats were randomly received oral distill water or Esomeprazole (3.6 mg/kg/d) for 28 days.

Results: The were no significant changes in renal vascular reactivity to ET-1 after acute (Fig. A) and chronic (Fig. B) PPIs treatment in CBDL rats. Chronic PPIs treatment had no significant effects on systemic hemodynamics and renal function but decreased hemoglobin in both SHAM and CBDL rats (Table).

Conclusions: In conclusion, PPIs showed no renal vascular effects. The mechanisms of lower hemoglobin following PPIs treatment need further analysis.

Table. Hemodynamic and biochemistry data

	SHAM-DW	SHAM-PPIs	CBDL-DW	CBDL-PPIs
Mean arterial pressure (mmHg)	146±4	155±3	117±4§	123±6
Portal pressure (mmHg)	8.7±0.3	8.0±0.3	15.4±0.5§	15.2±0.9
Superior mesentery artery flow (ml/min/100g)	4.0±0.2	4.1±0.2	5.5±0.4§	6.2±0.5
Renal artery flow (ml/min/100g)	2.7±0.2	2.6±0.2	3.3±0.3	3.6±0.2
ALT (IU/L)	49±4	58±4	139±12§	146±10
Creatinine (mg/dL)	0.47±0.02	0.45±0.03	0.53±0.03	0.52±0.02
Hemoglobin (g/dL)	16.6±0.3	15.8±0.2¶	14.6±0.3§	13.5±0.3¶

Expressed as mean ± SEM

§, $P < 0.01$ vs DW-treated SHAM group

¶, $P < 0.01$ vs corresponding DW-treated group

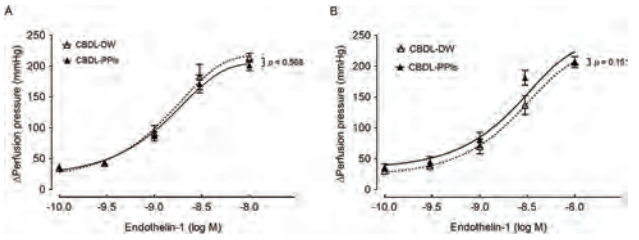

Fig. Concentration-response curves in perfuse kidneys of CBDL rats following (A) acute and (B) chronic PPIs treatment.

PO0417

Hospitalized AKI Is Associated with Long-Term Increases in TNFR1 and TNFR2: Findings from the CRIC Study

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Background: Evaluation of plasma biomarkers before and after AKI may yield valuable insights into the pathogenesis of progressive CKD after AKI. Markers of endothelial inflammation and injury, Tumor Necrosis Factor Receptors 1 and 2 (TNFR1 and TNFR2), are associated with progressive CKD, but it is unknown whether an episode of hospitalized AKI may cause long-term changes in these biomarkers.

Methods: Among participants in the prospective Chronic Renal Insufficient Cohort (CRIC), episodes of hospitalized AKI were identified using acute changes in inpatient serum creatinine values (peak/nadir ≥1.5). For each AKI hospitalization, we found the best matched non-AKI hospitalization (unique patients) using the following pre-hospitalization criteria: estimated glomerular filtration rate (eGFR), urine protein/creatinine ratio, duration between hospital discharge and next CRIC visit (max 1 year), diabetes, age, sex, and duration between hospital admission and prior CRIC visit (max 2 years). We measured plasma levels of TNFR1 and TNFR2 using banked plasma samples collected at CRIC study visits before and after the hospitalization. Biomarkers were measured using a customized U-Plex assay on a MesoScale Device.

Results: Study participants who did and did not have AKI were well matched (**Table**). Pre-hospitalization TNFR1 and TNFR2 levels were also similar. AKI was associated with greater increases in TNFR1 ($p<0.01$) and TNFR2 ($p<0.01$).

Conclusions: Hospitalized AKI was associated with increases in plasma TNFR1 and TNFR2 months after the hospitalization.

Funding: NIDDK Support

Characteristics Mean (std) or Median [IQR]	AKI Hospitalization (n = 198)	Non-AKI Hospitalization (n = 198)
Age, yrs	66 (9)	66 (9)
Female	39%	36%
Pre-hospitalization eGFR, mL/min/1.73m2	48 (17)	48 (17)
Pre-hospitalization UPCR, g/g	0.24 [0.10-0.99]	0.26 [0.08-0.90]
Duration between prior CRIC visit and hospital admission, days	221 [138-291]	220 [123-283]
Ln(TNFR1 (n pg/ml) pre- and post-hospitalization	7.23 and 7.44	7.27 and 7.33
Change in TNFR-1 (Ln(pg/ml))	0.21*	0.06*
TNFR-2 (pg/mL) pre- and post-hospitalization	50900 and 57255	50101 and 52626
Change in TNFR-2 (pg/mL)	6355*	2525*

*P <0.05 comparing AKI vs. non-AKI.

PO0418

Can Urinary Biomarkers at AKI Predict Progression to CKD?

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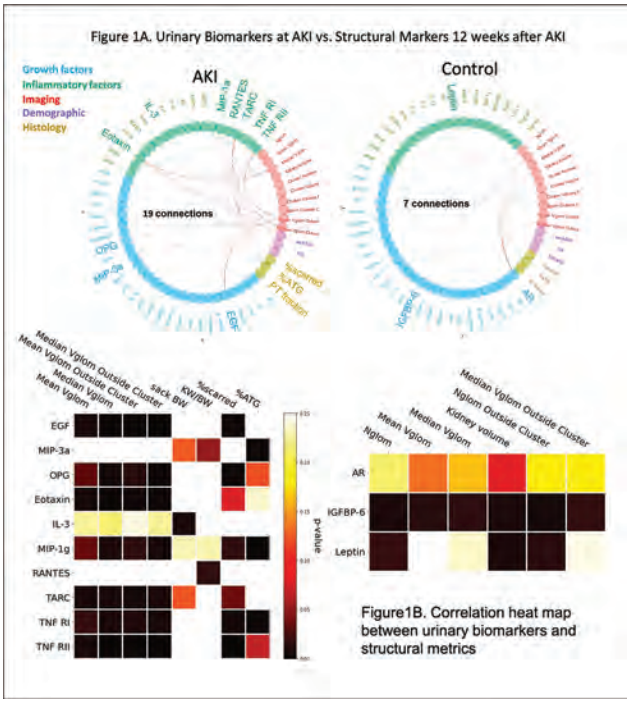
Background: Acute kidney injury (AKI) can cause permanent structural changes and progressive chronic kidney disease (CKD). If kidney function normalizes after AKI, it is difficult to distinguish who will progress to CKD. We evaluated urinary biomarkers from mice at the time of AKI and correlated them to a range of structural features derived from histopathology and cationic ferritin enhanced-MRI (CFE-MRI) in the kidney later in life. We investigated whether these biomarkers at AKI could predict future progression to CKD.

Methods: Adult male mice were injected with folic acid (AKI) or $NaHCO_3$ (controls), (n=8/grp) and urine was collected after 4 days. Biomarkers were measured using the Cytokine Array Q1000 (Ray BioTech). Mice received CF 12 wks after AKI and kidneys were imaged *ex vivo* using a 7T MRI. Structural metrics were derived by CFE-MRI (N_{glom} and aV_{glom}) and histology (proximal tubule (PT) content, atubular glomeruli (ATG), and scarred area).

Results: We performed a univariate analysis comparing the AKI and controls. Using hierarchical edge bundling, there were 19 connections between the urinary biomarkers and structural metrics at 12 wks and 7 connections in the control group (Fig 1A). EGF, OPG, TARC and TNF RII (correlation>0.8, Fig 1B) were correlated to structural metrics in AKI and only IGFBP-6 was correlated to the structural metrics in controls. We developed predictive models using the 13 urinary markers in Fig 1B. The best model predicted mean aV_{glom} (r^2=0.67), %ATG (r^2=0.50) and PT content (r^2=0.47).

Conclusions: Urinary biomarkers, alone or in combination, may provide noninvasive predictive markers for progression to CKD after AKI. We identified 13 urinary biomarkers that appear to predict structural changes in the kidney 12 weeks after AKI and may serve as candidate biomarkers to predict outcomes in patients.

Funding: NIDDK Support



PO0419

The Kidney Produces a Non-Polymerizing Form of Uromodulin That Associates with Reduced Risk of AKI

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Background: Uromodulin (Tamm-Horsfall protein, THP) is a glycoprotein uniquely produced in the kidney. It is released by cells of the thick ascending limbs (TAL) apically in the urine, and basolaterally in the renal interstitium and systemic circulation. Processing of mature urinary THP, which polymerizes into supra-molecular filaments, requires cleavage of an external hydrophobic patch (EHP) at the C terminus. However, THP in the circulation is not polymerized, and it remains unclear if non-aggregated forms of THP exist natively in the urine. We propose that an alternative processing path, which retains the EHP domain, can lead to a non-polymerizing form of THP.

Methods: We have generated an antibody that specifically recognizes THP with retained EHP (THP+EHP). Liquid chromatography, mass spectrometry and C terminal sequencing were performed to delineate potential sites of enzymatic cleavage of immunoprecipitated THP+EHP. Immunofluorescence confocal microscopy was used to localize this isopform in the human kidney. Finally, we finally developed a customized ELISA to measure THP+EHP and used it on urine and plasma samples from a small cohort of patients hospitalized with liver cirrhosis.

Results: Using native and denaturing Western blots, we established the presence of THP+EHP in the urine in a non-polymerized native state. Proteomic studies confirmed the identity of THP+EHP and suggested that enzymatic cleavage occurred at Arg615, which is one amino acid beyond the GPI anchoring site. In the human kidney, THP+EHP predominantly co-localized with urinary THP in TAL cells, but it was also detected, at lower levels, in other tubular segments. In a cohort of patients with liver disease, admission urinary THP+EHP, but not total THP, was significantly lower in patients who subsequently developed acute kidney injury during hospitalization. THP+EHP was also detected in the plasma, albeit at very low concentrations.

Conclusions: Our findings uncover novel insights into uromodulin biology by establishing the presence of an alternative path for cellular processing. Our proof-of-principle findings in patients warrant further investigations to establish the utility of THP+EHP as a sensitive biomarker of kidney health and susceptibility to injury.

Funding: NIDDK Support, Veterans Affairs Support

PO0420

Air Pollution Aggravates Ischemia-Reperfusion-Induced AKI in Mice

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Background: The biggest city in Latin America is São Paulo (SP), where disorganized urbanization has had a negative impact on air quality and vehicle emissions are the main source of fine particulate matter ($PM_{2.5}$). Epidemiological studies have linked $PM_{2.5}$ exposure to an increased risk of CKD. The mechanisms mediating the adverse health effects of $PM_{2.5}$ include epigenetic changes, oxidative stress and inflammation. The role of $PM_{2.5}$ in AKI has yet to be described. We hypothesized that $PM_{2.5}$ exposure would aggravate renal ischemia/reperfusion (I/R) injury in mice.

Methods: In temperature-/humidity-controlled chambers within an ambient particle concentrator, animals were exposed to a concentrated $PM_{2.5}$ stream ($PM_{2.5}$) or to high-efficiency particulate air-filtered clean air (CA). Mass concentrations of PM were measured with an airborne particulate monitor, and the target dose was 600 μg m^{-3}/day (equivalent of the daily exposure in SP). After 12 weeks, some $PM_{2.5}$ and CA mice underwent bilateral 30-min clamping of the kidney hila and subsequent reperfusion. All studies were performed 48 h after I/R. Groups: CA, $PM_{2.5}$, CA+I/R and $PM_{2.5}$+I/R. Data are mean±SEM.

Results: Renal TLR4 protein expression was higher in CA+I/R and $PM_{2.5}$+I/R than in CA and $PM_{2.5}$ (128±2.1 and 146±2.0 vs. 97.5±2.1 and 98.0±0.9%; P<0.05), also being much higher in $PM_{2.5}$+I/R than in CA+I/R (P<0.05). Manganese superoxide dismutase levels were higher in $PM_{2.5}$+I/R than in CA+I/R, AF and $PM_{2.5}$ (146±12 vs. 99±3.6, 102±3.9 and 96±2.8; P<0.05).

Conclusions: $PM_{2.5}$ aggravates I/R-induced AKI by decreasing renal Klotho protein, leading to increased renal TLR4 expression and inflammatory cell infiltration. (FAPESP, NWO)

Funding: Government Support - Non-U.S.

Biochemistry and histology

	CA (n=4)	PM2.5 (n=7)	CA+I/R (n=11)	PM2.5+I/R (n=14)
Creatinine Clearance (mL/min)	0.67±0.20	0.83±0.33	0.76±0.34	0.28±0.26[a]
FENa (%)	0.13±0.03	0.10±0.03	0.12±0.02	0.30±0.07[a]
Urinary Osmolality (mOsm/kg)	2045±244	1949±175	1764±300	1106±184[a]
Tubular Injury Score	0.00	0.00	1.0±0.56	3.6±0.64[a]
Klotho* (%+area/high power field)	4.7±0.8	4.8±0.4	2.2±0.15[b]	1.1±0.24[a]
F480*(%+area/high power field)	0.71±0.15	0.44±0.04	0.83±0.11	1.35±0.16[b]
Ki67* (+cells/high power field)	1.55±0.41	1.32±0.38	15.4±7.7	30.6±5.44[b]
ly6G* (+cells/high power field)	0.67±0.10	1.10±0.20	12.19±6.55[b]	61.84±11.29[a]

*Immunohistochemical analysis;

[a]P<0.05 vs. CA, PM2.5 and CA+I/R; [b]P<0.05 vs. CA and PM2.5.

PO0421

Proteogenomic Effects of Environmental and Uremic Toxin Acrolein on Mouse Kidneys

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Background: Acrolein is present in the environment, water, food and is a uremic toxin endogenously produced through lipid peroxidation and polyamine oxidation. Its mechanism of action involves cellular thiol reactivity and glutathione depletion-induced oxidative stress. However, direct effects of acrolein on kidneys are not known. The current study conducted RNA-seq and proteomic analysis on mouse kidneys exposed to acrolein.

Methods: C57BL/6 mice were subjected to filtered-air (control) or inhaled-acrolein (1.0 ppm), 6h/day, 5 days/week for 12 weeks. Total-RNA and kidney homogenates from all mice were subjected to RNA-seq and proteomic analysis. Immunoblotting, H&E and Sirius-Red staining of kidneys was performed.

Results: RNA-seq analysis detected activation of profibrotic pathways including TGFb/TGFbR/SMAD3/TEAD4/Autotaxin and down-regulation of anti-fibrotic pathways including STAT5A/FGF21/PPARb/IL-22. Proteomic analysis identified fibrotic pathways, activation of oxidative stress, mitochondrial dysfunction, proteasomal degradation, apoptosis, and inflammatory pathways. Proteomic analysis demonstrated acrolein-decreased expression of antioxidant proteins, non-erythroid hemoglobin and glutathione synthetase (GSS), targets of transcription factor Nuclear Factor-Erythroid derived-2 (NF-E2). Accordingly, acrolein decreased renal NF-E2 expression and increased cleaved caspase-3 and profibrotic connective tissue growth factor (CTGF) expression. H&E staining demonstrated damaged tubules while Sirius-Red staining demonstrated increased collagen deposition in kidneys of acrolein exposed mice. Over-expression of NF-E2 in immortalized human renal proximal tubule (HK-11) cells, inhibited acrolein-induced CTGF expression and caspase-3 cleavage.

Conclusions: Our studies demonstrate activation of oxidative stress, apoptotic and profibrotic pathways in acrolein treated kidneys. Chronic exposures of acrolein may lead to progressive fibrosis-induced End Stage Renal Disease (ESRD). *In vivo* modulation of NF-E2 expression may slow-down progressive fibrosis-induced ESRD.

Funding: Other NIH Support - NIH/NIEHS P30 ES030283

PO0422

Impaired Renal Hemodynamic Reserve Following Ischemic AKI Is Associated with Inflammation and Capillary Rarefaction and Reversed by Retrograde Hydrodynamic Isotonic Fluid Delivery

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Background: We have previously shown that retrograde hydrodynamic delivery of isotonic fluid (HIFD) improved renal function in established AKI between 24-48 hours following ischemia and reperfusion injury (IRI). This improvement was associated with decreased inflammation and vascular congestion and improved microvascular perfusion. However, it is unknown whether HIFD results in sustained effects on renal hemodynamic reserve and CKD progression

Methods: Male Sprague Dawley rats underwent left unilateral IRI-35 min with right unilateral nephrectomy to induce AKI. 24 hours later, serum creatinine (SCre) was measured and rats received either HIFD via the renal vein or 0.5ml of isotonic saline into the vena cava (VC) as control. After 5 weeks, renal hemodynamic responses were assessed in response to i.v. L-arginine infusion (450 mg/kg/hr) in anesthetized rats. Kidneys were evaluated for further analysis

Results: At 5 weeks of recovery from surgery, baseline renal blood flow (RBF) and renal vascular resistance (RVR) were similar in the experimental groups (sham-, HIFD-, and VC-treated rats). Following 40 minutes of arginine infusion RBF increased similarly in both the sham group and the I/R HIFD group (22.6% and 19.8% compared to their corresponding baseline value (P<0.001). However, I/R-VC treated rats showed an impaired response to arginine infusion relative to the sham group (P<0.001). As expected, RVR to blood flow was decreased significantly by 14% and 17% in sham operated and HIFD treated rats compared to their corresponding baseline respectively. In the kidney, HIFD treatment attenuated recruitment of inflammatory CD4+IL17+ cells (777659 vs. 417609, p<0.05), as assessed by flow cytometry compared to the VC-treated rats. Peritubular capillary density in medulla, measured by cablin immunofluorescence, was significantly reduced by (41%) in VC-treated rats compared to sham group. HIFD treatment significantly improved capillary density after 35 days of IRI

Conclusions: HIFD treatment shown improved impaired renal blood flow response to arginine infusion following 35 days IRI. This is associated with improved capillary density and attenuated infiltration of CD4+IL17+ cells. This data shows that HIFD treatment has long-term protective effects following I/R injury

Funding: NIDDK Support, Veterans Affairs Support

PO0423

Evidence for a Critical Role of ARNT Homodimerization in Renal Regeneration and Attenuation of Fibrosis

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Background: Based on the organ-spanning effectiveness of ischemic preconditioning we hypothesized that underlying mechanisms could be utilized to aid the kidney in realizing its endogenous regenerative capacity and to circumvent kidney fibrosis. Previous studies implied that ARNT, also known as HIF1beta, plays an important role independent of HIF1alpha in ischemic preconditioning. Here we aimed to explore the mechanisms underlying the reno-protective activity of ARNT and to exploit these mechanisitc insights for novel therapeutic strategies.

Methods: ARNT homodimerization in vivo and in vitro was studied by mass spectrometry, immunoprecipitation, proximity ligation assays, native gel analysis and the use of mutant ARNT variants. Control of ARNT expression was studies by use of qRT PCR, immunoblot and promoter assays. To study impact of ARNT homodimerization in vivo we utilzed mure models of UU and CCl4-induced liver fibrosis.

Results: We provide evidence that transcriptional induction of ARNT by administration of FK506 or Tacrolimus enhances renal regeneration and attenuates fibrosis in mice. This effect is not realized when ARNT is targeted by administration of in vivo morpholinos. We demonstrate that the protective effect of ARNT is only realized when it forms homodimers. ARNT homodimers acts as transcription factor on ALK3 and the protective effect of ARNT homodimers is not realized when ALK3 is lacking. We identify that ARNT dimerization decision to form homodimers is controlled by phosphorylation of a critical serine 77 amino acid. ARNT Ser77 phosphorylation is controlled by PP2A. The PP2A inhibitor LB100 enhances Ser77 phosphorylation, ARNT homodimer formation and attenuates fibrosis in the kidney. Combination of GPI1046 (to induce ARNT transcription) and LB100 (to enhance ARNT homodimers) has additive effect to protect against fibrosis in kidney and liver.

Conclusions: Increased intracellular ARNT levels through enhanced transcription and augmented homodimerization through phosphorylation of ARNT Ser77 are pre-requisites to realize the reno-protective activity of ARNT. Utilization of this dual mechanism through combination therapy has potential to protect the kidney.

PO0424

TGF-βR1-Mediated Tubular Injury and Cell Death Requires Recruitment of Inflammatory Cells via CCL5

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Background: Activation of the TGFβ signaling pathway plays an important role in both AKI and CKD pathogenesis. We have previously shown that ligand-independent activation of TGFβR1 in proximal tubules results in rapid epithelial cell injury and death, as well as immune cell infiltration. This study aims to determine the drivers and mechanism of epithelial cell injury.

Methods: *In vivo* studies were performed in transgenic Pax8Tgfbr1 mice with proximal tubular activation of TGFβR1 signaling by +/- doxycycline (Dox) chow. Immortalized proximal tubular epithelial cells (PTECs) from Pax8Tgfbr1 mice were treated with Dox and with activated spleen derived leukocytes. Cell death was determined by TUNEL or AnnexinV/PI staining, lipid-derived free radicals by electron paramagnetic resonance (EPR) spin resonance spectroscopy and *in vivo* spin trapping, and mitochondrial superoxide was determined by mitoSOX. Gene and protein expression were determined by RT-PCR, western blotting and immunofluorescence.

Results: Canonical TGFβ signaling induced by Dox was confirmed in Pax8Tgfbr1 mice and in isolated PTECs cells by increased Tgfbr1 gene expression and phospho-SMAD2 or nuclear translocation of SMAD2/3. Markers of tubular cell injury and inflammation were prominent in kidney sections from Pax8Tgfbr1 mice after 5 days of Dox. There was also increased oxidative stress and cell death after 5 days. TGFβR1 signaling activation in cultured Pax8Tgfbr1 PTECs did not induce cell death, but showed an increase in CCL5/RANTES expression, a chemokine involved in recruitment of several immune cell types, among them monocytes and T-cells. PTECs co-cultured with leukocytes isolated from spleens resulted in mitochondrial oxidative stress and cell death of PTECs. Cell death and mitochondrial oxidative stress was ameliorated by a mitochondrial superoxide scavenger in co-cultured PTECs.

Conclusions: Our studies show that induction TGFβR1 signaling in tubular epithelial cells triggers recruitment of inflammatory cells which mediate mitochondrial stress and cell death.

Funding: Other NIH Support - NIH grant R01DK097253

PO0425

Kidney-Draining Lymph Node Fibrosis Following Unilateral Ureteral Obstruction

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Background: Although the primary organ has been the subject of intense investigation in the field of organ fibrosis over the past several decades, the presence of lymph node fibrosis due to persistent activation of the immune response in its partner organ remains largely unknown. Previously, we demonstrated that activation of the immune response following ischemia-reperfusion injury and crescentic glomerulonephritis in the kidney was associated with extracellular matrix (ECM) production by fibroblastic reticular cells (FRCs) of the kidney-draining lymph node (KLN). Here, we sought to determine whether FRCs in the KLN become similarly fibrogenic following unilateral ureteral obstruction (UUO) of the kidney.

Methods: We subjected 6–8-week-old C57BL/6J mice to UUO for 2, 7, and 14 days. We examined the microarchitecture of the kidney and KLN by immunofluorescence staining at each timepoint, and we quantified immune cell populations in the KLN by flow cytometry. The contralateral kidney unaffected by UUO and its partner KLN were used as controls.

Results: We found through immunofluorescence staining that FRCs increased production of ECM fibers and remodeled the microarchitecture of the UUO KLN, contributing to fibrosis that mirrored the changes in the kidney. We also observed by flow cytometry that the populations of $CD11b^+$ macrophages, $CD11c^+$ dendritic cells, and activated $CD4^+$ and $CD8^+$ T cells were significantly higher in the UUO KLN than the KLN draining the unaffected contralateral kidney.

Conclusions: These findings for the first time highlight the association between fibrosis both in the kidney and the KLN during UUO, and they lay the groundwork for future studies that will investigate more deeply the mechanisms behind KLN fibrosis.

Funding: NIDDK Support, Other NIH Support - NIAID, Commercial Support - Dialysis Clinic, Inc.

PO0426

The Irradiation-Induced Renal Ischemic Preconditioning Is Blunted by the Oral Administration of the Anti-Angiogenic Agent Sunitinib

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Background: Whole-body irradiation has been suggested to induce renal ischemic preconditioning(RIP) in mice, possibly via angiogenesis. First, we comprehensively investigate the pathways involved in renal irradiation. Next, we assess the functional impact of renal irradiation applied before renal ischemia/reperfusion(I/R) injury. Finally, we test whether Sunitinib-mediated inhibition of the angiogenesis prevents irradiation-associated RIP.

Methods: Exp1: Renal irradiation(8.56 Gy) was performed in male C57bl/6 mice(n=10). One month later, total kidney RNA was extracted from irradiated and control(n=5) mice for comparative RNA-Seq. Exp2: After renal irradiation, the right kidneys were removed, and the left kidneys undergo ischemia(30min)/reperfusion(48h) at Days 7-14-28 post irradiation(n=8). Exp3: Following the same protocol of I/R at Day14, 3 groups were compared(n=8): 1/irradiation; 2/irradiation and gavage with Sunitinib from Day2 to 13; 3/control group without irradiation or gavage.

Results: Exp1: RNAseq showen up-regulation of angiogenesis signalling pathways. Expressions of angiogenesis markers(CD31, VEGF) showed an increase at both mRNA and protein levels in irradiated kidneys($p<0.01$). Exp2: Following I/R, Blood Urea Nitrogen(BUN) and Creatinine(SCr) levels were lower in the irradiated mice compared to controls: (BUN: 86.2±6.8 vs. 454.5±27.2mg/dl; SCr: 0.1±0.01 vs. 1.7±0.2mg/dl, $p<0.01$). The renal infiltration by CD11b-(187±32 vs 477±20/mm^2) and F4-80-positive cells(110±22 vs 212±25/mm^2) was reduced in the irradiated group. VEGF and CD31 expression was increased in irradiated kidneys at both mRNA and protein levels($p<0,01$). Exp3: One-way analysis of variance followed by Tukey's test showed that, following I/R, BUN and SCr levels were lower in the irradiated group compared to controls(BUN: 106.1±33.6 vs. 352.2±54.3mg/dl; SCr: 0.3±0.13 vs. 1±0.2mg/dl), and in irradiated group compared to the irradiated-exposed group to Sunitinib(BUN: 106.1±33.6 vs. 408.4±54.9mg/dl; SCr: 0.3±0.12 vs. 1.5±0.3mg/dl; $p<0.01$).

Conclusions: Renal irradiation induces the activation of angiogenesis in mice. Renal irradiation leads to RIP, with preserved renal function and attenuated inflammation post I/R. Exposure to the anti-angiogenic drug Sunitinib post-irradiation prevents the irradiation-induced RIP.

Funding: Government Support - Non-U.S.

PO0427

Inhibition of 12/15 Lipoxygenase (12/15 LOX) Improves Renal Recovery and Function Post Ischemia-Reperfusion in Male Spontaneous Hypertensive Rats (SHR)

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Background: Acute kidney injury (AKI) due to ischemia-reperfusion (IR) is a serious and frequent complication with high mortality rates. The mechanisms mediating renal IR injury leading to increased risk of later developing cardiovascular and renal diseases in either sex remain poorly understood, although elevated 12/15-LOX activity has been reported to contribute to the progression of numerous kidney diseases. The goal of the current study was to test the hypothesis that enhanced activation of 12/15-LOX leading to impaired recovery post-IR.

Methods: 13-week old male and female SHR were subjected to sham or 30-minute warm bilateral IR (n=6/group). Additional male SHR were randomized to receive vehicle or the specific 12/15-LOX inhibitor ML355 (30 mg/kg i.p.; n=5/group) 1 hr prior to sham/IR and every other day up to 7 days post-IR. Blood and urine were collected from all rats 24 hrs and 7 days after IR; kidneys were harvested 7 days post-IR for biochemical, histological, and Western blot analysis.

Results: IR increased plasma creatinine (Pcr) and blood urea nitrogen (BUN) in both male and female SHR compared to respective sham controls at 24 hrs (P_{IR}=0.0001; P_{sex*IR}=0.2). At 7 days post-IR, Pcr and BUN remained elevated in male SHR but returned to baseline levels in females (Pcr: P_{IR}=0.03; P_{sex}*$_{IR}$=0.04; BUN: P_{IR}<0.05; P_{sex}*$_{IR}$=0.05). Histological examination of kidneys 7 days post-IR showed greater tubular damage (P_{IR}=0.0003, P_{sex}*$_{IR}$=0.0019) and renal cell death (P_{IR}=0.001; P_{sex}*$_{IR}$=0.001) in male vs. female SHR. Delayed recovery of renal function in male SHR was associated with activation of renal 12/15-LOX (P_{IR}<0.05; P_{sex}*$_{IR}$=0.008), increased lipid peroxidation (P_{IR}=0.008; P_{sex}*$_{IR}$=0.018), and ER stress (P_{IR}=0.05; P_{sex}*$_{IR}$=0.01) compared to sham-controls. Pre-treatment of male SHR with ML355 reduced IR-induced lipid peroxidation (P_{IR*TxT}=0.02) and ER stress (P_{IR*TxT}=0.05), prevented IR-induced tubular damage (P_{IR*TxT}=0.02) and tubular cell death (P_{IR*TxT}=0.04), and improved renal function (Pcr: P_{IR*TxT}=0.0067; BUN: P_{IR*TxT}=0.042) compared to vehicle-treated IR males 7 days post-IR.

Conclusions: In conclusion, our data demonstrate that enhanced activation of 12/15-LOX contributes to impaired renal recovery post-IR via ER stress and cell death in male SHR.

Funding: Other NIH Support - AHA and NHLBI, Private Foundation Support

PO0428

The Immunomodulatory Effect of LMWF5A on Infiltrating Immune Cells Supports Its Clinical Use for AKI

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Background: Infiltrating immune cells are critical to acute kidney injury (AKI) pathogenesis. They are activated to clear cellular debris, secrete pro-inflammatory mediators, and drive leukocyte recruitment, with a subsequent switch to produce anti-inflammatory mediators that promote tissue repair. However, dysregulated, continuous, or excessive immune activation can result in further tissue damage. The <5kDa low molecular weight fraction of human serum albumin (LMWF5A) has anti-inflammatory/pro-resolution effects. This *in vitro* study aimed to evaluate the ability of LMWF5A to treat AKI by examining its effects on immune cells relevant to AKI.

Methods: Peripheral blood mononuclear cells (PBMC) were treated with vehicle control or LMWF5A and activated with lipopolysaccharide (LPS), LPS + interferon (IFN) γ, or interleukin (IL)-4 + IL-13. Media and total RNA were collected at 24h. Secreted molecules were analyzed using multiplex cytokine arrays or prostaglandin E2 (PGE2) ELISA, and differential gene expression was determined by mRNAseq. Data were then subjected to *in silico* interrogation of known AKI signaling pathways and comparison to public datasets featuring human AKI samples.

Results: Cytokine release by PBMC was significantly modulated by LMWF5A treatment. While cytokine profiles differed depending on stimulant, the most highly downregulated cytokines included C-X-C chemokine ligand 10, IFNγ, IL-10, IL-12, IL-17, monocyte chemoattractant protein (MCP)-1, and MCP-3 (n=3; p≤0.05), which have been implicated in AKI. In addition, the release of PGE2, which has been proven to be beneficial to kidney injury, was potentiated with LMWF5A treatment. *In silico* secretome and transcriptome analysis of LMWF5A-treated PBMC displayed predicted inhibition of pathways known to drive AKI, notably IFN and IL-17 signaling. Further, comparison to public human AKI biopsy data revealed that pathways activated by AKI were predicted to be significantly inhibited in LMWF5A-treated PBMC.

Conclusions: These data reflect the ability of LMWF5A to reduce inflammatory cytokines and shift the immune response towards resolution. Moreover, global regulation of pathways activated by AKI in kidney tissue are predicted to be inhibited by LMWF5A. This preliminary study suggests a potential role for LMWF5A as an effective AKI therapeutic.

Funding: Commercial Support - Ampio Pharmaceuticals

PO0429

Mutation of Regulatory Phosphorylation Sites in PFKFB2 Does Not Affect Metformin's Protective Effects Against Renal Fibrosis

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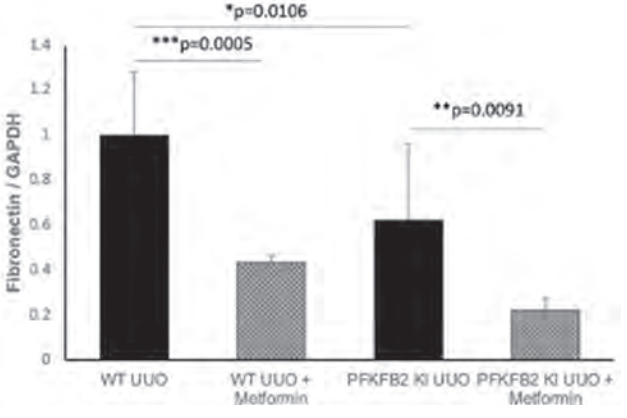
Background: Metformin has been shown to have protective effects in mouse models of renal fibrosis via its effects on fatty acid oxidation but the contribution of glycolysis to this effect is unclear. 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase (PFKFB) is a key regulator of glycolysis in the kidney and is not believed to have an effect on fatty acid oxidation. We aimed to determine if modification of glycolysis has a critical role in metformin's protective effects against renal fibrosis.

Methods: Mice with inactivating mutations of the phosphorylation sites in PFKFB2 (PFKFB2 KI mice) were generated, which is predicted to reduce the ability to increase the rate of glycolysis following stimulation. These were compared with wild-type controls. Mice were administered metformin via drinking water and a unilateral ureteric obstruction (UUO) model was used. The degree of fibrosis was assessed by Western blot and RT-PCR.

Results: In the PFKFB2 KI mice treated with metformin, there was decreased fibrosis following UUO as assessed by Western blot for fibronectin ($p<0.05$) and RT-PCR for alpha-SMA, collagen-3 and F4.80. There was no significant difference between WT and PFKFB2 KI mice treated with metformin in regards to the degree of fibrosis following UUO in any of the Western blot or RT-PCR parameters that were measured.

Conclusions: These data show that inhibition of the regulation of glycolysis by PFKFB2 does not prevent metformin from having protective effects against renal fibrosis in a UUO model.

Funding: Government Support - Non-U.S.



PO0430

Scaffold Protein Na+/H+ Exchanger Regulatory Factor 1 (NHERF1) Protect Tenofovir-Induced Nephrotoxicity by Regulating Na+/Pi Cotransporter (Npt) and Intracellular Phosphorus Balance

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Background: Tenofovir disoproxil fumarate (TDF) could cause proximal tubular (PT) dysfunctions and eGFR decline with mitochondria damages. PDZK1, MAP17, and NHERF1 are scaffold proteins that influence the localization and function of membrane proteins. We tried to investigate the changes of both membrane-associated proteins and proximal tubular transporters in TDF-induced nephrotoxic model.

Methods: C57/BL6 mice (n = 8) were gavaged daily with 10mg/kg/d, 50mg/kg/d of TDF for 8 weeks. The human renal tubular epithelial cells (HK-2) were grown and received 24 to 72 h exposure to 0–128 μM TDF or vehicle. NHERF1 was overexpressed in HK-2.

Results: Chronic TDF administration to mice resulted in swollen and exfoliated tubular epithelial cells, brush border cilia lodging and dissolving, and serum creatinine elevation ($P<0.05$, mean 10.23±2.683 vs. 27.18±18.41) compared to the control group. The protein expressions of scaffold protein NHERF1, Na+/Pi cotransporter (Npt), and sodium-glucose cotransporter type 2 (SGLT-2), but not PDZK1 and MAP17 were decreased in the kidneys of TDF-treated mice and cells. The intracellular phosphorus concentrations decreased dose-dependent with TDF concentration and the exposing time, companies with down-regulated Npt expressions. ATP levels reflected mitochondrial functions were also decreased with a time and dose-dependent exposure of TDF. NHERF1 overexpressing cells are well resistant to transporter damage and mitochondrial damage caused by TDF.

Conclusions: NHERF1 protects the TDF-induced AKI by Npt, intracellular phosphorus, and mitochondria dysfunction pathway.

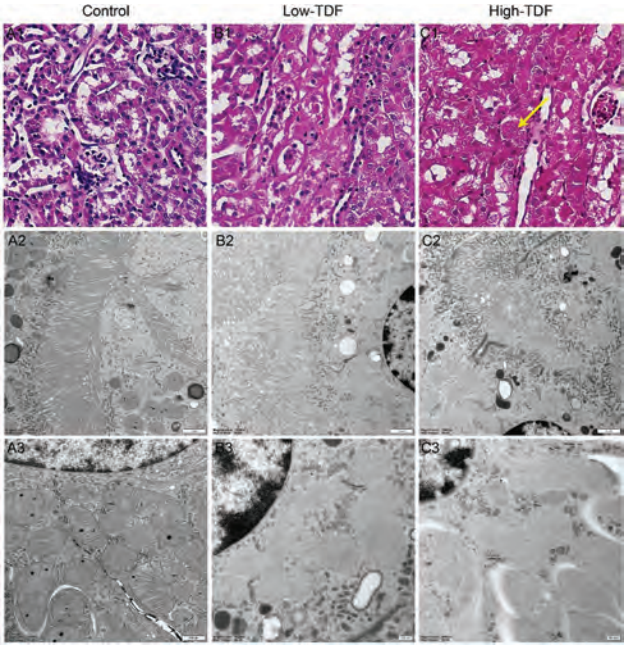

Figure 1. Representative light micrographs and electron micrographs of mice kidney.

PO0431

Renal Papillary Function and Repair After Reversible Ureteral Obstruction

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Background: Models of reversible UUO (R-UUO) have provided insight into the mechanisms of repair in the renal cortex, but little is known about the mechanisms or extent of renal papillary repair after reversal of obstruction. Here we characterize long-term functional and structural papillary repair in a new mouse model of R-UUO.

Methods: Vascular clamps are placed on the L ureter, removed on day 7, and a R nephrectomy (Nx) performed on day 17. We evaluated serial BUN; transdermal GFR (tGFR); urinary osmolarity (OSM) after water restriction; histology and fibrosis; tubules, interstitium, and capillaries by IF with segment-specific markers, markers of repair, and lineage analysis with Six2-CRE; R26R-td Tomato reporter mice to assess repair of nephronic epithelium.

Results: At clamp removal (day 0) all mice had hydronephrosis. 60-80% survived 48hrs after Nx, and day 14 BUN in Nx vs. R-UUO+Nx was 18.5 (0.9) vs. 42.6 (8.5) mg/dl, $p<0.001$, indicating reversal and consistent injury. tGFR was reduced at day 28 (991.0 (46.6) vs. 569.8 (82.6) ml/min/100gm, $p<0.001$), reversed by day 84, with decreased urinary OSM up to day 84 (3525 (106.9) vs. 1718 (175.7) mOsm/L, $p<0.0001$). There was cortical fibrosis from 0-84 days. Fibrosis increased day 0>28 in the papilla but was absent by day 84. There was papillary necrosis days 0-3; repopulation of tubular structures starting day 7 with disorganized tubulointerstitial repair by day 28 but normal histology by day 84. There was loss of AQP1 (descending thin limb, DTL) and AQP2 but not LTL staining (distal collecting duct, CD) days 3>28. AQP1 and 2 were restored by day 84, but there was a reduction in capillary density by CD31 staining days 14>84. Lineage analysis showed persistent Six2 lineage in the papilla at day 28, indicating effective repair of AQP1- DTL. There was a marked increase in Ki67+ Six2 lineage and LTL+ CD cells days 3-7 after reversal, but no expression of the de-differentiation marker, Sox9, in the papilla.

Conclusions: There is robust, Sox9-independent repair of tubules in the papilla that is initially disorganized but ultimately restores tubular organization after R-UUO. Despite this, a persistent defect in urinary concentrating capacity associated with decreased papillary capillary density, suggests that despite robust tubular repair, disorganized vascular integrity results in long-term papillary dysfunction after R-UUO.

Funding: NIDDK Support, Other NIH Support - DOD

PO0432

The Susceptibility Mechanism of AKI in Cirrhosis Through Regulation of miR-599 Mediated by SIRT1 rs4746720 Polymorphism

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Background: Previous study has confirmed that SIRT1/PGC-1α signaling pathway might be involved in the pathogenesis of acute kidney injury (AKI) in cirrhosis. This study aimed to analyze the association between *SIRT1* single nucleotide polymorphism (SNP) and the risk of AKI in cirrhosis in a Chinese Han population, and to further explore the molecular mechanism of *SIRT1* SNP *in vitro*.

Methods: A total of 29 patients in AKI group and 87 patients in control group were selected from a Chinese Han population. Genotypes of *SIRT1* rs4746720 and rs2273773 were detected by SnaPshot technology. Bioinformatics softwares predicted that miR-599 might bind to the rs4746720 loci within *SIRT1* 3′UTR. The dual luciferase reporter vectors pmir-GLO-SIRT1-3′UTR-T/C were constructed and respectively co-transfected with miR-599 mimic or NC into HK-2 cells. The overexpression recombinant plasmids pcDNA3.1-SIRT1-T/C were further constructed and respectively co-transfected with miR-599 mimic, miR-599 inhibitor or NC into HK-2 cells, and the expression of miR-599 and SIRT1/PGC-1α/NRF1/TFAM were detected by qRT-PCR and Western blot.

Results: There was no significant association between *SIRT1* SNP and the risk of AKI in cirrhosis (P>0.05). But stratified analysis based on risk factors showed that in the subgroup of hepatic encephalopathy, *SIRT1* rs4746720 polymorphism was significantly associated with the risk of AKI in cirrhosis (OR=6.00, 95%CI: 1.22-29.48, P=0.027). Analysis of liver and kidney function showed that Scr and BUN of TT genotype of *SIRT1* rs4746720 was significantly higher than that of CC+CT genotype in the AKI group, and eGFR was significantly lower than that of CC+CT genotype (P<0.05). Dual luciferase reporter vectors showed that rs4746720 T allele of *SIRT1* could increase the binding of miR-599, which resulted in significantly reduced luciferase activity (P<0.001). Overexpression recombinant plasmids showed that rs4746720 T allele of *SIRT1* could mediate the binding of miR-599, which resulted in significantly reduced expression of SIRT1 and its downstream pathway (P<0.05).

Conclusions: The rs4746720 polymorphism in *SIRT1* 3′UTR may be associated with the risk of AKI in patients with cirrhosis. The rs4746720 T allele of *SIRT1* may mediate the binding of miR-599, affect the expression of SIRT1 and its downstream pathway.

PO0433

RAP Inhibits Proximal Tubule Endocytosis and Protects Against Gentamicin-Induced Nephrotoxicity

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Background: The proximal tubule (PT) reabsorbs and concentrates filtered nephrotoxins by clathrin mediated (CME) and fluid phase mediated (FPE) endocytosis, leading to PT injury and AKI. The molecular chaperone RAP (Alpha-2-macroglobulin receptor-associated protein) a 39kDa protein inhibits LDL receptor family members ligand binding, including megalin. Our hypothesis was that RAP would inhibit megalin mediated CME, but not FPE, and reduce gentamicin nephrotoxicity.

Methods: We utilized daily injections of gentamicin (100mg/Kg, IP) in a uninephrectomy CKD model in Munich Wistar Fromter rats with a baseline serum creatinine (sCr) of 0.80 ± 0.23. Gentamicin was given with or without RAP (40mg/Kg, IV) to evaluate RAP's impact on function, sCr, 24 hr urinary creatinine clearance and proteinuria, and endocytosis, 2-photon microscopy to determine FPE i.e. 10 kDa Cascade Blue dextran, and Megalin mediated CRE, i.e. albumin, endocytosis.

Results: RAP injections markedly reduced S1 PT albumin uptake over 60 minutes (80%), dextran (67%) and gentamicin (62%) in normal rats in a rapid and fully reversible fashion. In rats treated with or without RAP, daily gentamicin treatment resulted in elevated serum Cr by day 5 (1.4 ± 0.2 vs 3.1 ± 0.4mg/dl, p<0.01) and day 6 (1.5 ± 0.5 vs 5.4 ± 0.8mg/dl, p<0.01). CrCl decreased on day 6 to 0.49 ± 0.16 ml/min vs 0.09 ± 0.07 ml/min and urinary protein increased to 488 mg/ml/100gm wt vs 2,512 mg/ml/100 gm wt in RAP treated and untreated rats, respectively.

Conclusions: These results indicate RAP treatment induced reductions of both CME and FPE PT endocytosis suggesting a link between megalin and FPE. Clinically, RAP may have direct relevance to preventing the harmful nephrotoxic effects of gentamicin treatment, and likely other nephrotoxins, especially in individuals more susceptible to aminoglycoside injury. Future studies will need to explore whether reductions in ototoxicity are also prevented.

Funding: Other NIH Support - DK 091623 and 079312

PO0434

Role of Protease-Activated Receptor 1 (PAR1) in Glomerular Filtration Barrier Integrity

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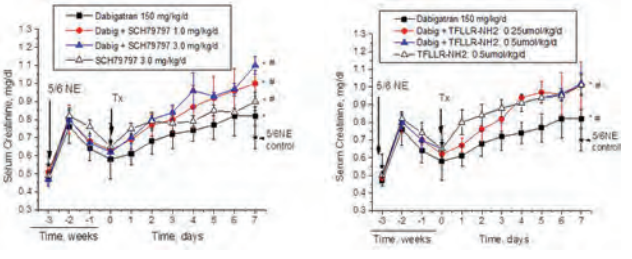
Background: Protease-activated receptors (PARs) play a significant role in the regulation of angiogenesis and fibrosis. Their role in the regulation of glomerular filtration barrier (GFB) function is incompletely elucidated. We had demonstrated that PAR1 inhibition with SCH79797 results in glomerular hemorrhage and acute kidney injury in the 5/6 nephrectomy rats (5/6NE), effects similar to those of a direct thrombin inhibitor (dabigatran) and mimic features of anticoagulant-related nephropathy in humans. The aim of the current study was to investigate potential synergistic effects of dabigatran with PAR1 inhibition or agonism in 5/6NE.

Methods: Three weeks after surgery 5/6NE rats were treated with dabigatran (150 mg/kg/day) alone or with PAR-1 inhibitor SCH79797 (1.0 mg/kg/day and 3.0 mg/kg/day) or PAR1 activation peptide, TFLLR-NH2 (0.25 mcmol/kg/day and 0.5 mcmol/kg/day). Serum creatinine (SCr), activated partial thromboplastin time (aPTT), and hematuria were measured daily; kidney morphology was evaluated at the end of the study.

Results: As expected, treatment with PAR1 modulators did not alter the anticoagulant effects of dabigatran and did not prolong aPTT when used alone. Both SCH79797 and TFLLR-NH2 aggravated increased SCr levels induced by dabigatran in a dose-depended manner in the 5/6NE. Interestingly, both PAR1 activation peptide and PAR1 inhibition increased SCr in 5/6NE when used alone (Fig 1). Neither SCH79797 nor TFLLR-NH2 significantly affected dabigatran-induced hematuria in 5/6NE. Morphologically, 5/6NE treated with dabigatran, SCH79797 and TFLLR-NH2 alone or in combination, had red blood cell casts in the tubules and acute tubular epithelial cell injury.

Conclusions: PAR1 homeostasis is necessary to maintain GFB integrity in 5/6NE. Pharmacological activation or inhibition of PAR1 results in glomerular hematuria and acute kidney injury in 5/6NE. These effects are similar to those of dabigatran-mediated thrombin inhibition in 5/6NE, suggesting that the thrombin-PAR1 signaling axis is important to GFB function.

Funding: NIDDK Support



*- p<0.05 compared to 5/6NE control

- p<0.05 compared to 5/6NE + dabigatran

PO0435

Renal GPNMB Is Highly Upregulated in Rodent Models of AKI and Is Further Elevated with Pharmacological AMPK Activation

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Background: Glycoprotein nonmetastatic melanoma B (GPNMB) is highly expressed in macrophages. GPNMB is an AMP-activated protein kinase (AMPK) up-regulated gene in whole bloods. GPNMB deficient mice fail to undergo repair and injury resolution following kidney ischemia reperfusion injury (IRI). Here we investigated GPNMB expression in the rat IRI and mouse cisplatin AKI models with or without an AMPK activator treatment. We also characterized GPNMB expression in human proximal epithelial cells, M1 and M2 macrophages.

Methods: RPTEC and HK2 cells were exposed to hypoxia for 24 h. GMCSF- or MCSF- primed human M1 or M2 macrophages were isolated from human LeukoPaks. Male SD rats were subjected to 40 min of bilateral renal ischemia. Kidneys were harvested 2 days after IRI. Male C57B mice were administered with a single injection of cisplatin. Kidneys were harvested 72 h after cisplatin injection.

Results: In human proximal epithelial HK2 and RPTEC cells, an AMPK activator treatment resulted in a dose-dependent increase of GPNMB mRNA. Significant increase of GPNMB mRNA was observed in HK2 and RPTEC cells cultured in hypoxic versus normoxic conditions. We also demonstrated that AMPK activation increased IFNγ and LPS-induced GPNMB secretion in human M2 but not M1 macrophages. After a single oral administration of an AMPK activator in normal mice or rats, a robust induction of GPNMB mRNA in the whole blood was seen starting 3 h and lasting up to 22 h. We found that GPNMB mRNA was expressed at low levels in the kidneys of normal mice or rats. GPNMB mRNA was markedly up-regulated following IRI in the kidneys at 48 h.

In a mouse cisplatin-induced AKI model, a dramatic increase of GPNMB mRNA was observed in the kidneys. Pharmacological activation of AMPK in both AKI models resulted in further increase of renal GPNMB.

Conclusions: GPNMB mRNA is highly up-regulated in the kidneys of rat IRI and mouse cisplatin AKI models and is further elevated after an AMPK activator treatment. GPNMB is a gene marker for AMPK activation in tubular epithelial cells, M2 macrophages, and whole bloods. Our results support that GPNMB could modulate macrophages polarization which may be involved in inflammation and immune response, contributing to injury and repair post AKI.

Funding: Commercial Support - Janssen Pharmaceutical Research & Development of Johnson & Johnson

PO0436

Loss of Stimulator of Interferon Genes (STING) Pathway Does Not Protect the Kidney Against Acute Injury or Inflammatory and Fibrotic Pathways Induced by Folic Acid

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Background: Acute kidney injury (AKI) greatly increases the risk for developing chronic kidney disease (CKD), but it is currently not well understood how this progression from injury to inflammation and fibrosis takes place. Recently it was discovered that with injury, damaged mitochondria in the kidney can leak mitochondrial DNA into the cytosol, where it activates the cyclic GMP-AMP synthase (cGAS) stimulator of interferon genes (STING) pathway causing inflammation and fibrosis. To explore the significance of this pathway in the setting of AKI and CKD transition we induced folic acid nephropathy in mice with no detectable STING activity and evaluated them for kidney function and inflammatory/fibrotic gene expression 7 days after administration.

Methods: 23-week-old Goldenticket (Gt)mice (no detectable STING protein due to a missense mutation) and age matched wild type (WT) littermate controls were injected with 250 mg/kg of folic acid. Seven days later plasma, urine, and kidneys were collected for analysis of plasma creatinine, blood urea nitrogen (BUN) and urinary albumin creatinine ratio (uACR). 8 mice were used for both WT and Gt vehicle groups and 11 mice were used for WT and Gt groups treated with folic acid.

Results: In WT control mice folic acid treatment significantly elevated plasma creatinine from 0.27±0.06 to 0.62±0.33mg/dl, BUN levels from 25.1±3.1 to 66.8±21.0mg/dl, and uACR more than doubled from 21.5±13.4 to 53.5±64.3ug/mg. This effect was not statistically different from what was observed in Gt mice (plasma creatinine increasing from 0.25±0.04 to 0.53±0.20mg/dl, BUN increasing from 20.9±1.9 to 54.7±21.1mg/dl, and uACR increasing from 15.9±13.8 to 140.2±313.5ug/mg with folic acid, respectively). Kidney gene expression for genes involved in fibrosis (*Tgf-β*, *Col1a1*), inflammation (*Tnf*, *Il6*, *Il1b*), and apoptosis (*Bax*, *Trp53*) were all elevated with folic acid treatment. Only *Il6* which is a direct effector gene of STING, was significantly decreased in the folic acid treated Gt mice as compared to the folic acid treated WT controls.

Conclusions: Ablation of STING did not protect kidney function, nor did it impact fibrotic or inflammatory gene expression. Our data suggest that the cGAS/STING pathway is not involved in the development of AKI and in the transition to CKD in the folic acid nephropathy model.

Funding: Commercial Support - Janssen Research & Development LLC

PO0437

Extracellular Matrix Protein 1 Organized Microenvironment Keys to Kidney Repair After AKI

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Background: In AKI, the kidney tubule is well-known as the epicenter of damages, yet little attention has been paid to changes in the microenvironment and associated repair processes. Amid this process, the extracellular matrix (ECM) is the principal organizing component for microenvironment construction and tubule repair, serving as a scaffold for remodeling. How ECM interacts with its surrounding materials to dictate the prognosis of AKI remains unclear in the field.

Methods: Kidney ischemia-reperfusion injury was employed to induce AKI in mice. *In vivo*, *in vitro*, and *ex vivo* translational experiments and quantitative proteomic analyses were performed.

Results: Quantitative proteomics revealed that extracellular matrix protein 1 (ECM-1) was the earliest activated matrix protein in ischemic AKI kidneys. Immunostaining revealed that ECM-1 was predominantly expressed in the activated kidney fibroblasts. In cultured fibroblast, knockdown ECM1 markedly repressed cell activation and proliferation, as assessed by the decreased expression of α-SMA, vimentin, PDGFR-β, and PCNA. *Ex vivo*, knockdown ECM1 in the decellularized AKI kidney scaffold directly reduced its capacities in promoting the proliferation of the seeded tubular cells. *In vivo*, loss of ECM1 caused elevated serum creatinine levels, more severe morphologic changes, and reduced inductions of α-SMA, vimentin, and PDGFR-β than the controls after AKI. By using affinity-purification mass spectrometry, we identified a vital mechanism that ECM1 could bind to an essential tubule-derived growth factor protecting against AKI, sonic hedgehog (Shh). *In vitro*, we confirmed that recombinant ECM1 promoted tubular cell proliferation and Shh expression.

Conclusions: Our finding implicated that ECM1 created a favorable microenvironment by interacting with Shh to promote AKI recovery.

Funding: NIDDK Support

PO0438

TNF Drives AKI-to-CKD Transition Downstream of Proximal Tubule EGFR

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Background: Inflammation is a key driver of fibrosis and progression of human chronic kidney disease (CKD), often caused or worsened by acute kidney injury (AKI-to-CKD transition). Sustained epidermal-growth-factor-receptor (EGFR) activation in injured proximal-tubule-cells (PTC) is strongly pro-inflammatory and has emerged as a key paradigm in AKI-to-CKD transition and CKD progression. Whether the key Type 1 inflammatory cytokine tumor-necrosis-factor (TNF) has a role in CKD progression and how TNF relates to the PTC-EGFR pathway is unknown.

Methods: We compared mice treated with control, TNF-inhibition (etanercept, TNF-scavenger), EGFR-inhibition (erlotinib, EGFR-kinase-inhibitor) or their combination in an AKI-to-CKD bilateral renal-ischemia-reperfusion model.

Results: TNF- or EGFR-inhibition did not affect initial kidney injury, but significantly overlapped in reducing kidney injury-upregulated cytokines and equally strongly reduced kidney fibrosis, while combination treatment had no additive effect, suggesting EGFR and TNF act in the same fibrosis pathway. TNF exerted its profibrotic effects downstream of PTC-EGFR, as TNF-inhibition did not affect tubular EGFR activation *in vivo*. Consistent with this, TNF-PTC-KO did not reduce inflammation or fibrosis, suggesting that PTC-derived TNF does not contribute to profibrotic PTC-EGFR activation. Kidney single-cell-RNAseq analysis identified macrophages, dendritic cells and T cells, but not PTC, as dominant TNF sources after AKI. Only EGFR-inhibition, but not TNF-inhibition significantly blocked injury-induced kidney ingress of macrophages, however, macrophage numbers where equal one month after AKI independent of treatment. Thus EGFR-inhibition reduces ingress and accumulation of TNF-producing proinflammatory and profibrotic immune cells whereas TNF-inhibition mechanistically largely acts by neutralizing their proinflammatory and profibrotic activities.

Conclusions: Our work provides mechanistic background to motivate examination of TNF pathway inhibition in human AKI or CKD.

Funding: NIDDK Support, Private Foundation Support

PO0439

Antioxidant Prevents Deleterious Heart-Kidney Cross-Talk in a Novel Experimental Model of Cardiorenal Syndrome due to Isolated Right Heart Failure

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Background: Since recognition of CRS, most studies have investigated left heart failure and CRS due to isolated RVF is under recognized. However, renal dysfunction is an independent predictor of death and hospitalization in RVF. To examine experimental models of CRS improve our understanding of the pathophysiology of RV-Kidney interaction and enable us to explore new therapeutic modalities.

Methods: In a alkaloid (ALK) injection induced CRS in rats we investigated whether antioxidant prevents deleterious interactions of RV-Kidney in CRS. Rats were treated with an antioxidant, 1 wk pre & post-ALK injection. At 3 and 4 wks post-ALK injection, serial echocardiography was performed to monitor cardiac function. RV systolic pressure (RVSP), RV hypertrophy (RVH), RV function, RV levels of superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx) and lipid peroxidation (LPX) were measured. After sacrificing animals, hearts and kidneys were removed for histopathology.

Results: At 4 weeks, ALK-induced CRS resulted in increased mortality, RVSP, RVH, and LPX in RV myocardium accompanied RVF as well as the kidney. Antioxidant enzymes activities including SOD and GSHPx were decreased in RV and the kidney. Kidney histopathology with Periodic acid-Schiff (PAS) staining demonstrated tubular epithelial denudation, a marker of ATN that was not seen at 3 weeks post-ALK injection. This excludes renal toxicity of the alkaloid. Antioxidant treatment prevents not only ALK-induced CRS and decreased oxidative stress but also increased the SOD and GSHPx levels in the RV myocardium and the kidney.

Conclusions: A reduction in oxidative stress by antioxidant may explain the prevention of ALK-induced CRS. Thus, targeting oxidative stress may lead to the development of novel therapies for CRS and antioxidants as an adjuvant therapy may be beneficial.

PO0440

Inability to Increase Fatty Acid Oxidation Worsens AKI and Impacts the Benefit of Metformin

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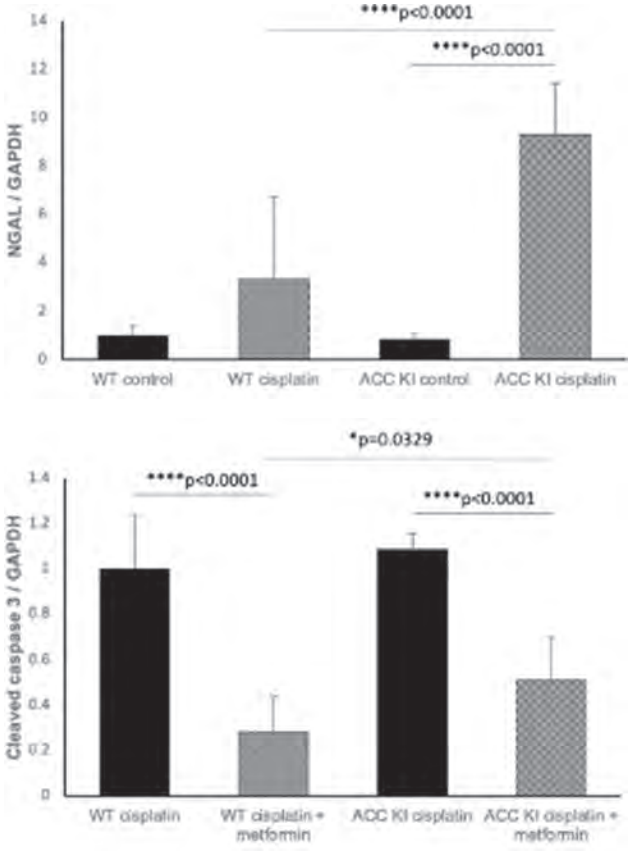
Background: Energy metabolism is critical to the pathogenesis of ischaemic acute kidney injury (AKI) - its role in nephrotoxic AKI is less understood. Fatty acid oxidation (FAO), the kidney's most important energy source, is regulated by acetyl-CoA carboxylase (ACC). Metformin increases FAO by increasing phosphorylation of ACC. We aimed to determine whether regulation of FAO affects the outcome of nephrotoxic AKI.

Methods: Cisplatin AKI was induced in ACC knockin (KI) mice, which have mutations of ACC phospho-sites that disrupt FAO regulation, and compared to wild-type (WT) controls. A primary tubular epithelial cell (TEC) culture model of cisplatin toxicity was used to further study the findings.

Results: ACC KI mice demonstrated more severe cisplatin-AKI versus WT as assessed by day 2 serum urea (ACC KI 40.5±11.6 mM vs WT 27.2±7.6 mM, p <0.005) and creatinine (ACC KI 0.09±0.03 mM vs WT 0.06±0.03 mM, p <0.05). Western blot for neutrophil gelatinase associated lipocalin (NGAL) was increased 9.3±2.1 fold in ACC KI compared to 3.3±3.4 fold in WT (p<0.0001 for ACC KI vs WT). WT and ACC KI TEC cultures exposed to cisplatin revealed increased apoptosis in ACC KI, as assessed by increased cleaved caspase-3 (cCasp3) (p<0.0001). In TECs, metformin was protective against cisplatin mediated apoptosis, however this was diminished in ACC KI cells (cCasp3 reduced 49.5%) versus WT cells (cCasp3 reduced 72%) (p=0.03 for ACC KI vs WT).

Conclusions: Severity of nephrotoxic AKI is dependent on maintaining regulation of FAO. Metformin reduces cisplatin-AKI severity by its ability to increase FAO.

Funding: Government Support - Non-U.S.



PO0441

Caloric Restriction Reduces the Pro-Inflammatory Eicosanoid 20-HETE to Protect from AKI

Karla J. Hoyer-Allo,[1,2] Martin R. Späth,[1,2] Susanne Brodesser,[2] Katrin Bohl,[2] Torsten Kubacki,[1] Katharina Kiefer,[1,2] Felix C. Koehler,[1,2] Franziska Grundmann,[1] Bernhard Schermer,[1,2] Thomas Benzing,[1,2] Volker R. Burst,[1,2] Roman-Ulrich Mueller.[1,2] *[1]Uniklinik Koln, Cologne, Germany; [2]Exzellenzcluster CECAD in der Universitat zu Koln, Koln, Germany*.

Background: Acute kidney injury (AKI) is a frequent complication in the clinical setting and associated with significant morbidity and mortality. Preconditioning with short-term caloric restriction (CR) is highly protective against kidney injury in rodent ischemia-reperfusion-injury (IRI) models, but the underlying mechanisms are unknown hampering clinical translation. The aim of this work was to further characterize possible mechanisms of protective effects of preconditioning.

Methods: 14-week-old male and female C57Bl6 wild-type mice underwent no preconditioning serving as a control group (CR) or four weeks of a calorie-restricted diet as a method of preconditioning prior to IRI. Afterwards, we compared control animals with animals after CR by phenotyping (histology, urea).

Results: We examined the molecular basis of CR-mediated protection to elucidate the principles of renal stress resistance. Analysis of an RNAseq dataset after CR identified *Cyp4a12a* – a cytochrome exclusively expressed in male mice - to be strongly downregulated after CR. Renal IRI robustly induced AKI in male mice and damage could be markedly attenuated by pre-treatment with CR. In females, the damage was significantly less pronounced and preconditioning with CR had only little effect. Tissue concentrations of the metabolic product of *Cyp4a12a*, 20-Hydroxyeicosatetraenoic acid (20-HETE), were significantly reduced by CR. Conversely, intraperitoneal supplementation of 20-HETE in preconditioned males partly abrogated the protective potential of CR.

Conclusions: Our findings provide an insight into the mechanisms underlying renal organ protection and implicate 20-HETE as a target of CR-based preconditioning. Understanding the mediators of preconditioning is an important pre-requisite for moving towards translation to the clinical setting.

Funding: Government Support - Non-U.S.

PO0442

The MLL1/WDR5 Complex Contributes to Cisplatin-Induced Renal Epithelial Death by Promoting p53-mediated E-Cadherin Repression

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Background: The mixed-lineage leukemia 1 (MLL1)/WD-40 repeat protein 5 (WDR5) complex is a methyltransferase deemed a positive regulator of histone H3 lysine 4 trimethylation (H3K4me3) and functions as an oncogenic factor in many cancer types. The role of the MLL1/WDR5 complex in acute kidney injury (AKI) and renal epithelial cell death is still unclear. In this study, we investigated the role and mechanism of this complex in the apoptosis of renal epithelial cells following cisplatin exposure.

Methods: Cultured mouse kidney proximal tubular (TKPT) cells were exposed to cisplatin in the presence or absence of MM102, a MLL1/WDR5 protein–protein interaction inhibitor or small interfering RNAs (siRNA) specific targeting MLL1 or WDR5.

Results: Expression of MLL1, WDR5 and H3K4me3 as well as phospho-p53 and cleaved caspase 3 were increased whereas that of E-cadherin was decreased in cultured TKPT cells exposed to cisplatin in a time dependent manner. Inhibition of the MLL1/WDR5 complex with MM102 or siRNA-mediated silencing MLL1 or WDR5 attenuated cisplatin induced cleavage of caspase 3 and cell death, which was coincident with downregulation of p-p53 and preservation of E-cadherin expression. Inhibition of p53 by pifithrin-α also alleviated cisplatin-induced cell death and restored E-cadherin expression in TKPT cells with or without MM102 treatment. In contrast, activation of p53 by Nutlin potentiated TKPT cell death and E-cadherin repression. Moreover, siRNA mediated silencing of E-cadherin attenuated the protective effect of MM102 following cisplatin treatment while expression of p-p53 was not affected. Finally, we found that pharmacological inhibition of MLL1/WDR5 reduced cisplatin-induced phosphorylation of ataxia-telangiectasia mutated protein, ataxia telangiectasia and Rad3-related protein, checkpoint kinase 1 (Chk1), checkpoint kinase 2 (Chk2) and γ-H2AX, which are activated in response to DNA damage and associated with p53 transcriptional activation.

Conclusions: These data suggest that the MLL1/WDR5 complex may contribute to cisplatin-induced apoptosis of renal tubular epithelial cells by promoting p53-mediated E-cadherin repression following DNA damage. Targeting the MLL1/WDR5 complex may have a therapeutic potential for the treatment of cisplatin-induced AKI.

Funding: NIDDK Support

PO0443

Comparison of Inflammatory Responses in Sepsis-Induced AKI Mouse Models and Response to Dexamethasone

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Background: AKI occurs in the majority of patients with severe sepsis and contributes to high morbidity and mortality. Despite the frequency of AKI, the underlying mechanisms of renal injury during sepsis are not fully understood, and no approved therapies to prevent or reverse this condition. Systemic and local inflammatory responses play a large role in the development of sepsis induced acute kidney injury (S-AKI).

Methods: To develop novel treatments for patients with S-AKI, animal models of polymicrobial sepsis are used; the most widely reported models being cecal ligation puncture (CLP) and cecal slurry (CS). We compared the acute (24h) renal function and inflammatory response of these two models, as well as the ability of dexamethasone (dexa) to prevent the development of S-AKI.

Results: CLP significantly reduced renal function, with increased plasma creatinine (0.18±0.11 mg/dL), blood urea nitrogen (BUN, 81.11±12.88 mg/dL), and increased inflammatory markers IL-6 (127±73 ng/mL), TNF-α (176±33 pg/mL), and IL-1β (164±141 pg/mL) compared to sham animals. Dexa (8 mg/kg) significantly decreased BUN but did not significantly decrease plasma creatinine or the inflammatory markers. Dexa (2.5mg/kg) had no significant effects on renal functional markers or circulating cytokines. CS significantly increased plasma creatinine (0.7±0.1 mg/dL), BUN (103±20 mg/dL), cystatin C (2443±947 ng/mL), IL-6 (124±63 ng/mL), TNF-α (134±39 pg/mL) compared to basal levels. Dexa treatment (2.5 mg/kg) significantly decreased creatinine, cystatin C, IL-6, TNF-α, and IL-1β. In this study, we have shown the CS model elicits a more robust increase in AKI and inflammatory measurements than the CLP model, with reduced variability. It also responds to a greater extent to the same dose of dexa. Our results suggest that the CS model may be provide a better window with less variability compared to the CLP model, to test novel treatments for S-AKI.

Conclusions: We have shown the CS model elicits a more robust increase in AKI and inflammatory measurements than the CLP model, with reduced variability. It also responds to a greater extent to the same dose of dexamethasone. Our results suggest that the CS model may be provide a better window with less variability compared to the CLP model, to test novel treatments for S-AKI.

PO0444

Prohibitin Ligand FL3 Protects Renal Proximal Tubular Cells Against ATP-Depletion-Induced Injury

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Background: FL3 is a synthesized ligand of prohibitins, a family of proteins located on and important for mitochondrial inner membrane. FL3 has been reported to protect neurons and cardiomyocytes by regulating mitochondrial function. Whether FL3 can protect kidney cells against cell stress remains unknown. This study aims to evaluate the effect of FL3 on ATP-depletion-induced cell death in renal proximal tubular cells (RPTCs).

Methods: RPTCs were pre-treated with 50nM FL3 for 3 hours and incubated with 10mM azide in glucose-free Krebs-Ringer bicarbonate solution for 3 hours to induce ATP depletion. The cells were then returned to a normal cultured medium for recovery. Cells were also exposed to the same concentration of FL3 throughout the ATP depletion and recovery phases. Mitochondrial changes including mitochondrial fragmentation, Bax translocation, cytochrome C release, prohibitin complex breakdown, OPA1 and OMA1 proteolysis were examined immediately after azide treatment; whereas apoptosis events including apoptotic morphology and caspase activation were examined after 2 hours of recovery.

Results: RPTCs with azide-induced ATP depletion developed apoptotic morphology, caspase 3 activation and PARP cleavage, which were suppressed by FL3. Mitochondrial fragmentation and membrane leakage of cytochrome C were increased in RPTCs during ATP depletion. FL3 suppressed mitochondrial fragmentation and inhibited mitochondrial injury. Under cell stress, the large prohibitin ring complex was disrupted to medium and small complexes, releasing OMA1 to cleave the inner membrane fusion protein OPA1. FL3 treatment decreased both the small prohibitin complex and the activation of OMA1. FL3 also partially prevented the degradation of the long isoforms of OPA1 during ATP depletion.

Conclusions: FL3 can protect against ATP-depletion-induced injury in renal tubular cells, likely through the regulation of mitochondrial dynamics.

Funding: NIDDK Support, Veterans Affairs Support

PO0445

Mechanisms of Aristolochic Acid I (AAI)-Induced Proximal Tubule Cell Injury

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Background: Aristolochic acids (AAs) are naturally occurring polyaromatic nitrogen compounds extracted from certain plants that were used to treat various diseases for centuries until their nephrotoxicity and carcinogenicity began to be recognized. Aristolochic acid I (AAI) is potentially one of the main pathogenic compounds and has been demonstrated to have nephrotoxic, carcinogenic, and mutagenic effects. Previous studies have indicated that AAI acts mainly on proximal renal tubular epithelial cells however investigation into the mechanisms of AAI-induced proximal tubule cell damage are still warranted.

Methods: Human kidney proximal tubule cells (PTCs; HK2 cell line) were exposed to AA1 at different time/dose conditions *in vitro*. Cell proliferation, ROS generation, NO production, m-RNA/ protein expressions and mitochondrial dysfunction was checked in HK2 cells after treating them with AA1.

Results: We found that AA1 treatment decreased HK2 cell proliferation significantly at 24hrs with 40μM concentration. AA1 exposure increased ROS generation and decreased NO production significantly. Furthermore, gene/ protein expression studies demonstrated activation of innate immunity (TLRs 2,3, 4 and 9, HMGB1), inflammatory (TNFA, IL6, IL18 and TGFB) and kidney injury (LCN2, KIM1) markers. In addition, our results indicated AA1 induced epithelial-mesenchymal transition (EMT) as well as mitochondrial dysfunction in HK2 cells.

Conclusions: AA1 treatment caused injury to proximal tubule cells (HK2) through ROS-HMGB1/mt DNA mediated TLRs activation and inflammatory response.

PO0446

AMPK Activation Alleviates TNF-α Induced Human Umbilical Vein Endothelial Cell Monolayer Permeability Increase

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Background: The abnormal structure and function of the renal microvasculature contributes to acute kidney injury (AKI) pathophysiology by reducing regional blood flow especially in the outer medulla. AKI results in marked increases in local and systemic cytokine levels. IL-1α, IL-6, and TNF-α orchestrate various inflammatory reactions increasing endothelial permeability due to loss of endothelial monolayer and alteration of endothelial cell-cell junctions. AMP-activated protein kinase (AMPK) has been reported to play a protective role in vascular function, mainly through eNOS phosphorylation, inhibition of ROS formation and stimulating mitochondrial biogenesis. In addition, AMPK has been reported to regulate the assembly and disassembly of epithelial tight junction. **Objectives:** Our aims were to investigate whether a direct small molecule AMPK activator could preserve endothelial cell monolayer integrity when challenged by TNF-α treatment, and to investigate the potential mechanisms.

Methods: Structural and functional integrity of human umbilical vascular endothelial cells (HUVECs) monolayer was evaluated by measuring permeability, and caspase 3/7 activity was measured to reflect apoptotic cell death. TNF-α was used to induce injury. AMPK activation was confirmed by measurement of pACC. Data were analyzed using 1-way ANOVA.

Results: 10, 30, and 100 ng/ml TNF-α significantly induced HUVEC monolayer permeability after 24 hr treatment, with 11.2-, 8.1-, and 8.1-fold increases, respectively. Direct allosteric AMPK activator (CpdA) protected against permeability induced by 24 hr of 100 ng/ml TNF-α treatment, with a maximum reduction of 57.6% permeability at 3 mM. SB 203580, a p38 MAPK inhibitor, decreased the permeability by about 62.5%. 100 ng/ml TNF-α treatment for 24 hr increased apoptosis by 2.8-fold. CpdA treatment significantly protected cells from apoptosis in a dose dependent manner. TNF-α treatment for 6 hr increased HUVEC permeability (~6.4-fold), which was reduced (40.6% reduction) by CpdA treatment. Cells incubated with CpdA maintained their shape and cell-cell contacts and showed less intercellular gaps when compared to those treated with DMSO vehicle control.

Conclusions: AMPK activation alleviated endothelial leakage, potentially via decreasing apoptosis and maintaining cell-cell contacts. Our data supports AMPK activation as a novel therapeutic approach for AKI.

Funding: Commercial Support - Johnson & Johnson

PO0447

SGLT-2 Inhibitor Dapagliflozin Does Not Improve Severe Ischemia-Reperfusion-Induced AKI

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Background: Acute kidney injury (AKI) is defined by a rapid decline in the kidney function, occurs in approximately 5-20% hospitalized patients and is associated with high mortality. Renal ischemia-reperfusion (IR) injury is a leading cause of AKI. Despite intensive research and progress in understanding the pathophysiological mechanisms, IR-AKI remains a critical problem without any effective treatment available. Dapagliflozin is a novel antidiabetic drug from the class of sodium-glucose cotransporter 2 (SGLT2) inhibitors that reduce glucose reabsorption in renal proximal tubules. SGLT2 inhibitors have been recently suggested to cause protection even in renal injury conditions beyond diabetes, such as AKI. In our work, we aimed to test the effectivity of dapagliflozin in decreasing kidney injury in a mouse model of severe IR-AKI.

Methods: We developed a mouse model of severe IR-AKI. C57BL/6J males underwent 35 minutes of renal ischemia by bilateral clamping of renal pedicles followed by 24h of reperfusion. The levels of blood urea nitrogen (BUN) and plasma creatinine at 24h after reperfusion were high but all mice undergoing IR surgery survived. Histological analysis showed severe tubular injury in the outer stripe of outer medulla. Mice undergoing IR surgery were divided into groups and received either no treatment, 1 mg/kg dapagliflozin, 10 mg/kg dapagliflozin or vehicle only administered by oral gavage 24h and 1h before the onset of ischemia. BUN and other parameters of kidney function were assessed 24h after reperfusion.

Results: In our preliminary data oral administration of dapagliflozin did not prevent kidney function decline in the model of severe IR-AKI. The BUN levels in plasma at 24h after reperfusion were not significantly different in groups of mice undergoing IR surgery. This is in contrast to previously published study[1] where, however, less severe model of IR-AKI with 27 minutes of renal ischemia was used.

Conclusions: Dapagliflozin did not improve severe IR-AKI. We hypothesize that dapagliflozin may be effective in improving less severe kidney injury, however, lacks effectivity in more severe cases of AKI. In our future studies, we would like to test the ability of dapagliflozin to prevent kidney injury at different stages of IR-AKI. [1]Chang et al. *PLoS One*. 2016;11(7):e0158810.

Funding: Other U.S. Government Support

PO0448

Establishment and Evaluation of a Primary Human Renal Tubular 3D Spheroid Model for AKI and CKD

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Background: The proximal tubule of the nephron is a prime site for tubular injury due to its high energy requirements and its dependence on oxidative metabolism to meet its energy needs. Our understanding of the central role of mitochondrial abnormalities and alterations in metabolism in both acute and chronic kidney injury has steadily improved with potential targets to improve mitochondrial dysfunction that occurs in AKI and in AKI to CKD transition. Two-dimensional (2D) monolayer cultures and rodent animal models are unable to fully recapitulate clinical drug response, hence 3D models are being developed to provide a physiologically relevant condition.

Methods: Here, we developed a primary human renal tubular 3D spheroid culture and established a cisplatin-injury model for therapeutic target evaluation. Human primary renal tubular cells (RPTEC) seeded in ULA plates showed aggregation after 4 hours and formed initial spheroids after 4 days and the primary cells can be cultured over 5 weeks without major physiological changes.

Results: In 3D setting, gene expression of tubular markers was significantly induced/ restored close to the human tissue level comparing to 2D culture (*AQP1, OAT, LRP2, PEPT2, SLC12A1*, etc.) suggesting a more physiologically relevant condition. As NAD+ level is a critical factor to maintain mitochondria functionality in tubular cells, we evaluated genes involved in *de novo* NAD synthesis pathway and observed increased

expression in 3D- vs. 2D culture (*AFMID, KMO, KYNU, HAAO, ACMSD, NMNATs*, etc.). Moreover, since TGF-β is activated in AKI and is involved in AKI to CKD transition, we confirmed that TGF-β treatment repressed *de novo* NAD pathway gene expression, suggesting a possible link to the decrease of *de novo* NAD+ in the cells producing TGF-β. Lastly, In our cisplatin-induced tubular cell injury model in 3D spheroid, cisplatin induces the dose-dependent increase of cell apoptosis associated with dose-dependent reduction of total cellular NAD+ and GSH.

Conclusions: Taken together, our 3D primary human spheroid model restored key marker gene expression and recapitulated in vivo response to the TGF-β treatment and cisplatin-induced injury, which provide a physiological and pathophysiological relevant tool and translational model to enable the quick screening and evaluation of therapeutic targets for AKI and CKD.

PO0449

Succinylation of Metabolic Enzymes Protects Against AKI

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Background: Acute Kidney Injury (AKI) is an increasingly prevalent outcome of hospitalizations, affecting up to 50% of ICU patients in America. Kidney function depends on the metabolic activity of Renal Proximal Tubule Epithelial Cells (RPTECs). To understand AKI pathology, we focused on a class of proteins that affect posttranslational modifications of major proteins, and especially the deacylase Sirtuin 5 which is highly expressed in RPTECs. Our previous studies indicate that knockout of this protein has a protective role in RPTECs post AKI which presents the exciting possibility of clinical translation in preventing or ameliorating any long-term damage from AKI.

Methods: Through independent pathway analysis and mass spectrometry we attributed the major protective effect of Sirt5 knockout to be succinylation of key mitochondrial and peroxisomal proteins, leading to a metabolic shift from mitochondrial Fatty Acid Oxidation (FAO) to peroxisomal-dependent FAO. To test this hypothesis in a less invasive manner than genetic knockdown, we used the mitochondrial FAO inhibitor Etomoxir and the peroxisomal stimulator Benzifibrate. In both cases we found a significant reduction in the kidney injury marker NGAL after ischemia-like injury.

Results: We postulate that the switch to more peroxisomal-mediated fatty acid oxidation is protective due to a decrease in the Reactive Oxygen Species. To promote this shift, we investigated the effects of supplementing the mouse diet with medium-chain fatty acids (10% dodecanedioic acid) pre or post ischemia-reperfusion-injury (IRI). Mass spectrometry of the succinylation signature of murine kidneys after diet treatment was similar to that of the Sirt5 KO mice, suggesting a functional phenocopy. We have preliminary evidence that there is less oxidative stress when the dodecanedioic acid diet is administered pre- or post-injury and there is less overall damage to the proximal tubule epithelia.

Conclusions: The data from these experiments suggest a simple but effective diet treatment could reduce the burden of AKI cases.

Funding: NIDDK Support

PO0450

Efficacy and Safety of Roxadustat in Patients with Anemia of Dialysis-Dependent CKD (DD-CKD) Treated Continuously for ≥3 Years

Chuan-Ming Hao,[1] Neera K. Dahl,[2] Stefan Tham,[3] Marcelo Orias,[2] Roberto Pecoits-Filho.[4] *[1]Huashan Hospital Fudan University, Shanghai, China; [2]Yale University School of Medicine, New Haven, CT; [3]Clinical Research, AstraZeneca, Gothenburg, Sweden; [4]Arbor Research Collaborative for Health, Ann Arbor, MI.*

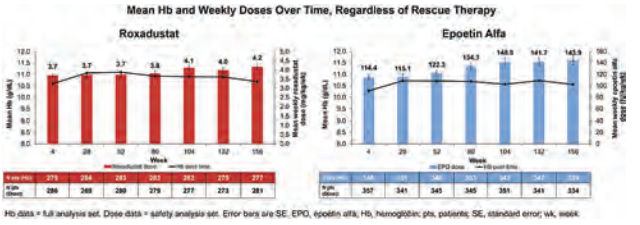
Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is in development in the US for chronic treatment of anemia of CKD. This pooled *post hoc* analysis explored outcomes in DD-CKD patients (pts) treated with roxadustat for ≥3 years (y).

Methods: Pts were randomized to open-label roxadustat (n=1943) or epoetin alfa (EPO; n=1947) for up to 4y in 3 Phase 3 DD-CKD trials (ROCKIES, SIERRAS, HIMALAYAS). Intravenous iron was given per local care for EPO and limited to need for roxadustat. Data were analyzed in pts treated continuously for ≥3y, regardless of rescue therapy use. P values are exploratory. Adverse events (AEs) were assessed.

Results: Overall, 288 roxadustat and 360 EPO pts were treated for ≥3y; of these, 95% and 94% completed treatment. Baseline (BL) values for roxadustat vs EPO were generally balanced: mean age 55 vs 57y, mean hemoglobin (Hb) 9.8 vs 9.7 g/dL, dialysis modality was predominantly hemodialysis (94% vs 93% pts), median dialysis vintage 21.9 vs 17.4 months. Over Weeks (wk) 28–52, change in Hb from BL was greater with roxadustat vs EPO (+1.3 vs +1.0 g/dL; P<0.001) and proportion of pts with Hb ≥10 g/dL was higher (95% vs 85%). To wk 156, roxadustat maintained higher Hb vs EPO, with 11% increase in mean roxadustat weekly dose from wk 25–28 vs 20% increase in mean EPO weekly dose (Figure). Need for red blood cell (RBC) transfusion appeared less with roxadustat vs EPO (11% vs 16% pts). Serious AE rates with roxadustat vs EPO were 18.0 vs 16.9 per 100 pt-exposure years, respectively.

Conclusions: In DD-CKD pts who remained on treatment for ≥3y, Hb stability with roxadustat was achieved with minimal dose change and less need for RBC transfusion vs EPO. Safety was comparable with roxadustat vs EPO.

Funding: Commercial Support - AstraZeneca, Astellas, and Fibrogen



PO0451

Efficacy and Safety of Roxadustat in Patients with Anemia of Non-Dialysis-Dependent CKD (NDD-CKD) Treated Continuously for ≥2 Years

Roberto Pecoits-Filho,[1] Neera K. Dahl,[2] Stefan Tham,[3] Marcelo Orias,[2] Chuan-Ming Hao.[4] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Yale University School of Medicine, New Haven, CT; [3]Clinical Research, AstraZeneca, Gothenburg, Sweden; [4]Huashan Hospital Fudan University, Shanghai, China.*

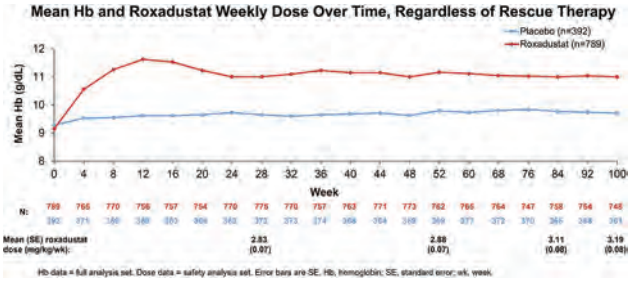
Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, is in development in the US for chronic treatment of anemia of CKD. This pooled *post hoc* analysis explored outcomes in NDD-CKD patients (pts) treated with roxadustat for ≥2 years (y).

Methods: Pts were randomized to double-blind roxadustat (n=2391) or placebo (PBO; n=1886) for up to 4y in 3 Phase 3 NDD-CKD trials (OLYMPUS, ALPS, ANDES). Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy. Data were analyzed in pts treated for ≥2y, regardless of rescue therapy use. P values are exploratory. Adverse events (AEs) were assessed.

Results: Overall, 789 roxadustat and 392 PBO pts were treated for ≥2y; of these, 87% and 85% completed treatment. Baseline (BL) values for roxadustat vs PBO were not balanced due to more discontinuation in PBO prior to 2y: mean hemoglobin (Hb) 9.2 vs 9.3 g/dL, 59% vs 78% of pts had hypertension, 56% vs 60% of pts had diabetes, mean eGFR 21 vs 24 mL/min/1.73 m^2. Change from BL Hb was greater with roxadustat vs PBO over Weeks (wk) 28–52 (+2.0 vs +0.5 g/dL; P<0.001), with differences seen from wk 4, and proportion of pts with Hb ≥10 g/dL over wk 28–52 was higher (95% vs 32%). Roxadustat maintained Hb ~11 g/dL to wk 100 (Figure). Mean roxadustat weekly dose increased by 11% from wk 25–28 to wk 97–100. Rescue therapy need (22% vs 34% pts), including red blood cell (RBC) transfusion (13% vs 18% pts), was less with roxadustat vs PBO; IV iron use was 9% for both. Serious AEs rates with roxadustat vs PBO were 20 vs 17 per 100 pt-exposure years, respectively.

Conclusions: In NDD-CKD pts who remained on treatment for ≥2y, roxadustat maintained Hb ~11 g/dL with minimal dose change and less need for rescue therapy, including RBC transfusion, than PBO.

Funding: Commercial Support - AstraZenecaAstraZeneca, Astellas, and Fibrogen



PO0452

Number Needed to Treat with Roxadustat to Avoid One Transfusion or Intravenous Iron Administration in Anemia of Non-Dialysis-Dependent CKD

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Background: Red blood cell (RBC) transfusion is the most common anemia treatment for non-dialysis-dependent chronic kidney disease (NDD CKD), but risks alloimmunization, which may delay or preclude kidney transplantation, and is associated with adverse events. Intravenous (IV) iron is recommended for poor response to oral iron, but requires travel to clinics. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor for anemia. It stimulates a coordinated erythropoietic response, increasing plasma endogenous erythropoietin levels and reducing hepcidin.

Methods: Data were pooled from 3 pivotal, randomized, phase 3 studies of roxadustat vs placebo NDD CKD populations. A phase 3 study of roxadustat vs darbepoetin alfa in NDD CKD was also analyzed. The number of patients needed to treat (NNT) with roxadustat for 1 year to avoid 1 RBC transfusion was calculated by taking the reciprocal

after subtracting the RBC transfusion annualized event rate in the roxadustat arm from the event rate in the placebo arm. The same analysis was done for RBC transfusion and IV iron incidence rates.

Results: Treating 4 patients with roxadustat vs placebo for 1 year is estimated to avoid 1 RBC transfusion. Treating 7 patients with roxadustat vs placebo for 1 year is estimated to avoid 1 patient needing 1 RBC transfusion, and treating 37 patients with roxadustat vs placebo is estimated to avoid 1 patient needing IV iron (Table). Rates of RBC transfusion (hazard ratio [HR]: 1.3 [95% CI 0.79, 2.11; p=0.3]) were comparable between roxadustat and darbepoetin alfa in the additional analyzed study, and a lower proportion of patients on roxadustat vs darbepoetin alfa required IV iron therapy use (HR: 0.45 [95% CI: 0.26, 0.78; p=0.004]).

Conclusions: In the pooled NDD CKD population, the NNTs to prevent RBC transfusion were low and indicative of patient benefit. Roxadustat reduced rates of RBC transfusions and IV iron use compared to placebo.

Funding: Commercial Support - FibroGen, Inc. and AstraZeneca

Table: Number needed to treat with roxadustat vs. placebo to avoid 1 RBC transfusion, 1 patient needing an RBC transfusion, and 1 patient needing IV iron

	Roxadustat arm rate	Placebo arm rate	Absolute risk reduction (ARR)	Relative risk reduction (RRR), %	1/ARR
RBC transfusion event (per 100 PFY)	15.5	45.5	30.0	65.9	3.3
RBC transfusion incidence (per 100 PEY)	6.1	20.4	14.3	70.1	7.0
IV iron usage, % patients	2.1	4.8	2.7	56.3	37.0

PEY: patient-exposure years, PFY: patient follow-up years

PO0453

Effects of Roxadustat in Patients with Dialysis-Dependent CKD (DD-CKD) Across All Baseline (BL) Hemoglobin (Hb) Values

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, increases Hb by stimulating endogenous erythropoietin synthesis and improving iron bioavailability. This pooled *post hoc* analysis evaluated the efficacy and safety of roxadustat in patients (pts) with DD-CKD across all available BL Hb values.

Methods: Pts were randomized to open-label roxadustat (n=1943) or epoetin alfa (EPO; n=1947) in 3 Phase 3 DD-CKD trials (ROCKIES, SIERRAS, HIMALAYAS). Across trials, Hb eligibility criteria were <10 or 8.5–12 g/dL at final screening. EPO and intravenous (IV) iron were given per local care for the EPO group; for roxadustat, dose was titrated to Hb 11±1 g/dL and IV iron limited to need. Pooled subgroup analyses were performed by selected Hb values (g/dL: <8.0, ≥8.0–<9.0, ≥9.0–<10, ≥10.0) at BL (mean of up to 4 pre-randomization values) regardless of study rescue therapy use. Adverse events (AEs) were assessed.

Results: Pt study discontinuation rates were similar across BL Hb ranges (Table). Pts with lower BL Hb had less time on dialysis (Table), suggesting pts incident to dialysis. At BL, pts with Hb <9 g/dL had the lowest weekly ESA doses, but by Weeks (wk) 49–52 their weekly ESA doses were highest (Table). Pts with BL Hb <8 g/dL received on average ~1 mg/kg/wk more roxadustat dose at wk 49–52 than pts with BL Hb ≥10 g/dL (Table). Rates of serious AEs (SAEs) and treatment-emergent SAEs per pt-exposure year were comparable for roxadustat vs EPO and appeared more common in pts with higher BL Hb (Table).

Conclusions: DD-CKD pts with more severe anemia at BL required more IV iron during the study. Roxadustat was effective and had comparable tolerability to EPO across all BL Hb studied.

Funding: Commercial Support - AstraZeneca, Astellas, and Fibrogen

Endpoint	Hb <8.0 g/dL		Hb ≥8.0–<9.0 g/dL		Hb ≥9.0–<10.0 g/dL		Hb ≥10.0 g/dL	
	Roxa	EPO	Roxa	EPO	Roxa	EPO	Roxa	EPO
ITT analysis set, n	**233**	**235**	**328**	**332**	**522**	**491**	**860**	**889**
Discontinued study, % pts	37	32	38	34	41	32	44	35
Dialysis vintage, median, months	2.6	2.7	2.8	2.7	6.3	6.6	29.6	30.2
Full analysis set, n	**232**	**233**	**327**	**325**	**520**	**487**	**850**	**883**
Δ Hb (wk 28–52), g/dL*	3.5 (3.3, 3.6)	3.2 (3.1, 3.4)	2.1 (1.9, 2.4)	1.8 (1.5, 2.0)	1.3 (1.2, 1.4)	1.1 (1.0, 1.2)	0.3 (0.1, 0.5)	-0.1 (-0.3, 0.1)
Hb ≥10 g/dL (wk 28–52), % pts	65	62	66	69	69	68	73	73
IV iron to wk 52, % pts	47	61	39	54	35	45	27	31
RBC transfusion to wk 52, % pts	7	6	3	5	3	6	5	7
Safety analysis set, n	**233**	**235**	**328**	**329**	**522**	**490**	**857**	**886**
ESA dose/wk, median, IU/kg/wk BL Wk 49–52	 65.6 -	 66.7 132.2	 60.0 -	 58.4 107.1	 69.5 -	 75.0 104.2	 70.0 -	 70.3 81.6
Roxa dose/wk (wk 49–52), mean, mg/kg/wk	4.3	-	3.6	-	3.8	-	3.4	-
SAE % pts IR (100 PEY)	 48 28.4	 45 23.5	 51 31.1	 49 27.0	 60 36.3	 59 31.5	 67 37.5	 64 32.0
TESAE % pts IR (100 PEY)	 45 26.6	 45 23.3	 48 29.1	 46 25.0	 55 33.3	 57 30.4	 62 34.9	 61 30.2

ITT = all randomized pts. Full analysis set = all randomized and treated pts with ≥1 Hb measurement. Safety analysis set = all randomized and treated pts. *Data are least-squares mean change (95% confidence intervals). BL, baseline; EPO, epoetin alfa; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IR, incidence rate; IV, intravenous; PEY, patient-exposure years; RBC, red blood cell; Roxa, roxadustat; SAE, serious adverse event; TESAE, treatment-emergent serious adverse event; wk, week.

PO0454

Effects of Roxadustat in Patients with Non-Dialysis-Dependent CKD (NDD-CKD) Across All Baseline (BL) Hemoglobin (Hb) Values

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Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, increases Hb by stimulating endogenous erythropoietin synthesis and improving iron bioavailability. This pooled *post hoc* analysis evaluated the effects of roxadustat in patients (pts) with NDD-CKD across all available BL Hb values.

Methods: Pts were randomized to double-blind roxadustat (n=2391) or placebo (PBO; n=1886) in 3 Phase 3 NDD-CKD trials (OLYMPUS, ALPS, ANDES). Hb eligibility criteria were ≤10 g/dL at final screening, study drug dose was titrated to Hb 11±1 g/dL. Oral iron was administered without restriction; intravenous (IV) iron was limited to rescue therapy (IV iron, red blood cell [RBC] transfusion or ESA). Pooled subgroup analyses were performed by selected Hb values (g/dL: <8.0, ≥8.0–<9.0, ≥9.0–<10, ≥10.0) at BL (mean of up to 4 pre-randomization values) regardless of study rescue therapy use. Adverse events (AEs) were assessed.

Results: Pts with lower BL Hb had higher study discontinuation rates and lower BL eGFR (Table). Across BL Hb ranges over Weeks (wk) 28–52, BL change in Hb and proportion of pts with Hb ≥10 g/dL were greater with roxadustat vs PBO (Table). Pts with BL Hb <8 g/dL were treated with ~2 mg/kg/wk more mean roxadustat dose at wk 49–52 than pts with BL Hb ≥10 g/dL (Table). IV iron or RBC transfusion need was less with roxadustat vs PBO and with higher BL Hb (Table). Lower rates of serious AEs (SAEs) and treatment-emergent SAEs per pt-exposure year were observed with increased BL Hb (Table).

Conclusions: NDD-CKD pts with more severe anemia had worse kidney function, required more treatment including RBC transfusion and experienced more SAEs than pts with less severe anemia. Roxadustat improved anemia vs PBO across all BL Hb studied.

Funding: Commercial Support - AstraZeneca, Astellas, and Fibrogen

Endpoint	Hb <8.0 g/dL		Hb ≥8.0–<9.0 g/dL		Hb ≥9.0–<10.0 g/dL		Hb ≥10.0 g/dL	
	Roxa	PBO	Roxa	PBO	Roxa	PBO	Roxa	PBO
ITT analysis set, n	**204**	**164**	**653**	**536**	**1421**	**1079**	**113**	**107**
Discontinued study, % pts	53	74	42	65	35	55	26	53
BL eGFR, mean, mL/min/1.73 m²	13.8	13.4	17.1	17.7	21.3	21.8	25.3	24.4
Full analysis set, n	**199**	**162**	**649**	**530**	**1410**	**1069**	**110**	**104**
Δ Hb (wk 28–52), g/dL*	3.3 (3.1, 3.5)	0.9 (0.6, 1.1)	2.3 (2.3, 2.4)	0.3 (0.2, 0.4)	1.6 (1.6, 1.7)	0.1 (0.0, 0.2)	1.2 (1.0, 1.3)	0.1 (-0.1, 0.3)
Hb ≥10 g/dL (wk 28–52), % pts	58	4	71	11	79	22	86	40
IV iron to wk 52, % pts	3	5	2	7	2	4	0	5
RBC transfusion to wk 52, % pts	14	34	5	18	4	8	2	7
Safety analysis set, n	**204**	**164**	**653**	**535**	**1418**	**1078**	**111**	**107**
Dose/wk (wk 49–52), mean, mg/kg/wk	4.2	-	3.5	-	2.7	-	2.3	-
SAE†								
% pts	71	68	64	57	54	51	40	42
IR (100 PEY)	51.0	82.3	40.6	53.0	32.4	37.7	23.6	29.8
TESAE								
% pts	68	57	61	44	51	44	38	38
IR (100 PEY)	48.9	69.0	39.0	41.2	30.7	32.4	22.5	27.1

ITT = all randomized pts. Full analysis set = all randomized and treated pts with ≥1 Hb measurement. Safety analysis set = all randomized and treated pts. *Data are least-squares mean change (95% confidence intervals). †ITT analysis set. BL, baseline; Hb, hemoglobin; IR, incidence rate; IV, intravenous; PBO, placebo; PEY, patient-exposure years; pts, patients; RBC, red blood cell; Roxa, roxadustat; SAE, serious adverse event; TESAE, treatment-emergent serious adverse event; wk, week.

PO0455

Roxadustat in Elderly Patients with Anemia of CKD

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Background: Elderly patients with anemia of chronic kidney disease (CKD) typically have several comorbidities requiring polypharmacy, but slower drug metabolism than younger patients. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that promotes coordinated erythropoiesis and increased iron availability. We explored roxadustat treatment in elderly (≥65 years) vs younger (<65 years) patients in dialysis-dependent-(DD) and non-dialysis-dependent-(NDD) CKD populations.

Methods: Data were pooled from pivotal phase 3 studies of roxadustat vs placebo (stage 3-5 NDD-CKD) and vs epoetin alfa (DD-CKD). Data were analyzed for patients <65 and ≥65 years old. The primary endpoint in the overall trials was mean change from baseline (CFB) in hemoglobin (Hb), weeks 28-52, regardless of rescue therapy. Least square mean difference (LSMD) was determined between treatments. Secondary endpoints were transfusion rate per 100 patient-exposure years (NDD and DD) and change in mean IV iron use (DD). Adverse events were monitored during treatment + 28 days post treatment (NDD and DD).

Results: In NDD (N=4277) and DD (N=3590) populations, the majority were female (NDD) or male (DD) (Table). Baseline Hb levels were higher in elderly vs younger patients (Table). Age did not affect improvements in Hb, but mean CFB was greater in elderly vs younger in DD and NDD patients (Table). Transfusion rates were lower in younger vs elderly DD patients and in elderly vs younger NDD patients (Table). Trends in mean IV iron use were lower with roxadustat vs epoetin alfa and similar among age groups (Table). Roxadustat was well tolerated, regardless of age (Table).

Conclusions: Roxadustat was effective and well tolerated, regardless of age, in patients with anemia of CKD.

Funding: Commercial Support - FibroGen, Inc. and AstraZeneca

Table: Baseline characteristics and efficacy and safety endpoints

Characteristic/ Endpoint	NDD population[1] N=4277				DD population[1] N=3590			
	<65 years old		≥65 years old		<65 years old		≥65 years old	
	Roxadustat n=1292	Placebo n=866	Roxadustat n=1049	Placebo n=900	Roxadustat n=1432	Epoetin alfa n=1420	Roxadustat n=611	Epoetin alfa n=527
Baseline characteristics								
Age, yrs, mean (SD)	51.7 (10.3)	52.2 (10.0)	73.9 (5.4)	74.3 (5.6)	48.0 (11.6)	48.7 (11.3)	72.2 (5.1)	72.5 (5.2)
Sex, female, n (%)	792 (61.3)	509 (57.7)	625 (59.6)	465 (53.9)	592 (41.3)	582 (41.0)	250 (45.0)	217 (41.2)
Hb, g/dL, mean (SD)	9.05 (0.77)	9.02 (0.75)	9.15 (0.7)	9.19 (0.7)	8.54 (1.5)	8.55 (1.5)	8.88 (1.2)	8.96 (1.2)
Efficacy endpoints	n=1282	n=974	n=1036	n=891	n=1422	n=1410	n=607	n=518
Mean (SD) CFB in Hb, g/dL	1.81 (1.0)	0.11 (1.1)	1.90 (0.9)	0.16 (1.0)	1.81 (1.5)	1.59 (1.5)	0.88 (1.4)	0.59 (1.4)
LSMD (SE) (95% CI), g/dL	1.71 (0.05) [1.62, 1.82] p<0.0001		1.73 (0.05) [1.63, 1.83] p<0.0001		0.23 (0.04) [0.16, 0.33] p<0.0001		0.28 (0.057) [0.164, 0.388] p<0.0001	
Transfusion incidence rate, per 100 PEY	6.5	21.8	5.5	18.9	4.7	5.5	7.0	9.3
IV iron use, Weeks 1–4, mg, mean (SD), median (range)	—	—	—	—	42 (161) 0 (0–2800.0)	70 (457) 0 (0–11200.0)	41 (159) 0 (0–1900.0)	66 (753) 0 (0–16300.0)
IV iron use, Weeks 48–52, mg, mean (SD), median (range)	—	—	—	—	43 (231) 0 (0–6000)	64 (194) 0 (0–2300)	42 (126) 0 (0–1200)	60 (147) 0 (0–1400)
Patients with ≥1 treatment-emergent adverse event, %								
TEAE (DT + 28)	n=1290 88.9	n=864 84.0	n=1040 89.9	n=900 86.8	n=1430 93.9	n=1418 94.8	n=610 90.2	n=524 86.3

PO0456

Roxadustat Effectively Treats Anemia in Dialysis-Dependent CKD (DD-CKD) Patients with Ferritin ≥500 ng/mL

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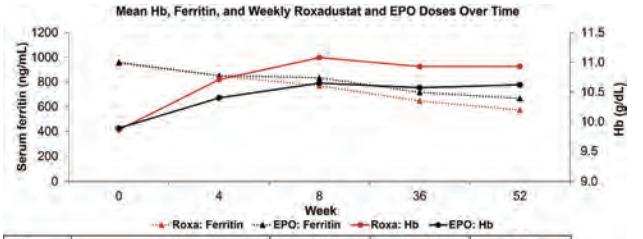
Background: Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, increases hemoglobin (Hb) by increasing erythropoietin and improving iron bioavailability. This pooled *post hoc* analysis evaluated roxadustat vs ESA in DD-CKD patients (pts) with high ferritin.

Methods: Pts were randomized to roxadustat (n=1943) or epoetin alfa (EPO; n=1947) in 3 Phase 3 DD-CKD trials (ROCKIES, SIERRAS, HIMALAYAS). Ferritin was ≥100 ng/mL at entry. EPO and intravenous (IV) iron were given per usual care for EPO; for roxadustat, dose was titrated to Hb 11±1 g/dL and IV iron limited to keep ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%. Pooled subgroup analyses were performed by baseline (BL) ferritin ≥500 ng/mL. P values are exploratory.

Results: At BL, 963 roxadustat and 937 EPO pts had ferritin ≥500 ng/mL: median (min-max) 838 (502-5186) vs 855 (501-4577) ng/mL. Roxadustat vs EPO BL values were balanced for mean age (56 vs 57 years), mean Hb (9.9 g/dL), and median hepcidin (305 vs 301 µg/L), serum iron (68 vs 66 µg/dL) and TSAT (34% vs 33%). Through Week (wk) 52, roxadustat maintained Hb ~11 g/dL with minimal weekly dose change; EPO maintained Hb ~10.5 g/dL with dose increases (Figure). Ferritin reduction from BL was greater with roxadustat vs EPO at wk 20 (-249 vs -202 ng/mL; P=0.01) and to wk 52 (Figure). For roxadustat vs EPO, serum iron (1.6 vs -10.7 µg/dL) and transferrin (0.35 vs 0.01 µg/dL) increased at wk 20 and hepcidin (-88 vs -51 µg/L) reduced at wk 24 (all P<0.01). IV iron use was less with roxadustat vs EPO (29% vs 37% pts).

Conclusions: In DD-CKD pts with high ferritin, EPO pts had lower Hb and impaired iron mobilization despite increased IV iron use and EPO dose. Roxadustat drove ferritin reductions and increased serum iron and transferrin, with minimal dose change, and is an alternative to ESA for DD-CKD pts with high ferritin.

Funding: Commercial Support - AstraZeneca, Astellas, and Fibrogen



Week	1–4	5–8	33–36	49–52
Roxa dose (mg/kg/wk)	4.0	4.0	3.7	3.8
EPO dose (IU/kg/wk)	116.3	121.2	135.4	137.8

Hb = ferritin data = full analysis set. Dose data = safety analysis set. Error bars are SE. EPO, epoetin alfa; Hb, hemoglobin; SE, standard error.

PO0457

Iron-Related Outcomes in Patients with Dialysis-Dependent CKD Randomized to Vadadustat vs. Darbepoetin Alfa

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD).

Methods: We conducted 2 global phase 3, randomized, open-label, active-controlled, noninferiority trials (INNO$_2$VATE) comparing once-daily oral dosing of VADA with the erythropoiesis-stimulating agent darbepoetin alfa (DA) in patients with anemia and incident (N=369) or prevalent (N=3554) dialysis-dependent (DD) CKD. Inclusion criteria: serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%. Safety and efficacy results of the INNO$_2$VATE trials were previously reported. Here we report iron-related outcomes, including the changes in mean serum hepcidin, ferritin, total iron-binding capacity (TIBC), iron, and TSAT from baseline to the primary (wk 24–36) and secondary (wk 40–52) evaluation periods.

Results: A total of 1958 patients received VADA and 1965 received DA. VADA treatment was associated with greater decreases in mean hepcidin and ferritin, and increases in TIBC from baseline to the primary and secondary evaluation periods (**Table**). Mean serum iron decreased more in the DA than the VADA group from baseline to wk 24–36 and 40–52. Oral and intravenous iron use was similar in the 2 treatment groups throughout both studies. Similar results were seen in the non–DD-CKD populations (PRO$_2$TECT studies).

Conclusions: The observed relative decreases in hepcidin and ferritin and the increase in TIBC are consistent with a VADA-induced facilitation of iron mobilization from intracellular stores that support erythropoiesis.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

Table. Changes From Baseline in Iron-Related Parameters

	Primary Evaluation Period (wk 24–36)				Secondary Evaluation Period (wk 40–52)			
Parameter, LS mean (SEM)	VADA (N=1958)	DA (N=1965)	Difference (VADA–DA) LS mean (95% CI)	*P* value	VADA (N=1958)	DA (N=1965)	Difference (VADA–DA)	*P* value
Hepcidin, ng/mL	−59.5 (4.4)	−40.7 (4.4)	−18.9 (−26.1, −11.6)	<0.001	−71.3 (4.8)	−50.5 (4.8)	−20.7 (−28.5, −12.9)	<0.001
Ferritin, ng/mL	−77.4 (15.9)	−39.6 (15.7)	−37.7 (−63.6, −11.9)	0.004	−84.6 (16.5)	−44.6 (16.3)	−39.9 (−66.3, −13.6)	0.003
TIBC, µg/dL	30.8 (1.3)	2.3 (1.3)	28.6 (26.5, 30.7)	<0.001	27.4 (1.4)	1.0 (1.4)	26.3 (24.0, 28.6)	<0.001
Serum iron, µg/dL	1.5 (1.1)	−3.5 (1.1)	5.0 (3.2, 6.9)	<0.001	−0.5 (1.2)	−3.6 (1.2)	3.1 (1.2, 5.0)	0.001
TSAT, %	−3.8 (0.5)	−1.9 (0.5)	−1.9 (−2.7, −1.1)	<0.001	−4.4 (0.5)	−1.8 (0.5)	−2.6 (−3.4, −1.7)	<0.001

PO0458

Associations Between Hepcidin and Laboratory Measures of Iron and Inflammation in Patients with Anemia and CKD Not on Dialysis in the Roxadustat Global Phase 3 Program

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Background: Hepcidin is the master regulator of iron homeostasis. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates coordinated erythropoiesis in part by reducing hepcidin. We investigated the associations between hepcidin levels and select laboratories in anemic patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) in the roxadustat studies.

Methods: This exploratory analysis used data from 3 similarly designed pivotal phase 3 studies (OLYMPUS, ANDES, and ALPS) of roxadustat vs. placebo in anemic patients with stage 3-5 NDD-CKD. Quintiles of baseline (BL) hepcidin levels and change from baseline (CFB) in hepcidin were evaluated for associations with select labs at BL and changes at weeks 20-28. Multivariate regression to hepcidin was performed at BL and after treatment using full analysis set.

Results: 2717 patients were assessed (1630 roxadustat, 1087 placebo). BL hepcidin (range 0.75 to 808.2 μg/L) was analyzed by quintile regardless of treatment group. Patients with higher BL hepcidin were observed to have a lower hemoglobin (Hb), lower eGFR, higher C-reactive protein (CRP), higher serum iron, higher ferritin, lower total iron binding capacity (TIBC), and higher transferrin saturation (TSAT) compared to lower BL hepcidin groups (Table). Further analysis of these relationships using multivariate regression models with minimalized AIC score model selection criteria showed that BL hepcidin (log-transformed) was significantly associated with the following BL parameters (log-transformed) in the descending order of importance (+/- indicated the direction): ferritin(+), TIBC(-), eGFR(-), albumin(+), Hb(-). The mean (SD) CFB in hepcidin at week 24 was -23.1 (86.0) μg/L in the roxadustat group vs. +12.3 (87.8) μg/L in the placebo group. Hepcidin associations after treatment will also be presented.

Conclusions: Baseline hepcidin was strongly associated with iron parameters like serum ferritin but not other known factors, such as CRP, in NDD-CKD patients with anemia.

Funding: Commercial Support - FibroGen, AstraZeneca, Astellas

Table: Baseline characteristics by baseline hepcidin quintile in NDD-CKD (roxadustat + placebo)

Mean (SD)	Q1 (0.75 - 32.7) N=543	Q2 (32.8 - 69.5) N=543	Q3 (69.7 - 115.8) N=544	Q4 (115.9 - 186.7) N=544	Q5 (186.8 - 802.8) N=543	P-value (ANOVA)
Age, years	62.1 (14.8)	62.9 (13.8)	62.5 (13.7)	63.3 (12.5)	60.6 (13.8)	0.0143
BL Hb, g/dl	9.2 (0.6)	9.2 (0.7)	9.2 (0.7)	9.1 (0.7)	8.9 (0.8)	<.0001
BL eGFR, ml/min/1.73 m²	22.2 (13.2)	21.7 (12.6)	19.8 (10.7)	19.8 (10.5)	15.8 (9.6)	<.0001
BL CRP, mg/l	5.8 (8.5)	6 (9.8)	6.8 (15.6)	7.6 (22.4)	9.1 (19.3)	0.0023
BL albumin, g/l	38.1 (3.9)	37.6 (4.6)	38 (4.3)	38 (4.6)	38.2 (5.0)	0.3092
BL iron, μg/dl	57.9 (24.3)	63.7 (23.6)	65 (23.8)	66 (25.6)	74.6 (32.7)	<.0001
BL ferritin, ng/ml	108.9 (107.8)	173.5 (141.7)	223.7 (194.2)	325.3 (283.1)	532.5 (446.9)	<.0001
BL TIBC, μmol/l	44.3 (13.1)	39.8 (12.6)	36.1 (11.9)	34.5 (11.5)	36.1 (13.7)	<.0001
BL TSAT, %	22.2 (10.1)	26 (10.6)	27.4 (10.4)	28.7 (10.6)	34.2 (14.4)	<.0001

PO0459

Associations Between Hepcidin and Laboratory Measures of Iron and Inflammation in Incident Dialysis Patients with Anemia Enrolled in the Roxadustat Global Phase 3 Program

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Background: Hepcidin is the master regulator of iron homeostasis. Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates coordinated erythropoiesis in part by reducing hepcidin. We investigated the associations between hepcidin levels and select laboratories in incident dialysis (ID) patients with anemia.

Methods: This exploratory analysis used data from three similarly designed, pivotal, phase 3 studies (ROCKIES, HIMALAYAS, and SIERRAS) of roxadustat vs. epoetin alfa in anemic patients with dialysis-dependent chronic kidney disease (CKD). Patients on dialysis for 2 weeks to ≤4 months prior to randomization (defined as ID) were included in the analysis. Quintiles of baseline (BL) hepcidin levels and changes from baseline (CFB) in hepcidin were evaluated for associations with select labs at BL and changes at weeks 20-28. Multivariate regression to hepcidin was performed at BL and after treatment using full analysis set.

Results: 1297 ID patients were assessed (646 roxadustat, 651 epoetin alfa). BL hepcidin (range 5 to 1118.7 μg/L) was analyzed by quintile regardless of treatment arm. Patients with higher BL hepcidin were observed to have higher C-reactive protein (CRP), higher serum iron, higher ferritin, lower total iron binding capacity (TIBC), and higher transferrin saturation (TSAT) compared to lower hepcidin groups (Table 1). Further analysis of these relationships using multivariate regression models with minimalized AIC score model selection criteria showed that BL hepcidin (log-transformed) was significantly associated with the following BL parameters(log-transformed) in the descending order of importance (+/- indicated the direction): ferritin(+), TIBC(-), albumin(+), CRP(+), iron(+). The mean (SD) CFB to week 24 in hepcidin was -63.47 (121.8) μg/L in the roxadustat group vs. -34.84 (141.6) μg/L in the epoetin group. Hepcidin associations after treatment will also be included in the presentation.

Conclusions: Baseline hepcidin was strongly associated with baseline iron parameters and CRP in ID patients with anemia of CKD.

Funding: Commercial Support - FibroGen, AstraZeneca

Table 1: Baseline characteristics by baseline hepcidin quintile in ID-CKD (roxadustat + epoetin alfa)

Mean (SD)	Q1 (5 - 78.5) (N= 260)	Q2 (78.9 - 130.5) (N= 259)	Q3 (130.6 - 184) (N= 259)	Q4 (184.3 - 261) (N= 260)	Q5 (261.8 - 1118.7) (N= 259)	P-value (ANOVA)
Age, years	54.3 (14)	54.1 (14.7)	53.9 (15.3)	54 (14.4)	54.3 (14.5)	0.9971
BL Hb, g/dl	8.8 (1.1)	8.8 (1)	8.8 (1.1)	8.7 (1.3)	8.6 (1.2)	0.1322
BL CRP, mg/l	7.5 (16)	6.8 (8.9)	8.5 (16.8)	10.8 (17.9)	22.1 (43.5)	<.0001
BL albumin, g/l	36.5 (3.8)	36.4 (4.5)	37.1 (3.9)	36.9 (4.2)	36.6 (4.8)	0.2304
BL iron, μg/dl	61.8 (21.9)	63.5 (22.4)	67.1 (33.7)	66.3 (24.4)	72.7 (30.2)	<.0001
BL ferritin, ng/ml	212.3 (171.9)	310.3 (190)	418 (261.4)	502.4 (292.6)	757.4 (382.7)	<.0001
BL TIBC, μmol/l	43.7 (9.8)	41.7 (8)	40.6 (8.4)	39.9 (9)	39.5 (8.9)	<.0001
BL TSAT, %	24.8 (7.2)	26.8 (7.8)	28 (9.5)	29.3 (9.9)	32.6 (12.3)	<.0001

PO0460

Comprehensive Safety Profile of Vadadustat from Global Phase 3 Clinical Trials

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD).

Methods: We pooled safety data from 4 global phase 3, randomized, open-label studies evaluating VADA vs darbepoetin alfa (DA) in patients from 2 dialysis- and 2 non–dialysis-dependent CKD trials (INNO$_2$VATE and PRO$_2$TECT, respectively) who received ≥1 dose of study drug. We summarized treatment-emergent adverse events (TEAEs) by MedDRA system organ class (SOC) and preferred term (PT). We retrieved AEs of special interest (AESIs) using Standardized MedDRA Queries and analyzed as groups of PTs (medical topics).

Results: A summary of TEAEs by treatment group is provided (**Table)**. The most common in the VADA and DA groups by SOC were infections and infestations (50.8%, 52.7%), gastrointestinal disorders (40.2%, 35.2%), metabolism and nutrition disorders (34.6%, 36.2%), and injury, poisoning and procedural complications (29.5%, 30.7%). The most common drug-related TEAEs in the VADA group were the PTs of diarrhea (2.2%) and nausea (1.2%), leading to study drug discontinuation in 0.4% and 0.2% of patients, respectively. The most frequent serious AEs (SAEs) in the VADA and DA groups occurred in the SOCs for infections and infestations (23.3%, 24.0%) and renal and urinary disorders (18.6%, 18.1%). TEAEs leading to death in the VADA and DA groups were cardiac arrest (1.7% in each group), end-stage kidney disease (1.8%, 1.3%), and cardio-respiratory arrest (0.9%, 1.0%). AESIs (>10%) in the VADA and DA groups were hypertension (18.0%, 21.0%), congestive heart failure (10.3%, 11.5%), and hyperkalemia (9.9%, 11.9%), all of which were more frequent with DA.

Conclusions: VADA exhibited a TEAE safety profile generally comparable to DA.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

Table. Summary of TEAEs in Pooled Phase 3 Studies of VADA (safety population)

	INNO$_2$VATE		PRO$_2$TECT		Total	
n (%)	VADA N=1947	DA N=1955	VADA N=1739	DA N=1732	VADA N=3686	DA N=3687
Any TEAE	1712 (87.9)	1739 (89.0)	1565 (90.0)	1553 (89.7)	3277 (88.9)	3292 (89.3)
Any drug-related TEAE	176 (9.0)	73 (3.7)	195 (11.2)	101 (5.8)	371 (10.1)	174 (4.7)
Drug-related SAE	30 (1.5)	31 (1.6)	36 (2.1)	24 (1.4)	66 (1.8)	55 (1.5)
Drug-related TEAE leading to discontinuation	44 (2.3)	5 (0.3)	29 (1.7)	6 (0.3)	73 (2.0)	11 (0.3)
Any TEAE leading to death	281 (14.4)	294 (15.0)	312 (17.9)	302 (17.4)	593 (16.1)	596 (16.2)
Drug-related TEAE leading to death	0	1 (0.05)	0	0	0	1 (0.03)

PO0461

Vadadustat, an Oral HIF-PHI, Is Not Associated with Increased Risk of Neoplasm in Patients with Anemia due to CKD

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that stimulates endogenous erythropoietin and red blood cell production. The downstream effects of the transcription of HIF-responsive genes prompted our investigation of the risk of malignancy in patients with chronic kidney disease (CKD) receiving VADA in four global phase 3 trials.

Methods: We examined reports of adverse events (AEs) and serious AEs (SAEs) suggestive of neoplasms according to Standardized MedDRA Queries (preferred terms [PTs]) from four phase 3, randomized, open-label trials evaluating VADA vs darbepoetin alfa (DA) in patients from the two dialysis-dependent (DD) and two non–dialysis-dependent (NDD) CKD (INNO$_2$VATE and PRO$_2$TECT, respectively) who received ≥1 dose of study drug. Patients with a history of active malignancy within two years prior to or during screening were excluded from the trials, except for those with treated basal

cell carcinoma of the skin, curatively resected squamous cell carcinoma of the skin, or cervical carcinoma in situ. Malignancies are reported here as events per 100 patient-years (PY).

Results: In total, 3686 patients were exposed to VADA and 3687 to DA for a median of 56.7 wk (25%, 75th percentile range 31.9–91.7 wk) and 70.0 wk (39.9–102.1 wk); 54.6% and 64.2% patients were exposed for ≥52 wk and 18.9% and 24.1% for >104 wk, respectively. Malignancies in the VADA and DA treatment groups were 2.1 events/100 PY and 2.7 events/100 PY, respectively (relative risk [RR], 0.81; 95% confidence interval [CI], 0.64–1.03). Specifically, malignancies in patients with NDD-CKD were 2.7 vs 3.0 events/100 PY (RR, 0.89; 95% CI, 0.65–1.21), and in patients with DD-CKD were 1.5 vs 2.4 events/100 PY (RR, 0.72; 95% CI, 0.50–1.03), for VADA vs DA, respectively. In both studies, no pattern was observed for any specific type of malignancy, including renal cell carcinoma in patients with DD or NDD CKD.

Conclusions: VADA was not associated with an increased risk of neoplasms compared with DA in patients with anemia and CKD.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

PO0462

Assessment of Thromboembolic Events with Vadadustat vs. Darbepoetin Alfa for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD). Two recently completed global phase 3, open-label, randomized (1:1), sponsor-blind, noninferiority trials (PRO_2TECT) compared the safety and efficacy of VADA with that of darbepoetin alfa (DA) in adult patients with non–dialysis-dependent (NDD) CKD. One of the studies (NCT02648347) was in 1751 patients previously untreated with an erythropoiesis-stimulating agent (ESA). The other study (NCT02680574) was in 1725 ESA-treated patients. The primary safety endpoint of the PRO_2TECT trials was time to first major adverse cardiovascular event (MACE; a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke), prespecified as a pooled event-driven analysis of both trials. As previously reported, the hazard ratio (HR; VADA:DA) for MACE was 1.17 (95% confidence interval [CI], 1.01–1.36), which did not meet the prespecified noninferiority margin of 1.25.

Methods: Here we describe the prespecified pooled analysis of the secondary safety endpoints of time to first thromboembolic event, including (1) any thromboembolic event (a composite of events of vascular access thrombosis, arterial thrombosis, deep venous thrombosis [DVT], and pulmonary embolism [PE]), (2) arterial thrombosis, DVT, or PE, and (3) venous thromboembolic events (DVT or PE).

Results: A total of 1739 patients received VADA and 1732 received DA in these two studies. A first thromboembolic event occurred in 33 patients (1.9%) in the VADA group and 38 (2.2%) in the DA group (HR [95% CI]: 0.88 [0.554–1.408]; *P* value of Gray's test=0.569). For arterial thrombosis, DVT, or PE, there were 21 (1.2%) and 25 (1.4%) patients with events, respectively (HR [95% CI]: 0.86 [0.480–1.544]; *P*=0.569), and for venous thromboembolic events, there were 18 (1.0%) and 23 (1.3%), respectively (HR [95% CI]: 0.80 [0.430–1.485]; *P*=0.445). Vascular-access thrombosis was reported as <1.0 event/100 patient years in both the VADA and DA groups.

Conclusions: In the phase 3 PRO_2TECT trial in patients with anemia and NDD-CKD, the rate of thromboembolic events was similar between the VADA and DA groups.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

PO0463

Thromboembolic Events with Vadadustat vs. Darbepoetin Alfa for Anemia Treatment in Patients with Dialysis-Dependent CKD

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD). Two recently completed global phase 3, open-label, randomized (1:1) noninferiority trials ($INNO_2$VATE) compared the safety and efficacy of VADA with that of darbepoetin alfa (DA) in adult patients with dialysis-dependent (DD) CKD. One trial randomized 369 patients with incident DD-CKD (Correction/Conversion trial; NCT02865850) and the other trial randomized 3544 patients with prevalent DD-CKD (Conversion trial; NCT02892149). The primary safety endpoint of the $INNO_2$VATE trials was time to first major adverse cardiovascular event (MACE; a composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke), prespecified as a pooled event-driven analysis of both trials. As previously reported, the pooled MACE risk (hazard ratio [HR]; VADA:DA) was similar between the VADA and DA groups (0.96; 95% confidence interval [CI], 0.83–1.11), which met the prespecified noninferiority margin of 1.25.

Methods: Here we describe the prespecified pooled analysis of the secondary safety endpoints of time to first thromboembolic event, including (1) any thromboembolic event (a composite of events of vascular access thrombosis, arterial thrombosis, deep venous thrombosis [DVT], and pulmonary embolism [PE]), (2) arterial thrombosis, DVT, or PE, and (3) venous thromboembolic events (DVT or PE).

Results: A total of 1947 patients received VADA and 1955 received DA in the 2 studies. A first thromboembolic event occurred in 169 patients (8.7%) in the VADA group and 148 (7.6%) in the DA group (HR [95% CI]: 1.20 [0.959–1.493]; *P* value of Gray's test=0.161). For arterial thrombosis, DVT, or PE, the number of patients with events was 26 (1.3%) and 32 (1.6%), respectively (HR [95% CI]: 0.86 [0.509–1.444]; *P*=0.462), and for venous thromboembolic events, there were 19 (1.0%) and 28 (1.4%), respectively (HR [95% CI]: 0.71 [0.400–1.269]; *P*=0.206). Vascular-access thrombosis was reported as 6.6 events/100 patient years in both the VADA and DA groups.

Conclusions: In the phase 3 $INNO_2$VATE trial in patients with anemia and DD-CKD, the rate of thromboembolic events was similar between the VADA and DA groups.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

PO0464

Vadadustat for Treatment of Anemia in Patients with Dialysis-Dependent CKD Receiving Peritoneal Dialysis

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD). In two recently completed global phase 3 trials in patients with dialysis-dependent CKD (DD-CKD) ($INNO_2$VATE), VADA was noninferior to darbepoetin alfa (DA) for the primary safety endpoint (time to first major adverse cardiovascular event [MACE: a composite of all-cause mortality, nonfatal MI, and nonfatal stroke]) and the primary and secondary efficacy endpoints (correction/maintenance of hemoglobin [Hb]). Here we describe safety and efficacy of VADA compared to DA in the subgroup of patients receiving peritoneal dialysis (PD).

Methods: We conducted two randomized (1:1), phase 3, global, open-label, sponsor-blind, parallel-group active-controlled noninferiority trials ($INNO_2$VATE) comparing VADA vs DA to determine safety and efficacy in patients with anemia of DD-CKD receiving dialysis (either PD or hemodialysis). The prespecified primary safety endpoint was time to first MACE, defined as all-cause mortality or nonfatal myocardial infarction or stroke. The primary and key secondary efficacy endpoints were the mean change in Hb from baseline to wk 24–36 and from baseline to wk 40–52, respectively, in each trial. We assessed the incidence of treatment-emergent adverse events (TEAEs). The efficacy endpoints and TEAE analyses were conducted post hoc.

Results: Of the 3923 patients randomized in the 2 $INNO_2$VATE trials, 309 were receiving PD (VADA, N=152; DA, N=157). Among patients receiving PD, MACE rates were similar in the VADA and DA groups (25/152 [16.4%] and 27/157 [17.2%], respectively). The least-squares mean difference in change in Hb from baseline was –0.10 g/dL (95% CI: –0.33, 0.12) to wk 24–36 and –0.19 g/dL (95% CI: –0.43, 0.05) to wk 40–52. Primary and key secondary efficacy endpoints met the prespecified noninferiority margin of –0.75 g/dL. The incidence of overall TEAEs was 88.2% vs 95.5% and of serious TEAEs was 52.6% vs 73.2% in the VADA and DA groups, respectively.

Conclusions: Among patients receiving PD in the $INNO_2$VATE phase 3 trials, safety and efficacy of VADA were comparable to DA.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

PO0465

Daprodustat Is Noninferior to Darbepoetin Alfa in Treating Anemia in Incident Dialysis Patients

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Background: Daprodustat (Dapro) is a hypoxia-inducible factor prolyl hydroxylase inhibitor that is being evaluated as an alternative to conventional erythropoiesis stimulating agent (ESA) therapy. Treatment with Dapro in incident dialysis dependent (ID) patients (pts) that are at high risk for co-morbidity and mortality has not been examined previously. This Phase 3 trial evaluated the efficacy and safety of Dapro vs darbepoetin alfa (Darbe) in the ASCEND-ID (NCT03029208) study.

Methods: Pts who started on hemodialysis (HD) or peritoneal dialysis (PD) were randomized to Dapro or Darbe to maintain hemoglobin (Hb) at 10–11 g/dL in an open-label (sponsor-blind) 52-week study. Eligible pts were ≤3 months from initiation of HD or PD, ESA naïve or of limited ESA exposure, Hb 8–11.0 g/dL, and iron replete. Primary endpoint tested non-inferiority of Dapro vs Darbe (analysis of covariance) for mean change in Hb between baseline (BL) and Evaluation Period (EP) in weeks 28–52. Secondary endpoint included IV iron use.

Results: 312 pts from 14 countries were randomized; of those, 81% started on HD and 31% had an unplanned dialysis start. Overall 99% (155/157) pts on Dapro and 97% (151/155) on Darbe completed the study. Major BL characteristics were balanced, except age (mean 53.7 y vs 55.8 y) and history of heart failure (16% vs 22%) in Dapro vs Darbe, respectively. Hb measurements from EP are shown below. Mean (SD) Hb in EP was 10.5 (1.0) g/dL and 10.6 (0.9) g/dL (Dapro vs Darbe). There was no significant difference in mean (SE) monthly IV iron use 145 (10.9) mg vs 125 (11.0) mg (Dapro vs Darbe). Rescue treatment was the same in both groups (3%). While the number of subjects with worsening of hypertension (24% Dapro vs 19% Darbe) was numerically higher, the overall effect of dapro on BP was similar to Darbe. Rates of AEs were similar (76% Dapro vs 72% Darbe).

Conclusions: In a high-risk incident dialysis population, Dapro was non-inferior to Darbe in maintaining Hb in the target range. Dapro was well tolerated and appears to be a safe alternative to Darbe.

Funding: Commercial Support - GlaxoSmithKline

Mean Difference in Hb Change from BL in Dapro vs Darbe groups

Hb analysis Weeks 28–52	Population	Arm	n/N (%)	Adjusted mean Hb (g/dL) difference (95% CI)*
Post-randomization (observed and imputed)	ITT	Dapro Darbe	157/157 (100) 155/155 (100)	–0.10 (–0.34, 0.14)
Evaluable	ITT	Dapro Darbe	133/157 (85) 133/155 (86)	–0.20 (–0.43, 0.04)
Evaluable	PP	Dapro Darbe	77/77 (100) 101/101 (100)	–0.12 (–0.38, 0.14)

*Non-inferiority was declared when the lower boundary of the 95% CI for the treatment difference was greater than the prospectively defined non-inferiority margin of 0.75 g/dL.
ITT, intent-to-treat PP, per-protocol

PO0466

Suboptimal Treatment of Anemia in CKD Non-Dialysis Patients: What Role Will HIF-PH Inhibitors Play?

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Background: The purpose of this study was to understand the real-world patient presentation and treatment priorities for CKD non-dialysis patients, focusing on the treatment of anemia of CKD.

Methods: Using a HIPAA-compliant, online chart audit tool, nephrologists (n=183) submitted de-identified clinical and non-clinical demographic information for 1,030 non-dialysis patients with CKD (eGFR<60) in Fall 2020. This independent, retrospective patient chart audit collected data beginning at the time of patient referral and concluded with details from the most recent visit.

Results: As CKD progresses so too does the prevalence of anemia, with nearly six-in-ten CKD Stage 5 patients identified by their physicians as having anemia. However, while anemia is a common comorbidity in CKD non-dialysis patients, physicians tend to deprioritize the disease when consulting with these patients in their offices. When asked about topics discussed during their most recent patient visit, anemia falls behind other topics such as hypertension, weight and diet, and quality of life. Although anemia is less of a priority, more than 60% of patients did have a hemoglobin test ordered at their most recent visit, indicating that physicians are monitoring hemoglobin levels somewhat regularly to help keep track of potential anemia. More than one-half of CKD non-dialysis patients treated with ESAs have a hemoglobin level below 10.0 g/dL; however, the most common reason for non-treatment in patients with levels between 9.0 and 9.9 g/dL is that the hemoglobin is "not low enough", indicating physicians are waiting until hemoglobin is substantially low before starting treatment with ESAs. HIF-PH inhibitors are a novel class in development for the treatment of anemia, and nephrologists express a willingness to use the agents in their CKD non-dialysis patients who are not currenlty treated (45% Stage 3, 52% Stage 4 and 60% Stage 5). More than one-half (58%) would also be willing to switch ESA-treated non-dialysis patients to a HIF-PH inhibitor once they are approved, indicating there is a large opportunity for this class to have an impact on the treatment of anemia.

Conclusions: Enhanced communication with non-dialysis patients about anemia, as well as earlier detection and intervention with novel HIF-PH inhibitors, could lead to better anemia outcomes.

PO0467

Renal Injury Biomarkers Are Elevated in Acute Hepatic Porphyria

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Background: Acute hepatic porphyria (AHP) is a group of rare genetic diseases caused by defects in enzymes in the heme biosynthesis pathway. Acute intermittent porphyria (AIP) is the most common subtype. In patients with AHP, accumulation of heme pathway intermediates, delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), lead to acute attacks and long-term complications including hypertension and chronic kidney disease which is present in 30-60% of patients with biochemically active AIP. Chronic high excreters (CHE) are a group of patients that carry a genetic mutation and have elevated levels of ALA and PBG but are not experiencing acute attacks.

Methods: Proteomic analysis (Olink® platform) was used to measure 1196 proteins in plasma from consenting AHP patients with recurrent acute attacks (>90% AIP) in the EXPLORE natural history study, the ENVISION Phase 3 study, and CHE patients in the ALN-AS1-001 Phase 1 study at baseline. A separate cohort of healthy controls, age- and gender-matched to EXPLORE patients was also analyzed. Linear regression accounting for age, and sex was used to determine the proteins that were significantly different between AHP patients or CHE patients and controls.

Results: 212 plasma proteins were significantly different between healthy controls and patients with AHP. Two proteins with the largest effect sizes, kidney injury molecule-1 (KIM1; 3.4-fold; p-value= 8.0e-13) and matrix metalloproteinase-7 (MMP7; 5-fold; p-value= 1.5e-25) were previously described as biomarkers of renal injury. Three additional kidney injury biomarkers (neutrophil gelatinase-associated lipocalin, cystatin C (CST3) and chitinase-3-like protein 1) showed significant elevations in patients with AHP. Moderate to strong correlations were observed between each of these biomarkers and eGFR (correlation coefficients -0.33 to -0.54). AHP patients with a diagnosis of renal disease demonstrated significantly higher levels of each of these biomarkers than patients without such a diagnosis (p-values <0.01). KIM1, MMP7, and CST3 were also significantly elevated in CHE patients compared to controls.

Conclusions: Renal injury biomarkers may aid in diagnosing and managing kidney disease in patients with AHP suffering from recurrent acute attacks as well as chronic high excreters.

Funding: Commercial Support - Alnylam Pharmaceuticals Inc

PO0468

A Contemporary View of Erythropoietin-Stimulating Agent Switching: Determining a Dose Conversion Ratio (DCR) from IV Epoetin Alfa to IV PEG-Epoetin Beta and SC Epoetin Beta to Preserve Haemoglobin Control in Haemodialysis Patients

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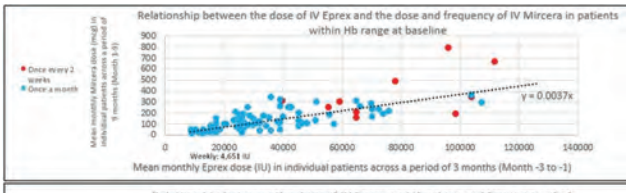
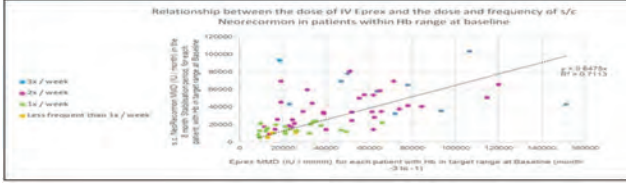
Background: Recent studies, such as PIVOTAL, in haemodialysis show the benefit of adequate iron repletion, including reduction in ESA dose. This study aims to determine the DCR to maintain Hb stability in a contemporary HD cohort, switch from IV epoetin alfa (Eprex®), to sc epoetin beta (Neorecormon ®) or IV PEG-epoetin beta (Mircera®).

Methods: This observational study from a UK single-centre analysed Hb stability and ESA requirements in 260 HD patients on IV epoeitin alfa, who switched to sc epoetin beta (n=118) or IV PEG-epoetin beta (n=142). Data from a 3 mth Baseline period were compared to a 9 mth post-switch Evaluation period. The DCRs were are calculated using Evaluation dose / Baseline dose. The target Hb was 100-120g/L. Iron requirements were determined from TSAT, Ret-He and Ferritin.

Results: The mean Hb, Hb in target, ESA dose, frequency and DCR were: For IV PEG-epoetin beta group 109g/L, 75%, 10418 iU/wk, 3/wk, at baseline;109g/L, 81%, 181mcg/mth, 1/mth, at evaluation; resulting DCR 1mcg:249iU. For sc epoetin beta 111g/L, 74%, 9717IU/wk, 3/wk, at baseline; 111g/L, 88%, 7528 iU/wk, 2/wk, at evaluation; resulting DCR of 0.8. At these DCRs the Hb stability was maintained throughout the study. Sub-group analysis for baseline Hb in the PEG-epoetin beta group were 1:255 (Hb in range), 1:239 (Hb below range), 1:253 (Hb above range).

Conclusions: These data show that the DCR of 0.8 for epoetin IV to sc, with a reduction in frequency for sc, is in keeping with published literature and product license. The DCR of 1mcg:249iU for PEG epoetin-beta IV: epoetin alfa IV is higher than the typical 1mcg:200iU reported in the literature. These dose conversion data will benefit clinicians wishing to switch ESA, and provide insight into the bio-equivalencies and reduced administration frequencies into any logistical or costing model.





PO0469

Anemia Care of Hemodialysis Patients: A National Study from Qatar

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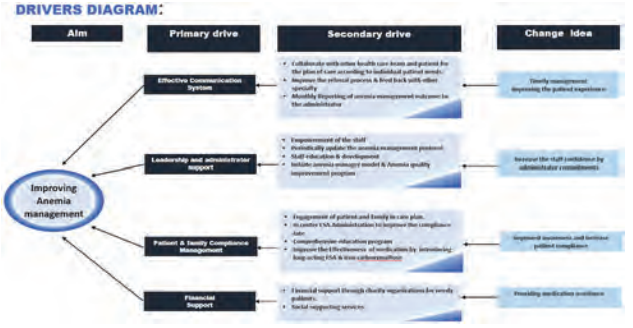
Background: Achieving anemia targets in dialysis patients is hard. Challenges like cost, compliance and erythropoietin stimulation agents (ESA) resistance can hamper anemia management. We established a new national anemia nurse manager model to improve care of anemia in dialysis patients in the State of Qatar. Key drivers of the new model are summerized in Figure below. We studied the effects of this program in improving anemia care in hemodialysis patients.

Methods: We did a retrospective study (IRB 01-20-158) to evaluate effectiveness of anemia nurse manager program in achieving anemia targets (percentage of patients with hemoglobin (Hg) in target (optimal range of 10-12g/dL)) and avoid extreme Hg (high (>13 g/dL) or low Hg (<9 g/dL) to avoid complications. We also studied effect of this model on ESA dosing. Our study included all adult ambulatory hemodialysis patients in the State of Qatar. Study duration was from July 2018-February 2020. Data was extracted from the Qatar national electronic medical rocord system.

Results: Our ambulatory HD patients increased from 535 to 575 during study duration. Age was 59+/-11 years with 59% male gender. Patients were mostly from the Middle East area 82% with 11% from South Asia and 5 % from East Asia. There was a significant improvement in patients with target Hg 10-12 g/dL (from 66% in July 2018 to 78% in February 2020, p=0.00001). Patients with extreme Hg were maintained at very low level throughout the study period (Hg<9 of 3.7% +/- 0.9% and Hg >13 of 4% +/- 0.7%). ESA dose was steady without much fluctuations (Darbepoietin 42.2+/-3.73 mcg/week and Mircera 149+/-18 mcg/month).

Conclusions: Our study showed that the new anemia care model improved anemia targets (Hg in range and low percentage of extreme Hg). ESA dose was steady during study period. Based on this result, we are implemnting similar models in different clinical areas in dialysis to improve patient care.

Funding: Government Support - Non-U.S.



PO0470

Anemia Treatment Patterns and First-Year Cardiovascular Outcomes in Incident ESKD Patients Undergoing Hemodialysis (2015-2018)

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Background: The first months of maintenance hemodialysis are characterized by a relatively high rate of death and by correction of anemia—mean hemoglobin (Hb) among incident end stage kidney disease (ESKD) patients is only 9.3 g/dL (source: 2020 USRDS Annual Data Report)—so it is hypothesized that new anti-anemia treatments could be utilized to improve outcomes. We assessed Hb, erythropoiesis-stimulating agent (ESA) dosing, and major adverse cardiac event-plus (MACE+) incidence during the first year of hemodialysis (HD), among users of either epoetin alfa (EPO) or darbepoetin alfa (DARB).

Methods: We analyzed United States Renal Data System Standard Analysis Files. The cohort comprised patients with newly diagnosed ESKD between 1 Jan 2015 and 30 Sep 2018 and whose primary modality was HD. We retained patients who used either EPO or DARB during the first month of HD, per CROWNWeb data. We followed patients until the earliest of kidney transplant, death, the end of the first year of ESKD, or 30 Sep 2019. During follow-up, we tabulated mean Hb and weekly ESA dose, by month. Among patients with Medicare coverage, we estimated the incidence of MACE+, as defined by death, myocardial infarction, stroke, or hospitalization for heart failure.

Results: Among 251,342 incident ESKD patients who initiated both HD and ESA treatment, 130,736 and 50,197 used EPO and DARB, respectively. Among EPO users, mean Hb was 9.9 g/dL in month 1 and between 10.6 and 10.7 g/dL thereafter. Mean weekly doses of EPO were 13,064 IU in month 1; 10,922 IU in month 4; 10,212 IU in month 7; and 9756 IU in month 10. Among DARB users, mean Hb was between 9.9 g/dL in month 1 and between 10.4 and 10.6 g/dL thereafter. Mean weekly doses of DARB were 39.3 mcg in month 1; 33.5 mcg in month 4; 32.5 mcg in month 7; and 31.7 mcg in month 10. Among EPO and DARB users, the cumulative incidence of MACE+ was 28.7% at 6 months and 49.1% at 12 months.

Conclusions: Anemia treatment among incident HD patients using either EPO or DARB is characterized by a brief increase in Hb, reaching a plateau of 10.5 to 10.7 g/dL, and steadily declining ESA doses during the first year. The incidence rate of MACE+ remains higher during the early versus late part of the first year. Real-world data are useful when evaluating benefits and risks of new anti-anemia treatments.

Funding: Commercial Support - Amgen Inc.

PO0471

Contemporary Anemia Treatment in Prevalent Patients Undergoing Hemodialysis

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Background: Anemia treatment remains a major area of focus in the management of maintenance dialysis patients. We assessed hemoglobin (Hb) and erythropoiesis-stimulating agent (ESA) dosing among hemodialysis (HD) patients with records in CROWNWeb, a national reporting system that captures data from all prevalent patients undergoing maintenance dialysis, regardless of whether patients carry Medicare coverage.

Methods: We analyzed United States Renal Data System Standard Analysis Files. For each calendar month from January 2015 to September 2019, we identified adult (age ≥18 years) patients who underwent HD during the entire month and whose CROWNWeb records included a valid measurement of single-pool *Kt/V*. In each patient-month, we identified Hb and ESA treatment (agent [epoetin alfa, darbepoetin alfa, or pegylated epoetin beta] and monthly cumulative dose). Subsequently, we tabulated the distribution of Hb in each month, incidence of 3-month and 6-month series with Hb <10.0 g/dL; utilization of ESAs, overall and by agent; and mean weekly ESA dose, by agent.

Results: Among 878,883 patients in the study period, 7.2% of patient-months had Hb <9.0 g/dL, 15.2% had Hb 9.0-9.9 g/dL, 35.3% had Hb 10.0-10.9 g/dL, 28.5% had Hb 11.0-11.9 g/dL, and 13.9% had Hb ≥12.0 g/dL. The prevalence of Hb <9.0 g/dL was relatively higher with age 18-44 years, Black race, and female sex. Among all 6-month series of Hb measurements, 5.8% had Hb <10.0 g/dL for 3 consecutive months and only 2.0% had Hb <10.0 g/dL for 6 consecutive months. Approximately 76% of patients received an ESA in each month. In 2019, 34% used epoetin alfa, 9% used darbepoetin alfa, and 33% used pegylated epoetin beta. Mean (median) weekly doses were 10,562 (7727) IU for epoetin alfa, 35.9 (23.0) mcg for darbepoetin alfa, and 33.6 (23.0) mcg for pegylated epoetin beta.

Conclusions: Between 2015 and 2019, despite substantial flux in the mix of ESAs used, distributions of hemoglobin and ESA doses among patients undergoing HD were stable, with only a small percentage of patients experiencing persistently low hemoglobin.

Funding: Commercial Support - Amgen Inc.

PO0472

Estimating Long-Term Survival Rates in Patients with Anaemia of Non-Dialysis-Dependent CKD: An Expert Elicitation

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Background: Clinical trials for the treatment of anemia of CKD provide mortality data. Cost-effectiveness analyses of new treatments require survival extrapolations over a lifetime time horizon. An expert elicitation was conducted to obtain estimates of long-term survival probabilities for patients with anemia of non-dialysis dependent (NDD) CKD.

Methods: Literature searches were used to identify clinical trials and observational studies that included patients with anemia of NDD CKD aged ≥ 18 years, that had > 500 participants per study arm and that reported all-cause death incidence and/or survival Kaplan–Meier (KM) curves. Study data were extracted and collated. KM curves were extrapolated to 20 years by calculating standardized mortality ratios (SMRs) compared to age- and sex-adjusted general population lifetables. A summary of relevant data was presented to six CKD experts. After an elicitation training, the experts made a judgment on the 10th, 50th and 90th percentile of 10- and 20-year survival of patients with anemia of NDD CKD. The individual judgments were combined into an overall assessment.

Results: From the literature, all-cause death incidence in patients with anemia of NDD CKD was 3.5–39.4 per 100 patient-years (five studies). From SMR-extrapolated KM curves, estimated survival at 10 and 20 years was 30–57% and < 1–13%, respectively (three studies; median age of 80 and 68 years in two studies, and mean age of 66 in the third). The aggregated elicited survival values were 50% (80% confidence interval [CI]: 34–64%) at 10 years and 21% (80% CI: 8–36%) at 20 years.

Conclusions: The elicited survival estimates could be used to model long-term survival and complement results from other extrapolation methods to inform and validate cost-effectiveness analyses. Long-term survival extrapolations are also likely to support patients and physicians with treatment decisions.

Funding: Commercial Support - AstraZeneca

PO0473

The Effect of a Patient Blood Management Program on Renal Outcome in Patients with CKD

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Background: Transfusion burden is high in CKD patients to treat anemia. However, transfusions had risks including volume overload, alloimmunization, blood stream infections and thromboembolism. We evaluated the effect of a monitoring program to identify appropriate transfusions in CKD patients.

Methods: Based on the guidelines of the Korean Society of Blood Transfusion, Korea University Anam Medical Center developed a verification program to assess the adequate indication of transfusion (patient blood management(PBM)) in August 2018. We analyzed 1,192 CKD patients admitted to the department of nephrology from August 2016 to July 2020. Patients were divided into two groups: patients who admitted before the implementation of PBM (pre-PBM(n=592)) and after the implementation of PBM (post-PBM(n=600)).

Results: The amount of blood transfused was 628 units in pre-PBM group and 443 units in post-PBM group. The patients who received more than 2 units was significantly lower in post-PBM group (20.1% vs. 13.5%, p=0.002). There were no differences in the administered doses of erythropoietin and iron between the groups. Although hemoglobin(Hb) (10.5±2.0 vs. 10.3±2.2) were not different between the two groups at admission, Hb levels were significantly lower in post-PBM group at discharge (10.4±1.8 vs. 10.1±2.0, p=0.010) and 6 months after admission (11.5±1.9 vs. 11.1±2.0, p=0.007). Kaplan-Meier analysis showed a survival benefit of CKD progression (≥50% increase in serum creatinine) (p<0.001) and percutaneous coronary intervention (p=0.030) in the post-PBM group. The incidence of end stage kidney disease or mortality was not different between groups. In multivariate analysis, PBM was associated with lower risk for CKD progression (HR of 0.587; 95% CI 0.416-0.830).

Conclusions: Patient blood management program may reduce inappropriate RBC transfusion. Implementation of PBM was associated with lower risk of CKD progression in hospitalized CKD patients.

PO0474

Ferric Pyrophosphate Citrate (Triferic® AVNU): Alternate Intravenous Dosing Strategies Compared to Continuous Infusion over 3 Hours

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Background: Ferric pyrophosphate citrate injection (FPC-IV) is an iron replacement product to maintain hemoglobin by intravenous infusion over 3 to 4 hours. The aim of this study was to investigate FPC-IV pharmacokinetics and confirm safety of alternate dosing strategies.

Methods: An open-label, randomized, multiple period single dose study was conducted in 23 CKD-5HD patients to establish the equivalence of doses between FPC-IV as a 3-hour infusion using the on-machine syringe pump and 5 alternate dosing strategies. The treatments were A) Baseline FPC-IV 6.75 mg Fe/3 hours (approved rate); B) FPC-IV 3.38 mg Fe bolus injections at t=0 and t=3 hours; C) FPC-IV 6.75 mg Fe bolus injection at t=0 hours over 0.5 - 5 min. and D) FPC-IV 2.25 mg Fe bolus injections at t=0, t=1.5 and t=3 hours and E) FPC-IV 6.75 mg Fe by infusion using a spring-driven syringe pump with flow restrictive tubing to deliver 2 mL/hr]. Blood samples were obtained to assess total iron (Fe_{tot}), transferrin bound iron (TBI), transferrin saturation (TSAT) and iron binding capacity (TIBC).

Results: The results for TSAT (Fig.1) track the administration group. FPC-IV was generally well tolerated in all treatments. There was transient flushing and abdominal discomfort of mild to moderate severity associated with treatment C (bolus injection of FPC over 0.5-5 min.) experienced by 15 of 16 patients. All symptoms spontaneously resolved over 2 to 5 minutes and no adverse events or intolerance was reported with any other treatment.

Conclusions: The results of this study demonstrate that FPC-IV can be safely administered as a continuous infusion over 2.5 to 4 hours or as IV bolus administration of 1/2 or 1/3 of the total dose at intervals during the course of dialysis. Bolus administration of the entire dose is not recommended due to the transient intolerance associated with the rapid administration. The study expands the dosing strategies for the administration of FPC.

Funding: Commercial Support - Rockwell Medical Inc.

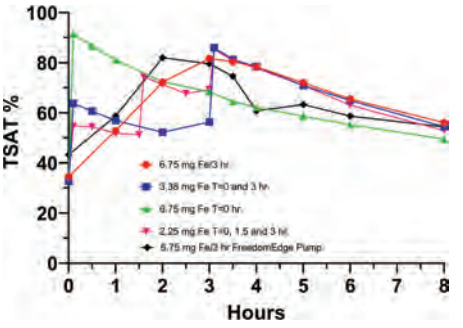

Fig.1. TSAT profile

PO0475

Ferric Pyrophosphate Citrate (Triferic® AVNU) Injection: Alternate Intravenous Dosing Using a Spring-Driven External Infusion Pump

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Background: Ferric pyrophosphate citrate injection (FPC-IV) is an iron replacement product to maintain hemoglobin by intravenous infusion (IV) over 3 to 4 hours. Some hemodialysis (HD) centers cannot use HD system syringe pumps for drug administration. We investigated the use of a spring-driven syringe pump to infuse FPC IV into the pre-or post dialyzer blood lines.

Methods: An open-label, study was conducted in 12 HD patients at 6 treatments. FPC-IV (6.75mg Fe/4.5 mL) was drawn up into 20 mL syringes. The syringe was attached to a flow-restrictor tubing 2 mL/hr (nominal rate) and then attached to the the pre-Dialyzer blood line port or to the venous drip chamber. The syringe was placed in the chamber of the FreedomEdge® Pump (FP) and the pump activated. Blood for serum iron (sFe) and transferrin saturation (TSAT) was collected pre-hemodialysis and immediately post infusion.

Results: FP Delivery of FPC took an average of 134 ± 31.7 minutes (Range 71 to 195 min). The mean increment in sFe pre- to post infusion was 202 ± 73.7 µg/dL. The pump set up, including loading the syringe, took an average of 109 ± 42.7 sec (Range: 48 to 251 sec.). The incremental sFe in this study is compared to the dialysate and IV FPC infusions over 3 hours in Figure 1. The sFe was rapidly cleared with no increase in pre-dialysis sFe. FPC-IV was well tolerated with no reported adverse events.

Conclusions: The results of this study demonstrate that FPC-IV can be safely administered as a continuous infusion using a spring-driven pump (FP) over 71 to 195 minutes. The increment in sFe is slightly greater than the 3 or 4-hour FPC infusions due to the shorter administration time. A spring-driven infusion pump to administer FPC IV is well-tolerated and a suitable alternative to use of the Hemodialysis machine syringe pump.

Funding: Commercial Support - Rockwell Medical Inc.

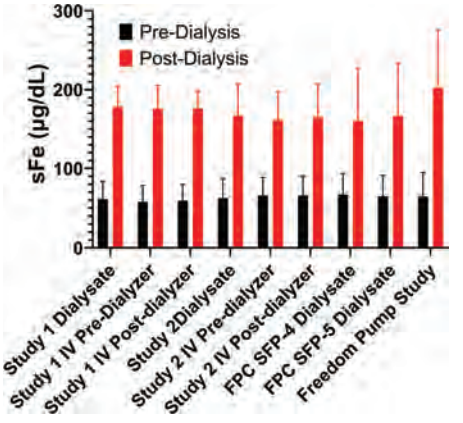

Figure 1. Comparison of pre- and post-dialysis sFe across FPC studies.

PO0476

Association Between Serum Indices of Iron Metabolism and Cardiovascular Morbidity in Patients with Pre-Dialysis CKD

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Background: The optimal ranges of serum iron markers are uncertain in predialysis chronic kidney disease (CKD) patients. Therefore, we aimed to investigate the association between serum indices of iron metabolism and the incidence of CVD events in patients with predialysis CKD using the CKD-Japan Cohort (CKD-JAC) data.

Methods: We prospectively followed 1,550 CKD patients aged 20-75 years with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 for a mean of 4.21 years. We set serum transferrin saturation (TSAT) and ferritin levels as the main exposures to be tested. Our main outcome measures were any of the CVD events including congestive heart failure (CHF) identified at each facility and adjudicated by the independent cardiac function evaluation committee. Multivariable Cox proportional hazards regression models were employed to examine the association between serum TSAT or ferritin levels with time to events. All models were stratified by facilities and adjusted for potential confounders. We also applied the multivariable fractional polynomial interaction (MFPI) approach to investigate whether serum TSAT or ferritin levels are the effect modifier of the association between iron supplementation and the outcomes.

Results: In the overall cohort, 208 (13.4 %) patients developed CVD events (including 97 CHF) during the follow-up period (26.6 events/1000 person-year). The incidence rate of CVD events was the highest in the TSAT < 20% category (33.0 events/1000 person-year). Compared to patients in the TSAT > 40% category, those in the TSAT < 20% category demonstrated an increased risk of CVD events (adjusted hazard ratio (AHR): 1.86, 95% confidence interval (CI): 1.06-3.26) and CHF events (AHR: 2.82, 95% CI: 1.15-6.89), respectively. There was no association between serum ferritin levels and the risk of CVD or CHF events. MFPI analyses showed a reduced risk of CVD in patients receiving iron supplementation only in patients with TSAT < 20% (P for interaction=0.02).

Conclusions: Maintaining TSAT > 20% could be effective to reduce the risk of developing CVD events (especially CHF) in patients with predialysis CKD. Our analyses also suggest that iron-deficient patients with predialysis CKD may benefit from iron supplementation for reduced risk of CVD events.

PO0477

Serum Erythroferrone and Serum Hepcidin 25 Are Associated with CKD

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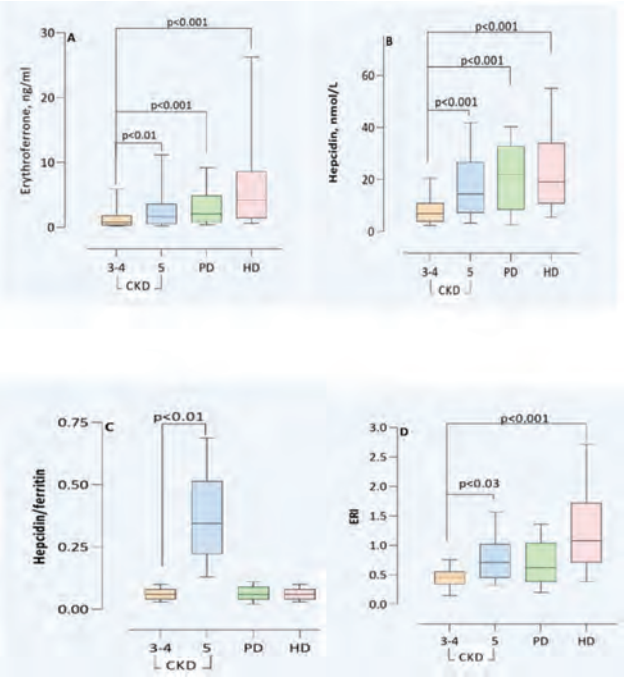
Background: Erythroferrone is a recently discovered hepcidin suppressor expressed in erythroblasts in response to erythropoietin (EPO) with the downstream effect of increased iron availability. In light of the central role of hepcidin-25 in the pathogenesis of anemia, we determined serum erythroferrone, serum hepcidin-25, the hepcidin/ferritin ratio, and the ESA hyporesponsivess index (ERI) in different stages of chronic kidney disease (CKD).

Methods: Erythroferrone was determined by ELISA in 602 CKD patients (97 CKD 3-4, 220 CKD 5 non-dialysis patients, 76 prevalent peritoneal dialysis (PD) patients, and 209 prevalent hemodialysis (HD) patients. The ERI was calculated as follows: ESA dose (international units) per kg/haemoglobin level (g/L) per week. Differences in levels of erythroferrone (ng/ml), hepcidin-25 (nmol/L), the hepcidin ferritin ratio, and ERI between stages of CKD were assessed by non-parametric ANOVA.

Results: Serum erythroferrone and serum hepcidin-25 increased with increasing CKD stage and was higher in patients with CKD 5, in PD patients, and in HD patients as compared to patients with CKD 3-4 (Figure A, B). When levels of hepcidin-25 were corrected for serum ferritin levels (hepcidin/ferritin ratio), only patients in CKD 5 had higher levels as compared to patients in CKD 3-4 (Figure C). Estimated ERI was higher in CKD 5 and HD patients as compared to CKD 3-4 patients (Figure D). The high tertile of erythroferrone in CKD 5 was associated with worse clinical outcome. No significant association with clinical outcome was observed in other cohorts.

Conclusions: Serum erythroferrone, serum hepcidin and ERI were linearly associated with deteriorating renal function. We found significant association of erythroferrone to all-cause mortality in CKD 5 patients.



PO0478

Cardiorenal Anemia Syndrome in Heart Failure Patients with Reduced vs. Preserved Ejection Fraction: An Insight from the Middle East

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Background: Patients with cardiorenal syndrome (CRS) have an increased risk of developing anemia, resulting in cardiorenal anemia syndrome (CRAS), which can lead to worsening renal and cardiac functions. This gets more complicated when multiple systemic conditions co-exist, such as in heart failure with preserved ejection fraction (HFpEF). To better understand the interplay between anemia, the heart, and the kidney, we aim to explore patients' characteristics of CRAS within different heart failure (HF) phenotypes, in the Middle East Region.

Methods: We included HF patients having stage 3-5 CKD (n=230) at their first visit to our HF clinic from October 2015 to January 2019. Patient characteristics were collected by a retrospective chart review. A comparison was made between HFrEF and HFpEF in CRAS patients in terms of baseline characteristics and iron deficiency anemia surrogates using appropriate parametric or non-parametric (for skewed variables) testing methods, and a p-value< 0.05 was considered statistically significant.

Results: Among 230 patients with cardiorenal syndrome, 138 (60%) of patients had anemia (Hb<120 g/L). There was no significant difference in the prevalence of anemia in the HFrEF- CRS group vs. HFpEF- CRS group (57.4% vs. 66.2%, p=0.2). When comparing HFrEF- CRAS patients with HFpEF- CRAS patients, the HFpEF group were more likely females, had lower hemoglobin, and higher rates of cardiovascular co-morbidities (Table). Furthermore, there was no significant difference in iron deficiency parameters between the two groups.

Conclusions: In this part of the world, where cardio-renal-metabolic conditions are highly prevalent, the prevalence of anemia among CRS patients is comparable to western countries and it was comparable among HFpEF and HFrEF CRS patients

Table. Baseline characteristics of patients with cardiorenal anemia syndrome according to their heart failure phenotype

Variable	HFrEF- CRAS patients (n=93)	HFpEF- CRAS patients (n=45)	P-value
Age (years)	66.9 ± 13.2	68.4 ±9.8	0.5
Female gender	26.9%	55.5%	0.001
Ischemic heart disease	66.7%	62.2%	0.7
Hypertension	85%	97.8%	0.02
Hyperlipidemia	74.2%	84.4%	0.2
Diabetes mellitus	76.3%	91.1%	0.04
Atrial fibrillation	30.1%	35.5%	0.5
Smoking	35.5%	31.1%	0.7
Vitals at baseline visit			
Baseline resting heart rate (bpm)	73 ±18.5	82.2 ±17.1	0.005
Baseline systolic blood pressure (mmhg)	118.7 ±22	135.2 ±20.6	<0.001
Weight (kg)	73 ±18.4	82.2 ±17.1	0.006
Medication at baseline visit			
RAAS inhibitors	59.1%	40%	0.04
Loop diuretics	84.9%	84.4%	1
Mineralocorticoid receptor antagonists	35.5%	13.3%	0.008
Aspirin	67.7%	53.3%	0.1
Statins	75.3%	91.1%	0.04
Haemoglobin (g/L)	103.3 ±10.6	96.7 ±17.4	0.001
Iron deficiency parameters			
Iron Saturation %*	20.1 ±14.8	16.7 ±8.1	0.19
Ferritin (mcg/L)*	167 [64.5-327]	117.5 [65-265]	0.3

Abbreviation: RAAS: Renin angiotensin aldosterone system
Note: Values presented as percentage %, mean ± standard deviation, or median (IQR)
*Data were missing for 10 patients

PO0479

Hypersensitivity Reaction to Epoetin-Alfa: A Therapeutic Challenge

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Introduction: Use of erythropoiesis stimulating agents (ESA) prevent the need for recurrent blood transfusions in patients with advanced kidney disease. Rarely, patients can have allergic reactions to the ESA components which can range from pruritic rash to fatal angioedema. We report a case of delayed-type hypersensitivity reaction (DTH) due to epoetin-alfa (EPO). Cross-reactivity between molecular structures of various agents raises a therapeutic challenge.

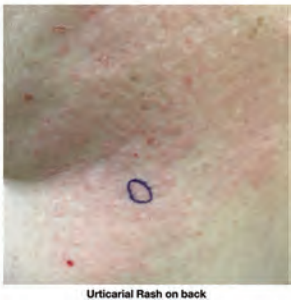
Case Description: A 78 year old man with anemia in the setting of chronic kidney disease stage 4 secondary to diabetes mellitus was initiated on EPO 10,000 units per month. He developed an urticarial rash in the back and chest after the first dose, which gradually worsened after receiving the second dose. Review of recent history was negative for any other new medication or chemical exposure. He underwent skin biopsy which showed dermatitis with eosinophils supporting a drug reaction. EPO was discontinued with resolution of the rash. Given known risk of cross-reactivity between various ESA molecules, he was subsequently referred to an allergist for desensitization protocol, followed by successful re-introduction of ESA therapy.

Discussion: Currently, ESA remains the treatment of choice for anemia of kidney disease, in order to limit need for blood transfusions. ESA-related DTH reactions can be due to excipients such as polysorbate, as well as the structural subunits of erythropoietin. Cross-reactivity has been reported between different ESA structures, which raises a therapeutic challenge in the care of such patients. Clinicians should consider desensitization, which can lead to successful re-introduction of ESA therapy.

Modified outpatient 17-day EPO desensitization protocol

Day	Dose (IU)
1	100
1	200
4	400
4	800
10	1,600
12	3,200
15	6,400
17	10,000

Doses were administered every 48–72 h



Urticarial Rash on back

PO0480

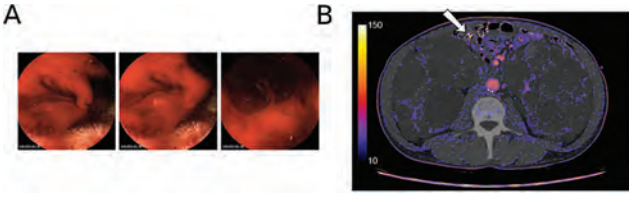
An Unusual Cause of Anaemia: Duodenal Compression by Polycystic Kidneys

Maithili Mehta, Fiona Duthie, Eoin D. O Sullivan. *Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.*

Introduction: We report a rare case of gastrointestinal bleeding due to extrinsic compression and shearing of bowel in a patient with autosomal dominant polycystic kidney disease (ADPKD).

Case Description: A 52-year-old male presented with progressive dyspnoea and melaena over one week. He was noted to have an eGFR of 9 ml/min/1.73 m^2, giant polycystic kidneys and a family history of ADPKD. A diagnosis of ADPKD was made and he was commenced on peritoneal dialysis. He was noted to have mitral regurgitation and hypertension. His haemoglobin at presentation was 39 g/L and his blood film revealed ovalocytes, without evidence of haemolysis. Haematinics were suggestive of iron deficiency. While uraemic at presentation, he had no other notable risk factors for bleeding. Upper GI endoscopy and colonoscopy were both unremarkable. He was treated with red cell transfusion, intravenous iron and commenced on an erythropoiesis-stimulating agent. He presented on four subsequent occasions over an 8 month period with recurrence of severe anaemia and melaena. A capsule endoscopy suggested bleeding at the duodenal-jejunal flexure, however no source was visualised. The cause of the bleeding was revealed by double balloon enteroscopy which demonstrated extrinsic compression of the scope at D3. Review of imaging confirmed this was due to a large right renal cyst. Ongoing tranexamic acid and lanreotide treatment has reduced the frequency of bleeds. While a nephrectomy would potentially provide a definitive solution to the underlying cause, this caries substantial risk and would need to be carefully coordinated with his mitral valve repair.

Discussion: While peptic ulcer disease is slightly increased in ADPKD, this is the first description of mechanical trauma to bowel by polycystic kidneys resulting in severe recurrent GI bleeding. **Teaching points** 1. Giant polycystic kidneys can rarely compress small bowel and cause GI bleeding 2. Correlation of advanced endoscopy such as double balloon enteroscopy with radiology may be required to make the diagnosis 3. Tranexamic acid and lanreotide may reduce bleeding.



Enteroscopy (A) and CT (B) show compression point.

PO0481

Targeted Literature Review (TLR) Exploring Adherence to Treatments, with Potential to Extrapolate to Patients with Anemia of CKD

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Background: Adherence to long-term treatment for chronic diseases, e.g. anemia of CKD, is problematic. Adherence to a patient's preferred treatment is critical to successful CKD management. We explored: availability of published best practice guidance for long-term disease; how analog scenarios from healthcare teams and patients provide learnings about treatment adherence and persistence; patient preferences; and how to measure adherence-related outcomes.

Methods: We conducted a TLR of analog scenarios where an oral therapy was introduced in a setting with injectable/subcutaneous therapy as standard of care. Embase and Cochrane searches included administration route, dosing frequency and titration, from 2016–2020. Searches were limited to literature reviews and clinical guidelines for adults with chronic disease from 10 countries.

Results: Of 1421 papers identified, 85 were relevant. Inspection of these papers revealed that non-adherence may be intentional or non-intentional, and can be linked to numerous factors, e.g. polypharmacy, treatment regimen complexity, number of daily tablets, lengthy treatment duration, and patient beliefs about treatment. Intentional non-adherence may link to patients' motivations/beliefs, and non-intentional non-adherence may link to patients' skill/ability to take a medicine. Regimen complexity can be influenced by drug dosage form, product characteristics, dosage schemes, specific additional instructions (e.g. fixed-time daily dosing), patient characteristics and administration errors. Discrete choice experiments and conjoint analyses provide robust means of measuring patient preferences, but evidence is conflicting of preference for injectable vs oral treatments, which is relevant to anemia of CKD management. Accurately documenting evidence of medication ingestion/administration is difficult. While several methods exist for assessing treatment adherence and persistence, no gold standard was identified.

Conclusions: In a competitive treatment setting, there remains significant opportunity to support patients in their treatment choice. Identifying best practice models of treatment adherence, persistence and measuring patient outcomes may prove important for differentiating between treatments.

Funding: Commercial Support - Astellas Pharma Inc.

PO0482

Iron-Related Outcomes in Patients with Non-Dialysis-Dependent CKD Randomized to Vadadustat vs. Darbepoetin Alfa

Mark Koury,[1] Pablo E. Pergola,[2] Prabir Roy-Chaudhury,[5] Youssef M. Farag,[3] Wenli Luo,[3] Robert Anders,[3] Christine Solinsky,[3] Dennis Vargo,[3] Wolfgang C. Winkelmayer.[4] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Renal Associates PA, San Antonio, TX; [3]Akebia Therapeutics Inc, Akebia Therapeutics Inc, Cambridge, MA, US, corporate/pharma, Cambridge, MA; [4]Baylor College of Medicine, Houston, TX; [5]UNC School of Medicine - W. G. (Bill) Hefner VA Medical Center, Salisbury, NC.*

Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for treatment of anemia due to chronic kidney disease (CKD).

Methods: We conducted 2 global phase 3, randomized, open-label, sponsor-blind, active-controlled, noninferiority trials (PRO_2TECT) comparing once-daily oral dosing VADA with the erythropoiesis-stimulating agent (ESA) darbepoetin alfa (DA) in 1751 patients with non–dialysis-dependent CKD (NDD-CKD) not previously ESA treated and in 1725 NDD-CKD patients previously ESA treated. Inclusion criteria included serum ferritin ≥100 ng/mL and transferrin saturation (TSAT) ≥20%. Safety and efficacy results were previously reported. Here we report iron-related outcomes, including the changes in mean serum hepcidin, ferritin, total iron-binding capacity (TIBC), iron, and TSAT from baseline to the primary (wk 24–36) and secondary (wk 40–52) evaluation periods (PEP and SEP).

Results: A total of 1741 patients received VADA and 1735 received DA. VADA treatment was associated with greater decreases in mean hepcidin, ferritin, and TSAT, and increases in TIBC from baseline at PEP and SEP (**Table**). A small increase in serum iron was seen in the VADA group as was a decrease in the DA group from baseline to PEP and SEP. Oral and IV iron use was similar in the 2 treatment groups throughout both studies.

Conclusions: Treatment with VADA resulted in relative decreases in hepcidin and ferritin and increases in TIBC and serum iron. Decreases in TSAT should be interpreted in light of a greater increase in TIBC than that of serum iron. These changes are consistent with a VADA-induced increase in iron mobilization from extracellular stores that support erythropoiesis.

Funding: Commercial Support - Akebia Therapeutics, Inc., and Otsuka Pharmaceuticals Development and Commercialization, Inc.

Table. Changes From Baseline in Iron-Related Parameters

	Primary Evaluation Period (wk 24–36)				Secondary Evaluation Period (wk 40–52)			
Parameter, LS mean (SEM)	VADA (N=1741)	DA (N=1735)	Difference (VADA–DA) LS mean (95% CI)	*P* value	VADA (N=1741)	DA (N=1735)	Difference (VADA–DA)	*P* value
Hepcidin, ng/mL	−38.2 (2.3)	−11.0 (2.3)	−27.2 (−32.1, −22.2)	<0.001	−40.4 (2.8)	−21.0 (2.8)	−19.4 (−25.5, −13.4)	<0.001
Ferritin, ng/mL	−77.5 (7.4)	−45.4 (7.3)	−32.1 (−48.1, −16.0)	<0.001	−64.8 (8.9)	−44.0 (8.8)	−20.8 (−40.0, −1.6)	0.03
TIBC, µg/dL	33.8 (1.1)	0.8 (1.1)	33.0 (30.6, 35.5)	<0.001	31.5 (1.3)	1.3 (1.3)	30.3 (27.5, 33.1)	<0.001
Serum iron, µg/dL	0.4 (0.8)	−2.4 (0.8)	2.8 (0.9, 4.6)	0.003	0.5 (1.0)	−1.9 (1.0)	2.39 (0.3, 4.5)	0.03
TSAT, %	−3.4 (0.3)	−0.5 (0.3)	−2.9 (−3.7, −2.2)	<0.001	−3.1 (0.4)	−0.4 (0.4)	−2.8 (−3.6, −1.9)	<0.001

PO0483

Elevation in Red Cell Distribution Width (RDW) Is a Risk Factor for Future Hyponatremia and Hypokalemia

Hiroshi Tanaka. *Mihara Sekijuji Byoin, Mihara, Japan.*

Background: Elevation in red cell distribution width (RDW), a marker of size variance in red blood cells, recently has been reported to predict mortality, future cardiovascular events, and faster CKD progression. Putative mechanisms in RDW elevation include factors such as inflammation, aging, oxidative streess or malnutrition. It has not been clearly reported whether elevation in RDW has any significant impact on future electrolyte metabolism.

Methods: A hospital-wide study with all the laboratory data for a period of 4 years and 2 months was conducted. First, for each patient, hemoglobin (Hb) measurements of the initial 365 days were retrieved and the maximum RDW was obtained. Then the latest measurements of serum sodium (Na) and potassium (K), at least 365 days apart from the initial Hb and RDW measurement, were obtained. Prevalence and odds ratio (OR) of hyponatremia and hypokalemia were calculated for each quartile of RDW. Statistical analysis was performed with R 3.6.0 on Ubuntu and with Microsoft Excel.

Results: A total of 5,537 patients were included in the study. Hb ranged from 7.7 to 20.2 (median 13.4) g/dL, MCV 55.7-124.5 (93.1) fL, and RDW 10.1-34.6 (12.7)%. Hyponatremia (<130 mEq/L) was observed in 2.65%/1.10%/0.49%/0.71% in patients in each quartile of RDW (from high to low; chi-squared, P <0.001); Patients in the highest quartile of RDW had hyponatremia with OR of 3.80 when reference was set to the lowest quartile of RDW. Hypokalemia (<3.5 mEqL) was observed in 6.99%/4.02%/2.17%/1.89% in each quartile of RDW (chi-squared, P <0.001); Patients in the highest quartile of RDW had OR of 3.90 as the reference at the lowest quartile of RDW. Likewise, in patients with the highest quartile of RDW, more severe hyponatremia (<125 mEq/L) and hypokalemia (<3.0 mEq/L) were seen in 0.61% (OR 2.59) and 1.49% (OR 19.2), respecively.

Conclusions: Elevation in RDW is a risk factor for future development of hyponatremia and hypokalemia

PO0484

IL-6 Inhibitor Ziltivekimab Increases Serum Hemoglobin and Iron Biomarkers in Patients with CKD Stage 3–5: A RESCUE Trial Analysis

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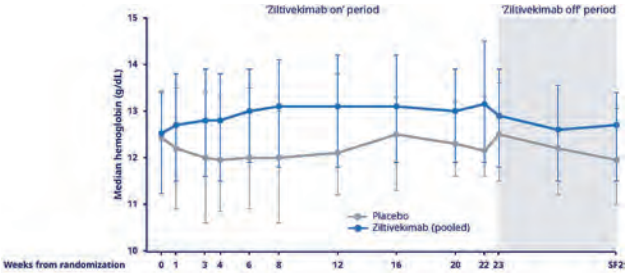
Background: Interleukin-6 (IL-6)-mediated inflammation causes functional iron deficiency and anemia in patients (pts) with chronic kidney disease (CKD). IL-6 inhibitor, ziltivekimab, reduced inflammation markers (RESCUE trial; NCT03926117) and improved anemia and serum albumin in hemodialysis pts (NCT02868229). We examined the effect of ziltivekimab on serum hemoglobin (Hb) and iron homeostasis in pts with CKD stage 3–5 in the RESCUE trial.

Methods: Changes in anemia markers from baseline (BL) to Week 12 were assessed in pts (CKD stage 3–5, high-sensitivity C-reactive protein ≥2 mg/L) treated with ziltivekimab 7.5, 15 or 30 mg vs placebo (PBO). The intention-to-treat population was analyzed using a mixed model for repeated measurements (no adjustment for multiplicity). Analysis by BL Hb level (<11 or ≥11 g/dL) was conducted.

Results: In the RESCUE trial overall, mean age was 66 years, median Hb 12.5 g/dL at BL (N=198, ziltivekimab; N=66, PBO). Ziltivekimab increased Hb from BL to Week 12 vs PBO (p<0.001 for each dose; Figure/Table), with numerically greater increases with ziltivekimab vs PBO in pts with BL Hb <11 g/dL than pts with BL Hb ≥11 g/dL (Table). Ziltivekimab increased serum iron levels (p<0.0001), total iron-binding capacity and transferrin saturation (both p<0.01) vs PBO. No major safety concerns were reported.

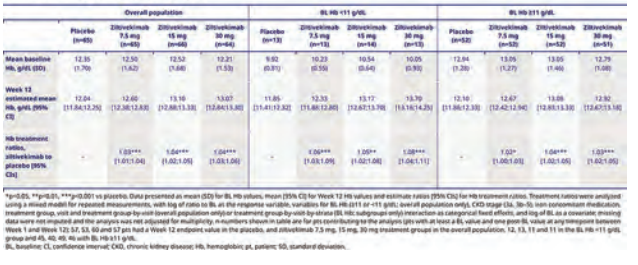
Conclusions: Ziltivekimab improved levels of Hb, serum iron and other iron biomarkers vs PBO in pts with CKD stage 3–5. By reducing inflammation and improving functional iron deficiency, ziltivekimab may improve anemia in pts with CKD.

Funding: Commercial Support - Novo Nordisk



Data are presented as median values and interquartile ranges (error bars) due to data distribution. Ziltivekimab data include pooled 7.5, 15 and 30 mg doses. n-numbers shown below the graph are for patients contributing to the analysis at that timepoint. SF2, safety follow-up 2 (11 weeks after last dose).

Table: Mean hemoglobin at baseline and Week 12



*p<0.05, **p<0.01, ***p<0.001 vs placebo. Data presented as mean (SD) for BL Hb values, mean (95% CI) for Week 12 Hb values and estimate ratios (95% CIs) for Hb treatment ratios. Treatment ratios were analyzed using a mixed model for repeated measurements, with log of ratio to BL as the response variable, variables for BL Hb (<11 or ≥11 g/dL; overall population only), CKD stage (3a, 3b–5), iron concomitant medication, treatment group, visit and treatment group-by-visit (overall population only)or treatment group-by-visit-by-strata (BL Hb; subgroups only) interaction as categorical fixed effects, and log of BL as a covariate; missing data were not imputed and the analysis was not adjusted for multiplicity. n-numbers shown in table are for pts contributing to the analysis (pts with at least a BL value and one post-BL value at any timepoint between Week 1 and Week 12); 57, 53, 60 and 57 pts had a Week 12 endpoint value in the placebo, and ziltivekimab 7.5 mg, 15 mg, 30 mg treatment groups in the overall population, 12, 13, 11 and 11 in the BL Hb <11 g/dL group and 45, 40, 49, 46 with BL Hb ≥11 g/dL.
BL, baseline; CI, confidence interval; CKD, chronic kidney disease; Hb, hemoglobin; pt, patient; SD, standard deviation.

PO0485

Sodium-Glucose Cotransporter 2 Inhibitors and Anemia Among Diabetic Patients in Real Clinical Practice

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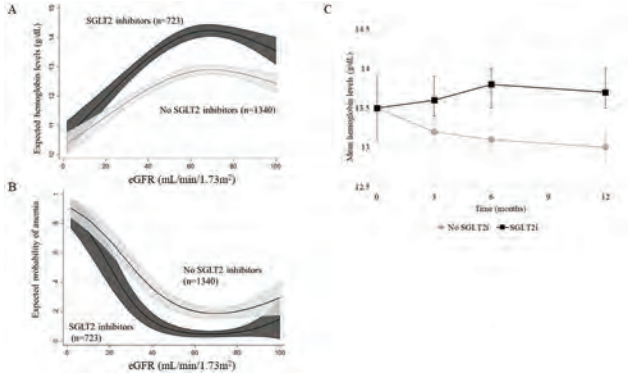
Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were reported to increase hemoglobin levels in short-term clinical trials. Whether it is also true in real clinical practice is unknown.

Methods: This is a retrospective cohort study. Inclusion criterion was diabetics who visited our outpatient clinic from January 2019 to August 2020. Exposure of interest was the use of SGLT2i. Outcomes were hemoglobin levels. For the cross-sectional analyses, non-linear regression models were fitted with restricted cubic splines to investigate the association between hemoglobin levels and estimated glomerular filtration rate (eGFR) for users and non-users of SGLT2i. For the case-control study, cases (anemia defined as hemoglobin <12 g/dL for men, <11g/dL for women or the use of erythropoiesis stimulating agents) and controls were matched by age, sex, and eGFR.

Results: Among 2063 diabetics, 723 were on SGLT2i. In the cross-sectional analyses, hemoglobin levels were higher among SGLT2i users compared with non-users at eGFR >15 mL/min/1.73m^2. For the case-control study, 197 cases and controls were

matched. Conditional logistic regression showed that the use of SGLT2i was associated with significantly lower prevalence of anemia (OR: 0.35 [0.21-0.58]). Adjusted mean differences (95% CIs) in hemoglobin levels between users and propensity score-matched non-users of SGLT2i were 0.7 (0.3-1.0) g/dL at 6 months. Among SGLT2i users, odds of increase in 6-month hemoglobin were similar across eGFR categories except for eGFR <15 mL/min/1.73m^2.

Conclusions: The use of SGLT2i was associated with higher hemoglobin levels and lower prevalence of anemia in real clinical practice.



PO0486

Pro-Inflammatory Signaling Alters Hematopoiesis in Anemic Mice

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Background: Iron deficiency anemia (IDA) is a common complication of Chronic Kidney Disease (CKD), associated with accelerated disease progression and death. IDA is the direct result of low circulating iron and total body iron stores, which are unable to meet the demands of erythropoiesis. To date, the effects of low iron bioavailability and anemia on hematopoiesis at the single cell level remain unexplored.

Methods: To investigate the effects of IDA on hematopoiesis, we fed three-week old mice a control or an iron deficient diet for 3 weeks. As expected, mice fed on a low-iron diet developed IDA, evidenced by low hematocrit count and severely reduced hemoglobin. We next analyzed the developing hematopoietic progenitors and identified molecular markers that are predictive of the cell differentiating status using single cell RNA sequencing of bone marrow (BM) and peripheral blood (PB) cells from control and IDA mice.

Results: We found that IDA increased the number of hematopoietic stem cells and restricted erythroid progenitors in BM and in PB. In contrast, IDA disrupted terminal erythroid differentiation, and particularly the differentiation of orthochromatic erythroblasts into reticulocytes. Compared to control mice, orthochromatic erythroblasts from IDA mice differentiated into an "alternate" reticulocyte cluster, overabundant in BM but quasi-absent in PB. Analysis of differentially expressed genes showed that iron deficiency increased pro-inflammatory signaling and resulted in the expression of pro-apoptotic markers in this alternate cluster, including the expression of *Ddit3* (+12 fold), *Trib3* and *Atf4* (+13 fold). The effects of IDA were not restricted to the erythroid lineage. IDA reduced the number of differentiated myeloid cells such as macrophages and neutrophils. Importantly, cells from IDA mice showed increased BM megakaryopoietic differentiation and higher number of circulating megakaryopoietic cells in PB. In contrast, IDA reduced lymphoid differentiation and thus, lowered the number of mature B cells, highlighting the importance of iron in adaptive humoral immune responses.

Conclusions: In aggregate, our data suggest that iron deficiency anemia alters hematopoiesis through inflammation-induced expansion of progenitors and apoptotic signaling in mature cell populations. Our results might help develop targeted therapies in CKD patients to correct anemia and improve outcomes.

Funding: NIDDK Support

PO0487

ASCEND-TD: A Randomized, Double-Blind, Active-Controlled Study of Daprodustat Administered Three Times Weekly in Hemodialysis Patients

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Background: Daprodustat (dapro) is a hypoxia-inducible factor prolyl hydroxylase inhibitor being investigated for the treatment of anemia of chronic kidney disease (CKD). This study evaluated the efficacy and safety of dapro administered three-times-weekly (TIW) vs recombinant human erythropoietin (rhEPO) for in-center prevalent hemodialysis (HD) patients.

Methods: This double-blind study (NCT03400033) randomized (2:1) HD patients with a baseline hemoglobin (Hb) of 8–11.5 g/dL already on rhEPO to dapro TIW (n=270) or rhEPO (n=137) for 52 weeks. A dosing algorithm aimed to maintain Hb between 10–11g/dL. The primary endpoint was a mean change in Hb in the evaluation period (EP; Weeks 28–52). The principal secondary endpoint was average monthly intravenous (IV) iron dose. Other secondary endpoints included blood pressure (BP) and Hb variability.

Results: Baseline characteristics in 407 randomized patients were balanced between the dapro and rhEPO groups. Dapro TIW was non-inferior to rhEPO for mean change in Hb (model-adjusted mean treatment difference [dapro-rhEPO] -0.05; 95% CI: -0.21, 0.10). In the EP, mean (SD) Hb was 10.45 (0.549) g/dL and 10.51 (0.849) g/dL for dapro and rhEPO groups, respectively. However, 80.0% in the dapro group were responders (mean Hb during EP in the analysis range [10–11.5 g/dL]) vs 63.6% in the rhEPO group, with a difference of 16.5% (one-sided nominal p=0.0007 after adjustment for region). Mean monthly IV iron dose was not statistically significantly lower with dapro vs rhEPO. While fewer BP elevations occurred with dapro vs rhEPO (one-sided nominal p=0.0093), the overall effect of dapro on BP was similar to rhEPO. In general, safety findings were comparable between treatment groups, with the incidence of treatment-emergent adverse events similar between dapro (75%) and rhEPO (79%).

Conclusions: Dapro was non-inferior to rhEPO in Hb response and was well-tolerated. Dapro administered TIW using the protocol employed in this study is a viable alternative to rhEPO in prevalent HD patients with anemia of CKD.

Funding: Commercial Support - GlaxoSmithKline

PO0488

Stabilization of Hypoxia-Inducible Factors Leads to Profound Epigenetic Changes in Primary Human Tubular Cells

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Background: Pharmacological stabilization of Hypoxia-inducible factors (HIFs) to induce erythropoietin expression presents a novel therapeutic approach to treat patients with renal anemia. Whereas general effects of HIFs on the transcriptome are well studied, insights in HIF-mediated alterations at the epigenetic level remain limited. The epigenetic landscape determines cellular identity and may be shaped by environmental factors such as hypoxia via HIF. In this study, we aim at generating a genome-wide atlas of the tubule-specific chromatin landscape while investigating the epigenetic plasticity of regulatory DNA elements provoked by HIF stabilization.

Methods: Primary tubular cells (PTC) were isolated from tumor nephrectomy specimens. We performed unbiased analyses of chromatin structure and HIF DNA-interactions using the Assay for Transposase Accessible Chromatin followed by sequencing (ATAC-Seq) and Chromatin Immunoprecipitation DNA-Sequencing (ChIP-seq), respectively. These epigenetic data sets were complemented with transcriptome information gained by RNA sequencing.

Results: ATAC-seq data generated in PTC obtained from four different individuals were combined to create a genome-wide landscape of chromatin accessibility comprising approx. 110 000 consensus regions. We validated cellular identity by benchmarking these sites against publicly available epigenomic data sets provided by ENCODE. Further characterization of chromatin activity was achieved by integration of ChIP-seq data for the histone mark H3K27ac. Pharmacological stabilization of HIF resulted in a remarkable change of chromatin accessibility yielding several hundred differentially open regions. Alterations of the chromatin coincided with HIF-binding events and HIF-mediated changes in mRNA expression suggesting a functional role for HIF in shaping chromatin accessibility in renal tubular cells.

Conclusions: Our genome-wide atlas of chromatin accessibility and activity in primary tubular cells represents a valuable reference data set for the investigation of tubule-specific features. Furthermore, our comprehensive approach allows for in-depth analysis of favourable as well as adverse epigenetic effects of HIF stabilizers in human tubular cells.

PO0489

Triferic (Ferric Pyrophosphate Citrate, FPC) Maintains Hemoglobin and Reduces Total IV Iron Requirement: Results from a Mid-Sized Dialysis Organization (MDO) Pilot Observational Analysis

Samuel L. Shull, Marc L. Hoffman. *Rockwell Medical Inc, Wixom, MI.*

Background: Triferic is approved as an iron (Fe) replacement product to maintain hemoglobin (Hb) in adult patients (pts) receiving chronic hemodialysis (HD). Randomized clinical trial data have demonstrated that FPC maintains Fe stores and Hb while reducing IV Fe usage with a safety profile similar to placebo. We now report the first 8 mos of an independent MDO's experience using FPC for all HD patients (pts) during a pilot implementation at 14 clinics.

Methods: FPC was added to centrally delivered liquid bicarb to provide 110 μg Fe/L dialysate. All patients received FPC at each HD. Anonymized prospective data were provided between Sep 2020—Apr 2021. Clinics added FPC into their anemia mgmt. practices per existing protocols and standards of care (SoC). Supplemental IV Fe, up to a max of 1000 mg Fe/mth, was administered according to a protocol based on serum ferritin and TSAT values. At baseline, the ave. utilization of IV Fe was 197 mg/pt/mo. During the first 3 mos of FPC, clinics saw a modest 23% reduction of IV Fe (151mg/pt/mo)). A new Fe mgmt. protocol was released specifically designed to guide IV Fe use in conjunction with FPC; this was adopted by 9 clinics while 5 clinics chose to maintain their SoC.

Results: Within 3 mos of initiation of the new protocol, Fe utilization in this group decreased by 81%, conversely Fe utilization increased by 19% in the SoC group. During this period, Hb remained stable in both groups (+/- 0.2 g/dL from baseline). Concurrent with these changes Mircera® (-epoetin beta) dose remained stable in the SoC group but was reduced 37% (from post-adoption baseline) in the new group.

Conclusions: Additional clinics continued to adopt the new protocol over time. Taking into account the staggered adoption of the protocol, after 8 mos, the aggregate Fe utilization across all 14 clinics was reduced by 51% and trending lower. Mircera dose was stable (decreased 5%) and Hb remains stable. This observational study demonstrates that FPC is a well tolerated replacement for IV Fe when administered to all patients in a HD unit. The findings of this real-world observational study align with pivotal clinical trials and previously reported real-world evidence in terms of reduction of IV Fe use and maintenance of Hb.

Funding: Commercial Support - Rockwell Medical

PO0490

Automated Tubular Morphometric Analysis in Kidney Biopsies

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Background: Tubular atrophy is prevalent in kidney disease. We automated tubular morphometric analysis and applied it to diabetic nephropathy (DN) and transplant biopsies.

Methods: Tubules (n = 302696) were segmented with a convolutional panoptic network (***Fig. 1***) from 57 native DN and 30 transplant surveillance renal biopsies. Distributions of digitally quantitated tubular diameter and basement membrane (TBM) were evaluated with respect to chronic kidney disease (CKD) stage and interstitial fibrosis and tubular atrophy (IFTA) severity.

Results: The trends in ***Fig. 2*** show that generally, as CKD and IFTA increase, tubular diameter decreases and TBM average width increases, with the DN trend being more prominent. However, significant distribution heterogeneity is observed.

Conclusions: High-throughput computation can be leveraged to automate morphometric analysis of tubules. Further data mining using a similar approach may reveal novel features that may have diagnostic or prognostic benefit.

Funding: NIDDK Support

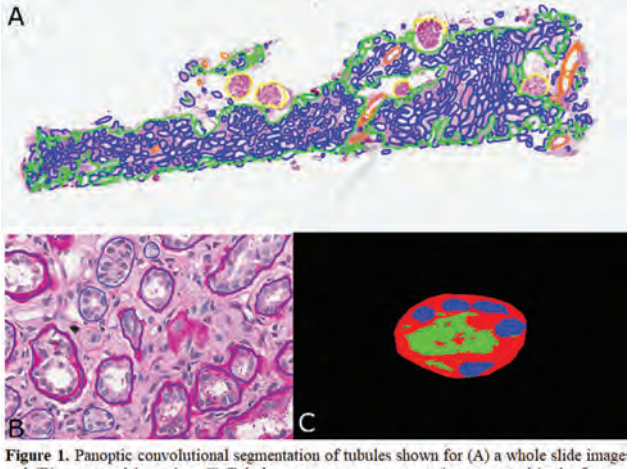

Figure 1. Panoptic convolutional segmentation of tubules shown for (A) a whole slide image and (B) a zoomed in region. C) Tubular compartment segmentation map used in the feature quantitation process showing Periodic acid-Schiff positive pixels in red, nuclei in blue and lumina in green.

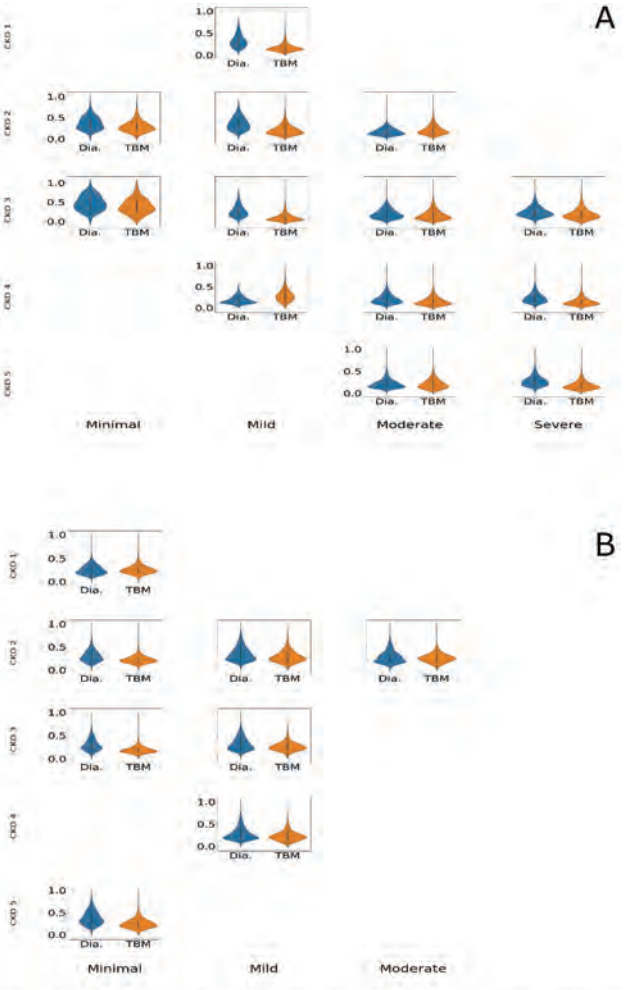

Figure 2. Distribution of tubular diameter and TBM thickness as a function of CKD and IFTA for A) DN patients and B) transplant surveillance patients.

PO0491

A Computational Pipeline for Estimating Renal Histologic Primitives

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Background: While a number of image segmentation approaches exist for digital pathology, in this study, we aimed to combine three complementary tools for enhanced quality assessment and segmentation of histologic primitives on kidney biopsy images. Specifically, we evaluated the integrated image analysis approach on two chronic kidney disease (CKD) renal tissue biopsy WSI cases from the curated Kidney Precision Medicine Project (KPMP) database.

Methods: HistoQC, an established tool for automated quality control (QC) of digital pathology images, eliminated staining and image artifacts from the biopsies. Next, two complementary computational tools were interfaced. HAIL (Human-AI-Loop), a supervised convolutional neural network, was used to isolate renal co mpartments (i.e., glomeruli, vessels, interstitium, and tubules). HAIL output was used to gate the training process of the second algorithm, VIPR (Vectorizing spatially-Invariant Pattern Recognition), a kernel-based, high-dimensional textural classifier capable of extracting distinct histopathological features as distinct sub-regions, ultimately allowing for the generation of a resulting pixel-level classification of all tissue compartments.

Results: The integrated pipeline precisely classified tubular basement membrane, brush border, nuclei, nucleoli, and tubular epithelial cytoplasm from CKD WSIs in a manner consistent with subject matter expert opinion for region fractionation, when resultant segmentation images were manually reviewed (***Fig. 1***).

Conclusions: We have shown the potential of our pipeline for image curation, and segmentation and sub-characterization of renal histologic primitives.

Funding: NIDDK Support

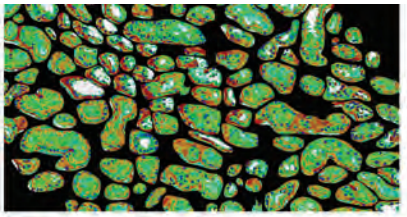

Figure 1. Renal tubular image descriptors using a combined HAIL-VIPR segmentation for a chronic kidney disease renal tissue image. Various colors stratify different image descriptors.

PO0492

A 3D Vascularised Tubule Model Improves the Phenotype of Cultured Cells

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Background: Modelling proximal tubule physiology and pharmacology is essential for mechanistic studies and drug discovery. As a consequence, a plethora of models have been developed. Despite this no comparative study between monocultures, co-cultures and 3D models has been reported. In this study we aimed to understand the differences of proximal tubule epithelial cells (PTECs) and glomerular endothelial cells (HGECs) alone or in co-culture when grown in static non-coated, static matrix-coated and 3D flow matrix-coated conditions.

Methods: We cultured PTECs under physiological flow in a 3D channel embedded within an engineered extracellular matrix (ECM) that is colocalised with an adjacent channel lined with HGECs to mimic a peritubular capillary. After a period of maturation under continuous flow, both cell types were harvested for RNAseq analyses.

Results: Our results revealed that PTECs' transcriptional profile is highly dependent on the matrix on which these cells are cultured, as well as the application of flow. Endothelial cells however demonstrated greater phenotypic plasticity, being affected by matrix, flow and co-culture. The transcriptional profile of PTECs grown on a non-coated surface presented an enrichment of inflammatory markers such as TNF-a, IL6 and CXCL6, resembling that of diseased tubular biopsies. This inflammatory effect was not seen in PTECs grown on a matrix, and the growth conditions of matrix under flow further resembled the transcriptional profile of healthy tubular biopsies. Unsurprisingly the presence of flow modulated the expression of kidney signature genes including drug/solute transporters. Likewise, HGECs' transcriptional profile more closely resembled the profile of in vivo glomerular cells when grown on a matrix under flow.

Conclusions: In conclusion, PTECs and HGECs grown under different culture conditions present considerable transcriptional profile changes; being enriched in inflammatory pathways when grown on a non-coated surface, but closely resembling *in vivo* homeostatic profiles when grown with matrix and/or flow. These findings guide future selection of translatable models investigating renal physiology and pharmacology.

Funding: Commercial Support - AstraZeneca

PO0493

Recreating Renal Function in a Human Glomerulus and Proximal Tubule Microphysiological System

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Background: Preclinical tests for pharmaceutical discovery extensively rely on static, 2D cultures and animal models. While these methods are commonly used, they poorly represent human responses due to the lack of architecture and physiological stimuli (2D culture), and human cells (animal models). Kidney microphysiological systems (MPS) better support renal function with controlled, 3D fluidic platforms, and serve as valuable tools in determining renal toxicity to new drugs. Current kidney MPS model individual regions of the nephron (glomerulus and proximal tubule or PCT) but fail to incorporate multiple filtration and reabsorption interfaces. Our study established a 7 day tri-culture of podocytes, endothelial, and PCT epithelial cells in a glomerulus and PCT MPS with key functional features.

Methods: The MPS consisted of: T-Junction, glomerulus housing (GH), and PCT chip. Media from the bloodstream flowed into the T-Junction, splitting 10% of flow to GH. The GH had a polyethersulferone membrane with human endothelial cells (HUVECs) and podocytes (CIHP-1) seeded at 10^5 cells/cm^2 on opposing sides. Connected to GH, PCT polycarbonate chip housed 10^5 cells/cm^2 of human PCT cells (HK-2) and outputs primary filtrate. At shear stress of 0.7-1.5 dyne/cm^2, velocity flow was measured based on daily filtrate output. Glomerular filtration was tested by challenging the system with 0.1 mg/mL of FITC-human serum albumin (FITC-HSA). PCT reabsorption was tested using fluorescent glucose analog (2-NBDG). Cultures were starved for 2 hrs, and later treated with media containing 200 mg/mL of 2-NBDG for 2 hrs. After 7 days of exposure, cell membranes were stained and imaged for F-actin, VE-cadherin, ZO-1, and nephrin.

Results: At a total pump flowrate of 45.3 μL/min, 17.7 μL/min (± 5.08 μL/min) exited as filtrate and 27.6 μL/min (± 7.63 μL/min) recirculated in the bloodstream. In the MPS, average daily filtrate output was 0.016 mL/min, filtration of FITC-HSA in the MPS was over 90%, and glucose output in the filtrate supported PCT reabsorption. Confocal images displayed cell type-specific protein expression.

Conclusions: Filtering of HSA, glucose reabsorption, and marker expression in the MPS indicates a physiological representation of renal filtration and reuptake in a human glomerulus and PCT. Our glomerulus and PCT MPS is a relevant preclinical tool for testing drug candidates for kidney toxicity.

PO0494

Renal Proximal Tubule Chip (RPTC) for Disease Modeling and Drug Toxicity Testing

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Background: Tissue chips are an emerging technology in disease modeling and screening therapeutics to address discrepancies between animal models and human clinical trials. They utilize tissue engineering, fluid mechanics, and biomaterials to replicate in vivo architectures and functions of complex organs and tissues. For the renal proximal tubule (PT), there are currently limited options in terms of human cell types, scalable platforms for evaluation of drug toxicity, and tissue engineered solutions where the complexity of the PT is accurately modeled.

Methods: We developed both 2D and 3D versions of the RPTC which incorporates immortalized human renal PT epithelial cells (hRPTEC-TERT1) under static and perfused conditions (i.e. physiological pressure, shear stress, and stretch). Additionally, we have begun generating peritubular vascular networks using a co-culture of human umbilical vein endothelial cells (hUVECs) and human dermal fibroblasts (hDFs) in gelatin methacryloyl (GelMA). These models were then used to investigate the effect of pressure and flow on nephrotoxicity by introducing drugs with known levels of toxicity. Our initial evaluations have been limited to non-invasive measurements such as transepithelial electrical resistance (TEER) and pro-inflammatory soluble factors, and ICC.

Results: Compared to static controls, hRPTEC-TERT1 subjected to fluid shear demonstrate that culture under physiologically relevant forces results in cytoskeletal reorganization, establishment of barrier function (adherens and tight junctions) and increased expression of transporters like aquaporin 1 and mechanosensors like α-tubulin. Additionally, noninvasive readouts such as TEER indicate the greater integrity of the renal proximal epithelium. Lastly, after 7 days, we can form dense microvascular networks to mimic the surrounding peritubular capillary networks which can actively reabsorb solutes from the glomerular filtrate. This network will enable us to test drugs in an environment where both reabsorption and secretion functions of the tubule are replicated.

Conclusions: These results provide preliminary evidence of our ability to subject hRPTEC-TERT1 to in vivo like flow conditions and demonstrate that replication of biomechanical cues from fluid flow significantly enhances the attainment of an in vivo–like phenotype which enhances the relevance of our in vitro models.

Funding: NIDDK Support

PO0495

Modeling Ischemia-Reperfusion in a High-Throughput Tubular/Microvascular Co-Culture-on-a-Chip

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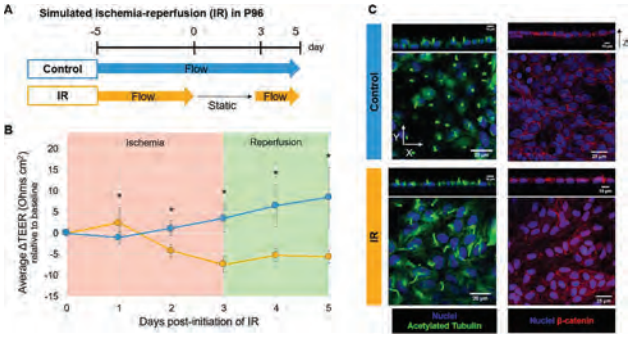
Background: Ischemia-reperfusion (IR) is a major cause of acute kidney injury (AKI). IR involves a period of inadequate perfusion that deprives highly metabolic kidney epithelia of nutrient and waste exchange impacting tissue structural integrity.

Methods: We demonstrate the potential of the PREDICT96 (P96) platform as a tool for examining tubule cell responses to IR. The oxygen-impermeable construction and robust pumping capabilities of P96 enable comparison of simulated IR and control conditions on a single culture plate. Here, primary human renal proximal tubule epithelial cells and human microvascular endothelial cells were cultured in adjacent microfluidic channels for 5 days under physiological fluid shear (0.07 Pa) to establish confluent layers. Subsequently, a portion of the tissue replicates underwent simulated IR consisting of 3 days of static conditions followed by 2 days of physiological flow. Transepithelial electrical resistance (TEER) was measured daily, and all tissues were fixed after 10 days in culture for structural characterization via immunofluorescence confocal microscopy.

Results: TEER measurements highlighted a transient increase in barrier function (relative to control tissues) in response to the onset of ischemia, followed by a reduction in integrity over subsequent days that persisted through reperfusion. IR tissues exhibited primary cilia that were on average less abundant but roughly double the length of those exhibited by control tissues. This is consistent with previous observations of cilia lengthening among IR-injured kidney epithelia in vivo. IR tissues also displayed nuclear staining for β-catenin suggestive of a proliferative response to injury.

Conclusions: The described model has significant potential to clarify mechanisms of IR injury in the kidney.

Funding: Other U.S. Government Support



(A) Experimental scheme for simulated IR in P96. (B) Average change in TEER by group relative to baseline readings on day 5 at start of IR treatment. N=12 devices per group. *p<0.05 t-test. (C) Change in tissue morphology following IR treatment.

PO0496

Niacin Supplementation Increases In Vitro Apicobasal Volume Transport and Oxygen Consumption by Proximal Tubule Cells

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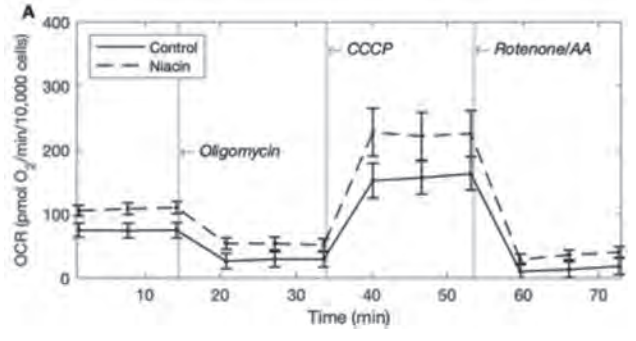
Background: Renal tubule cells are energetically demanding as they consume ATP to transport salt and water within the kidney. In vitro, renal tubule cells have an attenuated glycolytic phenotype described as cell culture stress. We hypothesized that Krebs cycle intermediates might be rate-limiting for ATP-dependent transport. We tested the influence of supplemental niacin as a source for NAD+/NADH on mitochondrial oxygen consumption.

Methods: Primary human renal tubule epithelial cells (HREC) were seeded on polystyrene tissue culture plates and cultured with normal (2 mg/L) or high niacin (4mg/L). After two weeks of treatment, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XFe96 analyzer. Respiratory inhibitors oligomycin (2μM), CCCP (2μM), rotenone (0.5μM), antimycin A (0.5μM) and 2-deoxyglucose (2-DG, 50mM), and glucose (10mM) were used to probe mitochondrial and non-mitochondrial respiration. Statistical differences between control and experimental groups were estimated by two-tailed Student's t-test. Results are considered significant at p<0.05. Cells from the same lot were seeded on permeable supports and cultured with an inhibitor of TGF-b receptor 1 and low or high niacin concentrations. Apicobasal volume transport was measured gravimetrically.

Results: High-dose niacin was associated with increased oxygen consumption compared with normal dose niacin (225 vs 157 uMol/min, p < 0.01), and with increased transport (187 +/- 83 vs 87 +/- 2.8 uL/cm2/day; p < 0.0004).

Conclusions: Our observation that mitochondrial oxygen consumption increased with addition of supplemental niacin supports the hypothesis that Krebs cycle intermediates may be rate-limiting in tubuel cell function. The significant increase in apicobasal transport with added niacin suggest that some of the dysfunctional phenotype induced by cell culture stress may be mitigated by nutritional supplementation.

Funding: Private Foundation Support



PO0497

Microenvironmental Influences on 3D Embedded and Bioprinted Induced Renal Tubular Epithelial Cells (iRECs)

Ludovica Rizzo,[1] Kevin Tröndle,[3] Michaela Bühler,[2] Roman Pichler,[2] Soeren S. Lienkamp.[1,2] *[1]Universitat Zurich, Zurich, Switzerland; [2]Universitatsklinikum Freiburg Abteilung Innere Medizin IV Nephrologie und Allgemeinmedizin, Freiburg, Germany; [3]Albert-Ludwigs-Universitat Freiburg Institut fur Mikrosystemtechnik, Freiburg, Germany.*

Background: Conventional cellular models of renal tubular origin only partially maintain their functional properties. Recent advances in 3D culture techniques and bioprinting technology promise to improve physiological conditions by reconstituting the tissue architecture in vitro. We previously described that direct reprogramming with a defined lentiviral cocktail of four transcription factors (Hnf1b, Hnf4a, Pax8, Emx2) can convert fibroblasts to induced renal tubular epithelial cells (iRECs). We analyzed how the microenvironment influences behavior, expression profile and the cellular function of iRECs to determine their utility for bioprinting applications.

Methods: iRECs were subjected to manual pipetting and inkjet bioprinting methods, embedded in three ECM-like microenvironments (Matrigel, Fibrin and Collagen I), and two culture media (DMEM and REGM). Morphology and viability of multicellular structures were assessed at several time points after seeding. Moreover, RNA-Seq was carried out to describe differentially regulated genes, and their protein products analyzed via immunofluorescence.

Results: iRECs showed high viability and biocompatibility with dispensing methods and bioinks. However, the morphology of multicellular aggregates was dramatically influenced by the microenvironment (e.g. they formed smaller spherical aggregates in Matrigel, but elongated tubule-like structures in Collagen I). Transcriptomic analysis revealed differentially expressed signature genes in each of the used biomaterials. For example, expression of apical endocytic machinery components was elevated in Matrigel embedded cells. In contrast, transcripts of ECM components showed strongest expression in the Fibrin condition. In addition, the tubule segment identity of iRECs was altered by the microenvironment. Microdispensing (drop on demand) bioprinting achieved perfusable tubule-like structures.

Conclusions: The design of specific tubule microenvironments for reprogrammed kidney tubule cells can be tailored to better reflect physiological conditions and to the desired purpose of vitro applications. This will facilitate the use of appropriate biomaterials to optimize the construction of biomimetic kidney tubule models at scale.

Funding: Government Support - Non-U.S.

PO0498

Biomimetic Thin Film Scaffolds Support Renal Cell-Based Filtration and Reabsorption

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Background: End stage renal disease affects millions of patients worldwide. Allotransplantation is the only curative treatment, yet it is only accessible to a fraction of patients. Hemodialysis does not adequately replace lost renal function. Engineered kidney replacing devices could be an alternative, however, excepting native extracellular matrix, no biologic scaffolding system to support cell-based filtration and absorption has yet been developed.

Methods: Biomimetic thin film scaffolds were fabricated by 3D printing, embedding, and leaching opposing networks of sacrificial material across 5μm thick microporous biologic membranes. The separate channel systems were co-seeded with primary glomerular microvascular endothelial cells and immortalized podocytes (glomerular grafts, N=3), or human umbilical vein endothelial cells and immortalized proximal tubule epithelial cells (tubular grafts, N=4) to recapitulate glomerular and proximal tubule anatomy and physiology.

Results: Scaffolds supported cell engraftment, polarization, and barrier formation in vascular and epithelial channels, and enabled filtration and reabsorption. Acellular scaffold vascular perfusion at 30mmHg resulted in a flow rate of 5.82mL/min/cm 2 (N=9), producing filtrate at 8.01μl/min/cm 2 of membrane. Confluent glomerular grafts produced filtrate at a rate of 3.76μL/min/cm 2 (48h, N=3). At 1 week, mature tubular grafts retained 96.8% of Inulin-FITC in the tubular epithelium (N=3). At maturity, glucose was transported into the vascular channel at a 24 hour rate of 0.11mg/mL/cm 2 (N=4).

Conclusions: Biomimetic thin film scaffolds support formation of perfusable 3D tissues and higher level renal cell based functions such as filtration and reabsorption in vitro. At scale, cellular constructs could enable fabrication of a fully biologic implantable renal replacement device.

Funding: Other U.S. Government Support

Figure 1. Recent developments in transplantable biologic and artificial filtration devices. Transplantation is the only permanent ESRD treatment while mechanical filtration requires ongoing treatments. Fully biological organ replacement devices are a long sought after therapeutic.

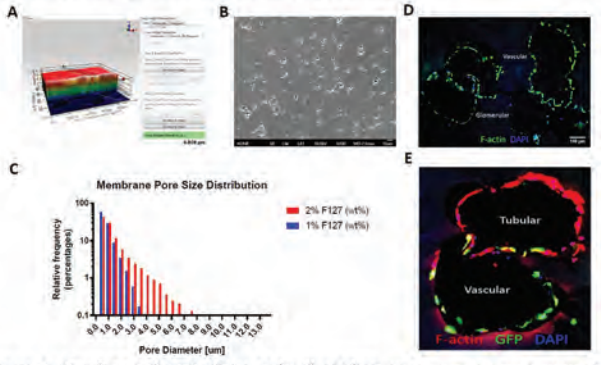

Figure 3. Membrane characteristics and cell seeding. (A) Membrane thickness is assessed by optical profilometry. (B) Porosity is imaged using SEM and can be quantified using image analysis techniques (Fiji/ImageJ). Stained histological sections show cells lining the channels glomerular and proximal tubular scaffolds. Podocytes and primary GMECs are shown by F-actin in green (D) and in HUVECs and PTECs in red (E). The HUVECs are GFP+.

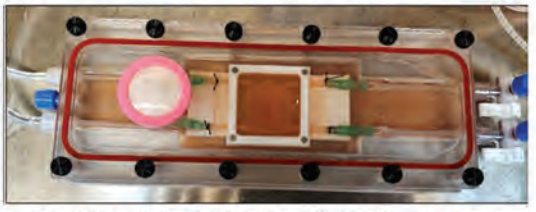

Figure 4. Perfusion culture of cellularized scaffolds in bioreactors. Scaffolds were cultured with separate perfusion into the vascular and epithelial channels. The cell seeded constructs were cultured for up to two weeks.

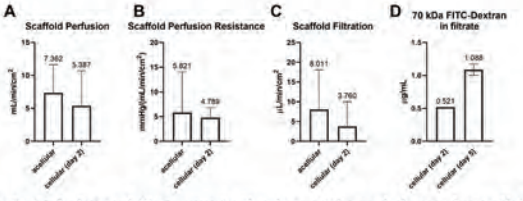

Figure 5. Perfusion and filtrate production in acellular and glomerular scaffolds. (A) PBS perfusion at 30mmHg pressure flowed through acellular (N=4) and glomerular (N=3) scaffolds at 7.3 and 5.3 mL/min/cm². Glomerular scaffolds (N=3) had slightly lower resistance to perfusion than acellular scaffolds (N=9) (B) but produced less than half of the filtrate into the epithelial channel (C). (D) At 2 (N=1) and 5 days (N=3) high molecular weight dextran at 1µg/mL was perfused through the vascular channels of glomerular cell seeded scaffolds. At 2 days, the filtrate macromolecular concentration was less than input, while at 5 days macromolecular concentration of filtrate matched input. Graphs represent means ± SD.

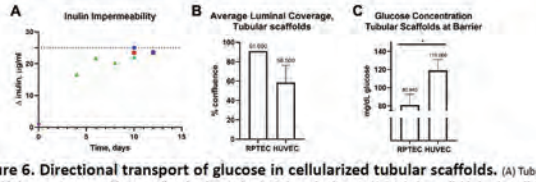

Figure 6. Directional transport of glucose in cellularized tubular scaffolds. (A) Tubular scaffolds become impermeable to small molecules at about 10 days of culture in N=3 tubular scaffolds (each scaffold a separate color). Fluorescent inulin at 25µg/mL in the tubular channel did not move into the vascular channel, while it quickly came to equilibrium in acellular scaffolds (N=1, purple triangle day 0). Delta inulin is epithelial channel concentration minus vascular channel concentration. (B) Luminal coverage of epithelium was nearly complete (N=2). (C) At inulin impermeability glucose was transported from the epithelial channel to the vascular channel, deviating from the initial concentration of 100mg/mL in each channel (N=4), P=0.0495 in a paired T-test. Graphs represent means ± SD.

PO0499

Tunable Stiffness Amino Functionalized Polyacrylamide-Based Hydrogels for Renal Cell Tissue Culture

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Background: Tunable stiffness polyacrylamide (PA) based hydrogels have been utilized for tissue engineering studies. PA gels require functionalization for cell attachment. Reagents such as sulfo-SANPAH or acrylic acid NHS ester are often used to attach protein to the gel surface. However, these methods do not provide adequate binding to maintain cell attachment for studies involving fluid shear stress or long-term culture. In order to produce PA gels with uniform surfaces and robust cell attachment, we tested gels incorporating N-(3-Aminopropyl) methacrylamide (APMA) to create a positively charged polylysine-like biocompatible surface.

Methods: APMA was substituted in varying amounts in PA mixes previously reported to produce gels with expected stiffnesses of 2.6 kPa or 40 kPa. Gels were produced by free radical polymerization under nitrogen, using TEMED (1:300) and 10% ammonium persulfate (1:100). Gels were cast on glass coverslips soaked overnight in 2M NaOH, dried and treated with a 5% solution of 3-aminopropyltrimethoxy silane in isopropanol, then 1% glutaraldehyde. Gels were sterilized with 70% ethanol for 30 minutes, and then placed in sterile PBS. Different amounts of APMA were tested using primary human renal tubule cells (Lonza). The elastic modulus of the modified gels was measured using an Electroforce 3100 mechanical analyzer.

Results: Cells attached rapidly to gels in standard medium with 10-20% APMA substitution at both stiffness levels, and maintained excellent attachment for at least 6 weeks, under both static and shaking conditions. Cells proliferated on gels until confluent. Higher APMA amounts were less effective with softer gels. Cells initially attached to 5% APMA gels, but detached after 2-3 days. The addition of APMA decreased the stiffness of the softer gels by ~25%, while it increased by ~25% for the harder gels.

Conclusions: Primary human renal tubule cells were found to attach rapidly and robustly to polyacrylamide hydrogels containing 10-20% APMA. Cells proliferated well on APMA based gels, and remained attached for at least 6 weeks, even under fluid shear stress (~2 dyn/cm2). We conclude that the addition of APMA to PA gels provides a very simple and reproducible method of functionalizing PA gels for renal cell attachment, and allows for the testing of soft, tissue-like substrates under physiological fluid flow conditions.

Funding: Private Foundation Support

PO0500

Canonical TGF-β Signaling Mediates Renal Tubule Epithelial Cell Differentiation In Vitro

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Background: Transforming growth factor-β (TGFβ) initiates multiple signaling pathways involved in the regulation of epithelial cell fate and cell plasticity. Here we identify canonical TGFβ signaling as a critical regulator of renal tubule epithelial cell membrane transporter expression in vitro.

Methods: Primary human renal tubule epithelial cells (HREC) were cultured on permeable supports on an orbital shaker. After two weeks in culture, cells were supplemented with TGFβ receptor I (TβR1) inhibitors SB431542 or A8301, Smad3 inhibitor SIS3, PI3K inhibitor LY294002, Rapamycin, p38 MAPK inhibitor SB203580, Takinib (2nM), Trametinib. After four weeks, apicobasal fluid transport and gene expression by RT-PCR was measured. Statistical differences were estimated by two-tailed Student's t-test in MatLab.

Results: Canonical TGFβ inhibitors SB431542 and A8301 increase apicobasal fluid transport, while Smad3 inhibitor SIS3 does not. Non-canonical TGFβ inhibitors LY294002, Rapamycin, SB203580, Takinib, Trametinib do not increase apicobasal fluid transport. SB431542 and A8301 suppress Snail1 transcription, while SIS3 does not. SB431542 and A8301 increase AQP2 transcription, while SIS3 does not, and have a greater effect on NHE3 transcription.

Conclusions: Increased inhibitable transport by renal tubule cells in vitro appears to be mediated by canonical TGF-β signaling. The lack of response to SIS3 suggests that Smad2, ratehr than Smad3, is responsible.

Funding: Private Foundation Support

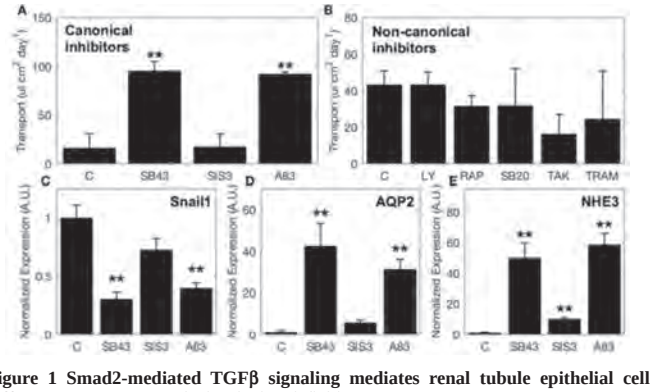

Figure 1 Smad2-mediated TGFβ signaling mediates renal tubule epithelial cell differentiation A. Canonical apicobasal fluid transport; Data are mean ± SD (n=4). **B.** Non-canonical apicobasal fluid transport. Data are mean ± SD (n=3). **C-E.** Snail1, NHE3, and AQP2 transcription. Data are mean ± SEM (n=4). *p<0.05, **p<0.01, ***p<0.001.

PO0501

TGF-β Mediates In Vitro Renal Tubule Cell Fatty Acid Oxidation

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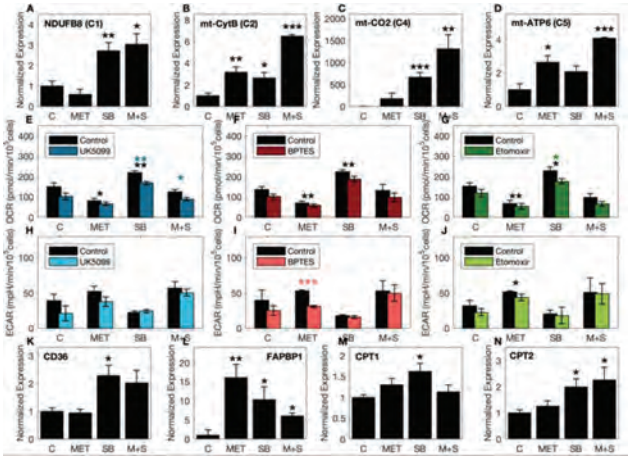
Background: Renal tubule cells (HREC) are energetically demanding due to their role transporting solutes., but undergo a shift toward glycolysis and away from oxidative phosphorylation of fatty acids in vitro. We identified Transforming Growth Factor-β (TGFβ) as a critical modulator of HREC differentiation. Here, we find that TGFβ inhibition increases HREC fatty acid oxidation.

Methods: Primary HREC were seeded on polycarbonate Transwells or polystyrene Seahorse XFe96 tissue culture plates. Cells were supplemented with AMPK activator metformin, TGFβ receptor I inhibitor SB431542, or a combination of both. After four weeks, cell oxygen consumption (OCR) and extracellular acidification rates (ECAR) were assessed using a Seahorse XFe96. Glutamine oxidation inhibitor BPTES, fatty acid oxidation inhibitor etomoxir, and glucose oxidation inhibitor UK5099 were used to probe HREC substrate utilization. Gene expression was measured using RT-PCR. Statistical differences were estimated by two-tailed Student's t-test. Results are considered significant at $p<0.05$.

Results: MET and SB43 stimulate transcription of electron transport chain Complexes I, II, IV, and V. Control and MET OCR did not respond to inhibitors. MET cells have diminished basal OCR and decreased ECAR in response to BPTES. SB43 increases basal OCR and cellular responses to UK5099 and etomoxir, implying increased glucose and fatty acid oxidation. SB43 increases transcription of fatty acid transporter CD36 and fatty acid oxidation genes FABP1, CPT1, and CPT2.

Conclusions: Inhibition of TGFβ increases in vitro transcription of mitochondrial genes and oxidative phosphorylation of fatty acids by HREC.

Funding: Private Foundation Support



Metformin and SB431542 module substrate oxidation dependency A-D. RNA expression of NDUFB8, mt-CytB, mt-CO2, and mt-ATP6. Data are mean ± SEM (n=4). **E-G.** OCR and **H-J.** ECAR of substrate inhibition assays. Data are mean ± SD (n=5). **K-N.** RNA expression of CD36, FABP1, CPT1/2. *p<0.05, **p<0.01, ***p<0.001.

PO0502

Investigating the Use of Smartwatch-Based Self-Assessments to Monitor Fluid Consumption of Hemodialysis Patients

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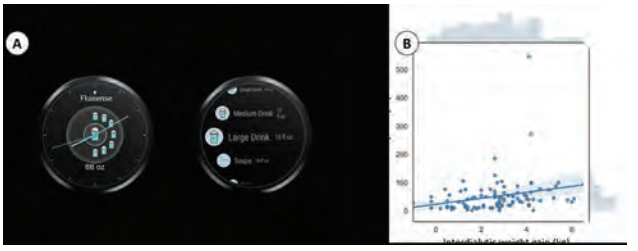
Background: Fluid intake control is a bedrock component of treatment for End Stage Kidney (ESKD) Patients, but continues to be a major challenge for patients, healthcare providers, and organizations. The ramifications of poor fluid control include increased mortality and morbidities, frequent hospitalizations and increased total cost of care. The goal of this work is to investigate the feasibility of leveraging self-assessments based on smartwatches to monitor fluid consumption of ESKD patients.

Methods: ESKD patients on hemodialysis (n=11) were given an Android smartwatch with an in-house developed app pre-installed (Fluisense, available on Android play store). Patients were asked to log their fluid intake through the app by choosing from a list of predefined volumes each time they consume any liquid. The app computed and displayed the self-reported daily volume intake to help patients monitor their own fluid consumption (Figure 1-A). Patients received text messages twice a day (9am and 8pm) to remind them to use the watch. We also recorded patients' weights before and after each of the thrice weekly dialysis sessions. The sum of self-reported interdialytic fluid intake was computed and compared against the interdialytic weight gain recorded in the clinic.

Results: Patients recorded fluids in 214 days out of 259 total days (i.e., 83% compliance rate). The average self-reported interdyalitic fluid consumption is 51 oz +/- 64, and the average interdialytic weight gain is 2.67 kg +/- 1.56. We found a moderate but significant correlation between the self-reported fluid volumes and the interdialytic weight gain ($r=0.363$, $P<0.001$, $r2=0.06$).

Conclusions: Leveraging smartwatches for the self-assessment of fluid intake is a promising solution for fluid monitoring of ESKD patients. This can be related to the ease of utilization of this technology and the ecological validity of its measurements given they are collected close to when they happen, reducing recall biases. In the future, we will leverage low-burden sensor data to monitor patients' fluid intake continuously and unobtrusively.



PO0503

Heterogeneous Local Hemodynamics in Rat Arteriovenous Fistula with Sildenafil Treatment

Hannah M. Northrup,[1] Yan-Ting E. Shiu,[1,2] Savanna Cahoon,[1] Isabelle D. Falzon,[1] Maheshika S. Somarathna,[3] Timmy C. Lee.[3,4] *[1]University of Utah, Salt Lake City, UT; [2]SLCVA, Salt Lake City, UT; [3]University of Alabama at Birmingham, Birmingham, AL; [4]Birmingham VA, Birmingham, AL.*

Background: Arteriovenous fistula (AVF) maturation failure is an unmet clinical need. Aberrant blood flow is thought to impair AVF remodeling, but previous literature has largely focused on hemodynamics averaged over the entire AVF. We hypothesize that hemodynamics is not uniform and thus any treatment's effect size is not uniform in AVF. We used the PDE5A inhibitor sildenafil and performed MRI-based computational fluid dynamics (CFD) to test our hypotheses.

Methods: Femoral AVFs were created in young male Sprague-Dawley rats. Sildenafil was given daily starting at 14 days before AVF creation and continuing for 21 days, at which time rats underwent MRI. MRI scans were used for measuring cross-sectional lumen area (CSA), and for CFD to derived flow rate, wall shear stress (WSS), oscillatory shear index (OSI), and vorticity. Results were split into 4 zones: 0-5, 5-10, 10-15, and 15-20mm away from the anastomosis.

Results: Sildenafil treated rats had significantly larger CSA, flow rate, WSS, OSI and vorticity than control rats in all zones ($p<0.05$)(Fig. 1). In both groups: (1) While flow rate remains constant in all zones, CSA increased from 0-5 to 15-20 zone. (2) Velocity, WSS and vorticity were the highest in the 0-5 zone, and each parameter drops significantly thereafter. (3) OSI increases at the 5-10 zone and then decreases gradually.

Conclusions: Sildenafil increased CSA and hemodynamics parameters in AVF. The magnitudes of increases are heterogenous along the AVF. Thus, the effect size of sildenafil on AVF remodeling and the association between hemodynamics and AVF remodeling depends on location. Increased knowledge of local hemodynamics and effect size may lead to treatments to improve AVF maturation.

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

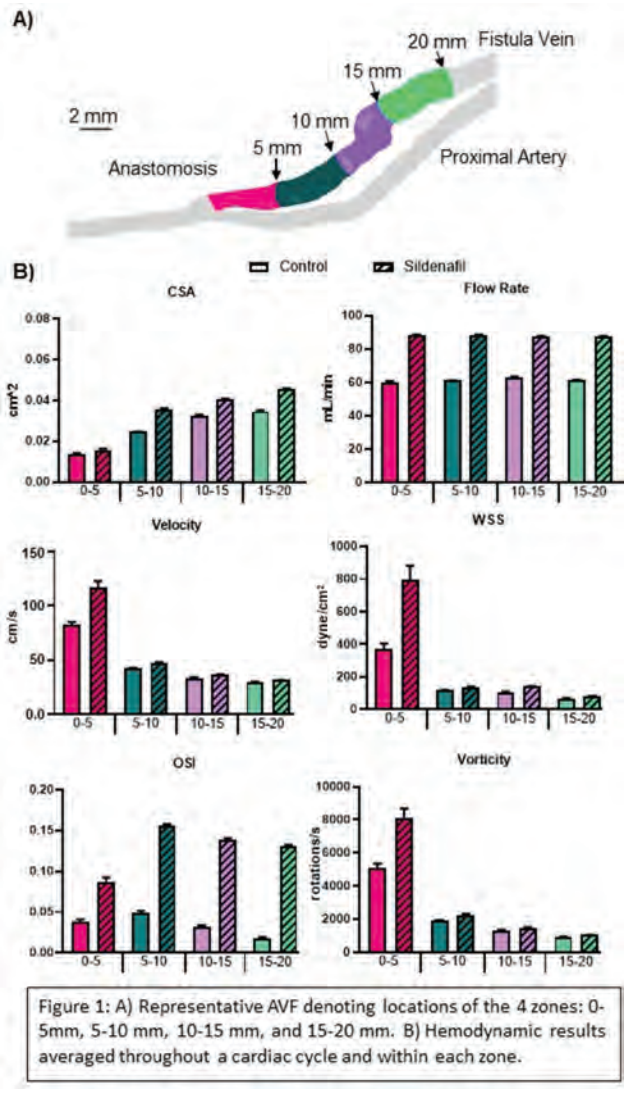
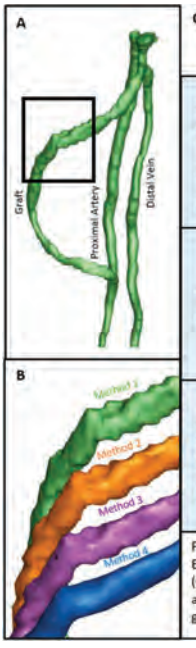


Figure 1: A) Representative AVF denoting locations of the 4 zones: 0-5mm, 5-10 mm, 10-15 mm, and 15-20 mm. B) Hemodynamic results averaged throughout a cardiac cycle and within each zone.



C

	Method	Cross-sectional Area (mm^2)	Velocity Magnitude (m/s)	WSS ($dyne/cm^2$)	OSI
Proximal Artery	1	38.5	1.44	148	0.044
	2	39.2	1.35	144	0.061
	3	37.7	1.53	184	0.059
	4	41.2	1.59	181	0.059
	Average	39.1	1.48	164	0.056
	SD	1.3	0.09	18	0.007
	RSD	**3%**	**6%**	**14%**	**12%**
Graft	1	25.2	0.72	100	0.055
	2	25.5	0.64	84	0.052
	3	24.8	0.79	116	0.054
	4	26.8	0.80	122	0.053
	Average	25.6	0.74	106	0.054
	SD	0.8	0.06	15	0.001
	RSD	**3%**	**9%**	**14%**	**2%**
Distal Vein	1	29.5	0.22	23	0.379
	2	30.4	0.23	19	0.344
	3	28.6	0.28	24	0.340
	4	30.7	0.24	26	0.355
	Average	29.8	0.24	23	0.355
	SD	0.8	0.02	3	0.015
	RSD	**3%**	**9%**	**12%**	**4%**

Figure 1: (A) View of the entire AVG reconstruction of Method 1. (B) Enlarged graft area of boxed section in (A) for each smoothing method. (C) Results for WSS, OSI, velocity magnitude, and cross-sectional area averaged over the entirety of each segment of the AVG (proximal artery, graft, distal vein) for each smoothing method.

PO0504

Effects of Smoothing Methods on Hemodynamic Assessment of a Human Arteriovenous Graft

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Background: Aberrant hemodynamics contribute to the formation of neointimal hyperplasia in arteriovenous grafts (AVG) for hemodialysis, but the detailed hemodynamic environment in an AVG is unclear. Computational fluid dynamics (CFD), while a useful tool for hemodynamic analysis, is influenced by lumen geometry. 3D vascular lumens reconstructed from medical images must be smoothed to remove surface deformities and improve their uniformity before being used in CFD. We investigated whether different smoothing methods may cause different hemodynamic analysis results.

Methods: MRI scans were performed on a dialysis patient's AVG and then used to reconstruct a 3D AVG lumen, on which four smoothing methods were applied that vary in their uses of interpolation, unconstrained smoothing, and additional surface smoothing (Fig 1A, B). The four smoothed lumens were used in the same CFD protocol to calculate velocity, wall shear stress (WSS), and oscillatory shear index (OSI). Results from different methods were compared using standard deviation (SD) and relative standard deviation (RSD = SD/mean x 100%) (Fig 1C).

Results: All methods give similar AVG lumen areas (RSD<3%). Although velocity has RSDs of 6-9%, their SDs are <0.1 m/s, and thus the differences are not considered biologically significant. Along the same line, all methods do not give biologically significant differences in OSI, as the SDs are <0.01. However, different smoothing methods give very different WSS, with RSD >12% and large SDs.

Conclusions: A variety of smoothing methods can be used to create AVG lumen reconstructions for CFD and hemodynamic analysis. These different methods can lead to significantly different WSS values. Therefore, researchers should consider the smoothing techniques used to characterize the hemodynamic environment in an AVG.

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

PO0505

Transdermal Glomerular Filtration Rate Measurement in Conscious Pigs Using the Novel Fluorescent Tracer Agent Relmapirazin

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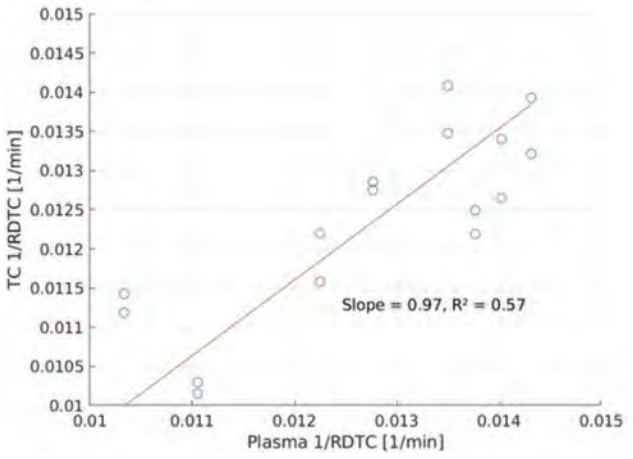
Background: Transdermal measurement of glomerular filtration rate (tGFR) using a miniaturized fluorescence detector ("TGFR Mini Monitors") in combination with a fluorescent exogenous GFR tracer agent is a common technique to measure kidney function in the preclinical setting, most commonly employed with rodents. However, larger animals are used in translational research on the way to human applications. The employ of an exogenous tracer agent in the preclinical setting which will also be amenable for seamless transition to human use would enhance the applicability of the preclinical data to clinical data.

Methods: The renal function of three healthy pigs (35-40 kg) was measured for 3 consecutive days. The novel fluorescent exogenous tracer agent Lumitrace™ (relmapirazin) was used in combination with two TGFR Mini Monitors per animal (MediBeacon, Germany). Excretion kinetics were measured transdermally, as well as in plasma, over the course of 4 hours. After attachment of the devices on the animal's skin, relmapirazin was administered intravenously. Seventeen blood samples were collected to measure plasma pharmacokinetics.

Results: The slopes of the single-exponential decay of the plasma kinetics and the transdermal kinetics of relmapirazin are in agreement (Slope 0.97; R^2=0.57). No statistical differences were detected using a paired t-test.

Conclusions: The collected data supports the suitability of the TGFR Mini Monitor to measure relmapirazin excretion kinetics in pigs, thus providing an important tool for translational research of GFR in larger animals.



Transcutaneous vs. Plasma renal decay time constant

Blue circles indicate the reciprocal RDTC derived from the transcutaneous and plasma measurement. The red line indicates the linear regression forced through the origin.

PO0506

Modeling Rare Human Tuberous Sclerosis Complex-Associated Kidney Angiomyolipomas In Vivo with Induced Pluripotent Stem Cell-Derived Renal Organoid Xenografts

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Background: Currently there are no animal models of renal angiomyolipoma (AML) for the study of tumor mechanisms *in vivo*. This is partly due to the fact that biallelic inactivation of *TSC1* or *TSC2* during development causes embryonic lethality, while previous attempts to ablate *TSC1* or *TSC2* by means of tissue-specific Cre-mediated recombination have not succeeded in recapitulating the lesions.

Methods: We induced nephric differentiation of isogenic *TSC2*$^{-/-}$, *TSC2*$^{+/-}$, and *TSC2*$^{+/+}$ human iPSCs derived from a TSC patient, under three-dimensional tissue culture conditions for 21 days. Next we transplanted the resulting renal organoids under the kidney capsule of immunodeficient RNU Nude rats. We next tested the a novel formulation for delivery of the mTOR inhibitor rapamycin using nanocarriers, on xenograft growth and ablation.

Results: Orthotopically transplanted *TSC2*$^{-/-}$ AML organoids displayed significantly higher growth rate compared to *TSC2*$^{+/-}$ or *TSC2*$^{+/+}$ kidney organoids, at Day 14 post-transplantation. Histological analysis of organoid xenograft tissues using antibodies against human nuclear antigen (HNA) or the human isoform of Lamin A/C (hLamin A/C), revealed prominent presence of human AML-like cells expressing smooth muscle and melanocyte markers in *TSC2*$^{-/-}$ but not in *TSC2*$^{+/-}$ or *TSC2*$^{+/+}$ organoid xenografts, indicating that the myomelanocytic phenotype of *TSC2*$^{-/-}$ AML organoids was maintained *in vivo*. mTOR activation was observed in ACTA2^{+} PMEL^{+} cells of *TSC2*$^{-/-}$ AML organoid graft cells, but not in the adjacent normal rat tissue or in *TSC2*$^{+/+}$ or *TSC2*$^{+/-}$ organoid xenografts, indicating that metabolic activation in the absence of TSC2 was consistent with xenograft growth. The rat kidney critically provided vascularization, supporting the growth of *TSC2*$^{-/-}$ organoids, and promoting the proliferation of AML cells. In our drug testing experiments, 3mg/kg rapamycin delivered orally significantly slowed *TSC2*$^{-/-}$ organoid xenograft growth, while local injections of low-dose rapamaycin-loaded nanoparticles resulted in organoid AML cell apoptosis and xenograft abrogation after 7 days, without affecting the rat kidney.

Conclusions: *TSC2*$^{-/-}$ hiPSC-derived AML organoid xenografts recapitulate key features of human TSC-associated AML *in vivo* with a high degree of anatomical and molecular fidelity. This model can be used to study tumor mechanisms and to test new therapies.

Funding: NIDDK Support

PO0507

Functional Maturation of Kidney Organoid Tubules: Mechanosensitive Ca2+ Signaling

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Background: When grown under static conditions, kidney organoids derived from human pluripotent stem cells exhibit glomerular- and tubular-like structures. However, static organoids possess an "immature" gene expression profile and their vascular development is limited (Homan et al., 2019; Takasato et al., 2015). As the technology for culturing organoids advances, aiming to promote terminal differentiation, the need to better characterize their physiological function has become a priority. To begin to functionally phenotype static organoids, we focused on characterizing mechano-induced changes in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) and signaling pathways in tubules isolated from maturing static organoids.

Methods: Tubular structures, microdissected from organoids between 21-57 d of culture, were microperfused in vitro or affixed to the base of a specimen chamber, and loaded with Fura-2 AM (20 μM) to measure $[Ca^{2+}]_i$. Digital ratio imaging was performed in individually identified cells by epifluorescence microscopy using commercial software.

Results: The average baseline $[Ca^{2+}]_i$ in microperfused tubules was 189±13 nM (n=6). A rapid increase in $[Ca^{2+}]_i$ was observed when tubules were subject to luminal filling, sufficient to cause circumferential stretch and turbulent flow, reaching values of 404±186 and 719±78 nM in organoids at 40 and 57 d of culture, respectively (n=3, p≤0.002 vs. baseline). Luminal flow-induced increases in $[Ca^{2+}]_i$ were not detected in tubules isolated from organoids <40 d in culture (n=3). Mechanosensitive *Piezo1* channels contribute to the flow-induced $[Ca^{2+}]_i$ response in the fully differentiated distal tubule (Carrisoza-Gaytan et al., EB 2019). Nonperfused organoid tubules exposed to basolateral *Piezo1* activator Yoda 1 (20 μM) exhibited increases in $[Ca^{2+}]_i$ from 110±36 to 272±114 nM (24-31 d in culture; n=4, p≤0.00001) and from 130±36 to 504±197 nM (43-67 d in culture; n=4, p≤0.002).

Conclusions: These preliminary results are consistent with a maturational increase in flow/stretch-sensitive Ca^{2+} channels, including *Piezo1*, and/or associated signaling pathways, in tubules of static organoids in culture.

Funding: NIDDK Support, Other NIH Support - R56 DK122380, UC2 DK 126023

PO0508

Human Primary Renal Tubuloids as Tools for Pathophysiology and Nephrotoxicity Assessment

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Background: Kidney organoids derived from human induced pluripotent stem cells can be used to study pathophysiology and nephrotoxicity using human kidney tissue. We have developed an efficient alternative way to generate homogeneous epithelial-like structures from kidney tissue derived from patients.

Methods: Human primary renal tubular epithelial cell (hRTEC) cultures were generated using non-tumor cells from partially resected human kidneys for renal cancer. Primary cells were cultured on ultra-low attachment plates for several days. The cells were then transferred into media containing matrigel, hepatocyte growth factor, fibroblast growth factor-2 and 5% fetal bovine serum. Tubuloids were treated with multiple nephrotoxicants. Morphological changes and KIM-1 expression were evaluated. Functional assays to characterize permeability and selective cellular absorption by tubuloids were conducted using fluorescent inulin and albumin. Co-culture experiments of tubuloids with bEnd.3 endothelial cells were performed.

Results: hRTEC tubuloids were generated based on the method above. We have generated a library of hRTECs derived from 25 patients. Tubuloids had polarized expression of cell surface markers, LTL, KIM-1 (apical) and Na-K-ATPase (basolateral). It took only a week to establish hRTEC cultures from patient kidneys and 2-4 weeks to form tubuloids from hRTECs. Cisplatin and palmitate-bound albumin altered the 3D structure of tubuloids. Treatment with aristolochic acid increased KIM-1 expression in a dose-dependent manner. Functional assays revealed that tubuloids reabsorb albumin from the apical side and release it into basolateral side, while being impermeable to inulin. Coculture of tubuloids and bEnd.3 cells resulted in formation of 3D capillary-like structure of bEnd.3 cells around tubuloids.

Conclusions: We generated renal tubuloids using hRTECs derived from patients. This strategy can recapitulate pathophysiology, enable nephrotoxicity screening of human kidney tissue and offers an additional approach to personalized kidney medicine.

Funding: NIDDK Support, Other NIH Support - NCATS

PO0509

Nephrotoxicity Assessment with Human Kidney Tubuloids Using Spherical Nucleic Acid-Based mRNA Nanoflares

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Background: Drug-induced nephrotoxicity represents an important cause of acute kidney injury with associated patient morbidity and mortality and is often responsible for termination of drug development, after extensive resource allocation. Current platforms for testing nephrotoxicity are limited and require disruptive end-point molecular assays. We have paired a 3D human kidney tubuloid system which phenocopies kidney proximal tubules with spherical nanoflare (NF) mRNA nanosensors to achieve facile, real-time assessment of drug nephrotoxicity.

Methods: Primary human tubuloids were generated from tubule cells isolated from patients' kidney tissue and cultured in 3D matrigel settings using serum-free media. NF nanosensors targeting kidney injury molecule-1 (KIM-1) mRNA and GAPDH mRNA were assembled and used to label tubuloids through overnight incubation. KIM-1 NF signal on tubuloids were monitored over time following drug exposure through fluorescence microscopy imaging. Quantitated NF signals were compared with quantitative polymerase chain reaction (qPCR) to verify the accuracy of NF signals.

To demonstrate utility, the proposed NF-tubuloid platform was applied to screen the nephrotoxicity of 10 representative anti-cancer drugs.

Results: Specificity of KIM-1 NF sensors were demonstrated by studying a cell line constitutively expressing KIM-1 mRNA and adenovirus-transfected tubuloids. NF ability to thoroughly label kidney tubuloids and report tubular injury were evaluated by applying several concentrations of aristolochic acid and cisplatin, two well-known nephrotoxicants. Compared against its respective mRNA expression from qPCR, quantitated NF fluorescence showed a positive linear correlation with R^2=0.931, indicating its accurate representation of tubuloid status. Finally, the platform was used to facilitate nephrotoxicity screening of anti-cancer drugs, with significant tubuloid KIM-1 upregulation induced by 5-fluorouracil and paclitaxel.

Conclusions: We demonstrated the utilization of NF nanosensors to monitor injury on human kidney tubuloids. This platform enables facile and personalized nephrotoxicity assessment *in vitro*.

Funding: NIDDK Support, Other NIH Support - NCATS, Government Support - Non-U.S.

PO0510

Physiological Replication of the Glomerulus Using a Triple Culture Microphysiological System

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Background: The glomerulus is a complex structure highly adapted for its function. A true representation of the in vivo cell-cell/ECM interactions, which provide the semi-permeable filtration barrier, is essential to interrogate physiological and pathophysiological processes and for understanding the impact of novel therapies.

Methods: We have developed a human microphysiological system with high fidelity to glomerular physiology and structure. For the first time the three resident cell types (glomerular endothelial cells (GECs), induced pluripotent stem cell (hiPSC)-derived podocytes and mesangial cells (MCs)) reside in a relevant 3D structure under flow conditions. Analysis was performed on the individual cell types using both transcriptomics (NGS) and high content imaging to shed light on the impact of each cell type on its neighbors. Inulin and albumin permeability assays (fluorescent) were performed to evaluate the integrity of the glomerular barrier.

Results: Transcriptomic analyses demonstrated crosstalk between cells in our microfluidic tri-culture system. An influence of MCs was observed on both podocytes and GECs. For GECs, MCs increased tight junction proteins (CLDN7) and for podocytes there was modulation of cell cycle control (WDR70). The differentiation of podocytes in the chip was able to regulate matrix and cell adhesion in MC (COL6A3, ITGA2) and influence angiogenic signals in GEC (KDR, THBS1). Analysis of pathways expressed in cells in the less complex comparator systems showed that they displayed transcriptomic signals akin to human disease phenotypes (comparison with signatures found in Nephroseq). Imaging showed increases in maturation markers such as synaptopodin in podocytes in triculture. Permeability assays revealed that as cell maturity increased barrier function improved and the passage of molecules was selectively hindered.

Conclusions: Our tri-culture model provides a highly physiologically relevant tool to study healthy glomerular function. This will enable improved understanding of the mechanisms underlying glomerulopathies and improved qualification of new therapies.

Funding: Commercial Support - AstraZeneca

PO0511

Biomimetic Platform for Quantitative Drug Screening of Podocyte Cytoskeletal Dynamics and Morphology

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Background: Foot process effacement is driven by dysregulation of cytoskeletal dynamics. Currently, there are no drugs that primarily target the podocyte cytoskeleton due to dearth of *in vitro* model systems. To address this limitation, we designed a 3D drug discovery platform with a morpho-mimetic milieu that allows high-throughput quantitative measurements of drug-induced cytoskeletal changes in podocytes.

Methods: Immortalized human podocytes were differentiated on micropatterned surfaces fabricated via photolithography. High-resolution microscopy including confocal, TIRF, SEM and atomic force microscopy (AFM) were used to characterize morphometric and biophysical properties. Protein expression was quantified using automated immunofluorescence, cell proliferation via EdU, and basal motility via fluorescent live-cell imaging. High-throughput analytical capabilities of the system were tested with cytoskeletal dose response against puromycin aminonucleoside (PAN).

Results: Cells cultured in 3D micropatterns for up to 14 days show a significant reduction in morphometric variability compared to unpatterned controls. During differentiation, micropatterned podocytes achieve cell cycle arrest faster and more robustly with reduced motility. Furthermore, the increased speed and the extent of cell cycle arrest is also observed in low serum, suggesting that the effects of morpho-mimetic culture are independent from biochemical stimuli. AFM elastography shows primarily a peripheral distribution of stiff actin fibers in micropatterned podocytes, mimicking *in situ* conditions. A cohesive cytoskeletal dose response was observed against PAN in the micropatterned cells only.

Conclusions: 3D micropatterns increase the speed and efficiency of podocyte differentiation while reducing cell-to-cell variability by up to 5-fold. Through its increased reproducibility, our automated system allows for quantitative *in vitro* study of podocyte morphology, cytoskeleton and biomechanics in response to drugs and pathogens with high fidelity and reproducibility.

Funding: NIDDK Support, Other U.S. Government Support

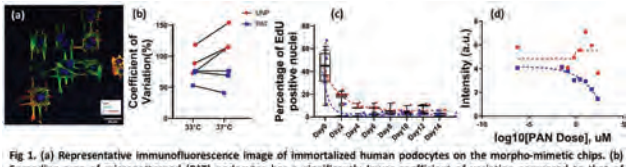

Fig 1. (a) Representative immunofluorescence image of immortalized human podocytes on the morpho-mimetic chips. (b) Spreading area of micropatterned (PAT) podocytes has a significantly lower coefficient of variation compared to that of unpatterned control (UNP) cells.(c) A more rapid decrease in cell division was observed during differentiation for PAT vs. UNP (2.1 ± 1.3 days vs. 6.4 ± 1.8 days) with a significantly lower number of dividing cells at the differentiated state (2.6 ± 1.8% vs. 5.4 ± 4.1%). (d) PAN dose response for cellular actin expression in UNP was mostly indiscernible due to high variability whereas it was clearly visible and quantifiable in PAT.

PO0512

Monitoring Mitochondrial Dynamics Within a Kidney-on-Chip Platform for Investigating Disease Progression and Potential Therapeutics

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Background: The kidneys rely on an abundant number of mitochondria to produce energy to drive key functions, such as fluid/electrolyte balance. Mitochondrial dysfunction has been linked to the progression of renal diseases including acute kidney injury and diabetic nephropathy. Thus, the mitochondria are a key target for therapeutic development. Kidney-on-chip platforms provide a dynamic *in vivo*-like tissue culture environment to investigate renal pathophysiology. Yet, it is difficult or impossible to investigate mitochondrial dynamics due to lack of real-time measurements. Here, we present a sensor integrated kidney-on-chip platform with real-time cell oxygen consumption rate (OCR) readouts for monitoring the dynamics of mitochondrial function.

Methods: Human primary renal proximal tubule epithelial cells (hRPTEC) were cultured in PREDICT96 (P96), a high-throughput organ-on-chip platform. Integrated optical- based oxygen sensors enabled measurement of dissolved oxygen. Flow was turned off to measure decreases in oxygen and compute OCR. hRPTEC were treated with mitochondrial inhibitors Oligomycin and Antimycin A and un-coupler FCCP. OCR was measured prior to and following the drug treatments.

Results: hRPTEC basal OCR was monitored under flow at 70 uL/min over a 10 day culture period. OCR decreased by 58% and 39% following treatment with Antimycin A and Oligomycin, respectively, and increased 64% following treatment with FCCP (**Fig.1**).

Conclusions: We demonstrated real-time and label-free monitoring of drug-induced shifts in mitochondrial respiration within a high-throughput kidney-on-chip platform. Our work enables new investigations into mitochondrial dynamics in response to nephrotoxic agents or disease progression, as well as potential therapeutics that target the mitochondria.

Funding: Other U.S. Government Support

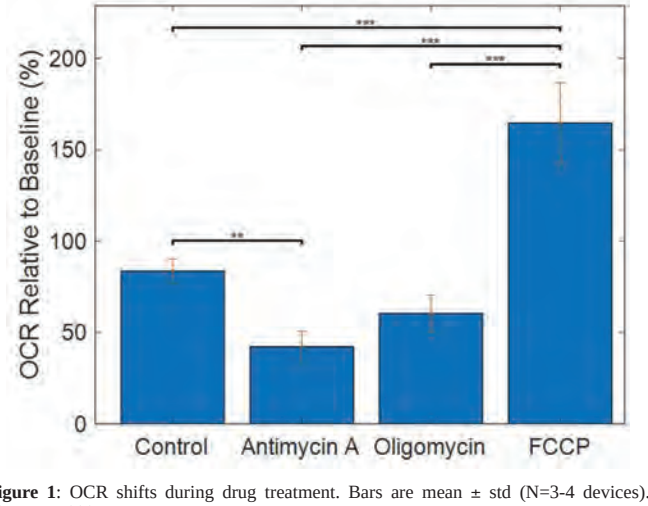

Figure 1: OCR shifts during drug treatment. Bars are mean ± std (N=3-4 devices). **p<0.01, ***p<0.001, one-way ANOVA.

PO0513

Demonstrating Preclinical Proof of Concept of an Implantable Bioartificial Kidney (iBAK)

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Background: An implantable bioartificial kidney (iBAK) would provide continuous and convenient treatment while overcoming the challenges of dialysis and renal transplant. We previously demonstrated small-scale operational versions of an immunoprotective renal tubule cell-containing bioreactor and a pumpless hemofilter utilizing biomimetic silicon nanopore membranes (SNM). Here we report the successful integration of bioreactor and hemofilter components into an iBAK prototype that demonstrated operational feasibility in swine.

Methods: Designs of the bioreactor and hemofilter were optimized using computational fluid dynamics. Porcine renal (LL-CPK1) cells were cultured on collagen-coated Transwell® (Corning) membranes and inserted into the bioreactor. A hemofilter containing SNM with ~10 nm-wide pores was connected to the bioreactor in series through the hemofilter blood outlet and bioreactor blood inlet. The iBAK was implanted into the retroperitoneum of a healthy Yucatan mini-pig, with anastomoses from the hemofilter blood inlet and bioreactor blood outlet to the iliac artery and vein, respectively, and the bioreactor ultrafiltrate outlet connected to the bladder. The pig did not receive systemic anticoagulation or immunosuppression. After 3 days, patency was assessed via angiogram and the device was explanted for further analysis. Cell viability was assessed using a LIVE/DEAD™ Cell Viability Assay (Invitrogen).

Results: The iBAK was successfully assembled and implanted with no procedural complications. Post-operatively the pig did not demonstrate signs of seroma/hematoma, thromboembolism, infection, or other adverse reactions. 3 days after implant, the device was patent. Ultrafiltrate was noted at both implant and explant, with a flow rate of 0.28 uL/min measured at explant. Cells demonstrated ~80% viability, relative to *in vitro* controls. No gross thrombi or protein films were observed on the SNM.

Conclusions: We successfully integrated hemofilter and bioreactor components to create a small-scale iBAK. The hemofilter generated ultrafiltrate from blood while the bioreactor sustained renal cells and delivered ultrafiltrate ("urine") to the bladder. This feasibility study will guide future development of a clinical-scale iBAK.

Funding: Other NIH Support - NIBIB Quantum Grant, Private Foundation Support

PO0514

A 20-lb Portable Continuous Renal Replacement Therapy (PCRRT) Machine Battery Operated Using 300 mL Fluid: CRRT Anywhere, Any Time

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Background: CRRT is challenging due to needing large amounts of sterile fluids excessive labor and cost. Prescribed treatment is frequently interrupted when patients are transported out of the ICU for tests and procedures. Hence the unmet need for a light and portable battery operated CRRT machine that uses less fluids and nursing labor and can be used anytime at any place, including during procedures or transportation.

Methods: The machine connects to a central venous catheter and blood is heparinized and propelled through the blood compartment of a 0.6 sqm dialyzer and recirculated back to the central vein. 300 ml of sterile 0.45 N is circulated into the dialysate compartment of the dialysate. Calcium, magnesium, and sodium bicarbonate are added to the dialysate. Potassium and other additives may also be added. Blood and the dialysate are propelled by a double channel pulsatile pump. The volume of fluid removal is controlled by a volumetric separate pump. The spent dialysate coming out of the dialyzer is circulated through sorbents that regenerate the dialysate allowing for the use of only 300 ml of fluid instead of 30 liters, or more, of sterile fluid. Spent dialysate coming out of dialyzers during treatment of renal failure patients and with added urea, creatinine and lactic acid was circulated through the sorbent canisters. Lactate, urea, creatinine, and electrolytes were measured in the dialysate after recirculating through the sorbents.

Results: Urea, creatinine, potassium, and lactate were undetectable in the dialysate after it recycled through the sorbent canisters.

Conclusions: Less sterile fluid and less nursing labor, make it cost-effective. Current machines weigh more than 100 pounds, and have a large footprint, making it impossible to use them out of the ICU, or during ambulance or helicopter transportation. This machine, weighs 20 pounds, is battery powered and uses 300 ml of sterile fluid. The size and weight, and sterile fluid requirements allow uninterrupted use in ICU, on a stretcher, during ambulance or aircraft transportation.

Funding: Other U.S. Government Support, Commercial Support - Wearable Artificial Organs Inc

PO0515

High Sodium Reduced the Expression of PTH1R and Klotho by Inhibiting 1,25 (OH)2D3 Synthesis

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Background: The proximal tubule is not only the sensing site of sodium and phosphorus, but also the main place for the synthesis and metabolism of 1,25 $(OH)_2D_3$. Sodium may share the sensing mechanism with phosphate in proximal tubule epithelial cells, whether sodium cooperates with phosphate, or it plays an independent role in the regulation of phosphorus homeostasis remains unknown. In this in vitro study, we were to investigate the effects of high sodium on the synthesis and function of active vitamin D and local phosphorus regulation in proximal tubular epithelial cells.

Methods: Human proximal tubule epithelial (HK-2) cells were treatment with different concentrations of sodium/phosphorus. The expressions of 1α-OHase (Cyp27b1) and 24-OHase (Cyp24a1) were determined by RT-PCR and Western Blot respectively. LC/MS and ELISA were used to detect the levels of 1,25 $(OH)_2D_3$. Intracellular Ca2+ ([Ca2+]i) was detected with the Ca2+ indicator dye Fura-4. Chromatin samples were immunoprecipitated with antibodies against PTH1R and klotho.

Results: High sodium decreased the expression of 1,25 $(OH)_2D_3$ through reducing 1α-OHase and 24-OHase in HK-2 cells. Sodium phosphorus transporter inhibitor (PFA) and sodium hydrogen transporter inhibitor (Caliporide) increased the expression of 1α-OHase and 24-OHase, while ouabain decreased their expressions. High sodium intervention increased intracellular calcium concentration, and chelating extracellular calcium reversed high sodium induced 1α-OHase and 24-OHase expression. High sodium reduced the expression of PTH1R and klotho, combined use of PFA and Caliporide significantly increased the gene and protein expressions of PTH1R and klotho, while ouabain intervention further decreased their levels. Vitamin D receptor agonists significantly increased the recruitment of VDR to the VDRE of PTH1R and klotho promoter, thus increased the expression of PTH1R and klotho.

Conclusions: High extracellular sodium can not only lead to a decrease in the synthesis of active vitamin D in the proximal tubules, but also affect the gene regulation of 1,25 $(OH)_2D_3$/VDR, and significantly reduce the expression of PTH1R and Klotho. It suggests the influence of high sodium diet on mineral metabolism and the core role of vitamin D in kidney mineral metabolism.

PO0516

Enhancement of In Vitro hPTH1-84 Bioactivity by hPTH38-84 and hPTH45-84

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Background: Recent research using high resolution mass spectrometry demonstrates that serum concentrations of full-length parathyroid hormone (hPTH1-84) and its fragments (hPTH28-84, 34-77, 34-84, 37-77, 37-84, 38-77, 38-84, and 45-84) are increased significantly in CKD patients with an eGFR of ≤17-23 mL/min/1.73m^2 (Kritemetapak *et al.* Clin Chem. 2021 Mar 6:hvab013. doi: 10.1093/clinchem/hvab013. Online ahead of print.PMID: 33693557). Information about the bioactivity of these newly discovered hPTH fragments is lacking.

Methods: Recombinant hPTH1-84 was synthesized in *Escherichia coli* and purified by immobilized metal-ion affinity chromatography. hPTH28-84, hPTH38-84, and hPTH45-84 were synthesized by solid phase peptide synthesis. The identity of hPTH1-84 and hPTH fragments was confirmed by mass spectrometry. To determine whether different-sized hPTH fragments modulate the bioactivity of hPTH1-84, we studied their effects on the generation of the cellular second messenger, cAMP, which mediates the intracellular signaling of hPTH1-84, in murine preosteoblasts (MC3T3-E1) *in vitro*. Forskolin, an adenylyl cyclase activator, was used as a positive control for cAMP production. All experiments were performed in triplicate.

Results: In MC3T3-E1 cells, cAMP increased to 28.5±5.5, 64.4±9.9, 91.5±11.6, 114.6±15.5, and 109.1±6.5 pmol/mL 30 minutes after treatment with 1, 3, 10, 50, and 100 nM,hPTH1-84. The same concentrations of hPTH28-84, hPTH38-84, and hPTH45-84 had no effects. When hPTH1-84 was added to cells concurrently with 100 nM hPTH38-84 or hPTH45-84 in 1:100, 3:100, 1:10, 1:2, and 1:1 molar ratios, cAMP responses to hPTH1-84 increased by 65.3% (95% CI, 63.2% to 67.4%; $P<0.01$) in the presence of hPTH38-84 and increased by 77.0% (95% CI, 65.2% to 88.8%; $P<0.01$) in the presence of hPTH45-84. hPTH28-84, added concurrently with PTH1-84, did not enhance cAMP generation in MC3T3 cells.

Conclusions: The small hPTH fragments, hPTH38-84 and 45-84, but not hPTH28-84, enhance the hPTH-induced generation of cAMP in MC3T3-E1, suggesting a novel biological role and a novel mechanism of action for these PTH fragments in osteoblast-like cells. It is plausible that *in vivo* these fragments may enhance the activity of full-length PTH by novel mechanisms. These findings may partly explain the discrepancy between PTH levels and bone histology in patients with CKD.

Funding: Other NIH Support - Fred C. and Katherine B. Andersen Foundation; and NIH, grants 5R01DK107870 and DK125252 (to RK), Private Foundation Support

PO0517

Bone Expression of Sclerostin in CKD and Dialysis Patients

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Background: Sclerostin, a 22-kDa glycoprotein secreted by osteocytes, negatively regulates bone formation through the inhibition of the Wnt/β-Catenin pathway. In patients with CKD, circulating sclerostin correlates negatively with bone formation but the impact of bone expression of sclerostin requires further investigation.

Methods: 87 pediatric patients with CKD underwent iliac crest bone biopsy with the quantification of sclerostin bone expression using immunohistochemistry (IHC). Subjects with circulating sclerostin values at the upper and lower extremes of each population (n=6 CKD and n=6 dialysis) underwent staining with two β-catenin antibodies that recognize the phosphorylated/unphosphorylated states.

Results: The median (IQR) age of the cohort was 17 (14, 20) and 39% had pre-dialysis CKD (Table). Significant correlations between IHC sclerostin and bone histomorphometry were limited to the dialysis group: IHC sclerostin correlated with bone formation rate (r=-0.34, p=0.02) and osteoid thickness (r=-0.3, p=0.03). In the sub-group undergoing β-catenin staining, dialysis patients demonstrated low bone staining of sclerostin independent of circulating sclerostin. CKD subjects with high circulating sclerostin levels (ranging from 58 to 110 pmol/L) demonstrated increased sclerostin staining in osteocytes when compared with CKD patients with lower serum sclerostin (ranging from 30 to 36 pmol/L). Phosphorylated β-catenin staining was higher and unphosphorylated β-catenin levels lower in bone tissues with high circulating sclerostin.

Conclusions: Together, these data support a model whereby high levels of circulating sclerostin from osteocytes contributes to altered bone remodeling through aberrant Wnt signaling activity in CKD and may provide a rationale to target therapeutic strategies using monoclonal antibodies towards sclerostin.

Funding: NIDDK Support

Table: Cohort Characteristics

	CKD	Dialysis
N (%)	34 (39.1)	53 (60.9)
Age, median (IQR)	15 (12.7, 17.1)	18.3 (16.4, 19.7)
Gender, n (%)		
Male	23 (67.7)	37 (69.8)
Female	11 (32.3)	16 (30.2)
Race, n (%)		
Black	2 (5.9)	5 (9.4)
White	14 (41.2)	6 (11.3)
Hispanic	18 (52.9)	39 (73.6)
Asian	0	3 (5.7)
Disease, n (%)		
CAKUT	23 (67.7)	15 (28.3)
GN	10 (29.4)	21 (39.6)
Unknown	1 (2.9)	17 (32.1)
Calcium, mg/dL	9.4 (9, 9.7)	9.2 (8.7, 9.7)
Phosphate z score	1.5 (0.3, 2.3)	5 (2.9, 7.7)
Alkaline Phosphatase, IU/L	171 (110, 265)	150 (92, 283)
Vitamin D, ng/mL	25.5 (23.5, 29.7)	21 (13.2, 29.6)
PTH, pg/mL	95 (50, 159)	411 (211, 991)
Intact FGF23, pg/mL	95 (64, 140)	1195 (286, 5718)
c-terminal FGF23, RU/mL	199 (101, 344)	1463 (705, 5577)
Sclerostin, pg/mL	40.4 (34.2, 52.6)	66.9 (48.3, 87.2)
IHC Sclerostin	1.6 (0,3.6)	1.7 (0,4.8)

PO0518

The Essential Role of miRNA in Maintaining an Intact Parathyroid in the Adult

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Background: miRNA are small noncoding RNAs with vital roles in homeostasis and development. Dicer mediates the final step of miRNA maturation. To study the roles of miRNA in the parathyroid, we generated parathyroid specific Dicer knockout (PT-*Dicer*$^{-/-}$) mice, to specifically delete parathyroid miRNA. The PT-*Dicer*$^{-/-}$ mice had normal serum PTH levels, but failed to increase PTH when stressed by hypocalcemia or kidney failure, unlike control mice and patients. We now show that in addition to parathyroid stimulation, miRNA are central to maintaining intact parathyroid glands throughout life.

Methods: We generated PT-*Dicer*$^{-/-}$ and control mice expressing YFP (Yellow Fluorescent Protein) in the parathyroid by cre lox recombination, to track parathyroid cells by fluorescence microscopy. Histological slides from P0 (day of birth) and older mice were immunostained. qRT-PCR and Western blots were performed on thyroid tissue that includes the embedded parathyroids.

Results: Surprisingly, adult PT-*Dicer*$^{-/-}$ mice had no YFP positive parathyroid glands detected by fluorescence microscopy, as opposed to easily detected intact glands in controls. However, the glands were present immediately after birth in P0 and P1 *Dicer*$^{-/-}$ mice. At P0 and P1 there were increased levels of the cleaved caspase-3 apoptotic marker in cells co-expressing PTH and the parathyroid transcription factor GCM2. From P3 to P12, there was a gradual loss of parathyroid glands in PT-*Dicer*$^{-/-}$ mice, with the left gland disappearing last. qRT-PCR of thyroid RNA, containing the parathyroid when present, showed reduced expression of PTH mRNA in adult PT-*Dicer*$^{-/-}$ mice, compared to controls. PTH levels were also decreased in thyroid extracts as determined by Western blots. There was no change in thymus PTH mRNA that has been proposed to provide an auxiliary source of PTH.

Conclusions: Mice that do not express miRNA in the parathyroid lose their parathyroid glands after birth, indicating that miRNA are not essential for parathyroid embryonic development by rather postnatally, for maintaining intact parathyroid glands. In the absence of parathyroid glands in adult PT-*Dicer*$^{-/-}$ mice, an additional source for PTH other than cells in the thyroid or thymus contributes to normal basal serum PTH that cannot be stimulated by hypocalcemia or uremia.

PO0519

PTH Suppression Improves Cortical Bone Parameters in Aging Mice with CKD

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Background: Chronic kidney disease (CKD) and aging are each independently associated with higher risk of fracture due to significant loss of bone mass and quality. In CKD, cortical thinning and cortical porosity are driven by elevated parathyroid hormone (PTH) and directly linked to increased fracture risk in CKD patients. Overlaying CKD and aging produces cortical porosity that is higher than either condition alone. Previously, we discovered potent suppression of PTH in rodents with CKD infilled existing pores; however, it is unknown if aged bone may react similarly given attenuated osteoblast function. The goal of this study was to assess the impacts of PTH suppression on cortical porosity in young and aging CKD mice.

Methods: Male C57Bl/6J mice were used at 16 and 66 weeks of age. CKD was induced via dietary adenine (AD, 0.2% for 6 weeks + 2 weeks of maintenance on control diet). Control mice were fed normal control diet for the duration of the study. After 8 weeks of CKD induction, calcium water was provided for 4 weeks to suppress PTH (n=8/group). Outcome measures included biochemical assays and bone architecture via μCT.

Results: Aging AD mice had more than six-fold higher PTH levels than age-matched controls and more than two-fold higher PTH levels than young AD mice. Administration of calcium water led to lower PTH in both young AD and aging AD mice, 85% and 82%, respectively. Regardless of age, AD mice showed lower cortical bone area (~32%) and cortical thickness (32-40%) versus age-matched controls; mice given calcium water had higher cortical bone area (11%, 8%) and cortical thickness (20%, 10%) compared to untreated age-matched AD. Due to large variability, there were no statistical differences in cortical porosity between groups, although porosity did trend lower in both calcium water-treated young AD (-74%) and aging AD (-29%) groups compared to age-matched controls.

Conclusions: These data demonstrate the beneficial impact of PTH suppression on cortical bone in young and aging animals; however, PTH suppression alone may not be enough to sufficiently reduce cortical porosity, particularly in aging bone. This lays the groundwork for future studies to assess clinically available therapies of PTH suppression and their efficacy in reducing cortical porosity in a broad spectrum of CKD patients.

Funding: Other NIH Support - T32-AR065971

PO0520

Calcimimetics Alter Periosteal and Perilacunar Bone Matrix Properties in Early CKD

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Background: Chronic kidney disease (CKD) patients have an elevated fracture risk due to hyperparathyroidism, cortical porosity, and reduced bone material quality. Calcimimetic drugs are used to lower PTH in dialysis patients, but their impact on bone matrix quality in early CKD remains unknown. We hypothesized that tissue-level bone quality is altered in early CKD and that calcimimetic treatment improves bone quality.

Methods: Male Cy/+ rats fed a casein-based diet undergo progressive CKD with mineral and bone disorder. 18-week-old rats (stage 3 CKD, N=12) were treated with the calcimimetic KP-2326 (0.6 mg/kg i.p. 3x/wk). N=12 normal littermates (NL) and untreated CKD rats received the casein diet to control mineral intake. Calcein was administered 4 and 14 days prior to sacrifice at 28 weeks (stage 4 CKD). Blood was drawn and femora were harvested for MicroCT and 4-point bending. Femur sections were cut and polished for colocalized Raman spectroscopy and nanoindentation. Colocalization was run in fluid in periosteal bone using calcein as a guide and in concentric ellipses around osteocyte lacunae.

Results: PTH was 284% higher in CKD vs NL and KP reduced PTH by 92% vs CKD. Neither CKD nor KP altered cortical porosity and KP did not improve structural mechanical properties vs CKD. In new periosteal bone, CKD reduced carbonate substitution by 20% and elastic modulus by 15% vs NL while KP increased mineral crystallinity by 4% vs NL and restored elastic modulus to NL levels. In perilacunar bone, KP reduced carbonate substitution and increased elastic modulus and hardness vs CKD.

Conclusions: This study demonstrates that CKD and KP alter bone matrix composition and material properties on the tissue level prior to structural changes such as cortical porosity. The perilacunar data suggests that osteocytes may actively alter their surrounding matrix in CKD and that calcimimetics may help prevent these changes prior to a decline in bone structural integrity.

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

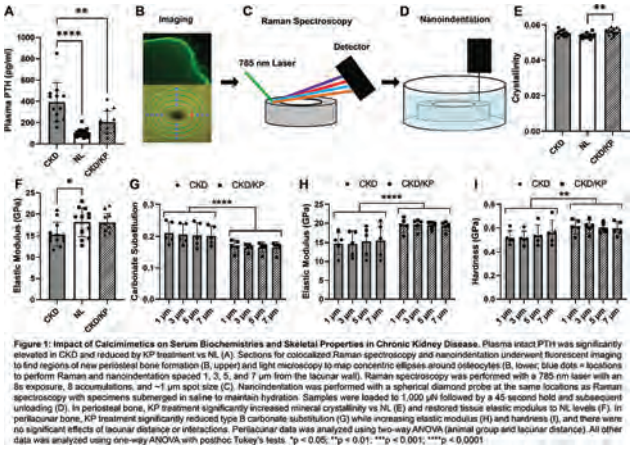

Figure 1: Impact of Calcimimetics on Serum Biochemistries and Skeletal Properties in Chronic Kidney Disease. Plasma intact PTH was significantly elevated in CKD and reduced by KP treatment vs NL (A). Sections for colocalized Raman spectroscopy and nanoindentation underwent fluorescent imaging to find regions of new periosteal bone formation (B, upper) and light microscopy to map concentric ellipses around osteocytes (B, lower; blue dots = locations to perform Raman and nanoindentation spaced 1, 3, 5, and 7 µm from the lacunar wall). Raman spectroscopy was performed with a 785-nm laser with an 8s exposure, 8 accumulations, and ~1 µm spot size (C). Nanoindentation was performed with a spherical diamond probe at the same locations as Raman spectroscopy with specimens submerged in saline to maintain hydration. Samples were loaded to 1,000 µN followed by a 45 second hold and subsequent unloading (D). In periosteal bone, KP treatment significantly increased mineral crystallinity vs NL (E) and restored tissue elastic modulus to NL levels (F). In perilacunar bone, KP treatment significantly reduced type B carbonate substitution (G) while increasing elastic modulus (H) and hardness (I), and there were no significant effects of lacunar distance or interactions. Perilacunar data was analyzed using two-way ANOVA (animal group and lacunar distance). All other data was analyzed using one-way ANOVA with posthoc Tukey's tests. *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001

PO0521

Integrated Transcriptomic and Proteomic Analyses for the Characterization of Oxyphil Cells in Patients with Uremic Secondary Hyperparathyroidism

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Background: Calcitriol and calcimimetics are the most powerful treatments for secondary hyperparathyroidism (SHPT); however, the mechanisms leading to calcitriol or calcimimetic resistance in oxyphil cell–predominant SHPT are unknown. Here we used transcriptomic RNA-seq and tandem mass tag (TMT) proteomic techniques to characterize oxyphil cells by comparing the differences between chief and oxyphil cell nodules of parathyroid glands in patients with uremia.

Methods: Transcriptomic and proteomic analyses were performed on chief and oxyphil cell nodules collected from uremic patients. We sought to verify the expression of differentially expressed genes (DEGs), and detect the expression of mitochondrion-associated proteins (voltage-dependent anion channel 1 (VDAC1) and mitochondrially encoded cytochrome c oxidase II (MT-CO2)), proliferation-related proteins (proliferating cell nuclear antigen (PCNA) and cyclinD1), parathyroid-specific factors (parathyroid hormone (PTH) and glial cells missing homolog 2 (GCM2)), and SHPT-regulating factors (vitamin-D receptor (VDR), calcium-sensing receptor (CaSR), and Klotho). The mitochondrion microstructure and mitochondrial DNA (mtDNA) copy number were measured to assess the mitochondrial mass. Freshly excised parathyroid tissues were incubated *in vitro* to detect PTH secretion levels.

Results: Compared to chief cell nodules, the most marked expression increases in oxyphil cell nodules were for proteins involved in mitochondrion-associated components and a series of metabolic processes. The mitochondria number, mtDNA content, and protein levels of VDAC1 and MT-CO2 were significantly increased in oxyphil cell nodules. Moreover, oxyphil cell nodules expressed PTH and GCM2, and exhibited lower protein levels of PCNA and Cyclin D1 but higher synthesis and secretion level of PTH. The protein expression of VDR, CaSR, and Klotho were significantly downregulated in oxyphil cell nodules.

Conclusions: Oxyphil cells characterized by enrich mitochondria in patients with uremic SHPT were parathyroid-derived and showed higher synthesis and secretion of PTH but lower expression of SHPT regulators than chief cells, which may contribute to the pathophysiology of SHPT and the treatment resistance to calcitriol and calcimimetics.

Funding: Government Support - Non-U.S.

PO0522

The Calcimimetic KP-2326 Alters the Gut Microbiota in a Rat Model of CKD-MBD

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Background: CKD-MBD therapies, including diet and phosphate binders, can alter the gut microbiota. However, it is unknown if calcimimetics alter the gut microbiota and their derived uremic toxins.

Methods: Cy/+ rats, a slowly progressive rat model of CKD-MBD (CKD hereafter, n=13) and normal littermates (NL, n=8) consumed a diet with 0.7% phosphorus from 18 wk of age (~ 60% of NL glomerular filtration rate (GFR)) to euthanasia at 28 wk of age (~30% of NL GFR). An additional CKD group received the pre-clinical form of etelcalcetide, KP-2326 (CKD+KP; 0.6 mg/kg IP 3 times/wk, n=13) for a total of 10 wk starting at 18 wk of age. DNA was extracted from cecal samples, the V4 region of the 16S rRNA gene was sequenced via Illumina MiSeq, and data were analyzed via QIIME2. Indoxyl sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine-N-oxide (TMAO) were quantified by ultra-performance liquid chromatography-tandem mass spectrometry.

Results: CKD or KP did not affect α-diversity, or diversity within samples. B-diversity, or diversity between samples, assessed by unweighted UniFrac distances was different across all groups (PERMANOVA p=0.001; q<0.013 between groups). Weighted UniFrac distances (presence/absence + abundance), differed between NL vs. CKD and CKD vs. CKD+KP (q<0.04), and there was a trend between NL and CKD+KP (q=0.07). At the phyla-level, CKD rats had a lower relative abundance of Firmicutes than NL (60.6±9.4% vs. 68.7±3.4%, p=0.03), but CKD+KP rats were comparable to NL (67.9±4.5%, p=0.96). Bacteroidetes relative abundance was higher in CKD vs. CKD + KP (22.1±5.3 vs. 17.7±3.2%, p=0.03). Several bacterial genera that were lower in CKD were comparable to NL rats with KP, including *Allobaculum, Bifidobacterium,* and *Blautia.* Similarly, CKD rats had a higher relative abundance of the mucin-degrader *Akkermansia* compared to NL, and while KP had a lower relative abundance, it remained higher than NL. Despite the gut microbial changes, IS, PCS, and TMAO levels were higher in the CKD and CKD+KP compared to NL rats (p<0.05).

Conclusions: KP-2326 changed the gut microbial composition without altering the levels of gut-derived uremic toxins. As the calcium-sensing receptor is expressed along the gastrointestinal tract, future studies should explore the effect of calcimimetics on host-microbe interactions.

Funding: NIDDK Support

PO0523

A New Physiological Model to Study Regulation of SLC26A6-Mediated Oxalate Transport in Mouse and Human Intestinal Tissue

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Background: Intestinal organoids have great utility in studying stem-cell self-organizing properties. However, barrier and transport functions cannot be determined readily in three-dimensional (3D) cultures. We converted 3D intestinal organoids to two-dimensional monolayers (2D) and studied oxalate transport physiology via the oxalate transporter SLC26A6. Furthermore, we investigated the response of intestinal organoids to high oxalate concentrations.

Methods: Mouse and human adult stem cell-derived 3D culture systems were grown onto 2D monolayers. Cell differentiation was compared by gene expression and western blotting. Plasma membrane transport was examined in mouse and human monolayers with radioactively labeled substrates. Monolayers were exposed to soluble oxalate and cell death was measured by Caspase-3 activation and lactate dehydrogenase (LDH) release.

Results: We demonstrate that 2D intestinal monolayers maintained the gene expression profile of 3D organoids. Furthermore, murine and human intestinal organoids demonstrated high Cl-oxalate exchange transport activity that was 4,4-diisothiocyanostilbene-2,2-disulfonic acid (DIDS)-sensitive. Chloride-oxalate exchange was abrogated in murine organoids deficient for Slc26a6, resulting in intracellular oxalate accumulation, Caspase-3 activation and LDH release.

Conclusions: We conclude that 2D intestinal organoid cultures are suitable *in vitro* models to study oxalate transport from mice and humans. Using these models we demonstrate that Slc26a6-mediated chloride-oxalate exchange protects from intracellular oxalate accumulation and cell death.

Funding: Government Support - Non-U.S.

PO0524

Optimization of Oxalobacter formigenes-Derived Small Peptides with Therapeutic Potential for Hyperoxalemia, Hyperoxaluria, and Related Kidney Stones

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Background: Most kidney stones (KS) are composed of calcium oxalate, and very small increases in urine oxalate enhance the stone risk. Besides KS, oxalate also potentially contributes to CKD progression and CKD - and ESRD-associated cardiovascular diseases, emphasizing the need for plasma and urinary oxalate lowering therapies, and enhancing the bowel's ability to secrete oxalate may effectively do so. We previously discovered *Oxalobacter*-derived secreted factors stimulating oxalate transport by human intestinal Caco2-BBE (C2) cells and reducing urinary oxalate excretion in hyperoxaluric mice by inducing colonic oxalate secretion. We identified the small peptides P8 and P9 as the major secreted factors and they have significant therapeutic potential for hyperoxalemia and hyperoxaluria. Natural peptides are often not suitable therapeutics due to rapid degradation by proteolytic enzymes, and P8 & 9 peptides have multiple enzymatic cleavage sites.

Methods: Described under Results.

Results: To optimize P8 & 9 peptides and make them resistant to proteolytic degradation, there were subjected to the following structural modifications. N-terminal acetylation (P8-Ac & P9-Ac), C-terminal amidation (P8-Am & P9-Am), retroinverso (P8-RI & P9-RI), and replacing several glycine and lysine sites with PEG6 (P8-P & P9-P) & ornithine (P8-O & P9-O), respectively. All of these modified peptides stimulated oxalate transport by C2 cells similar to the native P8 & 9, except P9-RI (47.3% less functional) and P8-RI (nonfunctional). The native and modified peptides were then treated with different enzymes (trypsin, proteinase K, and colonic lavage fluid [CLF: mimics the colonic environment]) to evaluate the impact of such modifications using LC-MS and/or HPLC in an *in vitro* stability assay. Native and modified (P8/9-Ac, P8/9-Am, & P8/9-P) peptides were completely degraded by the above enzymes. P8-O and P9-O have improved stability (~57-80%) against trypsin, but they were fully degraded by proteinase K and CLF. Importantly, P9-RI is completely resistant to degradation by the above enzymes.

Conclusions: P9-RI is the most stable optimized peptide, but is less functional compared to native P9. Studies are ongoing to evaluate its *in vivo* therapeutic effects in lowering plasma and urinary oxalate levels in hyperoxalemic and hyperoxaluric mice.

Funding: NIDDK Support

PO0525

Leaky Intestinal Epithelium Causes Hyperoxaluria in CA-MLCK Mice

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Background: Most kidney stones are composed of calcium oxalate, and very small increases in urine oxalate enhance the stone risk. The intestine plays a crucial role in oxalate homeostasis, and intestinal oxalate absorption is largely passive and paracellular. To evaluate whether enhanced intestinal paracellular permeability can increase urinary oxalate excretion, mice with augmented small and large intestinal paracellular leak (transgenic mice expressing intestinal constitutively active myosin light chain kinase = CA-MLCK) were used.

Methods: Described under Results.

Results: CA-MLCK mice have significantly higher (1.27-fold) urine oxalate compared to controls (μM/mg creatinine; Controls = 10.15±0.48; CA-MLCK = 12.86±0.65), reflecting that primary intestinal barrier dyscfuntion is sufficient by itself to cause hyperoxaluria. This 27% increase in urinary oxalate concentration is significant since minor increases enhance the stone risk. To see if the observed hyperoxaluria is due to enhanced passive paracellular intestinal oxalate absortion, jejunal and ileal tissues were isolated from control and CA-MLCK mice and mounted in Ussing chambers, and unidirectional ^{14}C-oxalate and ^{3}H-mannitol absorptive fluxes were assessed. CA-MLCK mice have signifincatly higher ileal ^{14}C-oxalate (1.65-fold) and ^{3}H-mannitol (1.70-fold) absorptive fluxes. CA-MLCK also have a statistically insignifcant higher jejunal ^{14}C-oxalate (1.31-fold) absorptive flux. To determine whether enhanced intestinal oxalate absorption is also active *in vivo* as observed *ex vivo,* control and CA-MLCK mice were orally gavaged with a single dose of ^{13}C-oxalate, followed by urine collection x 6 h. CA-MLCK mice have a statistically insignifcant higher (1.40-fold) ^{13}C-oxalate excreted in the urine compated to Controls in preliminary studies, suggesting that they absorbed higher amount of the administered ^{13}C-oxalate, which is likely due to the underlying intestinal barrier dysfunction leading to enhanced passive paracellular oxalate absorption.

Conclusions: CA-MLCK mice have significant hyperoxaluria due to mechanisms including enhanced small intestinal passive paracellular oxalate absorption. These findings are of significant interest since they provide new understanding into the role of leaky intestinal epithelium and hyperoxaluria, a feature of diseases such as obesity, DM, IBD, and celiac disease.

Funding: NIDDK Support

PO0526

Transcriptomic Mapping of the Human Kidney Papilla Reveals Myeloid Immune Activation and Matrix Remodeling Pathways in Stone Disease

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Background: The role of the kidney papilla in the pathophysiology of stone disease remains unclear. The aim of this study was to identify the cellular and molecular determinants of nephrolithiasis by molecular mapping of the stone forming papilla using integrated single nuclear and spatial transcriptomics.

Methods: Renal papillary biopsies were obtained from Calcium oxalate (CaOx) stone formers and reference non-stone formers. Tissue sections were prepared according to Visium (10x Genomics) spatial transcriptomic protocol. Single nucleus RNA sequencing from papillary frozen sections was used to spatially map the signature of specific cell types within the tissue. Data analysis and visualization were performed in R (seurat, ReactomePA, ClusterProfiler) and Loupe browser. In-situ mapping of cell distribution and pathway activation were quantified using 3D immunofluorescence imaging. The levels of select proteins in urine samples were quantified by ELISA.

Results: Genes and pathways associated with reactive oxidative stress, myeloid immune activation and extracellular matrix (ECM) remodeling were significantly upregulated in CaOx biopsies relative to non-stone forming reference. Spatial transcriptomic localized the signature of specific cell types and demonstrated the increased expression of genes from those pathways such as FOS, JUN, SOD2, CCL2, SPP1, MMP7/9 and MGP, particularly in areas within or adjacent to mineralized regions in the stone forming papillae. 3D immunofluorescence imaging confirmed the observed activated stress response and myeloid immune activation using phospo-c-JUN and CD68 staining, respectively. Additionally, the activation of myeloid and ECM remodeling pathways was validated by increased levels of MMP7 and MMP9 in the urine of patients with stone disease compared to healthy controls.

Conclusions: Using integrated transcriptomic and imaging approaches, we demonstrate that the papilla of stone patients is an active site of myeloid immune activation, oxidative stress and matrix remodeling. This immune active state had a molecular profile comparable to atherosclerotic disease. Our studies also uncover potential novel markers for screening and activity assesment of important pathogenic pathways in stone patients.

Funding: NIDDK Support

PO0527

Assessment of Vascular Calcification Using Micro-CT Quantification in a Vitamin D Rat Model

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Background: Micro-computed tomography (micro-CT) scanning could be an alternative technique of both visualization and quantification of calcium content in vessels. Our aim was to standardize the micro-CT calcium quantification methodology and evaluate its reliability in a rat model of calcification.

Methods: Six Sprague-Dawley rats were induced by three consecutively daily subcutaneous administrations of 150 klU/kg vitamin D3 and sacrificed 5 days after induction. Three of the rats were subcutaneously treated with 60 mg/kg SNF472 (G1), an inhibitor of calcification, and the rest were treated with saline (G2). One additional rat was not induced nor treated and served as negative control. Micro-CT was performed in aorta and femoral arteries with an isotropic resolution of 45 μm, 400 projections collected in one full rotation of the gantry in 10 min, x-ray tube at 80 kV and 150 μA. A phantom made of a laser cut aluminum skeleton was scanned with the same protocol to simulate bone. After the image analysis, the vessel samples were digested (1:1 HNO_3:$HClO_4$) and total calcium was quantified using an inductively coupled plasma atomic emission spectrometry (ICP-AES).

Results: The threshold for calcium detection was established at 153.8 Hounsfield Units (HU). Rats treated with vitamin D presented more calcium deposits than the control and SNF472 treated rats (7.6 ± 6.1 HU in G2 vs 3.3 ± 3.2 HU in G1). The volume of calcium deposits in femoral samples was similar between groups. The quantification of calcium by ICP-AES brought similar results in aorta (>50% inhibition with SNF472 treatment) but not in femoral samples, as in this tissue increased calcium content was quantified in vitamin D-treated rats when compared to the control rat. A significant correlation was obtained between the calcium deposits quantified by micro-CT and the total calcium quantified by ICP-AES.

Conclusions: The threshold-based quantification method by micro-CT can be a useful and reliable tool to evaluate vascular calcification and the efficacy of inhibitors of vascular calcification in rat models, especially in large-diameter vessels such as aorta.

Funding: Commercial Support - Sanifit Therapeutics

PO0528

The Effect of the Warfarin-TG2-MVs Axis in Vascular Calcification

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Background: Warfarin is a common anticoagulant drug. How to effectively reduce vascular calcification induced by warfarin while ensuring its anticoagulant effect is an urgent problem to be solved. Previous studies have found that warfarin enhances the expression and activity of transglutaminase 2 (TG2) in vascular smooth muscle cells (VSMCs), which mediates communication between cells and extracellular matrix (ECM). Matrix vesicles (MVs) are the center of hydroxyapatite crystal precipitation, which is released to ECM and interacts with ECM protein to initiate mineralization and form calcification core. This study observed the role of warfarin-TG2-MVs axis in vascular calcification by culturing VSMCs in vitro.

Methods: VSMCs were cultured in normal or osteogenic medium (OM) and stimulated with 10 μm warfarin for 3-14 days. The expressions of SM22α, Runx2, ALP, OPN and OPG were detected by RT-PCR, Western blot. Alizarin red and von Kossa staining were performed to evaluate calcification, and calcium content was determined. Meanwhile, the expression and activity of TG2 were detected. Differential centrifugation was used to extract MVs and evaluate their release. Type I collagen was coated in the culture dish to determine the calcification of MV-collagen.

Results: Warfarin stimulation promoted transdifferentiation of VSMCs, that the expression of osteogenic factors Runx2, ALPL and OPN were increased, while the expression of SM22α and calcification inhibitor OPG were decreased. When using OM, the above trend was more obvious. Alizarin red and von Kossa staining were performed when the cells were cultured for 14 days. The results of calcium staining in the warfarin intervention group were all positive. Warfarin promoted the expression and activity of TG2, and it gradually increased with the extension of the intervention time. The same amount of cells were cultured for 7 days under different stimuli, and the medium was changed every other day. Then, the supernatant was collected for differential centrifugation. The amount of MVs produced by the warfarin and OM group was significantly higher than that of other groups, and the ability to mineralize of MVs in type I collagen was increased.

Conclusions: Warfarin increased the expression and activity of TG2, promoted the release of MVs from VSMCs, and further cross-linked ECM to aggravate vascular calcification.

PO0529

Uremic Milieu Exacerbates Muscle Regeneration After Muscular Injury in Mice

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Background: In our life, skeletal muscle injuries occur not only in strenuous exercises but also in daily activities with unexpected excessive muscle contraction. In general conditions, injured muscles are repaired to normal structure, and muscle functions are rescued. However, whether this repair process is affected in the uremic milieu has not been fully elucidated yet.

Methods: In C57BL6 male mice fed with normal diet or 0.2% adenine-conjugated diet, the muscle injury was induced by intramuscular injection with vehicle (PBS) or barium chloride ($BaCl_2$) in tibialis anterior (TA) muscles. Then, we evaluated the TA muscle wet weight, histology, muscle strength, and marker gene expressions of $Pax7^+$ satellite cells and macrophages playing a pivotal role in muscle regeneration. We also treated differentiating mouse skeletal myoblasts with a representative uremic toxin, indoxyl sulfate (IS), and evaluated the cell morphology and marker gene expressions.

Results: In adenine-induced CKD mice, the $BaCl_2$-injected TA muscle showed reduction of muscle wet weight, muscle fiber size, instantaneous muscle strength, and Pax7 gene expression compared to control mice. Furthermore, the gene expression of DLL1 and Notch2 regulating the Pax7 expression, CCL5 accelerating the migration of macrophages, and cell surface markers of M1/2 macrophages (CD206, CD163, and CD86) also decreased in the injured muscle of CKD mice. Treatment of murine C2C12 myoblast with IS led to not only the myotube atrophy but also smaller number of nuclei per myotube. The gene expression of Pax7, DLL1, and CCL5 increased during the C2C12 myoblast differentiation, but IS treatment deteriorated these expressions as seen in vivo experiments.

Conclusions: Uremic milieu deteriorated muscle regeneration with the decline of gene expression associated with satellite cells and macrophages.

PO0530

Indoxyl Sulfate Induces Cardiomyocyte Hypertrophy via FGF23-FGFR4 Signaling Pathway

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Background: Both fibroblast growth factor 23 (FGF23) and indoxyl sulfate (IS) have been reported to relate with left ventricular hypertrophy (LVH) in patients with chronic kidney disease (CKD), but their inter-relationship remains unknown.

Methods: To induce LVH, 8-week-old-male C57BL/6J mice were fed high phosphorus diet after heminephrectomy for the induction of FGF23 and administrated with continuous subcutaneous dose of 100mg/kg IS per day for 4 weeks, and half of them were treated with continuous intraperitoneal administration dose of 7.5 mg/kg H3B-6527 (H3B), a fibroblast growth factor receptor 4 (FGFR4)- inhibitor. Moreover, rat cardiac myoblast (H9c2, 2-1) cells were incubated with 0, 0.25 or 1.0 mM IS and collected after 24 and 72 hours for RT-PCR and western blotting, respectively.

Results: IS promoted cardiac hypertrophy, and inhibition of FGFR4 reduced heart weight and left ventricular wall thickness in IS groups ($p < 0.05$). There was no significant difference in serum FGF23 level among experimental groups, but the expressions of FGF23 protein and mRNA in the heart were markedly increased in IS-injected mice compared to control mice ($p < 0.05$). In cultured H9c2 cells incubated with IS, intact FGF23 protein expression and phosphorylation of FGFR4 were elevated in cell lysate, but intact FGF23 protein level in the media didn't change. The mRNA levels of β-myosin heavy chain (βMHC), α-smooth muscle actin (αSMA), brain natriuretic peptide (BNP), polypeptide N-acetylgalactosaminyltransferase 3 (Galnt3), and FGF23 were significantly up-regulated ($p < 0.05$), but collagen I was not.

Conclusions: IS increased intact FGF23 protein expression and activated FGF23-FGFR4 signaling in cardiomyocyte, leading to LVH, and FGFR4 inhibition suppressed IS-induced LVH.

PO0531

Hyperphosphatemia Contributes to Skeletal Muscle Atrophy in the Absence and Presence of CKD

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Background: Chronic Kidney Disease (CKD) is a public health epidemic and associated with elevated serum levels of phosphate (hyperphosphatemia) as well as skeletal muscle atrophy, and the interconnection is poorly understood. Elevated phosphate (Pi) has direct effects on smooth muscle cells and induces vascular calcification. We wanted to test if Pi directly induces atrophy in skeletal muscle cells. Furthermore, we analyzed skeletal muscle on a functional, histological and molecular level in three models of hyperphosphatemia – two CKD models, i.e. mice with global deletion of collagen 4a3 (Col4a3-/-) and wildtype mice receiving an adenine-rich diet, as well as wildtype mice on a high Pi diet with normal kidney function. Finally, we determined the effect of a low Pi diet on skeletal muscle in Col4a3-/- mice.

Methods: C2C12 myotubes were treated with 1-5 mM Pi for 24 hours, followed by qPCR expression analysis of atrophy genes (atrogenes), including MT1, Trim63, and Fbox32. Furthermore, we studied Col4a3-/- mice receiving normal chow or a 0.2% Pi diet at 10 weeks of age. We also analyzed C57Bl/6 mice receiving an adenine-rich (0.2%) diet for 14 weeks or a 3% Pi diet for 3 months. We analyzed grip strength, hindlimb area by MRI, muscle wet weight, cross-sectional area of individual muscle fibers immuno-labeled with anti-laminin by fluorescence microscopy, and expression levels of atrogenes by qPCR.

Results: Pi treatments increased the expression levels of atrogenes in C2C12 myotubes. In the three mouse models, grip strength and cross-sectional area of myofibers were significantly reduced, and the expression levels of atrogenes were significantly elevated when compared to respective controls. Additionally, the two CKD models showed significant reductions in muscle weight and hindlimb area. Administration of a 0.2% Pi diet protected Col4a3-/- mice from developing skeletal muscle atrophy.

Conclusions: Elevated Pi induces myotube atrophy in vitro. Mouse models with hyperphosphatemia develop skeletal muscle atrophy in the presence and absence of CKD, and a low Pi diet protects the skeletal muscle in CKD mice. Pharmacological approaches targeting Pi uptake or excretion, or inhibition of Pi's direct actions on tissues might alleviate various CKD-associated pathologies.

Funding: NIDDK Support, Other NIH Support - Research reported in this publication was supported by the National Institute Of Dental & Craniofacial Research of the National Institutes of Health under Award Number T90DE022736 to K.H.

PO0532

Renal FGF-23 Resistance by Phosphate Leads to NaPi-2a Internalization via Activated PiT-2/ERK1/2 Signaling in Proximal Tubule

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Background: The bone-derived hormone fibroblast growth factor (FGF) 23 targets the kidney to promote urinary phosphate (Pi) excretion by activating the FGFR1/Klotho/ERK1/2 signaling in renal proximal tubule (PT) cells. This reduces type II sodium phosphate cotransporters NaPi-2a and NaPi-2c in the apical brush border membrane (BBM) lowering serum Pi levels. In vitro data show that under high extracellular Pi, the type III sodium-dependent phosphate transporters PiT-1 and PiT-2 activate ERK1/2 in bone cells. Moreover, Pi-regulated osseous FGF23 secretion is facilitated via PiT-2. Here we aim to analyze Pi versus FGF23 regulated Pi transport in the setting of high phosphate load in renal PT cells.

Methods: We subject C57BL/6N male mice to increased dietary Pi load (0.8% vs. 2%) for 6 months to determine phosphate homeostasis and analysing kidneys by qPCR, immunoblot and histology. In addition, we study cultured renal PT cells treated with phosphate or FGF23 to examine the activation of downstream signaling events and

expression levels of specific target genes. Furthermore, we determine if co-treatment with the phosphate transporter inhibitor Foscarnet blocks the observed effects.

Results: A 2% Pi diet promotes the elevation of plasma FGF23 levels in mice. Despite reduced TRP, increased FEPi and urine Pi levels, the serum Pi levels are still enhanced. In animals fed a 2% Pi diet, we observed reduced renal *NaPi-2a* mRNA expression. Immunofluorescence staining revealed internalization of NaPi-2a from the apical BBM due to the high dietary Pi load. This is confirmed by analysing BBM vesicles. Interestingly, mice on 2% Pi diet have a diminished renal Klotho expression, but unaltered Fgfr1 expression. PiT-2 expression is increased and accumulated in the basolateral membrane of PT. In cultured PT cells, Pi enhanced *PiT-2* expression. The Pi-mediated increase in ERK1/2 phosphorylation was blocked by Foscarnet co-treatment.

Conclusions: Hyperphosphaturia might be a result of PiT-2/ERK1/2-mediated downregulation of NaPi-2a stimulated by Pi itself. Our study indicates these Pi-mediated effects may be independent of FGF23. We postulate that high dietary Pi load causes a resistance of renal FGF23/Klotho signaling.

PO0533

Recurrence of Hypophosphatemia Despite FGF-23 Reduction in Dmp1 Knockout Mice

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Background: Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone produced by bone. Hypophosphatemic rickets diseases, such as X-linked hypophosphatemia (XLH) and autosomal recessive hypophosphatemic rickets (ARHR), are associated with FGF23 excess, impaired skeletal growth and osteomalacia. Treatment with FGF23 blocking antibody has shown great promise to improve serum phosphate (Pi) levels and bone mineralization in XLH. Further studies need to determine if blocking FGF23 is efficacious in the long term and in other diseases associated with FGF23 excess, including ARHR.

Methods: We deleted *Fgf23* in osteocytes using a *Dmp1*-cre in wild-type (WT) and Dmp1 knockout ($Dmp1^{KO}$) mice. We studied the bone and mineral phenotype of WT, $Fgf23^{cKO}$, $Dmp1^{KO}$ and $Dmp1^{KO}/Fgf23^{cKO}$ mice at 12 and 20 weeks of age.

Results: $Fgf23^{cKO}$ mice showed a 40% reduction in serum intact FGF23 levels and a 25% increase in Pi levels (vs. WT), confirming successful deletion. As expected, DMP1 deficiency in $Dmp1^{KO}$ mice induced significant elevations in serum FGF23 levels (+15-fold) and PTH levels (+5-fold), phosphaturia, hypophosphatemia, rickets and osteomalacia (vs. WT). At 12 and 20 weeks, osteocyte specific deletion of *Fgf23* in $Dmp1^{KO}$ mice partially corrected FGF23 levels (-80%), PTH levels (-50%), and ameliorated the bone phenotype (+50% in femur length and bone mineral density) (vs. $Dmp1^{KO}$). Partial reduction of FGF23 levels was sufficient to fully correct serum Pi levels in 12 week-old (NS vs. WT), but not in 20 week-old $Dmp1^{KO}/Fgf23^{cKO}$ mice which showed recurrent hypophosphatemia despite nearly normal FGF23 levels. In contrast, phosphaturia persisted in $Dmp1^{KO}/Fgf23^{cKO}$ mice at 12 and 20 weeks (vs. $Dmp1^{KO}$), suggesting that lowering FGF23 and PTH is insufficient to prevent phosphaturia in $Dmp1^{KO}$ mice.

Conclusions: These data suggest that in $DMP1^{KO}$ mice, hypophosphatemia is only partially responsible for the bone defects and that blocking FGF23 might not be sufficient to prevent hypophosphatemia in the long term.

Funding: NIDDK Support

PO0534

Linking CKD with COPD: Kidney-Lung Cross-Talk and the Role of Phosphate and FGF-23 in the Bronchial Epithelium

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Background: Dysregulation of phosphate homeostasis and increased circulating FGF23 levels are associated with chronic kidney disease (CKD); however, their role in pulmonary pathology remains poorly defined. Hyperphosphatemia is associated with increased mortality in patients with chronic obstructive pulmonary disease (COPD). Human bronchial epithelial cells (HBECs) are key effector cells in the pathogenesis of COPD, making them essential for assessing the comorbid association of COPD with CKD. Smoking is the leading cause of COPD and dramatically accelerates kidney disease occurrence. We have previously shown that FGF23 can directly affect the COPD bronchial epithelium. With the goal of improving outcomes for patients with concomitant CKD and COPD, we aimed to study the effects of phosphate, FGF23, and cigarette smoke on HBECs and their underlying mechanisms.

Methods: HBECs were treated with 1 to 5 mM sodium phosphate, FGF23, and/or cigarette smoke extract (CSE). Expression levels of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and IL-8 were analyzed by RT-qPCR. Concentration of these cytokines in the conditioned media was also quantified via enzyme-linked immunosorbent assay. In addition, wild type and FGFR4 knockout ($FGFR4^{-/-}$) mice were fed a high phosphate diet for a total of three months or exposed to cigarette smoke for three weeks. Lung tissue was then analyzed by western blotting and RT-qPCR.

Results: Increased phosphate concentrations induced an inflammatory response in HBECs, which was further exacerbated by the addition of CSE but attenuated by FGF23 treatment. Furthermore, mice on a high phosphate diet showed increased FGF23 and IL-6 levels in their lung. The increase in IL-6 was not observed in the $FGFR4^{-/-}$ mice. Subacute cigarette exposure led to an increase in IL-1β and IL-8 in total lung tissue, which was abrogated in the $FGFR4^{-/-}$ mice.

Conclusions: Our in vitro data suggest that CKD-associated hyperphosphatemia may increase cigarette smoke induced airway inflammation, whereas our in vivo data demonstrates a role of both phosphate and FGF23 signaling in mediating lung inflammation. In summary, our results show that in CKD, there seems to be kidney-lung crosstalk with both FGF23 and phosphate as mediators of an inflammatory airway response, which seems to be mediated by FGFR4.

PO0535

Plasma Biomarkers of Mineral and Bone Disorder in ADPKD Patients Treated with Tolvaptan

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Background: Autosomal-dominant polycystic kidney disease (ADPKD) is characterized by a unique bone and mineral phenotype. Patients affected by ADPKD show parathyroid hormone (PTH) resistance, a better-preserved cortical bone mass, higher sclerostin levels, lower bone turnover and total alkaline phosphatase compared to other chronic kidney disease (CKD) aetiologies. To date, the association between tolvaptan administration, plasma biomarkers of mineral and bone disorder (CKD-MBD) and bone mineral density has not been investigated.

Methods: We conducted an analysis of patients enrolled in the Bern ADPKD registry, a prospective observational cohort study. Plasma parameters for CKD-MBD and 24-hour urine analyses were performed at baseline and every 12 months thereafter. DEXA scans were obtained at baseline and after 3 years. Multivariable fixed-effects regression models adjusted for age, sex, BMI, eGFR, urinary sulfate excretion (a marker of acid intake) and NGIA (a marker of alkali intake) were applied to study changes in CKD-MBD parameters and bone mineral density associated with tolvaptan treatment.

Results: A total of 167 participants (56 with and 111 without tolvaptan treatment) were included in the analysis. Median follow-up time was 24.5 months. After adjusting for potential confounders, tolvaptan treatment was associated with a significantly reduced plasma PTH (β -14.84; 95%CI, -28.61 to -1.07; p=0.04), increased total plasma calcium (β 0.05; 95%CI, 0.01 to 0.09; p=0.01), plasma magnesium (β 0.02; 95%CI, 0.00 to 0.04; p=0.03) and femoral but not lumbar bone mineral density (β 0.10; 95%CI, 0.01 to 0.19; p=0.04 and β 0.22; 95%CI, -0.04 to 0.08; p=0.49, respectively). In contrast, tolvaptan treatment was not associated with changes in plasma phosphate, ionized calcium, TmP/GFR, serum intact fibroblast growth factor 23, plasma alkaline phosphatase, blood pH or serum 1,25(OH)2 and 25(OH) vitamin D.

Conclusions: Tolvaptan treatment is associated with changes in mineral metabolism parameters and increased bone mineral density at the femoral neck. Long-term prospective studies are needed to assess the impact of tolvaptan on fracture risk.

PO0536

Call for Harmonization of the Histomorphometric Reference Ranges for Bone Turnover in Renal Osteodystrophy

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Background: Knowledge of bone turnover helps guide fracture preventive treatment in patients with chronic kidney disease (CKD). Bone histomorphometry remains the gold standard to assess bone turnover, while non-kidney retained bone biomarkers are considered a valid, but imperfect alternative. Published reports show marked variation in the histomorphometric reference values of bone turnover. Our aim was to investigate the impact of different diagnostic cutoffs on the categorization of bone turnover in a CKD population.

Methods: 199 patients with successful bone biopsies before or after kidney transplantation were categorized for bone turnover according to diagnostic cut-offs as published by Salusky *et al* and Malluche *et al*, recently published normative histomorphometric data by Recker *et al*, as well as population-based normal ranges for bone-specific alkaline phosphatase (BsAP), tartrate-resistant acid phosphatase type 5b (TRAP5b), and trimeric procollagen type I N-terminal propeptide (Intact PINP; all IDS-iSYS).

Results: Major differences in the distribution of bone turnover categories were seen depending on the reference method used, for both kidney transplant candidates (n = 80, Figure) and recipients (n = 119, data not shown). Compared to the categorizations based on biochemical bone turnover markers, the bone biopsy diagnosis was skewed towards lower bone turnover when using cut-offs as proposed by Salusky or Malluche.

Conclusions: These findings call for harmonization and calibration of bone histomorphometry for the categorization of bone turnover. This will require a collaborative effort to first, construct a repository of bone histomorphometric data from healthy controls across ages, sexes, and ethnicities, and second, to reach a consensus on the diagnostic cut-offs for bone turnover in renal osteodystrophy.

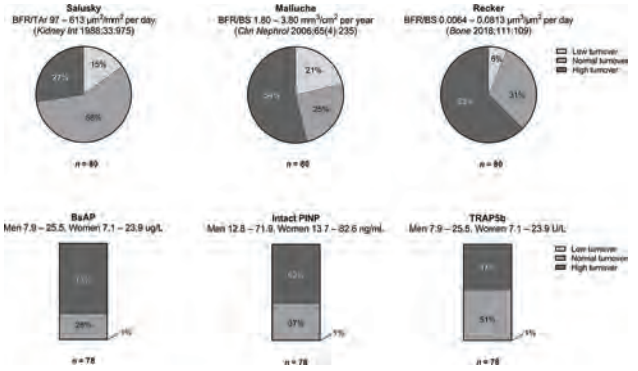

Figure Distribution of bone turnover by different references in kidney transplant candidates with chronic kidney disease stage 5-5D

PO0537

Effects of Patiromer on Serum Phosphate over 4 Weeks of Treatment in Hyperkalemic Patients with Hyperphosphatemia: Pooled Analysis of the AMETHYST-DN, OPAL-HK and TOURMALINE Trials

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Background: Elevated serum phosphate (sP) is associated with increased mortality in non-dialysis CKD. KDIGO guidelines suggest elevated sP should be lowered into the normal range: 2.5–4.5 mg/dL. Patiromer is a non-absorbed, sodium-free, potassium (K^+) binder that uses calcium as the exchange ion which, when released, likely binds to intestinal phosphate. We conducted a *post-hoc* analysis of pooled data from AMETHYST-DN, OPAL-HK and TOURMALINE to evaluate patiromer's effect on sP over 4 weeks in patients with sP>4.5mg/dL.

Methods: Eligible patients had CKD and hyperkalemia (HK; serum K^+ [sK^+]>5.0 mEq/L). Prescription of phosphate binders was not allowed. Hyperphosphatemia subgroup was defined as baseline sP>4.5mg/dL. Patients in the analysis received ≥1 dose of patiromer (8.4–33.6 g/day to start) and had ≥1 post-baseline sP assessment. Mean (± SD) changes from baseline in sP, sK^+, serum magnesium and serum calcium at weeks 2 and 4 were evaluated.

Results: 86/578 (15%) patients had baseline sP>4.5mg/dL: 56% were male, mean (SD) age was 63.9 (10.5) years, 84% had diabetes, mean (SD) eGFR was 25.9 (17.2) mL/min/1.73m^2 and 76% had stage 4/5 CKD. Mean (SD) baseline sP and K^+ were 5.0 (0.5) mg/dL and 5.5 (0.4) mEq/L, respectively. At 2 or 4 weeks of patiromer treatment, both mean sP and sK^+ levels decreased into the normal range (**Table**). Most frequent adverse events (AEs) were constipation (8/86; 9%) and diarrhea (6/86; 7%); most cases were mild or moderate in severity. AEs leading to study discontinuation occurred in 3/86 (4%) patients.

Conclusions: Patiromer decreased both sP and sK^+ into the normal range in patients with elevated sP and sK^+. Patiromer was well tolerated with mild/moderate gastrointestinal events. The ability of patiromer to normalize sP may be therapeutically useful in hyperkalemic patients with CKD and hyperphosphatemia.

Funding: Commercial Support - Vifor Pharma Ltd

Table: Serum phosphate, potassium, calcium, and magnesium at baseline, and after 2 and 4 weeks of patiromer treatment

Patients with baseline serum phosphate >4.5mg/dL	Baseline		Week 2		Week 4		Week 4: Change from baseline
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD) [95% CI]
Phosphate, mg/dL	5.04 (0.496)	86	4.43 (0.785)	72	4.44 (0.995)	71	-0.62 (1.089) [-0.87, -0.36]
Potassium, mEq/L	5.50 (0.350)	86	4.80 (0.415)	77	4.77 (0.480)	75	-0.71 (0.513) [-0.83, -0.59]
Calcium, mg/dL	9.02 (0.742)	86	9.11 (0.618)	74	9.08 (0.574)	71	0.04 (0.631) [-0.10, 0.19]
Magnesium, mg/dL	2.26 (0.347)	86	2.06 (0.338)	74	2.00 (0.268)	71	-0.25 (0.226) [-0.30, -0.19]

CI, confidence interval; SD, standard deviation

PO0538

Circadian Changes in Serum Phosphate Among Patients with ESKD on Hemodialysis

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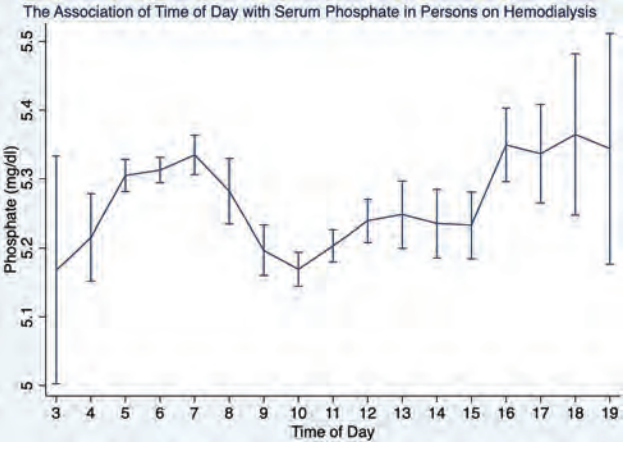
Background: Serum phosphate concentrations are known to have a circadian rhythm in healthy adults and in CKD, with a nadir in the late morning and a peak in the afternoon. Circadian changes in serum phosphate concentrations among persons on chronic hemodialysis may have important treatment implications, as serum phosphate concentrations are a therapeutic target in these patients.

Methods: We assessed serum phosphate concentrations in 118,440 persons with ESKD treated with in-center hemodialysis at Fresenius Kidney Care centers across the United States in July 2017. We used linear regression to assess the relationship between time of day and serum phosphate concentrations. We assessed unadjusted models and models adjusting for age, sex, race, region, weight, diabetes and use and dose of vitamin D analogs, calcimimetics and phosphate binders.

Results: The cohort had mean age 63 ± 13 years, 44% were female, 53% were white and 33% were black. The mean serum phosphate concentration was 5.3 ± 1.5mg/dl. In both the unadjusted and fully adjusted models, serum phosphate concentrations varied over the day with a peak at 6:00 pm and a nadir at 10:00 am (p<0.001). In the unadjusted model the difference from peak to nadir was 0.6mg/dl. This difference was attenuated in the fully adjusted model to 0.2 mg/dl (Figure).

Conclusions: In a large and diverse cohort of adults with ESKD treated with hemodialysis, serum phosphate concentrations varied depending on the time of day in which serum phosphate levels were measured. Thus, the target serum phosphate range for patients treated with hemodialysis should account for when serum phosphate is being measured.

Funding: NIDDK Support, Commercial Support - Fresenius Medical Care North America



PO0539

Association of Combined Urinary Fractional Excretion of Phosphate and Serum FGF-23 with Adverse Events in Moderate and Advanced CKD: An Analysis from the CRIC Study

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Background: High levels of FGF23 are associated with adverse events in CKD. The urinary fractional excretion of phosphate (FePi) might modify this association, although data are limited in moderate and advanced CKD. We investigated the association of combined FePi and serum FGF23 with mortality, renal and cardiovascular events in patients with prevalent CKD 2-4.

Methods: Patients from the Chronic Renal Insufficiency Cohort (CRIC) were divided into four groups according to the median of FePi and FGF23: 1) low-FePi/low-FGF23, reference group; 2) high-FePi/low-FGF23; 3) low-FePi/high-FGF23; 4) high-FePi/high-FGF23. Primary outcomes were: incident heart failure; a composite atherosclerotic cardiovascular disease (ASCVD) outcome of myocardial infarction, ischemic stroke or peripheral artery disease; CKD progression; and all-cause mortality. The association of groups with the longitudinal outcomes was assessed through unadjusted and adjusted Cox proportional hazards models.

Results: We analyzed 3684 patients with a mean age of 58±11 years, 45% were male, and 42% were Black. Baseline mean eGFR was 44.3 ± 14.9 ml/min/1.73 m2. Median FePi and FGF23 were 26.5% (IQR, 19.5-36.8) and 145 (IQR, 95.6-238.3) RU/ml, respectively. The median time of follow-up was 12 (IQR, 7-13) years. The total number of events was 796 for incident heart failure, 717 for composite ASCVD, 1233 for CKD progression and 1328 for all-cause mortality. The adjusted relative risk of incident heart failure was higher in the low-FePi/high-FGF23 group (HR, 1.31; 95%CI, 1.03 to 1.67) and higher in the high-FePi/high-FGF23 group (HR, 1.58; 95%CI, 1.23 to 2.02), comparing to the low-FePi/low-FGF23 group. Composite ASCVD was higher in the high-FePi/high-FGF23 group (HR, 1.42; 95%CI, 1.11 to 1.80), but not in the low-FePi/high-FGF23 group (HR, 1.25; 95%CI, 0.98 to 1.59). All-cause mortality was higher in the low-FePi/high-FGF23 group (HR, 1.56; 95%CI, 1.30 to 1.89) and higher in the high-FePi/high-FGF23 group (HR, 1.57; 95%CI, 1.29 to 1.90). The adjusted risk of CKD progression was not different between groups.

Conclusions: In contrast to previous reports in patients with mild renal disease, the combination of high FePi and high FGF23 was associated with the highest risk of heart failure and ASVCD events in moderate and advanced CKD.

PO0540

Pill Burden and Changes in Mineral Bone Disorder (MBD) Markers in Hemodialysis (HD) Patients Switched from Sevelamer to Sucroferric Oxyhydroxide (SO): A One-Year Follow-Up in a Contemporary Cohort

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Background: About 80% of US dialysis patients are prescribed phosphate binders (PB) for serum phosphorus (sP) control; however, PB high pill burdens are associated with non-adherence and elevated sP levels. Clinical and observational studies have demonstrated that SO is effective in lowering sP with similar efficacy to sevelamer (Sev), but with a lower pill burden. The present study aims to assess the long-term changes in MBD markers and pill burden in a contemporary HD cohort switching from Sev to SO.

Methods: The study included adult, Fresenius Kidney Care maintenance HD pts receiving Sev during a 91-day baseline (BL) and first prescribed SO monotherapy during 5/2018- 5/2019. The one year follow up (FU) on SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Comparisons of PB pill burden and MBD markers between BL and FU were carried out using mixed-effects linear regression and Cochran's Q test.

Results: On average, patients (n=841) were 56.2 (13.3) years old with dialysis vintage of 50.5 (48.6) months. At BL, the % of pts was 21.2% for sP ≤ 5.5 mg/dL and 4.5% for sP≤ 4.5 mg/dL with 8.4 Sev pills/day; after switching to SO, the % of patients increased to 35.4%- 44.0% for sP ≤ 5.5 mg/dL and 11.4%-16.1% for sP≤ 4.5 mg/dL with 4.4- 4.9 pills/day. Mean iPTH and serum calcium (Ca) decreased progressively after SO conversion.

Conclusions: Maintenance HD patients switching PB prescription from Sev to SO during 2018 and 2019 as part of routine care showed significant reductions in sP and PB pill burden, and increases in the number of patients with sP ≤5.5mg/dL and sP ≤ 4.5 mg/dL. A trend toward decreased serum Ca and iPTH levels during SO therapy was also observed.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	BL: -Q1 (ref)	SO Q1	SO Q2	SO Q3	SO Q4	P- value
PB, pills/day	8.4	4.4**	4.6**	4.9**	4.9**	<.001
sP≤ 5.5 mg/dL, %	21.2	35.4**	44.0**	43.8**	41.1**	<.001
sP≤ 4.5 mg/dL, %	4.5	11.4**	15.8**	16.4**	15.1**	<.001
sP, mg/dL	6.55	6.14**	5.92**	5.92**	5.98**	<.001
iPTH, pg/ml	628	592**	579**	578**	565**	<.001
Calcium, mg/dL	9.14	9.13	9.09**	9.04**	9.02**	<.001

*P<0.05; **P<.001 (vs. BL)

PO0541

Serum Phosphorus (sP) and Pill Burden Among Hemodialysis (HD) Patients Prescribed Sucroferric Oxyhydroxide (SO): One-Year Follow-Up on a Contemporary Cohort

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Background: A previous real-world analysis included HD patients (pts) prescribed SO during 2014-2015 followed for 1 year. Improvements in sP were observed along with fewer phosphate binder (PB) pills/day after pts switched from their previous PB to SO (2014 Cohort, Kendrick). To examine how PB prescription (Rx) patterns have changed over time, the present study compares the long-term effectiveness of SO in a contemporary cohort (prescribed SO in 2018-2019; 2018 Cohort) with 2014 Cohort results.

Methods: Adult Fresenius Kidney Care HD pts first prescribed SO monotherapy during 5/2018- 5/2019 as part of routine care and followed for one year were included. All pts were on a non-SO PB during a 91-day baseline (BL) before SO Rx. Mean PB pills/day and labs were compared for BL and SO follow-up (divided into 4 consecutive 91-day intervals; Q1-Q4) using mixed-effects linear regression and Cochran's Q test. These results were compared with findings from the 2014 Cohort.

Results: Compared to the 2014 Cohort (n=530), the 2018 Cohort (n=1793) was older (57 vs 55 yrs) with shorter HD vintage (34 vs 45 months), more likely prescribed calcium acetate (36 vs 28%) and ferric citrate (6% vs 0) and less likely prescribed sevelamer (47 vs 60%). The 2018 Cohort had better BL sP control; both cohorts showed reductions in sP and PB pills/day after SO conversion. During SO FU, iPTH decreased in the 2018 Cohort.

Conclusions: Despite different pt characteristics and treatment patterns in the 2014 and 2018 cohorts, HD pts from both cohorts had improvements in sP and % pts achieving sP ≤ 5.5 mg/dL or sP ≤ 4.5 mg/dL with fewer PB pills/day after SO conversion.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

	Cohort	BL: -Q1	Q1	Q2	Q3	Q4	P- value
sP, mg/dL	2018	6.38	6.10**	5.88**	5.88**	5.93**	<.001
	2014	6.82	6.54**	6.37**	6.25**	6.19**	<.001
sP≤ 5.5 mg/dL, %	2018	27.0	37.8**	45.1**	44.7**	44.0**	<.001
	2014	17.7	24.5**	30.5**	36.4**	36.0**	<.001
sP≤ 4.5 mg/dL, %	2018	8.4	12.7**	16.8**	17.4**	17.0**	<.001
	2014	4.7	6.6	11.6**	12.1**	13.7**	<.001
PB, pills/day	2018	7.7	4.4**	4.6**	4.8**	4.9**	<.001
	2014	8.5	4.0**	4.1**	4.2**	4.3**	<.001
iPTH, pg/ml	2018	564	560	558	545*	528**	<.001
	2014	611	627	622	636	643*	0.16
Corrected Calcium, mg/dL	2018	9.64	9.61*	9.58**	9.53**	9.52**	<.001
	2014	9.25	9.21*	9.16**	9.16**	9.10**	<.001

*P<0.05; **P<.001 (vs. BL)

PO0542

One-Year Follow-Up of Maintenance Hemodialysis (HD) Patients Who Switched Phosphate Binder (PB) Prescription from Ferric Citrate (FC) to Sucroferric Oxyhydroxide (SO)

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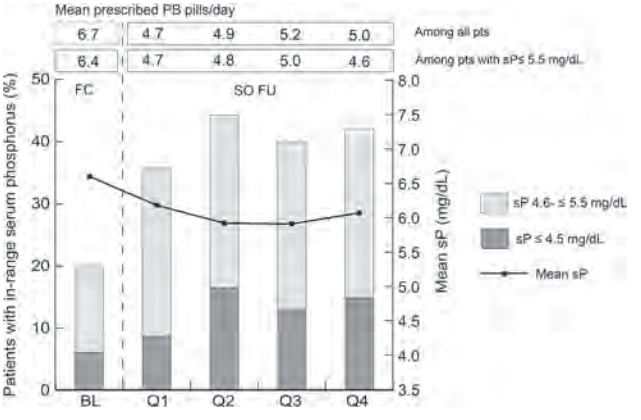
Background: A new class of iron based PBs have been prescribed to HD patients for hyperphosphatemia management. This one-year real-world data analysis in a contemporary cohort of HD patient who switched from FC to SO as part of routine care investigates changes in serum phosphorus (sP) and pill burden.

Methods: Adult Fresenius Kidney Care HD patients included in the analysis were first prescribed SO monotherapy between 5/2018-5/2019 and were on FC for 3 months (baseline; BL) prior to SO therapy. The one year SO therapy was divided into four consecutive 91-day intervals (Q1-Q4). Changes in lab measurements and PB pill burden were compared between BL and Q1-Q4, using mixed-effects linear regression and Cochran's Q test.

Results: Patients (n=115) were on average 55.5 (12.6) years old with 52.8 (46.4) months HD vintage, 38% female, 54% had diabetes and 20% had CHF. There were consistent improvements in pts achieving sP ≤ 5.5 mg/dL (from 20% at BL to 35.7%- 44.3% with SO; p<.0001) and in patients achieving sP≤ 4.5 mg/dL (from 6.1% at BL to 8.7%-16.5% with SO; p=0.02). Pts were prescribed 6.7 pills/day at BL and 4.7-5.2 pills/day with SO. SO conversion was associated with decreases in mean iPTH (620 pg/mL at BL, 496 pg/mL at Q4; p<.0001) and serum calcium (9.18 mg/dL at BL, 8.93 mg/dL at Q4; p<.0001).

Conclusions: Maintenance HD pts switched PB prescription from ferric citrate to sucroferric oxyhydroxide experienced significant increases in % patients achieving in-range sP (+111% for sP ≤5.5mg/dL and +144% for sP ≤4.5mg/dL) with a lower pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group



PO0543

Effects of Lanthanum Carbonate on Whole-Body Phosphorus Balance in Patients with Stage 3b-4 CKD and Normophosphatemia

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Background: In CKD, elevated phosphorus, even within the normal range, is associated with cardiovascular disease (CVD) and mortality. However, in normophosphatemic CKD, phosphate binders do not improve vascular function, an independent predictor of CVD. Whether long-term treatment with phosphate binders affects phosphorus balance in CKD is unknown. Our objective was to determine phosphorus balance in normophosphatemic subjects with CKD 3b-4 after 12 weeks of treatment with lanthanum carbonate (LC) or placebo.

Methods: A subset of 15 subjects with CKD 3b-4 and serum phosphorus within normal limits randomized to receive 12 weeks of LC or placebo investigating effects of phosphate lowering on vascular function (NCT02209636) volunteered to participate in this ancillary aim. At the end of 12 weeks, participants consumed a controlled diet (1000 mg/day phosphorus and 800 mg/day calcium) for 9 days and continued their randomly-assigned study drug (N=7 LC, N=8 placebo). Fasting morning blood samples and all stool and urine were collected during a 48-hour inpatient clinical research center stay at the end of the 9-day balance period. Phosphorus balance (mg/d) was determined by values averaged over the 48-hour period: Dietary phosphorus intake minus urine phosphorus minus fecal phosphorus. T-tests were used to compare means.

Results: Mean age was 65±7y and mean eGFR was 33±6 mL/min/1.73m^2. One patient randomized to LC was excluded from fecal phosphorus and phosphorus balance results due to insufficient stool. 24-hour urine phosphorus was lower with LC compared with placebo, but this did not reach statistical significance (388±60 v. 513±51, p=0.15). Fecal phosphorus was higher with LC compared with placebo (775±163 v. 259±141, p=0.03), and whole-body phosphorus balance was lower with LC compared with placebo (-131±163 v. 320±141, p=0.06).

Conclusions: These results provide evidence that long-term treatment with the phosphate binder lanthanum carbonate may reduce whole-body phosphorus balance in patients with stage 3b-4 CKD and normophosphatemia. Whether this translates into beneficial clinical outcomes relevant to chronic-kidney disease-mineral and bone disorder warrants further investigation.

Funding: NIDDK Support, Veterans Affairs Support

PO0544

Impact of Tenapanor in Peritoneal Dialysis

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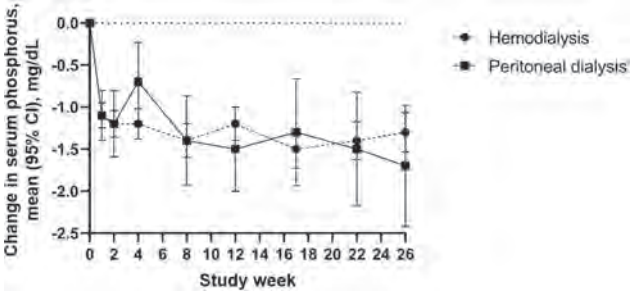
Background: Peritoneal dialysis (PD) utilization is being promoted worldwide as more emphasis is placed on the advantages and reduced cost of home dialysis. Serum phosphorus (sP) control for PD patients remains a challenge, particularly as residual kidney function is lost. Many PD patients receive stool softeners or laxatives to prevent constipation which may impede the treatment. Tenapanor (TEN) is a first-in-class phosphate absorption inhibitor (PAI) that targets the paracellular pathway of phosphate absorption by inhibiting the sodium-hydrogen exchanger 3 (NHE3) antiporter on the luminal surface of gastrointestinal epithelium. As a side effect of inhibiting NHE3, the sodium and water content of the stool is augmented, increasing stool frequency and volume. Here we compare the control of sP and the adverse event (AE) profile of TEN in the PD and hemodialysis (HD) subgroups in the phase 3 PHREEDOM trial.

Methods: PHREEDOM evaluated the safety and efficacy of TEN in patients on HD or PD with hyperphosphatemia. Following washout from phosphate binders, patients whose sP increased by 1.5 to ≥6.0 mg/dL were enrolled. Those randomized to the TEN arm received TEN 30 mg orally twice daily for 26 weeks. Counseling to discontinue stool softeners or laxatives was not provided to patients entering the trial. sP and AEs were recorded per protocol.

Results: Over the 26-week treatment period, the change in sP was similar for patients treated by PD (n=42) and HD (n=365) (figure). Diarrhea was the most common AE (56.1%) in the PD subgroup (with a similar incidence in the HD subgroup [51.6%]); no PD patients reported diarrhea as a serious AE.

Conclusions: These findings demonstrate that TEN may be a useful agent in reducing sP levels for patients treated with PD and have an added benefit of assisting with the management of constipation, which can be problematic for the PD patient. Prior counseling to discontinue stool softeners and laxatives when initiating TEN may decrease the AE of diarrhea and further reduce the number of medications when patients are switched from phosphate binders to TEN.

Funding: Commercial Support - Ardelyx, Inc.



PO0545

Management of Serum Phosphorus (sP) Over One-Year Follow-Up in Peritoneal Dialysis (PD) Patients Prescribed Sucroferric Oxyhydroxide (SO) as Part of Routine Care

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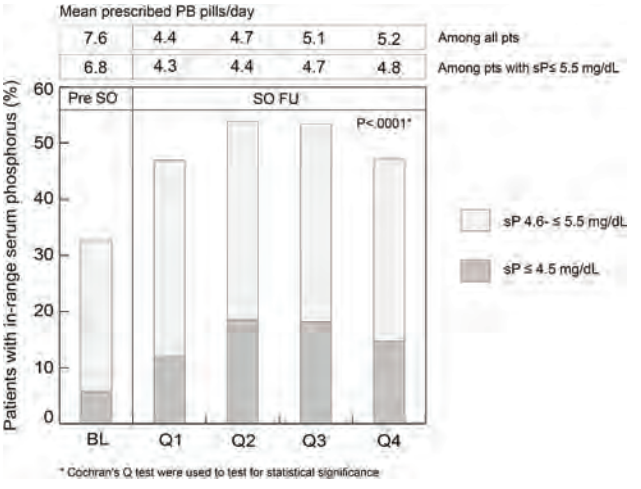
Background: Clinical and observational studies have shown the effectiveness of SO in controlling sP in PD patients (pts). A real-world retrospective analysis in a PD cohort prescribed SO for 6 months demonstrated an association between SO prescription and lower sP. The current analysis examines the changes in sP and PB pill burden over a one-year period in PD patients converting to SO.

Methods: We included adult Fresenius Kidney Care (FKC) PD pts (n=260) first prescribed SO monotherapy during 5/2018- 5/2019 who had sP measured 91 days before SO prescription (baseline; BL). Comparisons were made between BL and the four consecutive 91-day intervals of SO treatment (Q1-Q4). Means of PB pill burden and lab measures were calculated using mixed effects linear regression.

Results: At BL, mean age was 54 years old with PD vintage 18 months, 37% pts had no PB prescriptions recorded and the remaining pts were prescribed sevelamer (36%), calcium acetate (33%), lanthanum (1%), ferric citrate (13%), switched between PB (10%), or >1 PB recorded (6%). After switching to SO, % of pts achieving sP<= 5.5 mg/dL increased from 32.7% at BL to 46.9%- 53.8% during SO FU, % of pts achieving sP<= 4.5 mg/dL increased by 153% from BL to Q4, along with fewer PB pills per day (7.6 at BL vs 4.4-5.2 at FU).

Conclusions: During a one-year observation period, PD pts prescribed SO as part of routine care during 2018-2019 had significant reductions in sP and PB pills/day and increases in % of pts with sP≤ 5.5 mg/mL or sP≤ 4.5 mg/mL, suggesting improved sP management with concurrent reduction in pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group



PO0546

US Hemodialysis Facilities Switching from Cinacalcet to Etelcalcetide: Impact on Parathyroid Hormone (PTH) Levels

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Background: Some US hemodialysis (HD) facilities switched from oral cinacalcet (Cina) to intravenous (IV) etelcalcetide (Etel) as the primary calcimimetic therapy to control parathyroid hormone (PTH) levels after the introduction of Etel in 2017. While clinical trial data have indicated superior efficacy of Etel vs. Cina, real-world evidence is lacking.

Methods: We evaluated facility calcimimetic use during 6-month intervals before (Period 1: May-October 2016) and after (Period 2: March-August 2019) introduction of Etel using US-DOPPS data. We compared the pre-post difference in outcomes – PTH, Ca, P – over the 6 months after each exposure period among calcimimetic users in HD facilities that "switched" from treating >75% of calcimimetic users with cinacalcet ("Cina-first") in Period 1 to treating >75% of calcimimetic users with etelcalcetide ("Etel-first") vs. facilities that remained Cina-first in Period 2.

Results: Among 32 US HD facilities that switched to Etel-first in Period 2, mean PTH decreased from 671 to 484 pg/mL and % PTH >600 pg/mL decreased from 39% to 21%. Among 34 facilities that remained Cina-first in Period 2, mean PTH increased from 632 to 698 pg/mL and % PTH >600 pg/mL increased from 37% to 43%. The adjusted difference-in-difference between switch to Etel-first and remain Cina-first was -169 (95%

CI: -249, -90) pg/mL for mean PTH and -14.5% (95% CI: -22.4%, -6.7%) for PTH >600 pg/mL. Serum Ca levels were slightly lower in facilities that switched to Etel-first, while serum P was not associated with facility calcimimetic type [*Table 1*].

Conclusions: In this natural experiment, we observed better PTH control in facilities that switched to etelcalcetide (vs. remained cinacalcet) as the primary calcimimetic therapy. Further research is needed to evaluate whether this clear difference in real-world effectiveness translates to a reduction in hospitalizations and mortality.

Funding: Other NIH Support - Agency for Healthcare Research and Quality (AHRQ), Commercial Support - This analysis was supported by Amgen. Other support includes: Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical CO., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torii Pharmaceutical Co.,Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd

	Switched to Etel-first		Remained Cina-first		Adjusted diff-in-diff (95% CI)	p-value
	Period 1	Period 2	Period 1	Period 2		
N facilities	32	32	34	34	--	--
N calcimimetic users	612	793	536	673	--	--
Median N per facility	17.5	21.5	11.0	18.5	--	--
Continuous outcomes						
PTH (pg/mL)	671 ± 580	484 ± 379	632 ± 463	698 ± 534	-169 (-249, -90)	<0.001
Serum Ca (mg/dL)	9.1 ± 0.6	8.9 ± 0.6	9.1 ± 0.5	9.0 ± 0.6	-0.10 (-0.20, -0.01)	0.04
Serum P (mg/dL)	5.5 ± 1.3	5.5 ± 1.4	5.6 ± 1.4	5.8 ± 1.5	0.04 (-0.17, 0.25)	0.71
Binary outcomes						
PTH >600 pg/mL	39%	21%	37%	43%	-14.4% (-22.0, -6.8)	<0.001
Ca <8.4 mg/dL	12%	19%	10%	13%	5.5% (-0.2, 11.3)	0.06
P >5.5 mg/dL	48%	46%	48%	53%	-1.9% (-9.6, 5.8)	0.62

Crude mean ± std dev and prevalence (%) shown in Period 1 and Period 2 columns; Linear mixed models with random facility intercept adjusted for HD facility characteristics (dialysis organization size, facility size, facility % Black race, hospital-based, facility % total calcimimetic use) and patient characteristics (age, sex, Black race, dialysis vintage, BMI, serum albumin, hemoglobin, serum potassium, 13 summary comorbidities, catheter use); Adjusted diff-in-diff (95% CI) parameter derived from the interaction effect between period and facility calcimimetic preference.

PO0547

A Real-World Observational Study of Calcimimetic Use in Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT) in Europe

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Background: Calcimimetics, Cinacalcet (CIN) and Etelcalcetide (ETEL), are approved for treating SHPT in adult patients on maintenance HD. Data on real-world use are needed to provide guidance in clinical practice.

Methods: In this observational study, chronic HD patients treated with calcimimetics for SHPT with ≥1 parathyroid hormone (PTH) measurement recorded within 90 days before calcimimetic initiation were included. Medical history, PTH, calcium (Ca) and phosphate (P) measurements, and calcimimetic use data were extracted from medical charts. Baseline period was defined as 6 months before calcimimetic initiation.

Results: Interim data for 974 HD (198 CIN and 776 ETEL) patients across 15 countries in Europe, recorded from June 2018 to March 2021, are reported. 43% (334/776) of ETEL patients had switched within 90 days after stopping CIN. ETEL patients were younger than CIN (median age: 62 vs. 65 yrs.). Dialysis vintage was longer for ETEL than CIN patients (median: 4.4 vs. 2 yrs.). Starting dose was 30 mg for 95% of CIN; and 5 mg and 2.5 mg for 58% and 40% of ETEL patients respectively. At 12 months, median PTH had decreased by 41% in ETEL and 31% in CIN patients (**Table 1**), however 54% of ETEL and 57% of CIN patients achieved target PTH range (150-600 pg/mL). The cumulative incidence of hypocalcemia (Ca <2.1 mmol/L) at 6 months (66% vs. 59%) was higher in CIN than ETEL patients, but no difference was recorded at 12 months (74% vs. 73%). As recorded in medical charts, nausea (2.2% vs. 2%) and vomiting (0 vs. 1.3%) were low for CIN and ETEL patients. ETEL persistence (88%) was greater than CIN (76%) at 12 months. 16% switched from CIN to ETEL and 2% from ETEL to CIN during follow-up.

Conclusions: ETEL and CIN patients achieved target PTH range to a similar degree at 12 months, however PTH decrease over time was better in ETEL patients. Treatment persistence was higher with ETEL than CIN. No new safety signals were observed.

Funding: Commercial Support - AMGEN

Table 1: PTH, Ca, and P laboratory values at baseline and up to 12 months

	Etelcalcetide (N=776)				Cinacalcet (N=198)			
	Baseline	3 months	6 months	12 months	Baseline	3 months	6 months	12 months
PTH (pg/mL) Median (IQR)	690 (460, 1006)	512 (345, 875)	425 (265, 782)	381 (234, 649)	648 (468, 930)	417 (285, 668)	405 (260, 716)	456 (297, 660)
Ca (mmol/L) Mean (SD)	2.27 (0.17)	2.17 (0.19)	2.16 (0.19)	2.19 (0.19)	2.25 (0.18)	2.17 (0.20)	2.20 (0.20)	2.19 (0.22)
P (mmol/L) Mean (SD)	1.81 (0.46)	1.67 (0.49)	1.65 (0.49)	1.67 (0.53)	1.79 (0.46)	1.66 (0.50)	1.67 (0.50)	1.68 (0.48)

PO0548

Effects of Etelcalcetide on the Evolution of Cortical Porosity in Patients and Rats with CKD

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Background: Suppression of chronically elevated parathyroid hormone (PTH) is a key treatment goal in patients with chronic kidney disease–mineral and bone disease (CKD-MBD). High PTH leads to increased cortical porosity which is associated to increased fracture risk. We tested the hypothesis that etelcalcetide, a calcimimetic agent, suppresses cortical pore development in CKD.

Methods: For our clinical cohort, etelcalcetide was dose-titrated to maintain serum PTH at 2-5 times the upper limit of normal of the local PTH assay, corresponding to the lower half of the KDIGO recommended target level. Patients were scanned at the distal tibia by high resolution peripheral QCT before and after 9-months of treatment. For our preclinical cohort, etelcalcetide was administered to an established model of progressive CKD (Male Cy/+ rat) for 3-5 weeks with *in vivo* microCT scans at the distal tibia taken at baseline and endpoint. Clinical and preclinical scans were registered across the two timepoints and individual cortical pores tracked for their dynamic action (filled, contracting, expanding, developed).

Results: Etelcalcetide significantly suppressed PTH in both the clinical (-64%) and pre-clinical (-77%) cohorts. Total cortical porosity did not increase over the course of treatment in either humans (baseline 5.8%; endpoint 5.8%) or rats (baseline 3.3%; endpoint 3.7%). However, changes were detected at the individual pore level by individual cortical pore analysis. In humans, of the baseline pores, 3% were unchanged, 25% had completely infilled, 40% had become smaller and 27% had increased in size. Twenty-one percent of the total pores at the end of treatment were formed de novo during treatment. The preclinical data followed similar trends, 43% of baseline pores had completely infilled, 20% had decreased in size, 22% had increased in size and 63% of the total pores end of treatment had formed de novo.

Conclusions: PTH suppression by etelcalcetide stabilizes overall cortical porosity yet permits dynamic activity of individual cortical pores during treatment. Further studies are needed to determine if de novo cortical porosity can be prevented by more aggressive PTH reduction.

Funding: Veterans Affairs Support, Commercial Support - Amgen

PO0549

Etelcalcetide Improves Central Skeleton Bone Quality and Density in Patients on Hemodialysis

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Background: Secondary hyperparathyroidism (SHPT) is an important complication of dialysis. It is associated with osteoporosis and fractures. Etelcalcetide is an intravenous calcimimetic superior to cinacalcet in control of parathyroid hormone (PTH) in hemodialysis (HD) patients. The effects of etelcalcetide on bone quality and density are unknown. We hypothesized that etelcalcetide improves spine trabecular bone score (TBS), a marker of central skeletal trabecular bone quality, and bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) in HD patients.

Methods: Eligible subjects were ≥18 yo, on HD ≥1 year, normocalcemic, without calcimimetic exposure within 3 months of enrollment. Treatment included a 3-month dose titration phase to target a PTH level 2-5 times the upper limit of normal, followed by a 6-month maintenance phase. TBS and DXA were obtained at both baseline (pre-treatment) and at 9-months (end of study). Intact PTH was obtained at pre-treatment, 3- and 9-months post-treatment. Mixed models assessed change in TBS and age, sex, race Z-Scores adjusted for change in PTH.

Results: 22 subjects were enrolled;13 completed follow-up. Among the 13 subjects: mean±SD age was 51±14 yrs; 53% male; 15% white. Median (min-max) PTH (pg/mL) levels at baseline, 3- and 9-months were 692(456-959), 266(18-1256) and 156(40-885) respectively. From baseline to 9-months of treatment, TBS improved by 7.4±2.6% (p=0.008). Z-Scores at the spine, femoral neck and total hip increased by 0.5, 0.4 and 0.3 SDs respectively (Table). There were no changes at the forearm.

Conclusions: Treatment of SHPT with etelcalcetide for 9 months was associated with improvements in trabecular quality and central skeleton BMD. Further studies are needed to determine the effects of etelcalcetide on tissue-level bone quality, bone strength and fracture resistance.

Funding: Commercial Support - Amgen

Baseline DXA parameters and Change in DXA parameters following treatment with etelcalcetide

Parameter	Baseline (Mean±SD)	Change (Mean±SE)	p-value
Z-Score Lumbar Spine	0.2±1.7	0.5±0.1	0.001
Z-Score Femoral Neck	-0.1±1.0	0.4±0.2	0.03
Z-Score Total Hip	-0.5±1.1	0.3±0.1	0.006
Z-Score 1/3 Radius	-1.1 ±1.8	-0.2±0.1	0.07
Z-Score Ultradistal Radius	-1.2±1.2	-0.07±0.1	0.6

PO0550

Etelcalcetide Suppresses Trabecular and Cortical Bone Remodeling Without Altering Bone Quality in Patients with ESKD

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Background: A key treatment goal in chronic kidney disease–mineral and bone disease (CKD-MBD) is suppression of chronically elevated parathyroid hormone (PTH). High PTH in CKD is associated with high bone turnover and fracture risk. Calcimimetics, such as etelcalcetide, are pharmacologic agents used clinically to reduce PTH to target levels. The goal of this study was to test whether 9-months of etelcalcetide treatment suppresses bone remodeling in patients with end stage kidney disease (ESKD) on hemodialysis with renal hyperparathyroidism (rHPT).

Methods: Five patients were enrolled. Mean age was 52±16 yrs and 80% were female. A quadruple label method was used to quantify pre- and post-treatment effects of etelcalcetide on bone turnover and quality. Prior to treatment, patients underwent tetracycline double labeling (3 days, 15 day interval, 3 days). Over 3 months, etelcalcetide was dose-titrated to maintain serum PTH at the lower half of the KDIGO recommended target (2-9x the upper limit of normal of the PTH assay). Patients were maintained on etelcalcetide at the specified PTH level for 6 months. At end of treatment, demeclocycline was administered (3 days, 15 day interval, 3 days) followed by transiliac crest bone biopsy.

Results: Mean PTH (pg/mL) levels at baseline and 9-months were 616±135 and 282±340, respectively. Following 9-months of treatment, trabecular bone formation rate was 80% lower (range of -54 to -96%) while intracortical rate was 83% lower (range of -61 to -94%). Suppressed remodeling of both trabecular and intracortical bone occurred through a reduction in both the amount of bone undergoing remodeling (~65%) and the mineral apposition rate (-35%). Static histomorphometry showed osteoclast surfaces (~1%) and eroded surfaces (5.3%) were within normal ranges. Raman and nano-indentation measures showed no differences in trabecular bone mineral/matrix properties between the two timepoints.

Conclusions: This work shows that etelcalcetide corrects high bone turnover in patients with rHPT on dialysis without affecting bone quality. More research is needed to determine whether the potent remodeling suppression by etelcalcetide can be used as a primary strategy to reduce risk of fracture in patients with ESKD.

Funding: NIDDK Support, Commercial Support - Amgen

PO0551

Interim Analysis of Paricalcitol vs. Cinacalcet in Hemodialysis Patients with Secondary Hyperparathyroidism: A Multicenter, Randomized, Positive Controlled Study (PERMIT Study)

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Background: A randomized, controlled, open-lable, multi-center study was conducted in China to compare the safety, efficacy and cost effectiveness of paricalcitol-dominated therapy with cinacalcet-dominated therapy in maintainted hemodialysis (MHD) patients with secondary hyperparathyroidism.

Methods: Patients over 18 years old, accepted MHD over 3 months, serum intact parathyroid hormone (iPTH)>300pg/mL, serum calcium 2.1~2.5mmol/L and serum phosphorus≤1.78mmol/L were randomized into paricalcitol-dominated therapy group (GpP) or cinacalcet-dominated therapy group (GpC) for 24 weeks. Paricalcitol or cinacalcet monotherapy was prescribed at the beginning, and combination therapy would be carried out when monotherapy was unable to meet the expected target for 2 consecutive visits (Fig 1). The primary endpoint was iPTH maintained within 150~300pg/mL. The secondary endpoints were the combination therapy rate, more than 30% or 50% decline of iPTH from baseline.

Results: 271 patients in 23 centers were screened, 154 patients were enrolled and 93 patients completed the study up to May 2021. There was no statistical difference between groups in age, gender, iPTH, Ca and P at baseline. In GpP and GpC, 44.9% (22/49) *vs* 36.4% patients (16/44) achieved primary endpoint (*P*=0.406). 89.8% (44/49) *vs* 77.3% (34/44) and 73.5% (36/49) *vs* 63.6% (28/44) patients attained iPTH decline more than 30% (*P*=0.099) or 50% (*P*=0.306). 24.7% (19/77) patients in GpP have hypercalcemia, and 44.2% (34/77) patients in GpC have hypocalcemia. The incidences of hyperphosphatemia were similar (28.6% *vs* 26.0%, *P*=0.7174). Combination therapy rate had a rising tendency, 36.8% in GpP *vs* 59.1% in GpC.

Conclusions: Paricalcitol-dominated therapy was as effect as cinacalcet-dominated therapy with lower incidence of hypocalcemia and combination therapy rate. (chictr.org.cn registration number: ChiCTR2000031420)

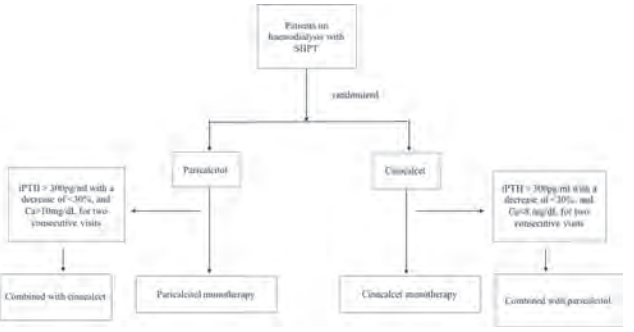

Fig 1: Study Design

PO0552

The Impact of Paricalcitol on Parathyroid Gland Size of Secondary Hyperparathyroidism Patients with Long-Term Maintenance Hemodialysis: An Observational Study

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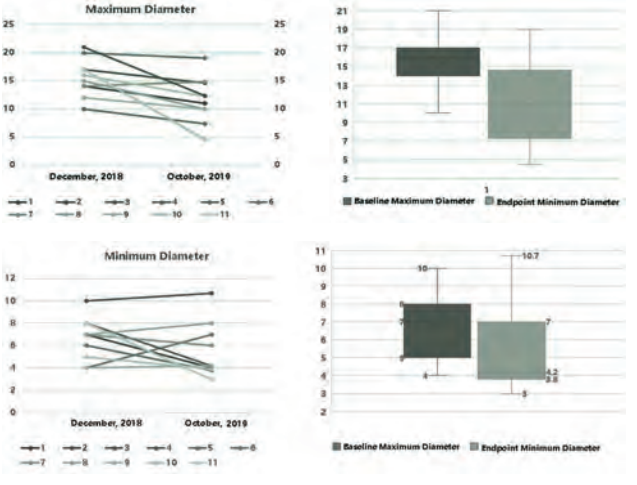
Background: This is an observational study to assess effectiveness of paricalcitol for treating secondary hyperparathyroidism (SHPT) patients with long-term maintenance hemodialysis, via changes in biochemical indexes, such as Calcium (Ca), Phosphate (P) and Parathyroid Hormone (PTH), and size of parathyroid gland (PG).

Methods: This single-centre and small sample study included 11 Long-term maintenance hemodialysis patients with SHPT, who were undergoing SHPT treatment with paricalcitol in the Blood Purification Centre of Fengdu people's hospital, Chongqing, China, from December 2018 to October 2019. We Administered Paricalcitol (Zemplar®) intravenously through a hemodialysis vascular access after dialysis as the following dosage: 5 ug tiw for iPTH<1000 pg/ml and 10 ug tiw for iPTH≥500 pg/ml. Titrations based on serum calcium and intact PTH levels. We collected biochemical indexes including Ca, P and iPTH, and imaging parameters of PG via ultrasonography (volume and number), evaluating variations between baseline and Month 11 of post-treatment.

Results: Compared to baseline, the maximum diameter lines of PG decreased significantly (mean 15.727 mm vs 10.936 mm, P=0.005) after 11 months' treatment, though the minimum diameter lines decreased without statistical difference (mean 6.727 mm vs 5.255 mm, P=0.089). The number of glands was less in Month 11 than that of baseline (mean 2.455 vs 2.182, P=0.277) and iPTH declined significantly (mean 1045.109 pg/ml vs 610.934 pg/ml, P=0.001). The overall effective rate of paricalcitol was 90.9% after 11 months' treatment. Moreover, there were no significant changes in serum calcium and phosphorus levels during the whole treatment.

Conclusions: Intravenous paricalcitol can decrease the size and number of parathyroid gland, and reduce iPTH concentrations in SHPT patients with Long-term maintenance hemodialysis, without significant influence for serum Ca and P levels.



PO0553

Burden of Secondary Hyperparathyroidism: A Matched Comparison Using Administrative Claims Data from Germany

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Background: Secondary hyperparathyroidism (SHPT) is a frequent, early, and progressive complication in chronic kidney disease (CKD) characterized by excessive parathyroid hormone production. SHPT independently predicts serious complications like cardiovascular diseases (CVD), fractures, progression to dialysis, and death. Analysis of data on the burden of CKD patients with SHPT in the German health insurance system is lacking.

Methods: A German health insurance claims database comprising data from 2014-2018 served as a source to identify CKD stage 3 and 4 patients, who were stratified by the occurrence of incident SHPT using ICD-10-GM diagnosis and ATC prescription codes. SHPT patients were matched 1:1 to non-SHPT patients in the same CKD stage using propensity scores. Index date was the first SHPT diagnosis quarter in the SHPT cohorts, and a randomly chosen quarter of a CKD diagnosis within the CKD-only cohorts. Patients with evidence of dialysis or kidney transplant prior to the index quarter were excluded. Matched groups were compared with respect to the prevalence of CVD (acute and recurrent myocardial infarction (MI), chronic ischemic heart disease, congestive heart failure (HF), and atherosclerosis (ATH)), dialysis, and CKD progression in a two-year follow-up period.

Results: Overall, 1,156 incident SHPT patients in CKD3 and 517 in CKD4 and their respective matches were identified. Prevalence of combined CVD conditions was higher in SHPT patients (46.8% vs. 41.9% p<0.05 in CKD3, 56.5% vs. 51.8% p=0.13 in CKD4). HF was more frequent among SHPT patients (34.6% vs. 28.6% p<0.01 in CKD3 and 46.4% vs. 39.3% in CKD4 p<0.05) while acute MI was observed significantly more often among CKD4 patients in the SHPT cohort (9.1% vs. 5.8% p<0.05). ATH was more frequent in SHPT patients in CKD4 (18.6% vs. 14.3% p=0.06). SHPT patients progressed to CKD5 more often (6.1% vs. 1.2% from CKD3, 26.7% vs. 2.9% from CKD4, both p<0.01) which resulted in a higher proportion of dialysis (6.1% vs. 1.3% in CKD3, 22.1% vs. 3.7% in CKD4, both p<0.01).

Conclusions: Patients with CKD3&4 and incident SHPT presented with a significantly higher disease progression to CKD5 and dialysis and had a higher prevalence of CVD compared to patients without SHPT during a two-year follow-up period.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma Ltd.

PO0554

Abstract Withdrawn

PO0555

Calcium-Based Phosphate Binders and the Regulation of FGF-23

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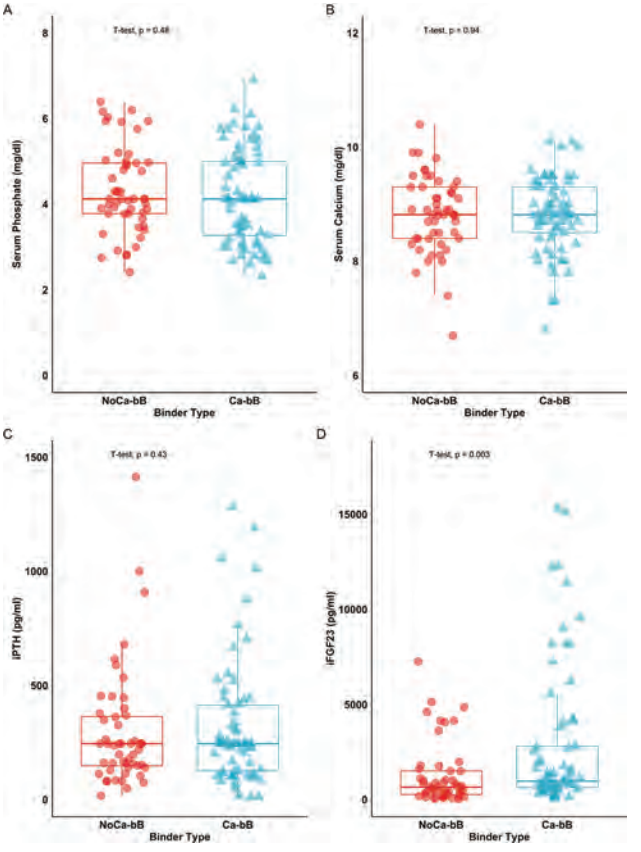
Background: Phosphate and calcium load are associated with FGF23 increase. Reduction of intestinal phosphate absorption by Calcium-based binders (Ca-bB) should decrease serum FGF23, but the opposed effect may result from calcium load derived from Ca-bB-administration. Since Ca-bB has been associated with vascular calcifications and FGF23 is an independent risk factor for cardiovascular disease (CVD), it is relevant to elucidate the effect of Ca-bB on FGF23. Thus, we aimed to determine the effect of Ca-bB on serum levels of FGF23 in hemodialysis (HD) patients.

Methods: We included 121 prevalent HD patients. Serum phosphate, Ca, iPTH and intactFGF23 were measured. 52 patients were on Calcium-free (NoCa-bB) binders, whereas 69 were on calcium-based (Ca-bB, n=69) binders. We also considered treatments with cinacalcet, paricalcitol and the calcium dialysate content. Multivariable regression identified the variables associated with FGF23 increase. Statistics were performed using R

Results: The mean age was 67.8±14.7. Serum levels of phosphate, Ca and iPTH were comparable between groups of binders (Fig 1A, B, and C). iFGF23 was higher in patients on Ca-bB than in NoCa-bB (2815.7vs1268.09 pg/ml, p<0.001). Multivariable regression, adjusted for iPTH, dialysate calcium, albumin, and the treatment with cinacalcet and paricalcitol, showed that the use of Ca-bB was associated with increased serum iFGF23 (beta=0.46, p=0.01).

Conclusions: At equivalent serum levels of serum phosphate, Ca, and iPTH, the use of Ca-bB is independently associated with higher serum iFGF23. This could partially explain the detrimental cardiovascular effects associated with Ca-bB use in HD patients.

Funding: Government Support - Non-U.S.



iFGF23 serum levels according to the different phosphate binders received

PO0556

Side Selective Renal Reduction of Intact and C-Terminal FGF-23

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Background: Relative abundance of FGF23 measured by the C-terminal (cFGF23, which measures both intact FGF23 & c-terminal fragments) vs intact (iFGF23) assays is higher in persons with higher eGFR. Mechanisms are unclear. Individuals with vascular disease often have asymmetric renal function. We compared side selective (R vs L) renal reduction of iFGF23 and cFGF23 within the same individual.

Methods: 162 patients were referred for renal angiography at Maastricht University, the Netherlands, for clinically suspected RAS. Participants were maintained off anti-hypertensive meds for 21 days. Blood samples were obtained from the aorta and right (RV) and left renal vein (LV), and renal blood flow was measured using ^{133} Xenon washout. Creatinine (Cr), cFGF23 (Immutopics), and iFGF23 (Kainos) were measured. Difference of side selective % reductions of each metabolite ([Aorta – (RV or LV)/Aorta]*100) was calculated among each participant. Mean "RV-LV metabolite reduction difference" was calculated across all participants.

Results: Mean age was 54±12 years, 54% were women, and all were white. Mean eGFR was 75±25 ml/min/1.73m^2 and directly measured Cr clearance during angiography was 72±48 ml/min/100g. Median (IQR) aorta concentrations of cFGF23 was 82 (59, 105) RU/mL, and intact FGF23 was 47(37, 65) pg/mL. The mean difference in R vs. L Cr clearance was 6.0 ± 36.2 ml/min/100g. Side selective reduction differences of both cFGF23 & iFGF23 were significantly related to side selective Cr reduction. Side selective phosphate reduction also associated with iFGF23 reduction independent of Cr reduction, but not cFGF23 (**Table**). Results were similar in models adjusted for age, sex & BMI.

Conclusions: In hypertensive individuals, the kidney with greater Cr reduction also reduced plasma cFGF23 and iFGF23 more than the contralateral kidney. The kidney that removes more iFGF23 also removes more phosphate, independent of Cr removal; a finding not observed for cFGF23.

Funding: NIDDK Support

Table: Mutually Adjusted Associations* of Variables with Side Selective Kidney FGF23 Reduction

	ΔRV-LV C-terminal FGF23 Reduction		ΔRV-LV Intact FGF23 Reduction	
Variable	β (95% CI)	p-value	β (95% CI)	p-value
Age	-1.75 (-4.57, 1.07)	0.20	-0.81 (-2.04, 0.42)	0.19
Male	1.09 (-4.96, 7.14)	0.72	-1.27 (-3.92, 1.39)	0.35
BMI	-0.18 (-3.22, 2.86)	0.90	0.41 (-0.92, 1.73)	0.54
ΔRV-LV creatinine difference	6.35 (2.92, 9.79)	<0.001	3.16 (1.63, 4.69)	<0.001
ΔRV-LV phosphate difference	-0.19 (-3.25, 2.87)	0.90	1.55 (-0.01, 3.11)	0.05
ΔRV-LV PTH difference	-0.08 (-3.09, 2.94)	0.95	0.94 (-0.50, 2.39)	0.19

*Variables are mutually adjusted in a linear regression model. Β reflects % change in ΔRV-LV FGF23 reduction difference per 1 SD higher of each variable except Β of male is average difference in FGF23 reduction b/w men and women

PO0557

Potassium Supplementation Decreases Plasma Fibroblast Growth Factor 23 and Increases Plasma Phosphate in Stage 3b-4 CKD Patients: Single-Arm Intervention Study

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Background: Advanced chronic kidney disease (CKD) is characterized by mineral and bone disorders (MBD) including elevated fibroblast growth factor 23 (FGF23). Recent studies in healthy subjects showed that potassium supplementation decreases FGF23. Here, we investigated whether potassium supplementation reduces FGF23 and other MBD parameters in patients with CKD.

Methods: We performed a post-hoc analysis of a 2-week open-label run-in phase from a clinical trial in patients with CKD stage G3b-G4 (NCT03253172). Patients received potassium chloride (KCl, 40 mmol/day). Baseline and post-treatment blood and urine samples were collected. Mixed model analyses were used to assess effects of potassium supplementation on MBD parameters.

Results: We included 135 patients in whom KCl supplementation increased plasma phosphate (from 1.0±0.2 to 1.1±0.2 mmol/L, *P*=0.001) and tubular phosphate reabsorption (from 0.64±0.20 to 0.69±0.20 mmol/L, *P*<0.001). KCl supplementation, when adjusted for estimated glomerular filtration rate, decreased C-terminal FGF23 (cFGF23) (from 140.5 [Interquartile range [IQR] 105.9–217.4] to 131.5 [IQR 105.8–212.8] RU/mL, *P*=0.03), intact FGF23 (from 69.6 [IQR 46.6–107.1] to 62.9 [IQR 41.7–104.6] pg/mL, *P*=0.003) and vitamin D (72.5 [IQR 43.9–92.9] to 70.2 [IQR 44.2–90.1] nmol/L, *P*<0.001). Parathyroid hormone, plasma calcium, 24hrs urinary calcium excretion, α-Klotho, and IL-6 did not change. At baseline, 37 participants were vitamin D deficient (<50 nmol/L). The decrease in cFGF23 by KCl supplementation depended on baseline vitamin D status (*P*-interaction=0.02), and was present in vitamin D sufficient (147.2 [IQR 108.3–216.8] to 130.9 [IQR 105.5–218.0] RU/mL, *P*=0.03), while it was not in vitamin D deficient patients (131.5 [IQR 104.0–230.7] to 133.0 [IQR 106.8–211.0] RU/mL, *P*=0.32).

Conclusions: In this short-term interventional study, KCl supplementation reduced FGF23 and coincided with increased plasma phosphate levels and vitamin D. Reduction in cFGF23 by KCl was only present in vitamin D sufficient patients. Dietary potassium intake might decrease FGF23 levels and vitamin D status should be sufficient before FGF23 lowering strategies could be applied in patients with CKD.

PO0558

The Dietary Supplement Chitosan Lowers Serum Phosphorus in a Hemodialysis Patient Not Tolerating Prescription Binders

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Introduction: Chitosan is a chitin derived, non-toxic, biodegradable biopolymer that binds negatively charged molecules. It's numerous industrial applications include phosphorus binding in agricultural wastewater. In humans it is used as a dietary supplement for weight loss, purportedly binding negatively charged lipids and bile acids and preventing their absorption. Here we report the case of a dialysis patient who did not tolerate prescription binders and who was able to control her serum phosphorus level for over a year by taking 3.5g of Chitosan with meals.

Case Description: A 66 y/o woman with no prior medical history and not taking any medications presented with emphysematous pyelonephritis with bilateral obstructing staghorn calculi requiring intensive care and hemodialysis. Her intial serum creatinine was 18 mg/dl. She recovered from sepsis but continued to require dialysis after discharge. Her residual creatinine clearance was 7.9ml/min six months after hospital discharge and 5.6ml/min two years later. The patient tried several prescription phosphorus binders but eventually decided to stop all prescription medications because of gastrointestinal side effects. Since over a year ago, at the recommendation of her dietitician, she purchased 500mg Chitosan tablets from the internet and used them like a phosphorus binder with meals, at a dose of 3.5 g per day. Her serum phosphorus levels have been stable and in a controlled range since (Figure 1). A quantitative analysis using urea kinetics to estimate phosphorus intake and removal reveals that Chitosan bind around 40 mg of phosphorus per gram, comparable to prescription binders.

Discussion: Chitosan acts as an over-the-counter non-calcium containing phosphorus binder that may provide an alternative option for patients who do not tolerate prescription phosphorus binders. Importantly, it may be psychologically more attractive for patients to take a dietary supplement for weight loss with their meals than a prescription medication.

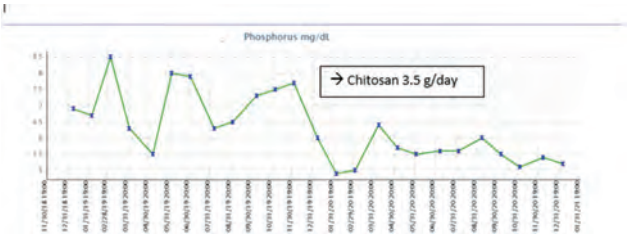

Figure 1: Effect of Chitosan on serum phosphorus levels

PO0559

Longitudinal Changes in FGF-23 in Children with CKD

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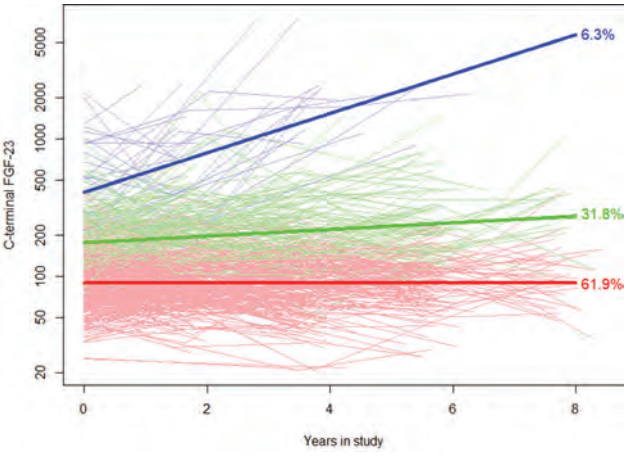
Background: Cross sectional studies show that plasma FGF23 is increased early in the course of chronic kidney disease (CKD) in children and adults and associates with disease progression and adverse cardiovascular outcomes. However, longitudinal changes in FGF23 have not been described in children with progressive CKD.

Methods: We measured C-terminal FGF23 and estimated GFR at baseline and every other year in 564 children with CKD stages 2-4 enrolled in the Chronic Kidney Disease in Children (CKiD) study. All subjects had 2 to 5 FGF23 measurements. We used linear mixed models to identify factors associated with baseline FGF23 level and longitudinal changes and latent group-based trajectory modeling to characterize distinct classes of FGF23 trajectories.

Results: Median age was 11 years and eGFR 55 ml/min/1.73m^2. In a univariate model with repeated measures, plasma FGF23 was 12% higher for every 10% lower eGFR (P<0.0001). In fully adjusted models, higher FGF23 at baseline was significantly associated with lower GFR, higher serum phosphorus, and glomerular diagnosis. Thereafter, FGF23 increased more rapidly in older subjects with lower GFR and higher proteinuria at baseline. We identified three distinct linear FGF23 trajectories: stable FGF23 in 62% of subjects (FGF23 slope 0% per yr); slowly rising in 32% (6% per yr) and rapidly rising in 6% (39% per yr). At baseline, median FGF23 in the trajectory groups were 90 [IQR:70,120], 166 [125, 242] and 461 [219, 924] RU/ml, respectively. Membership in the faster-rising trajectory groups was associated with lower eGFR, higher proteinuria and serum phosphorus, and glomerular diagnosis.

Conclusions: FGF23 was relatively stable in most children with CKD, but it increased more rapidly in those with traditional CKD risk factors. Further analyses of FGF23 trajectories will investigate whether FGF23 is a modifiable cause or a consequence of CKD progression and cardiovascular complications.

Funding: NIDDK Support



PO0560

Two Siblings with X-Linked Hypophosphatemia (XLH) Treated with Burosumab: Is Therapeutic Regimen Recommended Now Supported by Real-World Data?

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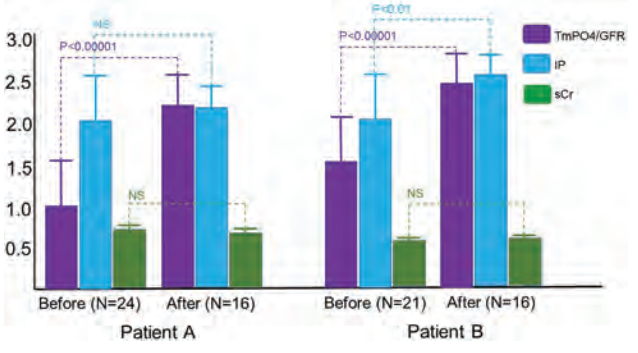
Introduction: Burosumab, a human monoclonal antibody to FGF 23, is used now to treat XLH. In phase III study, patients were selected and controlled. What is considered as "recommended" regimen of burosumab in that population within the controlled setting might be different from that in another population in real world. The present study was conducted in an attempt to address this issue.

Case Description: Patient A and patient B with XLH are siblings in their twenties. They were successfully managed in childhood, and have enthesopathy. They had had alpha calciferol and phosphate supplementation, and started to have 1 mg/kg BW burosumab 1.5 years ago. Changes in TmP/GFR, IP, and sCr after burosumab administration are shown (Figure). A significant increase in TmP/GFR ($p<0.00001$) was seen. IP and sCr levels almost did not change. Nephrocalcinosis, hyperparathyroidism, and vitamin D deficiency were mild and not worsened. Changes in bone mineral density (BMD) were assessed by DEXA scan. In 2018, young adult mean (YAM) of lumbar vertebra were 129% in Patient A, and 138% in Patient B. In 2021, these YAM values increased to 141% in Patient A and 140% in Patient B, respectively. ***Figure legend:*** Data for the past 6.5 years were retrospectively analyzed and shown as mean (colomn) plus standard deviation (bar). N numbers indicate the time they visited our hospital where they gave blood and spot urine samples. Dimensions of IP, and sCr are mg/dL. TmP/GFR; tubular threshold maximum for phosphorous per glomerular filtration rate.

Discussion: Using real-world data, we confirmed the efficacy and safety of recommended burosumab therapy regimen for 1.5 years, so far as laboratory indices used in phase III study were concerned. However, YAM values were above-the-average and increasing in the presence of hypophosphatemia and low TmP/GFR. The future consequence of this feature in relation to time-elapsed changes in renal physiological parameters including TmP/GFR, Ca, IP, and sCr should be seen.



PO0561

Burosumab in X-Linked Hypophosphatemic Rickets Adult Patients: An Italian Center Experience

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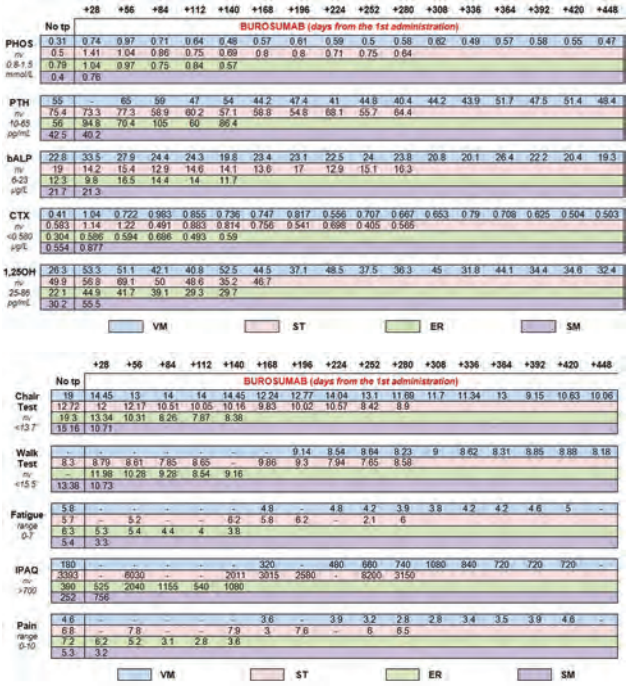
Background: X-linked Hypophosphatemic Rickets (XHR) is a rare disease caused by mutations in the PHEX gene leading to an increase in the serum levels of FGF23, which inhibits the tubular reabsorption of phosphates and the production of $1,25(OH)_2D$. This causes hypophosphataemia, rickets, bone deformities, growth retardation and muscle activity impairment.

Methods: Burosumab (B) is a monoclonal antibody against FGF23, used for the treatment of XHR patients. In Italy B can be employed in adults only as compassionate use. Starting in 2020 B (1 mg/kg sc every 4w) was administered to 4 adult subjects with XHR: VM (M, 32 yrs), ST (F, 47), ER (M, 46) and SM (F, 20) who showed legs deformities, musculoskeletal pain and severe movement limitations.

Results: In all patients, phosphorus levels were normalized by B, but tended to decrease during the 28 days following the administration. Plasma values of $1,25(OH)_2D$ and CTX (marker of bone resorption) also increased to a peak which then decreased over months. In contrast, PTH and bALP values did not change during B therapy. Scores provided by specific tests confirmed an improvement in the fatigue resistance and physical performance. Other tests showed the improvement of self-reported well-being and quality of life in all patients. These effects were not observed in adult patients on conventional therapy with phosphate salts and active vitamin D.

Conclusions: Despite the only temporary effect on phosphorus, Burosumab is right now the only therapy that improve the impact that XHR has on the quality of life of XHR patients.



PO0562

Regional Epidemiological Investigation of Calciphylaxis in Chinese Hemodialysis Patients

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Background: Calciphylaxis (calcific uremic arteriolopathy, CUA) is a grievous life-threatening vascular disease that commonly affects dialysis patients. This is the first epidemiological survey of CUA initiated in China.

Methods: In the cross-sectional survey during Oct. 2018 to Oct. 2019, a stratified sampling method was used to select 24 dialysis centers in Jiangsu Province in China. The participants were all adult patients in each center, who had been on hemodialysis for more than 6 months. This multicenter investigation was conducted in the form of questionnaires, which were filled in by doctors or nurses according to the actual situation of patients. CUA patients were uniformly diagnosed by the Calciphylaxis Study Group based on characteristic skin lesions and histopathological features.

Results: A total of 3867 hemodialysis patients (average age of 55.33±13.89 years; 61.81% of males) were included. 48 cases were diagnosed with CUA, and the prevalence was 1.24%. Among CUA patients, 68.75% of cases were male, and average age and median dialysis duration were 53.85±15.17 years and 84.00 (48.00, 138.75) months respectively. The average BMI of CUA patients was higher than that of controls, and patients with hyperparathyroidism, diabetes, atrial fibrillation, stroke, or tumors were more likely to suffer from the disease. Although only 4 CUA patients used warfarin therapy, there was still a significant statistical difference between two groups. Multivariate analysis indicated that increased BMI, prolonged dialysis duration, warfarin therapy, concomitant with hyperparathyroidism, diabetes mellitus or tumors, low ALB, and high serum ALP levels were high-risk factors for CUA. 394 (10.32%) of 3819 hemodialysis patients who didn't meet current diagnostic criteria for CUA had a variety of manifestations of skin lesions, mainly in lower limbs. 28.68% of these patients complained about a progressive deterioration of skin damage, and 44.67% suffered moderate to severe pain with potential CUA risks.

Conclusions: The prevalence of CUA in Chinese hemodialysis patients was 1.24% according to this regional epidemiological survey, but its actual prevalence would be presumably far beyond present data. Calciphylaxis, as a disease with such a high disability and fatality rate, should attract the attention of relevant specialists.

PO0563

Intraperitoneal Sodium Thiosulfate: Revisiting Route of Therapy for Calciphylaxis in Peritoneal Dialysis

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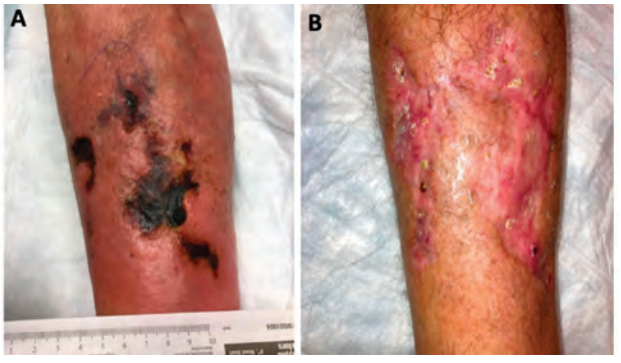
Introduction: Intraperitoneal (IP) drug therapy provides a convenient route for medication administration in patients on peritoneal dialysis (PD). IP sodium thiosulfate (STS) has been used for treatment of calciphylaxis with demonstrated enhanced calcium extraction. However, the use of this therapy has been limited after a reported incident case of chemical peritonitis. This reported complication did coincide with an FDA recall for

STS, and the possibility remains that peritonitis may have been due to particulate matter contamination. We present a case of calciphylaxis which was successfully treated with IP STS without evidence of peritonitis.

Case Description: An 80 yo woman on PD presented with bilateral lower extremity pain and erythema. This progressed to a necrotic eschar (Figure 1A). Labs were notable for PTH 1267, and Ca x Phos product of 110. Biopsy confirmed calciphylaxis. She underwent subtotal parathyroidectomy and was treated with IV STS. Severe nausea with IV infusions necessitated discontinuation of therapy. She transitioned to IP therapy, 12.5 g of STS in 1L of normal saline as a long dwell day-time exchange to maximize absorption and subsequent mobilization of calcium from tissue. The patient's pain significantly improved within 1 week. Therapy was completed after 3 months. The lesions almost completely healed 6 months after starting treatment (Figure 1B). Interval PD effluent cell counts, on several occasions, did not change in the PD effluent, although a modest, unexplained decrease in kt/V was noted.

Discussion: The use of IP medications in patients on PD minimizes venous access complications and reduces clinic visits. In our case, we were able to effectively treat calciphylaxis in a patient who could not tolerate IV STS therapy. No inflammatory activity appeared in the PD fluid, and it is unclear if STS had any other adverse effects. Further studies are needed to understand the impact of this therapy on peritoneal membrane transport characteristics.



Calciphylaxis lesion at diagnosis (A) and 6 months later (B)

PO0564

Calciphylaxis in a Cohort with Normal Kidney Function: Improved Survival Compared to ESKD

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Background: Calciphylaxis is a rare, devastating disease, characterized by vascular calcification and is associated with increased mortality.

Methods: We studied the baseline characteristics and outcomes of 78 patients with biopsy-proven calciphylaxis that were stratified according to glomerular filtration rate (GFR) into normal kidney function (NKF): GFR ≥ 90 mL/min/1.73 m^2, chronic kidney disease (CKD): GFR 15 – 89 mL/min/1.73 m^2, and end-stage kidney disease (ESKD): GFR <15 mL/min/1.73 m^2.

Results: Forty-seven patients (60%) with calciphylaxis had ESKD, compared to 22 patients (28%) with CKD and 9 patients (12%) with NKF. Patients with NKF were younger (median age 55 years compared to 69 years in CKD and 65 years in ESKD, p=0.006). Across all 3 groups, there was a predominance of female gender, obesity, multiple and peripheral lesions involving the extremities. Among patients with ESKD, 39 patients (83%) were on hemodialysis (HD) and 7 patients (15%) were on peritoneal dialysis (PD). The probability of survival was significantly higher in patients with NKF compared to ESKD (p = 0.039)(figure 1). Sepsis was the most common cause of death.

Conclusions: Calciphylaxis can occur in patients with normal or abnormal kidney function. Female gender, obesity, multiple, and peripheral lesions were predominant in our cohort. Patients with NKF were younger, which may have contributed to their increased survival compared to ESKD. Sepsis due to secondary infection of necrotic wounds appears to remain the most common cause of death.

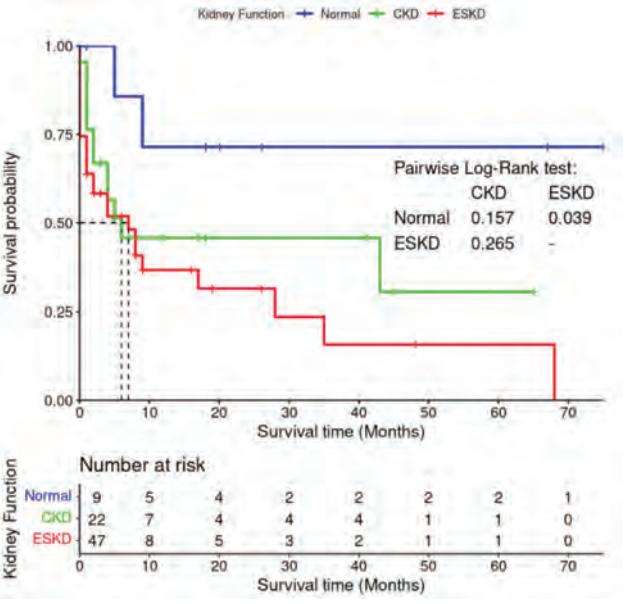

Figure 1: Kaplan-Meier curve showing survival in patients with calciphylaxis according to kidney function.

PO0565

Severe Tumoral Calcinosis of the Hip in a Hemodialysis Patient

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Introduction: Tumoral calcinosis (TC) is a rare complication of patients with end-stage renal disease (ESRD) on hemodialysis (HD) in which precipitation of calcium salts occurs in periarticular soft tissue. This manifestation can lead to painful and function restricting lesions. We herein describe a case of a severe presentation of TC with associated ulceration.

Case Description: A 47-year-old female with medical history of arterial hypertension, heart failure, hypothyroidism, focal segmental glomerulosclerosis and ESRD on HD for 15 years presented to the emergency department after a right hip ulceration. The patient described a right hip hard mass with ten years of progressive growth that suffered a sudden rupture associated with sand-like secretions. Medication and dialysis compliance was reported. Vital signs were unremarkable. Physical examination showed a right hip swelling and ulcer. Laboratories revealed WBC of 19.98 103/µL, Hgb of 8.70 g/dL, calcium 9.9 mg/dL, phosphorus 6.6 mg/dL, 25-hydroxyvitamin D 12.72 ng/mL and PTH 288.90 pg/mL. Calcium Phosphate Product (CPP) resulted in 65.34 mg/dL. Pelvic CT scan showed a 11.4cm x 9.6cm mixed density calcified cystic mass with multiple fluid-calcium levels in the right hip, suggestive of TC. Treatment with intravenous Sodium Thiosulfate, Sevelamer and antibiotics were provided. Cleansing and debridement were performed by the plastic surgery team without complications. Patient was discharged and sodium thiosulfate treatment was continued at the hemodialysis center.

Discussion: TC is associated with the dysregulation of calcium phosphate metabolism. Altered renal phosphate excretion along with vitamin D activation leading to hyperparathyroidism with elevated CPP is the proposed mechanism. The precipitation of large periarticular deposits of calcium salts leads to inflammation and chronic pain. Consequently, limiting functionality and impairing quality of life. Surgical excision can relieve symptoms, but the deposits can recur. Sodium thiosulfate has been described as a potential treatment, but further studies are necessary to assess its role in dialysis patients. The recognition of this rare disease is important as optimization of medical therapy and dialysis regimen can improve the evolution and outcome of this disorder.

PO0566

Case Series of Penile Calciphylaxis in a Large Urban Hospital

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Background: Calciphylaxis or calcific uremic arteriolopathy (CUA) is a complex syndrome of deranged mineral metabolism and vascular calcification with subsequent tissue ischemia predominantly in end stage kidney disease(ESKD) patients on dialysis. The disease has been categorized as central or peripheral but in rare cases of peripheral calciphylaxis there may be penile involvement. Due to the paucity of data on penile calciphylaxis, this study was done to ascertain the characteristics, management and mortality of patients with this condition.

Methods: An observational study involving retrospective analysis of medical records of six(6) patients with biopsy proven penile calciphylaxis treated in a large urban hospital between January 2000 and March 2021 was performed.

Results: All patients with penile calciphylaxis had ESKD with mean duration on dialysis of 5.2±3.5 years. The mean age at diagnosis was 54±9.7 years. Sixty six percent of patients were African Americans with the remainder being Caucasians. Only one of six patients was obese with mean BMI of 23.2±5.5 kg/m^2. Similarly only one patient was on warfarin. None of the patients was on systemic steroids or vitamin D at the time of diagnosis. All patients had secondary hyperparathyroidism with median PTH of 264.5pg/mL (IQR 175.5). Surprisingly all patients had normal calcium phosphate products with mean of 36.1±11.6mg^2/dL^2(normal range for our lab is 21.5-51.5). Penectomy was performed in 4 patients and 2 patients had treatment with hyperbaric oxygen. The mean survival at diagnosis was 4.0±1.2 months. Mortality was 20% and 100% at 3 and 6 months post diagnosis respectively.

Conclusions: Penile calciphylaxis is a very rare entity. Although obesity has been associated with calciphylaxis, majority of our patients with penile calciphylaxis were not obese. Interestingly all our patients had normal calcium phosphate products suggestive of heterogeneous mechanisms in the pathophysiology of the disease. The PTH was lower than our previously reported level of 569pg/mL in our calciphylaxis database. Our mortality rate was very high with 100% mortality within six months of penile calciphylaxis diagnosis.

PO0567

A Case of Severe Penile Pain

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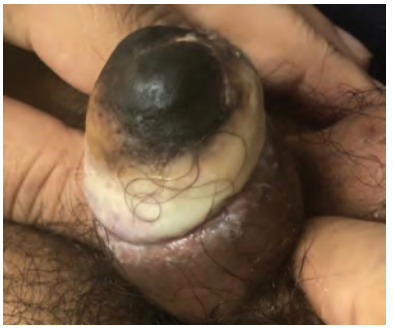
Introduction: Calciphylaxis is a rare disease with skin necrosis, tissue ischemia and small to medium-sized vessel calcium (Ca) deposition and thrombosis. The prevalence of penile calciphylaxis is 0.24% in end stage kidney disease (ESKD). Given its rarity and location, it can be difficult to diagnose and has a poor prognosis. Identifying it is imperative.

Case Description: 56 year old male with ESKD on hemodialysis (HD) due to diabetes mellitus with secondary hyperparathyroidism and peripheral vascular disease was admitted with a painful, necrotic penile lesion for 1 month. Since starting HD 1 year prior, his serum phosphorous ranged 7.8-9.0mg/dL, Ca 8.0-9.0mg/dL and parathyroid hormone downtrended from 611 to 127pg/mL on hectorol, phoslo and Ca carbonate. CTA showed atherosclerotic stenosis of internal pudendal arteries with patent penile arteries. Interventional angiogram showed severe stenosis occluding distal pudendal arteries. After consensus with nephrology, interventional radiology, vascular surgery, urology, dermatology and infectious disease, the diagnosis of penile calciphylaxis was made. Treatment goals included phosphate normalization by 4 weekly HD sessions, low Ca dialysate, non Ca based phosphate binders; vasodilators sildenafil and pentoxifylline, and sodium thiosulphate (blocks calcification of smooth muscle cells). He is in a clinical trial for SNF472, a selective calcification inhibitor, for wound healing and pain management. His severe pain has resulted in disability and income loss.

Discussion: Penile calciphylaxis is associated with hyperparathyroidism, ESKD, and normal body mass index. Neither parathyroidectomy nor penectomy have shown mortality benefits and current treatments are not based on interventional trials. Kidney transplant may be curative. It is essential that we identify penile calciphylaxis, given its significant morbidity and mortality.



Penile calciphylaxis

PO0568

Painful Facial Swelling in a 33-Year-Old Male with ESRD: Sagliker Syndrome with 2-Year Follow-Up

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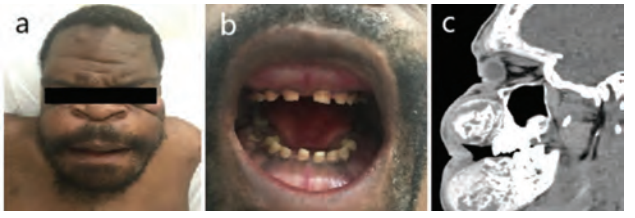
Introduction: Sagliker syndrome is a rare form of renal osteodystrophy seen in the setting of hyperparathyroidism. Disordered skeletal remodeling resulting in severe facial changes and possible psychological changes are seen

Case Description: We present a case of a 33 year-old African American male with end-stage renal disease on maintenance hemodialysis x3/week for 7 years and systemic lupus erythematosus on adalimumab, who presented with sudden onset severe facial swelling and pain. He has a history of tertiary hyperparathyroidism with intact parathyroid hormone level of 2,400 – 4,000 pg/mL (normal: 18.4 - 88.0 pg/mL). Cinacalcet (30 mg) dosing was inconsistent due to insurance difficulties. Laboratory studies showed a corrected serum calcium of 7.9 mg/dL, serum 25-hydroxy-vitamin D of 9.8 ng/mL (25.00 - 80.00 ng/ml), serum phosphorus of 5.9 mg/dL, intact parathyroid hormone of 1,206 pg/mL and alkaline phosphatase 427 U/L (35-150) with normal liver enzymes. The patient had severe facial pain, maxillary and mandibular enlargement with hypertrophic gums and widely-spaced teeth. Extensive brown tumor formation was detected with marked extension into the buccal spaces. Altogether, his presentation was consistent with an unsually severe Sagliker syndrome. Urgent subtotal parathyroidectomy was performed with immediate normalization of PTH (170, 75 pg/mL), but with subsequent severe postoperative hungry bone syndrome and a prolonged period of excessive calcitriol and calcium supplementation. At 2 year follow-up laboratory studies revealed corrected serum calcium of 7.5 mg/dL, serum phosphorus of 6.2 mg/dL, and intact parathyroid hormone of 36 pg/mL. While his facial abnormalities and pain improved, severe mandibular swelling persisted

Discussion: Genetic predisposition may be related to target exons of calcium-sensing receptors. Low vitamin D levels are thought to play a role in susceptible patients. Our case presents a rare documented long-term outcome for severe Sagliker syndrome. Furthermore, we are reviewing initial and follow-up pictures, with review of biochemical control and vitamin-D requirements over this period.



PO0569

Incident Diuretic Use and Subsequent Risk of Bone Fractures: A Large Nationwide Observational Study of US Veterans

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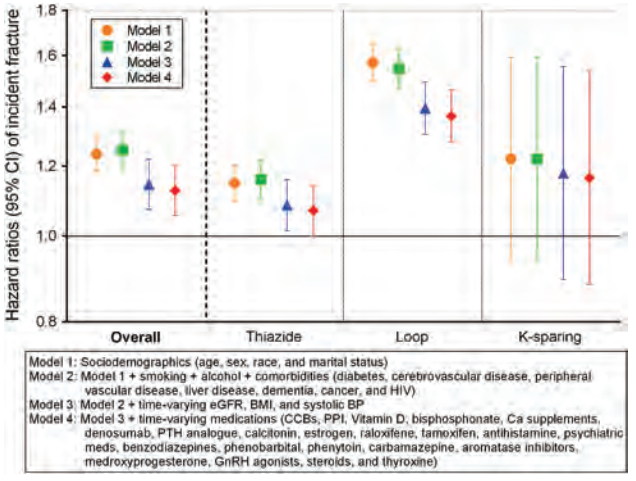
Background: Diuretics may affect bone metabolism by electrolyte imbalance (e.g., Ca and Na derangements). Inconsistent associations have been reported between diuretic use and risk of fracture, presumably due to the heterogeneity of study designs and populations.

Methods: In a nationwide cohort of 2,318,267 US veterans with an eGFR ≥60 mL/min/1.73m^2 from 2004-2006 and follow-up through 2018, we examined the association of incident diuretic use (thiazide, loop, and K-sparing diuretics, as time-dependent exposures) with incidence of any fractures (both vertebral and non-vertebral fractures), using time-dependent Cox models adjusted for sociodemographics, smoking and alcohol use, comorbidities, eGFR, vital signs, and medications (e.g., bone anabolic/antiresorptive agents, SERMs, steroids). Associations were also assessed by diuretic types.

Results: Patients were 59±15 years old; 91% were male; 14% were African American; and 18% were diabetic. Their baseline eGFR was 82±16 mL/min/1.73m^2. Among 2,318,267 patients, 835,054 (36.0%) started any diuretic therapy, and 146,017 (6.3%) experienced an incident fracture. After multivariable adjustment, incident diuretic use (vs. non-use) was significantly associated with higher risk of incident fracture (adjusted HR [95%CI], 1.13 [1.06-1.19]). The association was most pronounced for loop diuretics (1.37 [1.28-1.46]) but less evident for thiazide diuretics (1.07 [1.00-1.14]), and was not significant for K-sparing diuretics (1.16 [0.88-1.54]) (**Figure**).

Conclusions: Diuretic use, particularly loop diuretic use, was independently associated with higher risk of incident bone fractures. While our findings may be from confouding by medical indication, it might suggest a distinct pathogenic contribution of diuretics to bone metabolism and the need for careful attention to skeletal outcomes when initiating diuretics.

Funding: Veterans Affairs Support



PO0570

Low Magnesium Is Associated with Weak Bone Strength in Pre-Dialysis CKD Patients: Results from the KNOW-CKD Study

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Background: In patients with chronic kidney disease (CKD), bone strength was weakened as CKD progressed. There are still controversy of the association between magnesium (Mg) deficiency and osteoporosis in pre-dialysis CKD patients.

Methods: We investigated the association between serum Mg and a decrease of bone mineral density (BMD) from the prospective, multicenter cohort of pre-dialysis CKD patients (n=928). Patients were divided into tertiles according to serum Mg. The primary endpoint is a decrease of BMD, defined as decline of BMD of lumbar spine <-0.05g/cm^2. We performed sensitivity analysis with decline of BMD of femur neck.

Results: After 4 years of follow-up, BMD decreased in 267 (28.7%) patients. In a multivariable binary logistic regression model, the lowest tertile of Mg was associated with risk of the decrease of BMD of lumbar spine (T1, serum Mg ≤2.2 mg/dL, Odd ratio (OR) 2.79 [1.58–4.92]; *P*=<0.001; T3, serum Mg ≥2.3 mg/dL, reference group). Similar results were obtained when sensitivity analysis was performed with BMD of femur neck. Subgroup analyses showed that low Mg was particularly associated with risk of the decreased BMD of lumbar spine in patients <50 years of age, in those without diabetes mellitus, and in those with low physical activity.

Conclusions: Low level of Mg is associated with a weak bone strength in pre-dialysis CKD patients.

PO0571

The Vitamin D Metabolite Ratio May Serve as an Important Biomarker of Vitamin D Status in Patients Undergoing Therapeutic Plasma Exchange

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Background: Recent studies suggest that 25-hydroxyvitamin D [25(OH)D] may be a poor marker of vitamin D status due to variability in levels of vitamin D binding protein (VDBP). The vitamin D metabolite ratio (VMR) is the ratio of 24,25$(OH)_2D_3$: 25$(OH)D_3$ and is thought to be independent of variability in VDBP. Therapeutic plasma exchange (TPE) is a procedure that removes VDBP and thus may lower vitamin D metabolites. The effects of TPE on free vitamin D concentrations and the VMR remains unknown.

Methods: We measured total 25(OH)D, 1,25$(OH)_2D$, 24,25$(OH)_2D_3$, and VDBP using Liquid chromatography–mass spectrometry, and free 25(OH)D using a DIAsource ELISA assay in 45 patients undergoing TPE. Levels were measured before and after a single TPE. We used the paired t-test to assess changes in 25(OH)D, 1,25$(OH)_2D$, 24,25$(OH)_2D_3$, free 25(OH)D, VDBP and VMR across TPE.

Results: Study participants had a mean age of 55 ± 16 years; 67% were female; 76% were white; one of 45 had CKD. TPE caused a significant decrease in total 25(OH)D, 1,25$(OH)_2D$, 24,25$(OH)_2D_3$, and free 25(OH)D. There was no change in the VMR from before to after TPE (Table 1).

Conclusions: Changes in VDBP concentration across TPE parallel changes in 25(OH)D, 1,25$(OH)_2D$, and 24,25$(OH)_2D_3$ suggesting that levels of these metabolites may be markers of VDBP levels. The lack of change in VMR across TPE despite a significant change in VDBP suggests that VMR is independent of VDBP levels. The VMR may therefore serve as an important biomarker of vitamin D status in populations with a large spectrum of VDBP concentrations.

Changes in Vitamin D Metabolites, VDBP, and VMR from Before to After a Single TPE Procedure (N=45)

	25(OH)D	Free 25(OH)D	24,25$(OH)_2D_3$	1,25$(OH)_2D$	VDBP	VMR
% change after TPE (95% CI)	-66% (-70%,-62%)	-31% (-38%,-24%)	-66% (-72%,-60%)	-68% (-72%,-64%)	-65% (-68%,-63%)	6% (-2%, 14%)
p-value	<.001	<.001	<.001	<.001	<.001	0.160

PO0572

Childhood Hypercalciuric Hypercalcemia with Elevated Vitamin D and Suppressed Parathyroid Hormone: Long-Term Follow-Up

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Background: Hypercalcemia with low parathyroid hormone (PTH) level, hypercalciuria, nephrocalcinosis, or nephrolithiasis, was recently reported as caused by mutations in CYP24A1 and SLC34A genes. These encode for vitamin D-24A-hydroxylase and for the renal phosphate transporters NaPiIIa and NaPiIIc, respectively. We aimed to describe the course of these conditions during long-term follow-up

Methods: Ten patients with the above features were followed in our center during 1998-2019. Relevant laboratory and imaging data and results of genetic evaluation were retrieved from medical files

Results: The median age at presentation was 9.5 months (range 1 month-11 years), six were males, and the median follow-up time was 3.8 (1.1-14) years. Mutations in CYP24A1 and SLC34A3 were identified in three and one patients, respectively. Five patients presented with nephrocalcinosis, three with nephrolithiasis, and two had normal renal ultrasound. High blood calcium and 1,25-$(OH)_2D$ levels at presentation decreased during follow-up (11.1±1 vs 9.9±0.5 mg\dl (p=0.012), and 307±130 vs 209±65 pmol\l (p=0.03), respectively); this paralleled an increase in suppressed PTH levels (5.8±0.9 vs 11.8±7.3 pg\ml, p=0.2). Substantial improvements in hypercalciuria and renal sonography findings were not observed. Two patients had impaired renal function (eGFR 84-88 ml\min\ 1/73m^2) at the last follow up. Interventions included appropriate diet, citrate supplementation, and thiazides

Conclusions: In patients with the described clinical and laboratory profile, abnormal renal sonographic findings can persist despite appropriate treatment; and renal function may deteriorate. Long-term follow up and intervention to prevent nephrocalcinosis and nephrolithiasis are recommended in these children

PO0573

Performance Status (PS) as an Effect Modifier for Association Between Vitamin D Receptor Activator (VDRA) and Outcomes Among Hemodialysis Patients

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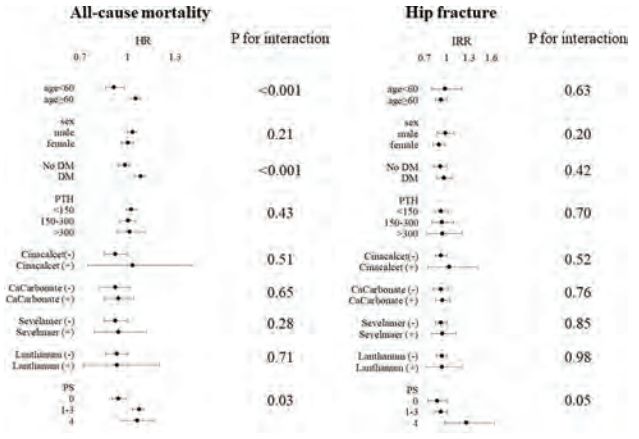
Background: VDRA use has been reported to be associated with lower mortality and fracture among hemodialysis patients. However, PS has not been considered in previous studies.

Methods: This is a prospective cohort study based on JSDT Renal Data Registry. Subjects on hemodialysis with age 20-100 at the end of 2009 were included. Exposure of interest was VDRA use. Outcome variables were two-year all-cause mortality and hip fracture. Associations between VDRA use and mortality or fracture were analyzed using Cox or poisson regression, respectively and interaction between VDRA use and PS was tested.

Results: Among 210,001 subjects, 80,492 (61.7%) were on VDRA. VDRA use was not associated with all-cause mortality (HR 1.02 [0.99-1.05]) or hip fracture (IRR 0.93 [0.86-1.00]) after adjustment for confounders including PS. The use of VDRA was associated with lower mortality and incidence of fracture among those with good PS (PS0) but not with poor PS (P interaction 0.03 and 0.05, respectively). Poor PS was associated with higher corrected calcium (Ca), lower parathyroid hormone (PTH) levels, and proportion of intravenous VDRA use was lower among those with poor PS. Linear regression analysis showed that the association between higher corrected Ca levels and VDRA use were stronger among those with poor PS compared with those with good PS (P interaction 0.01).

Conclusions: VDRA use was associated with better outcomes only among those with good PS. The reasons may be higher prevalence of adynamic bone among those with poor PS suggested by lower PTH levels and greater increase in Ca levels by VDRA, or preclusion of higher dose VDRA prescription due to higher Ca levels.



PO0574

Prevalence of Vitamin D Deficiency in a Predominantly African-American Hemodialysis Patient Population

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Background: Vitamin D insufficiency and deficiency are common abnormalities and high risk groups include kidney disease patients and African-Americans. Recommendations on the evaluation of vitamin D levels in CKD and ESKD are ambiguous due to a lack of studies examining epidemiology and treatment. The COVID-19 pandemic has disproportionately affected minorities and has highlighted the need for evidence as studies have examined vitamin D deficiency as a risk factor for COVID-19 complications. We present a case series examining the prevalence of vitamin D deficiency in a predominantly African-American hemodialysis patient population.

Methods: Retrospective chart review of all in-center hemodialysis patients at Emory Dialysis in Atlanta, GA. Data extracted from Sep to Nov 2020. We excluded any patients on home therapies. Serum 25(OH)vitamin D concentration total was analyzed. We defined vitamin D insufficiency as 20-29.9 ng/mL and vitamin D deficiency as a level<20 ng/ml.

Results: Patients receiving in-center hemodialysis(n=615). Average length of time on dialysis was 5 years and average age was 59.4 years. Patients were 52.5% male(n=323). 91.5%(n=563) of patients were African-American. Mean calcium level for all patients was 8.73 mg/dL and PTH level of 554 pg/mL. Mean vitamin D in all patients was 26.32 ng/mL. 98%(n=603) of patients had a vitamin D level available. All patients with vitamin D level<30 ng/mL=412(68.3%) and all patients with vitamin D level<20 ng/mL=244(40.5%). African-American patients with a vitamin D level was 552. African-American patients with vitamin D level<30 ng/mL=382 (69.2%) and African-American patients with vitamin D level<20 ng/ml=229(41.5%). Mean vitamin D in African-American patients 25.7 ng/mL and non-African-American patients 32.7 ng/mL, p=0.01.

Conclusions: In comparison to others such as the DIVINE trial, we present a larger and more diverse cohort. In our study, African-Americans had a statistically significant lower vitamin D level. A case for replacing 25(OH) vitamin D even in ESKD patients is based on the action of vitamin D beyond mineral metabolism, especially with regard to autocrine regulation of immune function. Future directions include examining effects of treatment on PTH and study of vitamin D deficient patients' risks for adverse events like COVID-19 infection.

PO0575

Prescription Patterns of Osteoporosis Medications in Patients with CKD Stages 4-5: A Retrospective Cohort Study

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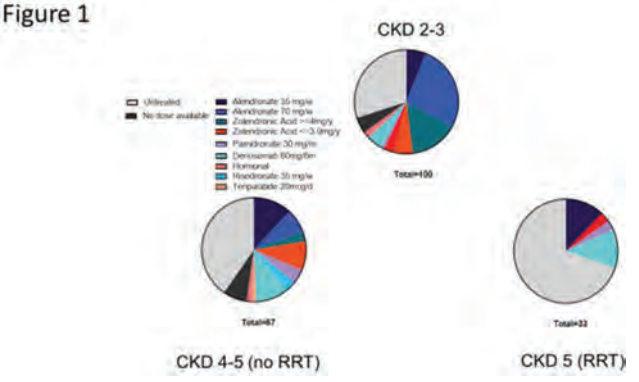
Background: Patients with CKD stages 4-5 are at greater than 2-fold risk of fractures than age-matched controls without CKD, but there is very limited data about the use of antiresorptive or bone anabolic medications in this population. Our goal was to compare the proportion of patients with CKD stages 4-5 vs CKD stages 2-3 who were prescribed these medications at our institution.

Methods: Using the Research Patient Data Registry (RPDR), a centralized clinical data registry at Mass General Brigham, we screened for all adults ≥55 years old with a diagnosis of CKD by ICD10 codes and a DXA scan available between years 2000-2019. We then identified CKD stages by eGFR and matched 100 patients with CKD stages 4-5 to 100 patients with CKD stages 2-3.

Results: Demographic characteristics were similar between the groups (Table 1). Despite having lower femoral bone density, patients with CKD stages 4-5 had lower rates of osteoporosis treatment than patients with CKD 2-3 (50% vs 72%, P=0.001). In all CKD groups, the most common class of medication used was bisphosphonates (Figure 1). Of note, 47% of patients using antiresorptive medications with stages 4-5 CKD had PTH levels lower than 100 pg/ml.

Conclusions: We found lower rates of osteoporosis treatment in patietns with CKD stages 4-5. Despite PTH levels consistent with normal or adynamic bone disease, most CKD patients are treated with antiresoprtive medicines. Our study calls attention to knowledge gaps in osteoporosis and CKD.

Figure 1



Demographics and outcomes	CKD 2-3	CKD 4-5 (all)	P-value vs. CKD 2-3	CKD 4-5 (No-RRT)	P-value vs. CKD 2-3	CKD 5 RRT	P-value vs. CKD 2-3
Total patients	100	100		67		33	
Age (yrs), +/- SD	68.9 ±7	68.2 ±7	0.5	69 ±8	0.67	67 ±6	0.17
Men, N (%)	19 (19)	19 (19)	0.9	13 (19.7)	0.9	6 (17.6)	0.9
White, N (%)	76 (76)	76 (76)	0.9	51 (76.1)	0.9	25 (75.8)	0.9
Black, N (%)	11 (11)	11 (11)	0.9	7 (10)	0.9	4 (12)	0.85
Hispanic, N (%)	5 (5)	5 (5)	0.9	3 (5)	0.9	2 (6)	0.84
T-score spine, +/- SD	-2.3 ±1.0	-2.2 ±3	0.5	-2.3 ±1.1	0.8	-2.0 ±1.6	0.2
T-score total hip , +/- SD	-2.1 ±.8	-2.6 ±.8	**<0.001**	-2.5 ±.8	**0.003**	-2.8 ±.61	**<0.001**
T-score femoral neck, +/- SD	-2.6 ±.7	-3.0 ±.6	**<0.001**	-2.9 ±.7	**0.001**	-3.0 ±.43	**0.001**
On medication, N (%)	72 (72)	50 (50)	**0.001**	40 (60)	0.09	10 (30)	**<0.001**
New Start, N (%)	23 (23)	6 (6)	**0.001**	5 (8)	**0.009**	1 (3)	**0.008**
Change in prescription, N (%)	4 (4)	2 (2)	0.65	2 (3)	0.99	0 ()	0.31
Antiresorptive, N (%)	72 (72)	49 (49)	**0.01**	39 (58)	0.06	10 (30)	**<0.001**
Anabolic, N (%)	0 ()	1 (1)	0.32	1 (2)	0.22	0 ()	N/A
Active Vitamin D, N (%)	21 (21)	37 (37)	**0.01**	20 (30)	0.17	17 (50)	**0.001**
Nutritional Vitamin D, N (%)	65 (65)	69 (69)	0.55	48 (73)	0.30	21 (62)	0.73
Calcium supplement, N (%)	59 (59)	53 (53)	0.39	40 (61)	0.84	13 (38)	**0.04**
Calcium carbonate or calcium citrate, N (%)	5 (5)	15 (15)	**0.02**	3 (5)	0.89	12 (35)	**<0.001**
Calcium or vitamin D, N (%)	83 (83)	85 (85)	0.70	57 (86)	0.56	28 (82)	0.93
Alive at 5 years, N (%)	87 (87)	72 (72)	**<0.001**	43 (65)	**<0.001**	29 (85)	**<0.001**
Fracture 5 y after DXA, N (%)	18 (18)	25 (25)	0.2	14 (21)	0.64	11 (33)	0.06
Hip Fracture, N (%)	2 (2)	8 (8)	0.05	5 (7)	0.08	3 (9)	0.06
Vertebral Fracture, N (%)	7 (7)	2 (2)	0.17	1 (2)	0.29	1 (3)	0.23

PO0576

Development of a Machine Learning Approach to Management of CKD-MBD Therapy

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Background: We developed a Quantitative Systems Pharmacology (QSP) model of CKD-MBD that predicts changes in mineral metabolism. We incorporate the CKD-MBD model into an Machine Learning (ML)-based simulation to optimize the dosing of three drugs used in CKD-MBD to test the hypothesis that Reinforcement Learning (RL) approach would improve therapeutic goals.

Methods: We performed a simulated 24 month study in a virtual cohort of 80 Stage 5d CKD patients using the QSP model of CKD-MBD treated by a simulated physician (AI-Agent 0) or RL (AI-Agent 1). Agent 0 was a Deep Neural Network trained on a set of 128,061 instances. Agent 1 was developed using RL rewarding concentrations within the target range for Ca, P, PTH and avoiding Ca < 7.0 and > 10.2 mg/dL. Results of the simulation were compared using regression analysis of the dependent variable (Ca, P, PTH, calcitriol (CTL), lnFGF23, bCa(bone efflux), and vCa(vascular influx) over time with the factors RL (Agent1 vs Agent 0), P binder adherence, and equilibrium vs. steady-state. Doses of agents used to treat were compared at 24 months.

Results: Results of the statitical analysis are shown in the Table. Agent 1 using RL resulted in a greater rate of change in the dependent variables in all cases and resulted in lower model predicted concentrations of P, PTH, and FGF23 and higher concentrations

of Ca, and CTL. The time effect on FGF23 was not significant. Ca flux from the bone and into the tissue was also decreased in Agent 1. Drug utilization was also different between methods tested at 24 months. Agent 1: 734 mg/day less P binder (p=0.015), 0.71 ug/day more calcitriol (p<0.001) and 3.84 mg/day less cinecalcet (p<0.001).

Conclusions: Through simulation we have shown that a machine learning approach using reinforcement learning is superior to an expert system mimicking physician dosing practices. Concentrations of Ca, P, and PTH came into equlibrium faster and at more optimal levels while predicting decreased unwanted Ca movement.

Funding: Veterans Affairs Support

	Coefficient			p Value		
	Time	RL	Adherance	Time	RL	Adherance
P	-0.053	-0.167	-0.603	<0.001	<0.001	<0.001
Ca	0.053	0.237	0.155	<0.001	<0.001	<0.001
PTH	-24.2	-53.7	-81.6	<0.001	<0.001	<0.001
CTL	1.53	19.6	-7.76	<0.001	<0.001	<0.001
lnFGF23	0.004	-0.329	-1.34	0.435	<0.001	<0.001
vCa	-0.006	-0.017	-0.118	<0.001	<0.001	<0.001
bCa	-0.017	-0.177	-0.08	<0.001	<0.001	<0.001

PO0577

Role of Current Proposed Algorithm to Guide Osteoporosis Treatment in CKD: A Bone Biopsy Study

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Background: Recently, algorithms have been proposed to guide osteoporosis treatment in chronic kidney disease population. As suggested by Kharaillah et al, evaluation of bone turnover level by bone specific phosphatase alkaline (bALP) will determine the use of anabolic or antiresorptive therapy with or without prior bone biopsy. The aim of this study is to use a cohort of CKD patients who had a bone biopsy to evaluate accuracy of this algorithm in a real-world setting.

Methods: Single-center retrospective cross-sectional study at CHU de Québec, Canada from 2017 to 2021. CKD 4-5 patients with bone fragility and suspicion of low bone turnover or mineralization defects who had a bone biopsy were included. Results of bone biopsy were categorized based on the TMV classification. We compared the performance of the algorithm to identify potential contraindications to antiresorptive or anabolic therapy vs bone biopsy results. Receiver operating characteristic (ROC) curves were used to explore the predictive ability of bALP and tALP regarding low bone turnover and potential contraindication to antiresorptive therapy in our cohort.

Results: Twenty-six patients included (mean age 67,7 years, 11 men, 14 HD and 1 PD, 11 diabetic patients). Eleven patients had low, 8 normal and 7 high bone turnover on biopsy. According to the algorithm, no patient would have received anabolic treatment, bone biopsy would have been proposed to 10 patients and 16 would have received antiresorptive therapy. Based on the biopsy results, 8 out of these 16 patients had potential contraindications: 4 with low bone turnover and 4 with presence of mineralization defects. ROC curve for bPAL to predict low bone turnover was 0,749 (similar to tPAL). However, the AUC for bPAL to predict the presence of potential contraindication to antiresorptive was lower at 0,6667 (0,6095 for tPAL).

Conclusions: Algorithm using bone turnover markers can guide clinicians in approaching these patients. However, bone biopsy is still needed in many patients to better tailor anti fracture therapy until more accurate non-invasive markers are available.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO0578

Different PTH Responsiveness and Bone Turnover in Japanese as Compared to European Patients Treated with Hemodialysis

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Background: Parathyroid hormone (PTH) targets are lower in Japanese compared to European patients on dialysis. Whether this translates to lower bone turnover may depend on PTH responsiveness. This study tested the hypothesis that skeletal PTH responsiveness differs between Japanese and European hemodialysis patients.

Methods: Whole PTH (Roche), bone-specific alkaline phosphatase (BsAP, IDS-iSYS), and tartrate-resistant acid phosphatase type 5b (TRAP5b, IDS-iSYS) were centrally assessed in 378 prevalent hemodialysis patients from Japan and Belgium, matched 1:1 on age, gender, diabetes, and dialysis vintage. Patients with PTH levels at the extremes (<normal range or >15 xUNL) were excluded.

Results: Patients were well matched in age (59±12 yrs), gender (66% male), diabetes (34%), and dialysis vintage (39 [22-63] months). Japanese patients had lower PTH levels (109 vs 161 ρg/mL, $p<0.001$) and bone turnover markers (BsAP 15.3 vs 24.5 ug/L; TRAP5b 3.35 vs 5.79 U/L, $p<0.001$ both). Scatterplots and linear regression revealed higher bone turnover markers in European patients for any given level of PTH (Figure). In a multivariable model, Japanese nationality, male gender, higher BMI, and higher PTH were negative predictors of the TRAP5b/PTH ratio (Table).

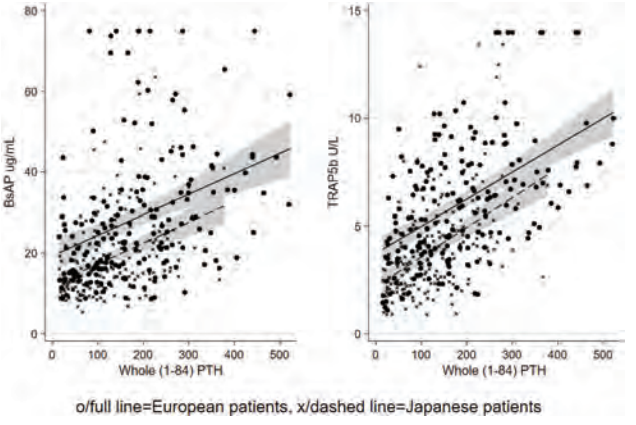
Conclusions: Skeletal PTH responsiveness is lower in Japanese as compared to European patients on dialysis; thus, differences in PTH sensitivity cannot reconcile the current discrepancies in PTH target range.

Funding: Private Foundation Support

Table: Determinants of Ln (TRAP5b/PTH) by multivariable linear regression

	β-coefficient	Standard error	p-value
Nationality, Japanese	-0.480	0.053	<0.001
Gender, male	-0.196	0.051	0.003
Body mass index, kg/sqm	-0.033	0.005	<0.001
Ln (1-84) PTH	-0.609	0.314	<0.001

Stepwise selection of variables. Model adjusted R-sq 52%, p<0.001.



Scatterplots of bone turnover markers over PTH

PO0579

Association of Metabolic Acidosis with Impaired Bone Quality

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Background: Chronic kidney disease (CKD) is a state of impaired bone quality and strength, usually presenting as renal osteodystrophy. Metabolic acidosis (MA) is an important complication of CKD that alters bone quality and strength and is associated with increased fracture risk. Few studies have investigated bone tissue-level effects of MA in humans with CKD. We hypothesized that CKD patients with MA would have altered bone-tissue level mineral content.

Methods: This retrospective cross-sectional analysis included 22 patients with eGFR <90 mL/min/1.73m^2, including those receiving kidney replacement therapy, recruited from the general nephrology clinics of Columbia University Irvine Medical Center. Patients were considered to have MA for serum bicarbonate ≤22mEq/L. Transiliac crest bone biopsy was assessed for bone formation and mineralization measures from quantitative histomorphometry of tetracycline double labels, tissue mineral density (TMD) by microCT and bone mineral density distribution (BMDD) by quantitative backscatter electron imaging (qBEI). Spearman correlations (ρ) were adjusted for eGFR. Univariate Wilcoxon tests assessed between group differences.

Results: Twelve participants had MA. There were no differences in age, sex or race/ethnicity. After eGFR adjustment, there was a correlation between serum bicarbonate and TMD (ρ=0.60, p=0.004). Bone formation and mineralization measures did not differ. TMD by microCT showed a trend. Measures of calcium content by BMDD differed between groups.

Conclusions: MA is associated with lower TMD and altered calcium content in patients with CKD. Further investigation is needed to determine whether impairments in TMD and BMDD are associated with decreased bone strength and are corrected by bicarbonate supplementation.

Funding: NIDDK Support

	Nonacidotic (HCO3 >22mEq/dL) (n=12)	Acidotic (HCO3 ≤22mEq/dL) (n=10)	p
microCT			
Tissue Mineral Density	1011±43.3	973.9±35.8	0.07
BMDD			
Trabecular			
Camean	22.5±0.6	21.7±0.86	0.06
Capeak	23.4±0.6	22.6±0.89	0.07
Cawidth	3.8±0.35	4.6±0.68	0.002
Calow	5.5±1.5	7.9±3.0	0.02
Cahigh	12.0±7.8	8.4±7.0	0.2
Cortical			
Camean	22.4±0.58	21.9±0.86	0.2
Capeak	23.4±0.50	23.0±0.77	0.2
Cawidth	4.1±0.33	4.4±0.50	0.1
Calow	5.8±1.9	7.4±2.9	0.3
Cahigh	12.8±5.1	10.3±7.8	0.2

PO0580

Impact of Urinary Calcium Excretion on Bone, Cardiovascular System, and Kidney Function in Caucasian Osteoporotic Patients: A Longitudinal Long-Term Follow-Up Study

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Background: Urinary Calcium excretion (UCaE) is expected to reflect the bone activities, however this relationship in osteoporotic (OP) patients (pts) is not well understood. Moreover, the influence of UCaE on kidney function and cardiovascular (CV) system is controversial.

Methods: Longitudinal study for OP pts who had bone biopsies between January 2008 and December 2013. All pts were white, had 24 urine collection for UCaE, DEXA scan for BMD, bone histology, and at least two follow ups with a minimum of 1-y. Exclusion criteria included active malignancies and infections, liver failure, ESKD, organ transplant, or secondary OP.

Results: Study included 118 OP pts with median follow up of 5.3 (1-11) y. The mean age was 61 ± 12 y and 89% of pts were women. The mean eGFR at baseline was 83 ± 19 ml/min Trabecular bone volume was low in 95% of pts, 39% had high turnover bone turnover disease (HTBD) and 61% had low turnover bone disease (LTBD), while mineralization was defective in 9%. Serum calcium and 25 vitamin D were within normal range in vast majority of pts. At baseline, lumbar spine (LS) T-score was -1.9 (-5.5 to 3.9), and total hip (TH) T-score was -1.6 (-4 to 2). Pts with HTBD had lower LS T-scores (p=0.02). Hypercalciuria found in 23%. Mean UCaE was 195 ± 116 mg/d with no difference between LTBD and HTBD pts. CKD pts were older (p<0.001), had higher PTH (p<0.001), and lower UCaE (p=0.04). BMD significantly declined (>2%) in 46% of pts at TH, and 42% at LS. BMD losers at TH were older, had lower UCaE, and lower serum albumin. Lower UCaE was significant predictor of BMD loss after adjustment of age, eGFR, and serum albumin (p=0.039, β=1.01, 95% CI (1-1.01)). Fractures occurred in 18% of pts during follow up. Fractures were higher in pts with UCaE<100. GFR declined (>3.3%/y) in 19% pts with no difference in UCaE in pts with declined vs stable GFR. Pts with kidney stones (13%) tended to have higher UCaE. New CV events occurred in 14% of pts. Pts with CV events tended to be older (64 vs 61 y) and had lower UCaE (169 vs 199 mg/d).

Conclusions: LTBD is common in OP pts. UCaE is not different between LTBD, and HTBD pts. CKD pts had less UCaE. Lower UCaE predicted bone loss and fracture risk in white OP pts.

PO0581

The Incidence of Hypocalcemia After Denosumab Administration in Patients with CKD

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Background: Patients with chronic kidney disease (CKD) are at increased risk of fragility fracture and its complications. Denosumab is an antiresorptive agent approved for use in CKD, but has been associated with hypocalcemia in those with advanced disease although the incidence is unclear. We examine the real-world incidence of hypocalcaemia in patients with CKD newly prescribed denosumab.

Methods: Using linked healthcare databases (ICES), we conducted a population-based cohort study of adults >65 years newly prescribed denosumab or bisphosphonates from 2012-2017 in Ontario, Canada. We captured the incidence of hypocalcaemia within 180 days of drug dispensing, stratified by eGFR.

Results: We identified 9,319 new users of denosumab and 9,052 new users of oral bisphosphonates. Compared with bisphosphonate users, denosumab users were older (78.8 vs 75.0 years), more often from long-term care, had a history of fragility fracture, and had more advanced CKD. Approximately one third of patients dispensed denosumab had a calcium level checked within 180 days of their prescription. The risk of hypocalcemia (<2.00mmol/L) with denosumab was low (0.74% 95% CI 0.58-0.93). One third of those had a calcium <1.8mmol/L (0.28% 95% CI (0.19-0.41). The risk of hypocalcemia increased substantially in those with eGFR <30 (8.4% [95% CI 5.5-12.0]). In new users of bisphosphonates, the risk of hypocalcemia was low across all eGFR groups.

Conclusions: In the largest population-based cohort of denosumab users with CKD to date, we found a modest increase in the risk of hypocalcemia with denosumab in those with stage 4 and 5 CKD. These rates are lower than reported in smaller cohort studies. This study was limited by the low numbers of patients with end stage renal disease. Our study emphasizes the importance of awareness of denosumab-induced hypocalcemia, routine monitoring post-denosumab, and benefit-risk assessment before prescribing this treatment to patients with kidney disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

The cumulative incidence of mild hypocalcemia (Ca <2.00 mmol/L) at 180 days

eGFR Category (mean GFR ml/min/1.73m2 [SD])	Denosumab % (95% CI)	Bisphosphonate % (95% CI)
All	0.74 (0.58-0.93)	0.38 (0.27-0.52)
eGFR ≥60 (80 [10.4])	0.46 (0.32-0.65)	0.32 (0.21-0.47)
eGFR 30 - <60 (49 [8.1])	0.65 (0.39-1.03)	0.52 (0.27-0.93)
eGFR <30 or chronic dialysis (23 [6.0])	8.39 (5.49-12.06)	1.33 (0.26-4.35

PO0582

The Efficacy and Safety of Denosumab for Osteoporosis in Advanced CKD with or Without Dialysis

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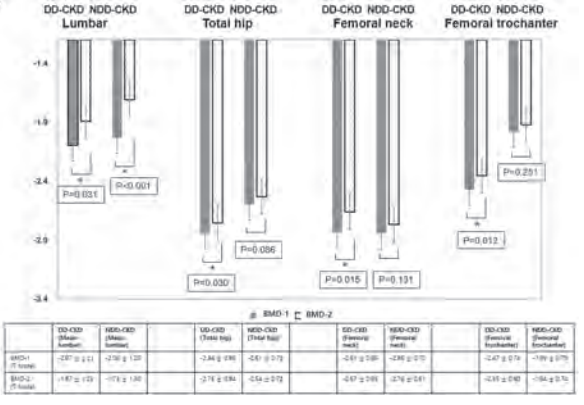
Background: Chronic kidney disease (CKD) is associated with an increased risk of osteoporosis and fragility fractures. However, studies assessing the optimal risk stratifications and treatments for osteoporosis in patients with advanced CKD are limited. This retrospective analysis evaluated the efficacy and safety of denosumab in patients with CKD and those on dialysis using data from a single-center

Methods: A total of 96 CKD patients with or without dialysis (CKD stages G3-G5D) in our hospital, who had osteoporosis diagnosed by dual-energy X-ray absorptiometry and received denosumab 60mg subcutaneously every 6 months at least twice, were enrolled. Annual changes in bone mineral density (BMD), annual incidence rate of new fractures (vertebral or non-vertebral) and adverse events focused on hypocalcemia were the major outcomes. The subjects were classified into non-dialysis dependent or dialysis-dependent CKD (NDD-CKD or DD-CKD) groups.

Results: The annual changes in BMD (T-score) at the lumbar spine from baseline were significantly increased in both groups. The annual changes in BMD at the total hip and femoral neck were increased in both groups, although only the DD-CKD group showed significantly improved changes (Figure 1). The annual incidence rate of new fractures was similar (4.7 % for DD-CKD vs. 7.5 % for NDD-CKD, p = 0.688). The incidence rate of severe hypocalcemia was comparable between both groups (2.3 % vs. 0.0 %, p = 0.448), whereas those of mild to moderate hypocalcemia were significantly higher in DD-CKD (25.6 % vs. 1.9 %, p = 0.000; 20.9 % vs. 1.9 %, p = 0.005). None required hospitalization due to severe symptoms such as tetany and seizure.

Conclusions: Denosumab significantly increased BMD and was safe in advanced CKD patients with osteoporosis. Although severe hypocalcemia or other severe adverse outcomes were rare, physicians should keep in mind that the patients essentially need adequate vitamin D and calcium replacement prior to administration of denosumab.

Figure 1



PO0583

A Rare Cause of Reversible Granulomatous Lung Disease Leading to Hypercalcemia in a Peritoneal Dialysis Patient

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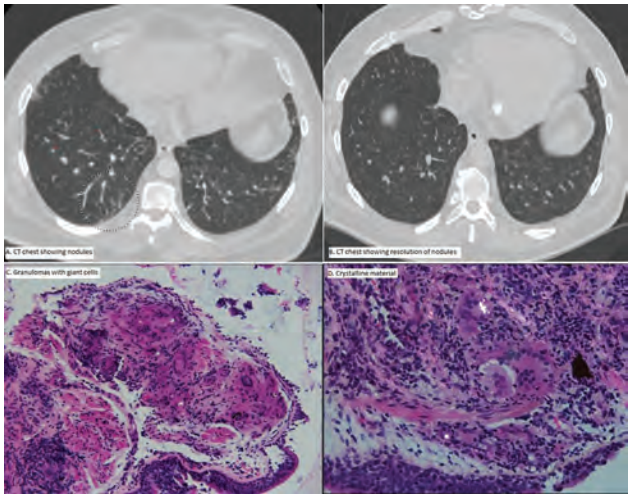
Introduction: Hypercalcemia is associated with poor outcomes in patients with end-stage kidney disease (ESKD). A meticulous work-up is essential to deduce the etiology and initiate appropriate management. We present a report where comprehensive work-up revealed a rare, environmental exposure as a cause of hypercalcemia: exposure to drywall dust.

Case Description: A 59-year-old man with ESKD had longstanding well-controlled mineral bone disorder. He developed worsening hyperphosphatemia of unclear etiology, and eventually presented with symptomatic hypercalcemia with corrected calcium level of 12.9 mg/dL. Biochemistry and imaging were consistent with hypercalcemia of granulomatous lung disease. CT chest showed numerous conglomerations of centrilobular nodules in multiple lobes of both lungs (Figure 1A). Transbronchial biopsy showed giant cell granulomas containing crystalline material and calcified inclusions (Figure 1C, 1D). Infectious and rheumatological work-up was unrevealing. Detailed patient interview revealed that he had been sanding drywall without respiratory protection due to N95 mask shortage in the global pandemic. No treatment was initiated because the environmental exposure had already terminated. Over a few months, the imaging (Figure 1B) and biochemical findings resolved. A year later, the patient has well controlled mineral bone disorder on calcium-containing phosphate binders again.

Discussion: Our report demonstrates how systematic work-up and careful history-taking are critical in diagnosing esoteric conditions associated with hypercalcemia. It also illustrates indirect health-related effects of the coronavirus-19 pandemic on non-infected ESKD patients.



A: CT scan showing granulomas, B: Resolution of granulomas in 4 months, C: Transbronchial biopsy with granulomatous inflammation, D: Crystalline material in granulomas

PO0584

Holy Fanconi, My Bone Is Breaking!

Anum Hamiduzzaman, Wei Ling Lau. *University of California Irvine, Irvine, CA.*

Introduction: Tenofovir-induced Fanconi syndrome can be insidious with severe hypophosphatemia from renal losses leading to subclinical fractures.

Case Description: A 72 y/o woman with CKD stage 3a, chronic hepatitis B and osteoporosis was referred for hypophosphatemia. She had recently presented to the ER with dizziness/weakness, chronic bone pain and poor appetite. She was found to have a critically low phos of 1.0 mg/dL. X-rays revealed old C-spine and femur fractures. Labs were also notable for K 3.2 mmol/L, CL 111 mEq/L, bicarb 18 mEq/L, Cr 1.1 mg/dL, Ca 8.4 mg/dL, PTH 120 pg/mL and normal vit D. Medications included tenofovir disoproxil fumarate (TDF) started 5 years prior for hep B, and ibandronate for osteoporosis. The hypophosphatemia was initially attributed to poor nutrition vs bisphosphonate therapy. However, fractional excretion of phos (FEphos) resulted at 78% consistent with urinary phos wasting. Proteinuria and glucosuria in combination with hypokalemia and hyperchloremic metabolic acidosis led to a diagnosis of proximal renal tubulopathy (Fanconi syndrome) from TDF nephrotoxicity, with hypophosphatemic osteomalacia. The patient was started on Na bicarbonate, K, Ca, vitamin D and phos supplementation. Osteoporosis therapy was switched to denosumab. The patient's hepatologist switched TDF to tenofovir alafenamide (TAF) given the requirement for lifelong hepatitis B therapy. Phos improved to 3.2 mg/dL one month after TDF was discontinued, with decrease in FEphos. PTH normalized in tandem with Ca repletion (Figure).

Discussion: Tenofovir nephrotoxicity occurs via disruption of proximal tubular mitochondrial function. In our patient, prolonged 5-year exposure to TDF with renal phos wasting led to inadequate bone mineralization and subsequent osteomalacia, which may have been aggravated by concurrent bisphosphonate therapy. Subclinical bone fractures led to chronic pain, deconditioning and poor nutritional status. TAF is a prodrug of tenofovir thought to be less nephrotoxic than TDF because its pharmacokinetics requires lower doses for efficacy. Other forms of tenofovir nephrotoxicity include ATN, chronic interstitial nephritis and nephrogenic diabetes insipidus.

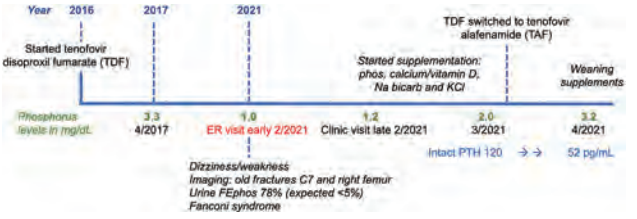


Figure: Case presentation of tenofovir-induced Fanconi syndrome.

PO0585

An Unusual Culprit of Severe Acute Refractory Symptomatic Hypocalcemia: Keyboard Cleaner

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Introduction: 1,1-Difluoroethane is commonly found in gas dusters and aerosol products. It has emerged as a recreational drug due to its acute euphoric effect. Side effects from difluoroethane abuse include hypocalcemia, acute kidney injury, cardiac arrhythmias and seizures. We report a case of 1,1-difluoroethane abuse presented with severe acute symptomatic hypocalcemia post Zoledronic acid therapy for Paget's disease.

Case Description: A 35 year old male with a past medical history of Paget's disease presented with generalized muscle cramps, facial twitching and upper extremities spasms for a day. He received IV Zoledronic acid as outpatient a day prior to the onset of symptoms. He also reported a significant history of inhalant abuse with keyboard cleaners. Physical examination were unremarkable other than a positive Trousseau sign. EKG showed prolonged QTc interval of 523 ms. Initial labs revealed corrected serum calcium 4.50 mg/dL, phosphorus 1.8 mg/dL, alkaline phosphatase 455 U/L, parathyroid hormone (PTH) 201 pg/mL, 25-Hydroxyvitamin D 7.0 ng/mL and 1,25-Dihydroxyvitamin D 146 pg/mL. Over the course of 5 days, he received a total of 24 g of IV calcium gluconate and 30 g of oral calcium carbonate. His symptoms subsequently resolved and serum corrected calcium normalized to 8.04 mg/dL and PTH decreased to 169.7 pg/mL on day 5 of hospitalization. He was discharged on day 6 with plans to follow up with primary care physician for monitoring of serum calcium level.

Discussion: Incidence of severe symptomatic hypocalcemia related to Zoledronic acid therapy in Paget's disease is uncommon (1%). Our patient was treated with Zoledronic acid in the past without complication. Besides, he lacks the risk factors for bisphosphonate-induced hypocalcemia which include hypoparathyroidism, hypomagnesemia and renal failure. Low 25-Hydroxyvitamin D on presentation is likely due to the effect of secondary hyperparathyroidism in response to hypocalcemia. Thus, we conclude that 1,1-difluoroethane is most likely the major precipitating factor for hypocalcemia seen in this case. Healthcare provider should be aware of uncommon causes of hypocalcemia such as difluoroethane as a differential once common causes have been ruled out, especially in certain susceptible populations given the ease of access for abuse and potentially fatal associated adverse effects.

PO0586

Severe Hypercalcemia in a Patient with Acute Lobar Nephronia

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Introduction: Acute lobar nephronia is a form of focal acute bacterial pyelonephritis without abscess formation or liquefaction.

Case Description: A 62-year-old Native American woman with a childhood history of left nephrectomy and treatment for tuberculosis was admitted for sepsis due to pyelonephritis and pan-sensitive E. coli bacteremia. Her creatinine was 5.2 mg/dL on admission, improved to 3.5 mg/dL with intravenous ceftriaxone, then increased to 4.2 mg/dL after transitioning to oral antibiotics six days later. At the same time, she developed hypercalcemia, which peaked at 13.7 mg/dL (ionized calcium 1.83 mmol/L). PTH was undetectable. Her 1,25-dihydroxy vitamin D (1,25-Vit D) was elevated at 120 pg/mL. The ultrasound showed right kidney hypertrophy to 16.3 x 9.9 x 10.5 cm, but no perinephric abscess or hydronephrosis. MRI abdomen showed wedge-shaped and cortical hyperintense striations through the kidney, the largest measuring 2.3 cm (Figure 1). Imaging showed no osteomyelitis, lytic lesions or suspicious masses. Kappa/lambda ratio was at 0.8 and IFE gel showed a faint band in lambda suggestive of a specific immune response or an early monoclonal protein. QuantiFERON Gold was indeterminate but imaging did not show pulmonary tuberculosis. Seven separate urine samples had negative acid fast stain and culture. Mycobacterium Tuberculosis PCR in urine was negative. She completed a prolonged course of antibiotics and over the six months of follow-up, her serum calcium and albumin normalized, and 1,25-Vit D fell to 16 pg/mL. Her serum creatinine decreased to 2.17 mg/dL. Right kidney size decreased to 9.8 x 5.7 x 5.4 cm and had normal contour and sonographic appearance.

Discussion: Acute hypercalcemia was likely due to a rare pathological activation of 1-alpha-hydroxylase (CYPb27b1) in renal proximal tubule cells due to inflammatory response. Common causes of severe hypercalcemia were ruled out. Supporting this etiology, resolution of hypercalcemia correlated with resolution of renal inflammation.

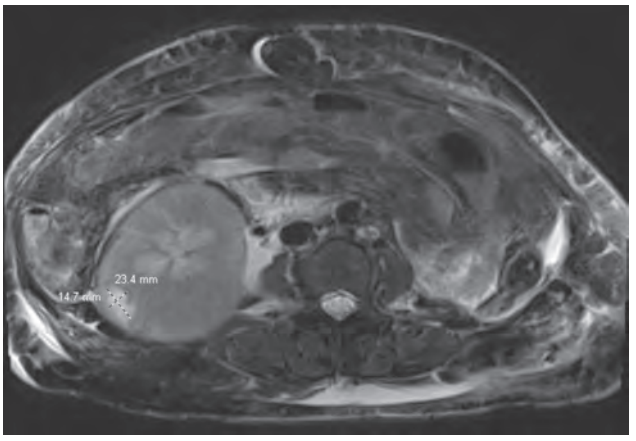

Figure 1.

PO0587

Identification of Factors Affecting Changes in the Agatston Coronary Artery Calcification Score in Maintenance Hemodialysis Patients

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Background: Coronary artery calcification (CAC) has been implicated in cardiovascular disease, one of the leading causes of death in patients on maintenance hemodialysis (MHD). The Agaston CAC score is the most widely used scoring system for CAC evaluation. The factors affecting changes in the CAC score in MHD patients remain unknown. We characterized the associations between change in Agaston CAC score and clinical parameters in MHD patients.

Methods: A total of 288 patients on hemodialysis at Ichiyokai group facilities between January 2018 to February 2021 were retrospectively analyzed. Clinical parameters and Agaston CAC scores, determined by multi-detector computed tomography, were assessed at baseline and after 1 year. Patients with Agaston CAC score ≥ 30 were enrolled. A multiple regression analysis for change in Agaston CAC score was performed. The independent variables were sex, age, Agaston CAC score, glucose, albumin-corrected serum calcium, serum phosphate, β2-microglobulin, hemoglobin, blood urea nitrogen, albumin, angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) use, calcimimetic use, and vitamin D use.

Results: The mean change in Agaston CAC score was 205.2 ± 545.1 and the mean percentage change in Agaston CAC score was 21.2% ± 43.5%. The multiple regression analysis for change in Agaston CAC score identified Agaston CAC score (regression coefficient [RC] = 0.3795, $p < 0.001$), serum phosphate (RC = 0.1230, $p = 0.0317$), albumin-corrected serum calcium (RC = –0.1165, $p = 0.0049$), and ACE inhibitor/ARB use (RC = –0.1262, $p = 0.0298$) as significantly related factors ($R^2 = 0.2011$, $p < 0.001$).

Conclusions: In patients on MHD, change in Agaston CAC score is positively associated with Agaston CAC score and serum phosphate, and negatively associated with albumin-corrected serum calcium and ACE inhibitor/ARB use.

PO0588

Qatar National Program for Screening and Management of Vascular Calcification in Hemodialysis

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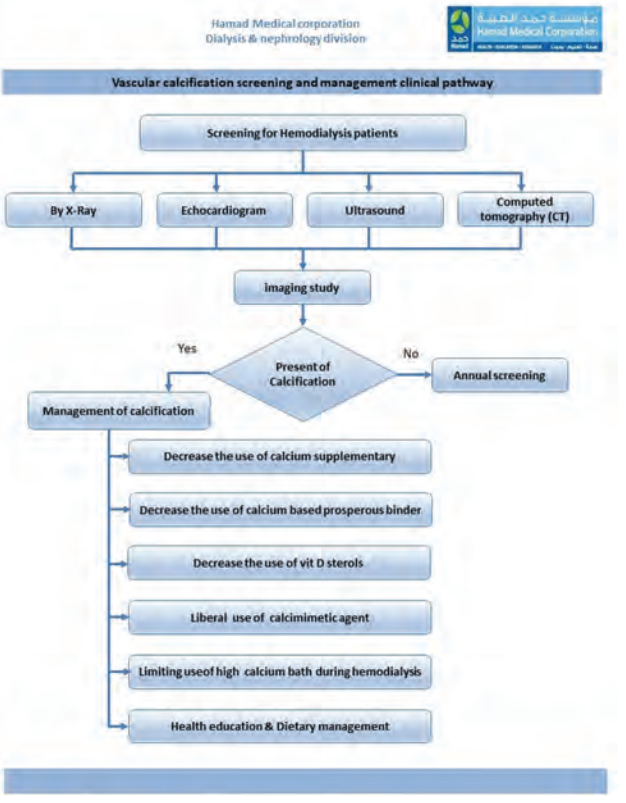
Background: Vascular calcification (VC) is an independent and important risk factor for cardiovascular events in (HD) patients. Trials aiming to reduce the progression of VC did not show a great success. We are presenting data from our national program for screening and management of VC in hemodialysis patients in State of Qatar.

Methods: All ambulatory HD patients in Qatar where included. Data were collected in 2020 from the Qatar national electronic medical record and it included all imaging studies (X-ray, echocardiogram, US, CT). VC then were classified into mild, moderate or severe. Patients with any VC were started on a newly created protocol to decrease calcium load (shift to non-calcium phosphate Binder, reduce active vitamin D, and liberalize calcimemitic dosing). Figure1 shows new pathway of screening and management of VC in HDpatients.

Results: Total patients were 650 During the study period. 559 were screened for VC (86%).423 (75%) had VC. We were able to classify 286 patients (67%) of them based on severity of VC on radiological findings to mild 201(70%), moderate 59(21%) or severe 26(9%). Following interventions, percentage of patients with calcium level of normal range (2.1-2.55mmol/l) increased by 5% from 83% in March 2020 to 88% in December 2020 (p value=0.004). Phosphorus level was maintained in the range 0.81-1.8mmol/l by 82% and PTH level in the range 150-500pg/ml by 72%. calcium based phosphate binder tables used weekly decreased by30%.

Conclusions: we created a screening and management protocol for VC in HD patients. Our protocol was successfully implemented and the initial outcomes was very promising. A follow up imaging to identify progression of VC should be considered in further studies.



PO0589

The Clinical Effect of Paricalcitol Treatment on Hemodialysis Patients with Secondary Hyperparathyroidism and the Influence of Abdominal Aortic Calcification

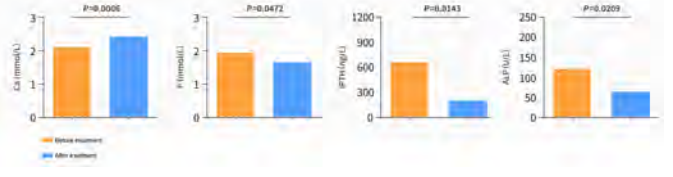
Yin Liu, Tao Yang. *Beijing Haidian Hospital, Beijing, China.*

Background: This is an observational study to investigate the clinical efficacy of paricalcitol in maintenance hemodialysis (MHD) patients with secondary hyperparathyroidism (SHPT) and its effect on the level of abdominal aortic calcification (AAC).

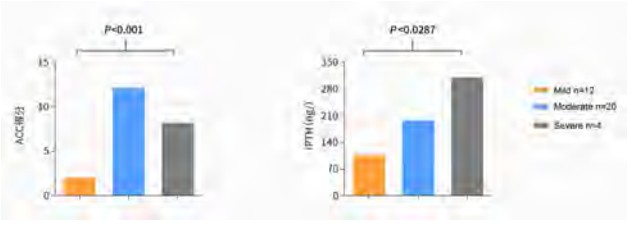
Methods: The study included 40 patients (24 males and 16 females) treated with regular MHD with SHPT in the hemodialysis clinic of Beijing Haidian Hospital from April 2019 to June 2020. After 12 weeks treated with Intravenous paricalcitol on the basis of regular hemodialysis, compared the blood calcium, blood phosphorus, and intact parathyroid hormone (iPTH) before and after the treatment and AAC score (Kauppila semi-quantitative method), and observed the clinical efficacy and the level of AAC after treatment with paricalcitol.

Results: Monitored blood calcium, blood phosphorus, and iPTH before starting treatment. Ande after 12 weeks of treatment, monitored blood calcium, blood phosphorus, iPTH, ALP changes and AAC score. The comparison found that the blood phosphorus, iPTH, and ALP levels after treatment were lower than the pre-treatment levels, and the blood calcium was higher than the pre-treatment levels, the difference was statistically significant ($P<0.05$)(Fig 1). At the same time, it is observed that patients with high levels of iPTH are often accompanied by severe AAC, while patients with mild to moderate AAC often maintain relatively low levels of iPTH. There were differences in the expression levels of iPTH among the three groups of patients with AAC with different conditions, and the differences between the groups were statistically significant ($P<0.05$)(Fig 2).

Conclusions: Intravenous paricalcitol has a significant effect on SHPT in hemodialysis patients, which can reduce the level of iPTH and reduce the risk of abdominal aortic calcification.



Biochemical indicators before and after treatment



Patient's ACC score and relationship with iPTH level

PO0590

Progression of Renal Osteodystrophy and Vascular Calcifications in Patients with CKD Stage II-IV

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Background: Vascular calcifications (VC) are associated with renal osteodystrophy (ROD) but limited data are available on ROD and VC with progression of CKD.

Methods: 23 pts with CKD II-IV underwent iliac crest bone biopsies for bone histomorphometry, Dual-photon absorptiometry (DXA) of hip and spine for bone mineral density (BMD), and MSCT of the aorta (AOC) and coronaries (CAC) for assessment of VCs. Tests were done at baseline and after 2-3 years of observation with continuation of the same clinical management following KDIGO guidelines.

Results: Pts age was 60 ± 12 y with 56% female, 70% white, 26% black, 4% Asian, 57% DM II, 96% HTN, 9% CKD II, 74% CKD III, and 17% CKD IV. Results are shown in Table 1. There was an increase in VCs. GFR declined in 12 and was stable in 11 pts. Pts with declining GFR had greater increases in AOC and more loss in hip BMD. AOC correlated better than CAC with BMD. At baseline there was low bone turnover (LTO) in 87% of pts, and bone volume (BV) was low in 22%. LTO decreased to 78% and low BV was increased to 45% of pts at end of study. Defective mineralization was not observed at any time.

Conclusions: LTO and low BV are seen in early stages of CKD. With progression of CKD, turnover increases and low BV is more frequently seen. VCs are also seen early in CKD, AOCs progress faster than CACs and there is a relationship between VCs and bone loss.

Funding: NIDDK Support, Private Foundation Support

Table 1

	Baseline	After 2-3 years	P
GFR(mL/min/1.73m2)	41.1±12.8	38.9±11.9	0.03
TH BMD(g/cm2)	1.01±0.17	0.99±0.18	0.03
FN BMD(g/cm2)	0.94±0.15	0.93±0.17	<0.01
Coronary calcifications			
- Agatston Score	119(0-3410)	132(0-4392)	0.06
- SqrtVolume	9.06(0-52.0)	10.6(0-58.3)	0.04
Aortic Calcifications			
- Agatston Score	130(0-5076)	263(0-6054)	<0.01
- SqrtVolume	11.0(0-63.8)	15.7(0-70.9)	<0.01
BFR(mm3/mm2/yr)	0.66(0.09-1.78)	0.98(0.40-2.01)	<0.01
ACF(Number/yr)	0.25(0.04-0.76)	0.41 (0.12-0.79)	<0.01
AR(μm/d)	0.30(0.09-1.76)	0.41(0.15-16.4)	0.02
MLT(days)	22.2(1.96- 134)	16.4(0.21-56.1)	0.01

Data given as Mean ± SD or Median(range). TH: Total hip, FN: Femoral Neck, SqrtVolume: Square Root of Volume, BFR: Bone Formation Rate, ACF: Activation frequency, AR: Apposition Rate, MLT: Mineralization Lag Time.

PO0591

Magnesium Supplements Reduce Arterial Stiffness in Patients with CKD Stage 3-4 but Do Not Affect Bone Mineral Density

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Background: Chronic Kidney Disease (CKD) entails to mineral metabolism disorders and vascular calcifications (VC). In vitro and in vivo, magnesium (Mg) supplements inhibits VC and show a beneficial effect on kidney function. However, some authors have suggested that Mg could affect bone turnover. We performed a study to evaluate the effect of dietary supplementation with Mg on arterial stiffness and bone mineral density in patients with CKD stage 3-4 and VC.

Methods: Randomized, open-label, parallel-group clinical trial (control/experimental) (n=8 per group). The experimental group received 360mg of Mg carbonate daily for 15±1.5 months. At the beginning and at the end of the study, blood and urinary biomarkers of bone mineral metabolism were measured; pulse wave velocity (PWV) was determined with Mobil-O-Graph device as an indicator of arterial stiffness, the Adragao index was calculated and bone mineral density was measured by densitometry.

Results: The included patients were in both groups mostly men and similar with respect to age and GFR. Serum Mg concentration were 1.9±0.1 vs 2±0.1mg/dl in control and experimental group respectively. At the baseline, no differences were found in demographic characteristics, comorbidities, treatments, PWV or biomarkers of bone mineral metabolism. The experimental group did not present hypermagnesemia or any other adverse event. The increase in urine Mg confirmed the therapeutic adherence. There was a decrease in GFR: 4ml/min in control and 1.71ml/min in experimental group, with no changes in serum Mg (both not statistically significant). An inverse correlation was found between urine Mg and the albumin/creatinine ratio (p=0.039). At the end of follow-up, serum Mg was inversely correlated with PWV (p=0.015). Urinary Mg was inversely correlated with iFGF23 (p=0.007). A non-significant trend of decrease in the Adragao index was observed in the experimental group. There were no changes in bone mineral density.

Conclusions: In CKD3-4 patients the Mg supplements reduce arterial stiffness without changes in bone mineral density.

PO0592

Phosphate, Blood Pressure, and Endothelial Cell Dysfunction in a Population Study

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Background: Hyperphosphatemia contributes to medial vascular calcification in chronic kidney disease (CKD) patients. There is emerging evidence that phosphate (Ph) is also associated with microvascular disease in individuals with normal kidney function, with in vitro data supporting a toxic effect of Ph on endothelial cells. We hypothesized there would be an association between serum Ph, blood pressure (BP), and endothelial cell dysfunction (ECD) markers in a large, diverse cohort.

Methods: Using data from the Dallas Heart Study, a multi-ethnic population-based cohort, we used serum Ph as the predictor variable and conducted linear regression analysis to determine its association with systolic BP and serum asymmetric dimethylarginie (ADMA) from a single visit. We controlled for numerous demographic and clinical variables including parathyroid hormone (PTH), calcium, vitamin D, estimated glomerular filtration rate (eGFR), and albuminuria.

Results: There were 3301 participants with a mean age of 43 years. The median systolic BP was 122 [112, 134] mmHg. The eGFR was 102 [88, 114] mL/min. Serum calcium, Ph, PTH, and vitamin D levels were 9.2 [9, 9.5] mg/dL, 3.2 [2.8, 3.5] mg/dL, 37.3 [27, 51] pg/mL, and 17 [12, 23] ng/mL. Serum Ph and PTH were independently associated with both systolic BP and ADMA (Table 1), although there was a negative relationship between Ph and BP.

Conclusions: Even in the physiologic range, serum Ph and PTH were independently associated with higher ADMA, an ECD marker, in a diverse population while accounting for known predictors of hypertension including age, diabetes, and kidney function. Higher systolic BP was predicted by higher PTH, but lower Ph. The presence of these associations in individuals with preserved renal function warrant further studies in CKD, where hypertension and hyperphosphatemia are both more prevalent.

Funding: Veterans Affairs Support

Multivariate Linear Regression Analysis

Predictor Variables	Outcomes			
	Systolic Blood Pressure (mmHg, reciprocal transformation)		Serum Asymmetric Dimethylarginine (μmol/L, square root transformation)	
	β	p-value	β	p-value
Serum phosphate (mg/dL)	6.1e-05	.049	0.0053	.045
Age (years)	-3.2e-05	<.0001	0.001	<.001
Serum parathyroid hormone (pg/mL)	-2e-06	.002	0.0001	.003
Serum vitamin D (ng/mL)	8e-06	<.001	-0.0002	.114
Serum calcium (mg/dL)	-8.2e-05	.129	0.005	.25

Model also controlling for race, sex, diabetes, serum albumin, estimated glomerular filtration rate, LDL cholesterol, urinary albumin to creatinine ratio

PO0593

Hyperphosphatemia Is Associated with Vasoconstriction and Endothelial Cell Dysfunction in Hemodialysis Patients

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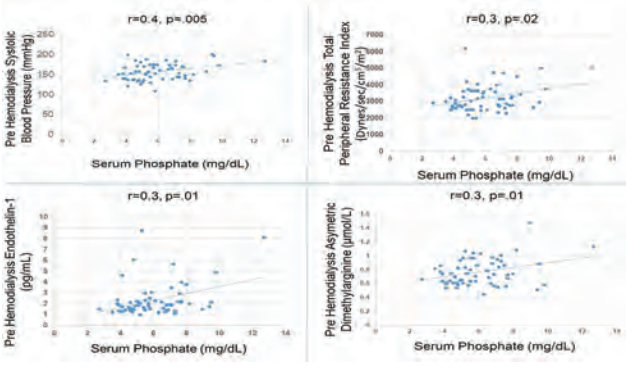
Background: Hyperphosphatemia is associated with increased mortality in hemodialysis (HD) patients. High phoshate (Ph) causes vascular structural changes including medial calcification. While there is in vitro evidence that high Ph can induce endothelial cell dysfunction (ECD), little is known about the relationship between Ph and vasoconstriction or ECD in HD patients.

Methods: We studied hypertensive HD patients with the following outcome data: pre-HD systolic blood pressure (BP), total peripheral resistance index (TPRI) obtained with non-invasive cardiac output monitor, and serum levels of endothelin-1 (ET-1) and asymmetric dimethylarginine (ADMA). The most recent pre-HD serum Ph was the predictor variable. We conducted correlation and multivariate linear regression analyses while controlling for other clinical variables.

Results: Among the 60 participants, the mean age was 50 years. There were 62% male, 58% Black, and 60% with diabetes. Serum Ph had significant correlations with systolic BP, TPRI, ET-1, and ADMA (Figure 1). Multivariate regression analysis showed independent associations for Ph with all outcomes except ADMA (Figure 2), but PTH did have an independent association with ADMA.

Conclusions: Hyperphosphatemia is independently associated with vasoconstriction in HD patients. Serum Ph is also associated with ECD, but this is in part confounded by PTH. These data show the adverse cardiovascular consequences of hyperphosphatemia extend beyond vascular calcification. Further human studies are needed to determine 1) if lowering Ph improves endothelial function in HD patients and 2) if pharmacologic therapy aimed at improving ECD reduces the cardiovascular burden associated with hyperphosphatemia.

Funding: NIDDK Support, Veterans Affairs Support



Multivariate Regression Analysis

	SBP		log [TPRI]		1/ET-1		ADMA	
	β	p-value	β	p-value	β	p-value	β	p-value
Serum Phosphate (mg/dL)	**3.2**	**.03**	**0.04**	**.02**	**-0.04**	**.02**	**0.02**	**.10**
Serum PTH (pg/mL)	0.003	.41	0.00004	.33	0.00002	.60	0.0001	.01
Percentage of Interdialytic Weight Gain	2.7	.06	-0.01	.46	-0.007	.65	-0.003	.82
Male Sex	-5.0	.32	-0.06	.32	-0.01	.86	-0.06	.20
Age (years)	-0.3	.17	0.002	.48	-0.002	.54	0.0009	.69
Black race	-0.8	.87	0.03	.62	0.04	.51	-0.06	.20
Diabetes	5.9	.27	0.1	.10	-0.01	.84	-0.08	.12

Models also controlled for serum albumin and protein catabolic rate; SBP=systolic blood pressure; TPRI=total peripheral resistance index, ET-1=endothelin-1, ADMA=asymmetric dimethylarginine; PTH=parathyroid hormone;

PO0594

Phosphate Indices and Atherosclerotic Cardiovascular Disease in CKD Patients: The CRIC Study

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Background: Phosphate (Pi) overload may induce vascular calcification and inflammation. We studied prospective association of Pi indices with ASCVD events in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Methods: 3939 CKD patients without cirrhosis were enrolled. 3096 were included in the analysis after excluding those with missing variables. ASCVD was defined as the first stroke, MI, or PAD. A new Pi burden index was calculated as [(urine Pi/Cr ratio) × serum Pi (sPi)× alkaline phosphatase (ALP)] to reflect the effect of high Pi diet on kidneys, cellular space, and bones. ALP was correlated with sPi and PTH. Cox proportional hazards models were used to study associations of Pi indices with ASCVD, adjusting for ACC/AHA ASCVD and other established risk factors.

Results: Over a mean of 9 years, 699 had ASCVD events. Pi burden index was correlated with 24-hr urine Pi. FGF23 and Pi burden index increased in early CKD. There were exposure-response associations of sPi, FGF23 and Pi burden index with ASCVD (**Table**). PTH, FEPi, and 24-hr urine Pi were not associated with ASCVD.

Conclusions: Pi burden is associated with ASCVD. FGF23 and Pi burden index increased in early CKD. They may be used for ASCVD risk classification and for monitoring phosphate overload. Future studies are warranted.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences (NIGMS)

Multivariable-adjusted Hazard Ratios of ASCVD Events Associated with Phosphate Indices

	HR (95% CI)
Quartiles of Serum Pi, mg/dL	
≤3.3	1.00
3.4 to 3.7	1.01 (0.81-1.27)
3.8 to 4.1	1.22 (0.97-1.54)
>4.1	1.28 (1.01-1.62)
P-value for linear trend	0.02
Quartiles of FGF23, RU/mL	
≤100	1.00
101 to 151	1.11 (0.88-1.40)
152 to 245	1.26 (0.99-1.60)
>245	1.54 (1.19-1.99)
P-value for linear trend	0.001
Quartiles of Pi burden index	
≤123	1.00
124 to 177	1.23 (0.98-1.54)
178 to 262	1.38 (1.10-1.74)
>262	1.59 (1.26-2.01)
P-value for linear trend	<0.0001

PO0595

Bone-Vessel Relationships, the Association Between Calcifications of the Iliac Arteries with Vertebral Fractures in Hemodialysis Patients: Results from the VIKI Study

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Background: Vascular calcification and fragility fractures are common age-related disorders and associated with high morbidity and mortality especially in end-stage renal disease. Skeletal disorders occur in dialysis patients. Few studies have provided data on the prevalence of vertebral fractures (VFs) and their association with large artery calcifications. We evaluated the relationship of iliac arteries calcifications (IACs) and abdominal aorta calcifications (AACs) with the risk for VFs in hemodialysis (HD) patients

Methods: The VIKI Study is a cross-sectional study involving 387 HD patients from 18 Italian dialysis centers. Biochemical data included bone health markers such as vitamin K levels, vitamin 25(OH)D, alkaline phosphatase, parathormone, calcium, phosphate, osteocalcin and Matrix Gla Protein. The presence of VF, IACs and AACs were determined through standardized spine lateral radiographs. A >20% reduction of vertebral body height was considered a VF. We quantified vascular calcifications by measuring the length of calcium deposits along the arteries classifying the degree of severity for the IACs and AACs with a specific score (mild: 0.1–3 cm; moderate: 3.1–5 cm; and severe >5 cm) previously validated for AACs.

Results: The prevalence of IACs was 56.1%, and of AACs 80.6%. After adjusting for confounding variables, the presence of IACs was associated with 73% higher odds of VF (p=0.028), whereas we found no association (p=0.294) for AACs. The presence of IACs associated with VF irrespective of calcification severity. Patients with IACs had lower levels of the vitamin K2, menaquinone 7 (MK7) (0.99 vs 1.15 ng/ml; p=0.003), and deficiency of this marker became greater when adjusting for triglyceride levels (0.57 vs 0.87 ng/ml; p<0.001).

Conclusions: The presence of IACs, regardless of their extent, appears to be a clinically relevant risk factor for VFs. The association is further enhanced by including vitamin K, a main player in bone and vascular health, in the model. Prospective studies are needed to confirm these findings both in chronic kidney disease patients and in the general population.

Funding: Private Foundation Support

PO0596

Oral Calcitriol Use, Vertebral Fractures, and Vascular Calcifications in Hemodialysis Patients: Results from the Vitamin K Italian (VIKI) Study

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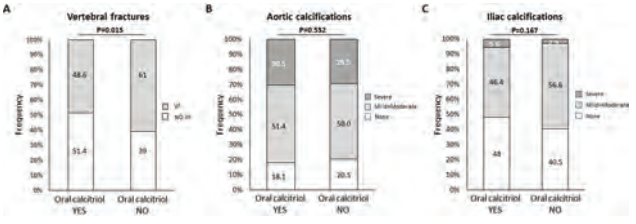
Background: Chronic Kidney Disease patients are characterized by alterations in bone and vascular metabolism associated to adverse clinical outcomes such as fractures, cardiovascular events and mortality. Dysregulation of vitamin D hormonal system, in levels of calcium, phosphate, PTH, FGF23/Klotho are the main responsible of these changes. We want to evaluate if oral calcitriol use can play a protective role on fractures in hemodialysis (HD) patients.

Methods: We included 387 HD patients of the VIKI database, a multicenter cross-sectional study. Biomarkers measured: vitamin K, VKDPs, vitamin 25(OH) D, ALP, PTH, Ca, P. Spine radiograph performed to define the presence of Vertebral Fractures (VF) and Vascular Calcification (VC). VF was indicated as >20% reduction of vertebral body height and VCs were quantified by measuring the length of calcium deposits along the arteries.

Results: 45.7% of patients were treated with oral calcitriol. No biochemical differences was observed between the treated and untreated patients. VFs were significantly lower in patients receiving oral calcitriol (48.6% vs 61%, **P=0.015**), the presence of VCs was similar (aortic: 81.9% vs 79.5% respectively, P=0.552; iliac: 52.0% and 59.5%, P=0.167). In a multivariable logistic regression analysis, after adjustment for all potential confounders, oral calcitriol was associated with a marked reduction (-40.2%) of the odds of fractures (OR: 0.598, 95% CI: 0.363-0.985, **P=0.043**).

Conclusions: In conclusion, we found a significant association between oral calcitriol use and lower VF rate in HD patients. Further prospective and interventional studies are needed to confirm these findings.

Funding: Private Foundation Support



PO0597

Significant Associations Between Vascular Calcification and Bone Mineral Density in CKD

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Background: Vascular calcification (VC) demonstrated as a predictor of cardiovascular mortality in chronic kidney disease (CKD) patients (pts). There are uncertainties in term of factors that may explain the links between low bone mineral density (BMD) and mortality in CKD. We aimed to study associations between VC and BMD in CKD pts.

Methods: We studied 90 consecutive CKD pts. The following VC assessments used: 1) lateral lumbar X-rays and the scoring system to assess VC of the abdominal aorta using a semi-quantitative scoring (Kauppila,1997); 2) Ankle-brachial index (ABI) assessment (Winsor,1950). A simple, non-invasive, accurate tool to evaluate arterial stiffness and peripheral arterial disease providing diagnostic and prognostic information with values ≥1.3 or⟨0.9 (Gu,2019); 3) Echocardiography; 3) BMD assessed by total body dual-energy X-ray absorptiometry (DXA).

Results: Study group pts (N=90, 41% male) median age was 64 years. Diabetes mellitus and hypertension were the common causes of CKD (29% and 28%, respectively). Kauppila score ⟩1 detected in 41% of cases. The evidence of peripheral VC measured by ABI detected in 23% of causes. The heart valves calcinosis and fibrosis found in 41% of pts. Table demonstrates multivariate regression analysis with variables entering the equation as correlates of DXA measurements with Kauppila score and ABI as dependent variables. In pts with heart valves lesions total body BMD is significantly lower than in those who have normal heart valves. In factorial regression analysis BMD of femur, femur neck and total body BMD were significantly associated with heart valves calcinosis/fibrosis. BMD of femur and femur neck also inversely associated with age.

Conclusions: BMD associated with VC in pts with different CKD stages. Multi-interventional approach for diagnosis of CKD-BMD is necessary for early detection to prevent complications. Total body DXA is more informative in clinical practice for evaluation of BMD.

Funding: Government Support - Non-U.S.

	R2	Coefficient	95% CI	p-value
Kauppila score	0.53			
BMD femur neck		-33.5	-49.1 - -17.7	0.001
BMD total spine		-25.1	-40.1 - -10.0	0.001
ABI	0.39			
BMD femur neck		-2.21	-3.09 - -1.23	0.001
BMD spine L1-L4		-0.77	-1.33 - -0.21	0.01
BMD ribs		-1.69	-2.74 - -0.65	0.002

PO0598

Increasing Bone Mineral Density Is Associated with Vascular Calcification in Children and Young Adults with CKD Stages 4-5 and on Dialysis

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Background: Bone mineral density(BMD) is inversely associated with coronary artery calcification(CAC) in older adults on dialysis. This association has not been shown in children and young adults where bone accrual may mitigate associations with vascular calcification

Methods: Multicenter longitudinal study in participants aged 5 to 30 years with CKD stages 4-5 and on dialysis. Measures included tibial cortical(Cort) and trabecular(Trab) BMD by peripheral quantitative CT, CAC, carotid intima-media thickness(cIMT), pulse wave velocity(PWV) and carotid distensibility, expressed as z-scores(BMDz, cIMTz, PWVz)

Results: 98 participants(age 13.8;IQR 10.7,16.5 yrs) were assessed at baseline and 55 again after 1.5(1.3 to 1.8) years. At baseline 10% had CAC, increasing to 18% at follow-up. Median cIMTz and PWVz were 2.17(1.14, 2.86) and 1.45(-0.16, 2.57) at baseline. At follow-up cIMTz and PWVz increased, and distensibility decreased in participants with static growth compared to children with linear growth (Fig 1A). TrabBMDz decreased from -0.26 to -0.38, p=0.01, particularly in growing children(Fig 1B); there was a non-significant decrease in CortBMDz (-0.47 to -1.13, p=0.09). On multivariable regression, baseline TrabBMDz was positively associated with cIMTz (β 0.35,p=0.001;Fig 1C). At follow-up, participants with increasing ΔTrabBMDz had 6-times greater odds of ΔcIMTz increase(95% CI 1.88 to 18.35). Growing people demonstrated greater declines in TrabBMDz but less progression of vascular calcification, compared to participants with static linear growth

Conclusions: In young people with CKD, an increase in vascular measures was seen despite an increase in BMD. Progression of vascular changes may be attenuated in the growing skeleton. Providing adequate calcium for optimal bone mineralization whilst avoiding vascular calcification remains challenging

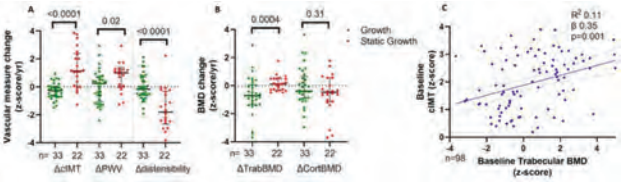

Fig1. Changes in (A) vascular measures and (B) BMD in growing children vs those with static linear growth; (C) Baseline trabecular BMDz and cIMTz

PO0599

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Assessing Efficacy of Standard and Low-Dose Hydrochlorothiazide in Recurrent Calcareous Nephrolithiasis Prevention: The NOSTONE Trial

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Background: Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8 % in men and 9.4 % in women. Without specific treatment, 5- and 20-year recurrence rates are 40 % and 75 %, respectively. Given the high cost of medical

treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach. Efficacy of thiazides for kidney stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses. In the case of recurrent nephrolithiasis, however, this practice is not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of kidney stones remains unclear.

Methods: NOSTONE is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial aiming to assess the dose-response relationship of three different dosages of hydrochlorothiazide (12.5mg, 25.0mg, 50.0mg) compared to placebo in the kidney stone prevention. The primary outcome incidence of stone recurrence at 3 years is a composite of symptomatic and radiologic recurrence (comparison of basal and end-of-study low-dose CT). The study included patients from 12 hospitals throughout Switzerland.

Results: The study was approved by all competent authorities by the end of February 2017. Recruitment started in Bern on March 9th 2017. All study sites are operative since June 30th 2017. The target number of 416 patients randomized in the trial was reached October 31st 2019 and recruitment stopped. In March 2020 the first patient randomized in the trial completed the treatment phase. All patients are expected to reach end of treatment by the end of August 2021 (www.nostone.ch).

Conclusions: The NOSTONE study will provide physicians with crucial information for the treatment of kidney stones. The impact of the results of this study will affect many patients currently under treatment with hydrochlorothiazide for the prevention of recurrent nephrolithiasis.

Funding: Government Support - Non-U.S.

PO0600

Body Mass Index (BMI) and Kidney Stone Risk in Calcium Kidney Stone Formers

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Background: The role of obesity among calcium kidney stone formers remains poorly defined, and it is unknown whether there are effect modifications of stone risk by diabetes and insulin resistance (IR).

Methods: We examined the independent associations between BMI and 24-hour urine stone risk profile among 167 calcium kidney stone formers (CSF), and analyzed the effect modifications by diabetes and IR measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in non-diabetics. Study participants were recruited from Lifespan Kidney Stone Clinic. We used linear regression and adjusted for demographics.

Results: The study population (n=167) had a mean age of 53 years, 77 (46%) were male, and 135 (81%) were Caucasian. 28 (17%) had diabetes. Mean BMI was 29 (Interquartile range (IQR) 25 to 33). Higher BMI associated strongly with diabetes ($p<0.0001$). Among 139 non-diabetic CSFs, mean BMI was 28 (IQR 25 to 31), and BMI had a strong positive association with HOMA-IR ($p=0.001$). 33% of nondiabetic CSFs had hypertension (vs. 100% in diabetics), 21% of nondiabetic CSFs had dyslipidemia (vs. 89% in diabetics). HOMA-IR ranged from 0.42 to 28.2 (mean 4.3). Overall, in the whole study population, BMI had significant positive associations with urine ammonium, urine uric acid (UUA), and UUA supersaturation ($p= 0.004$, <0.0001, <0.0001 respectively). The strong association between BMI and urine ammonium was only observed among diabetics ($p=0.006$), with a similar trend observed among non-diabetics with high IR ($p=0.09$ when HOMA-IR>10, $p= 0.9$ when HOMA-IR= 5-10, $p=0.2$ when HOMA-IR<5). On the contrary, the uricosuric effect of higher BMI was only observed in nondiabetics who had normal or near-normal IR ($p=0.3$ among diabetics, $p<0.0001$ when HOMA-IR<5, $p=0.003$ when HOMA-IR=5-10, $p=0.5$ when HOMA-IR>10). As a result, the UUA supersaturation tended to have weak associations with BMI among diabetics or non-diabetics who had high IR ($p=0.09$ in diabetics and those with HOMA-IR>10, $p= 0.2$ when HOMA-IR< 5, $p=0.9$ when HOMA-IR=5-10). Lastly, BMI did not have significant associations with serum levels of vitamin D and uric acid, plasma parathyroid hormone concentration and measurements of other urinary stone risk factors.

Conclusions: In our cohort of CSFs, higher BMI had strong associations with urinary uric acid and ammonium excretions, and these associations appeared to be modified by the presence of diabetes or IR.

Funding: Clinical Revenue Support

PO0601

Examining the Clinical Effectiveness of Calcium Oxalate Stone Treatments

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Background: Lowering urine calcium oxalate (CaOx) supersaturation (SS) is a primary clinical focus for CaOx kidney stone (KS) prevention and can be achieved by increasing urine volume, or decreasing urine calcium or oxalate excretions. Common clinical strategies to do this include advising patients to increase fluid intake, restrict dietary sodium, restrict dietary oxalate, or prescribing a thiazide-type diuretic. Several of these strategies have been validated in the controlled setting of randomized trials but efficacy in the real-world clinical setting is less clear. We investigated the efficacy of these treatment strategies in a clinical setting, observing whether trial-based findings on CaOx KS treatment hold true.

Methods: We reviewed medical charts for 204 CaOx KS formers with idiopathic hypercalciuria from University of Chicago Kidney Stone Clinic. Patients had three 24-hour urine collections before an initial clinic visit and one follow up 24-hour urine collection. Data collected included initial treatment advice and 24-hour urine composition. We analyzed patient groups based on treatment advice and used descriptive statistics and t-tests to analyze changes in urine variables from pre- to post-advice.

Results: Compared to those who did not receive the advice, advice to increase fluid intake resulted in a larger pre- to post-advice increase in urine volume (0.6 vs. 0.09L/day, $p<0.001$) and decrease in CaOx SS (-3 vs. -1, $p=0.001$). Compared with those who did not receive the advice, advice to restrict dietary sodium alone resulted in a larger pre- to post-advice decrease in urine sodium (-28 vs 13mg/day, $p=0.002$) but there was no change in urine calcium or CaOx SS without concurrent thiazide. Thiazide prescription resulted in a significant pre- to post-advice decrease in urine calcium for patients who also sodium restricted (-99mg/day, $p<0.001$) and those who did not sodium restrict (-58mg/day, $p<0.001$) with a trend towards a larger decrease in those who did both ($p=0.06$). Thiazide prescription resulted in a significant pre- to post-advice decrease in urine CaOx SS for patients who also sodium restricted (-3.3, $p<0.001$) and those who did not (-2, $p<0.001$).

Conclusions: In a real-world clinical setting, advice to increase fluid intake fluid or a thiazide diuretic prescription and reduction in sodium intake lowered CaOx SS and CaOx KS risk in follow up.

Funding: NIDDK Support

PO0602

Effect of Hydroxycitrate (HCA) on Urine Chemistry in Calcium Kidney Stone Formers

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Background: Potassium citrate is a mainstay of treatment to prevent recurrent calcium-containing kidney stones. However, it can increase urine pH and calcium phosphate (CaP) supersaturation (SS). HCA, extracted from *Garcinia cambogia,* is a potent inhibitor of calcium oxalate crystal growth in vitro and should not provide "potential base", as citrate does. Urine excretion of HCA has not been well-studied.

Methods: We enrolled 2 groups: calcium stone formers (SF; n = 9) and non-stone forming (NSF, n = 9) controls (after excluding 2 SF and 2 NSF whose urine creatinine excretion on the 2 collections differed by more than 20%). Mean age 49.3 years. Thiazides and citrate were held for 2 weeks prior to study. Participants recorded a self-selected diet for 2 days and performed 24-hour urine collection on day 2. HCA was purchased online from Amazon.com (Super CitriMax Garcinia Cambogia); 2 caps = 900 mg of HCA. Participants took 900 mg 3 times daily orally for 7 days. Diet from days 1 and 2 was replicated on day 6 and 7 of the HCA arm of the study. 24-hour urine was collected on day 7. Urine was sent to Litholink, Inc. (Chicago, IL) for analysis. Urinary excretion of hydroxycitrate and citrate were measured using LC/MS.

Results: According to label, 6 pills would provide 2700 mg (13.2 mmol) of HCA per day; we measured content as 3198 mg (15.6 mmol). Citrate content is supposed to be 0, but we found 126 mg (0.66 mmol) per day. Both NSF and SF had appearance of HCA in the urine: 1.86 ± 0.80 and 2.07 ± 0.67 mmol/day ($p = 0.56$). Urine chemistry seen in Table 1. In NSF, pH and citrate did not change. In SF, pH increased, citrate did not. K went up in both groups.

Conclusions: Administration of HCA, a potential inhibitor of Ca stone formation, leads to significant urinary HCA excretion. Citrate excretion was not affected. Urine pH increased, suggesting some alkalinizing effect. The difference in NSF and SF may be due to the lower starting pH in SF. The effect of HCA on stone formation remains to be determined.

Funding: Clinical Revenue Support

Urinary chemistry after HCA

	Baseline NSF	HCA NSF	p-value	Baseline SF	HCA SF	p-value
pH	6.67 +/- 0.62	6.63 +/- 0.50	0.87	5.81 +/- 0.57	6.32 +/- 0.57	0.007
Citrate (mg/d)	677 +/- 189	662 +/- 171	0.67	520 +/- 288	697 +/- 330	0.12
K (meq/d)	63 +/- 19	81 +/- 10	0.008	70 +/- 20	100 +/- 27	0.003

PO0603

Factors Reducing Kidney Stone Risk in Patients with Enteric Hyperoxaluria (EH)

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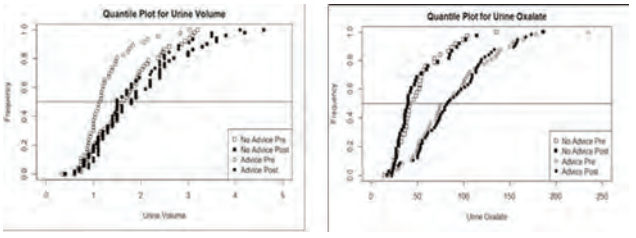
Background: There have been no trials examining efficacy of interventions aimed at decreasing stone risk in patients with EH. We drew upon data for patients in a kidney stone clinic who were treated with consistent methodologies over time. We asked how doctors made therapeutic choices and which therapies were effective at decreasing stone risk.

Methods: We selected 100 patients with EH from the Kidney Stone Evaluation and Treatment Program at the University of Chicago between 1970 and 2018. We analyzed 24-hour urine collections before and after patients' first clinic visit using multivariate linear regression and t-tests to compare effects of fluid intake and oxalate-focused interventions on outcomes.

Results: Patients told to increase fluid intake had low baseline urine volumes; volume increased from 1.3 to 2.0 L/day ($p < 0.001$). In those not told to increase fluid intake urine volume increased from 1.7 to 2.0 L/day ($p = 0.003$). Volume increased more in the advice group ($p = 0.03$). No interventions aimed at reducing oxalate absorption (low fat diet, calcium supplement, increased diet calcium, cholestyramine, and low oxalate diet) had a significant effect on urine oxalate. In those getting advice, urine oxalate was 88 mg/day at baseline and 91 mg/day on follow-up ($p = 0.90$) compared with 50 mg/day at baseline and 51 mg/day on follow-up ($p = 0.77$) in the non-intervention group. In a multivariate model, fluid intake advice was associated with a decrease in calcium oxalate supersaturation (95% CI -4.3 to -0.8), while oxalate-focused interventions were not (95% CI -1.2 to 2.3).

Conclusions: Physicians chose treatments based on baseline urine characteristics. Advice to increase fluid intake is associated with decreased risk of stone formation. Interventions aimed at reducing oxalate absorption are not associated with a decreased risk of stone formation on follow-up. This lack of effect may be the result of patient physiology or lack of compliance with treatments and advice.

Funding: NIDDK Support



Effect of advice to increase fluid intake (left panel) or lower oxalate absorption (right panel) in stone formers with EH.

PO0604

High Oxalate Concentrations Increase Risk for Sudden Cardiac Death in Dialysis Patients

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Background: The clinical significance of accumulating toxic terminal metabolites such as oxalate in kidney failure patients is imperfectly defined. Our study evaluated whether oxalate concentrations are associated with risk of all-cause mortality and cardiovascular events in a cohort of patients with kidney failure requiring chronic dialysis.

Methods: To relate all-cause death and cardiovascular events to serum oxalate, we performed a post-hoc analysis of a randomized controlled trial conducted between March 1998 and October 2002 that comprised 1255 European hemodialysis patients with diabetes who were followed up for a median of 4 years (4D Study). The results obtained via Cox proportional hazards models were confirmed by competing risk regression and restricted cubic spline modeling in the 4D cohort, and validated in a separate cohort of 104 US dialysis patients after a median follow-up of 2.5 years.

Results: A total of 1108 patients with a mean (SD) age of 66.3 (8.3) years had baseline oxalate measurements with a median (IQR) oxalate concentration of 42.4 (30) micromolar. During follow-up, 548 patients died, including 139 (25.4%) patients who died from sudden cardiac death. A total of 413 patients reached the primary composite cardiovascular endpoint, which comprised cardiac death, nonfatal myocardial infarction, and fatal or nonfatal stroke. Participants in the highest oxalate quartile (above 59.7 micromolar) had a 40% increased risk for cardiovascular events (adjusted HR 1.40, 95% CI 1.08-1.81) and a 62% increased risk of sudden cardiac death (adjusted HR 1.62; 95% CI 1.03-2.56), compared to patients in the lowest quartile (below 29.6 micromolar). The associations remained when accounting for competing risks, and with oxalate as a continuous variable, and could be reproduced in a separate cohort of 104 US dialysis patients.

Conclusions: Elevated oxalate concentrations are a novel risk factor for cardiovascular events and sudden cardiac death in dialysis patients. Further studies are warranted to test whether oxalate lowering strategies improve cardiovascular mortality in dialysis patients.

Funding: Other NIH Support - grant number DK33793, Private Foundation Support, Government Support - Non-U.S.

PO0605

Association of Serum Sclerostin Levels with Mortality in Maintenance Hemodialysis Patients: An 8-Year Prospective Cohort Study

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Background: Sclerostin is an osteocyte-derived inhibitor of bone formation and is increased in kidney failure. Sclerostin might be involved in the pathogenesis of vascular calcification, but few studies examined the association between sclerostin and mortality in hemodialysis patients.

Methods: We analyzed a cohort of 654 maintenance hemodialysis patients enrolled in the Tokai Dialysis Prospective Cohort Study. The primary exposure variable was the baseline serum sclerostin level, measured using a sandwich ELISA (Biomedica Medizinprodukte GmbH & Co KG). The primary outcome was 8-year all-cause mortality. Mortality risk was assessed using Cox regression models adjusted for potential confounders.

Results: aseline median (IQR) serum sclerostin level was 163 (120-215) pmol/L. Patients with higher sclerostin levels were likely to be male; have diabetes; have better nutritional status, higher hemoglobin, and lower intact PTH and bone turnover markers. No associations were observed between serum sclerostin and cardiovascular comorbidities. During a median follow-up of 7.6 years (IQR, 4.1-8.0 years), 229 of the 654 participants died. In univariate analysis, serum sclerostin levels were not associated with mortality (HR per doubling, 0.94; 95% CI, 0.76-1.17). This result was unchanged after adjustment for age, sex, dialysis vintage, diabetes, prior cardiovascular disease, body mass index, hemoglobin, albumin, and creatinine (HR per doubling, 1.07; 95% CI, 0.82-1.40).

Conclusions: Serum sclerostin levels were not associated with mortality in maintenance hemodialysis patients. Further research is required to determine the role of sclerostin in vascular calcification and cardiovascular disease in kidney failure.

Funding: Government Support - Non-U.S.

PO0606

Association Between 24-Hour Urine Sodium or Potassium Excretion and Cardiovascular Events in Veterans with Urinary Stone Disease

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Background: Urinary stone disease (USD) is associated with an increased risk of major adverse cardiovascular events. Recent studies that estimated 24-hour urine excretion from spot urine samples have demonstrated that high urine sodium excretion and low urine potassium excretion are independently associated with cardiovascular events. Since patients with USD undergo 24-hour urine testing for stone prevention, direct 24-hour urine testing for sodium and potassium excretion may provide insight into cardiovascular risk for patients with USD.

Methods: We identified 6,401 Veterans with USD and a 24-hour urine sodium measurement and 4,950 Veterans with USD and a 24-hour urine potassium measurement between 2007 and 2015 from national VHA data. We defined the primary outcome as an inpatient or emergency department diagnosis of acute myocardial infarction, unstable angina or stroke or a procedural code for percutaneous coronary intervention or coronary artery bypass graft surgery. We performed Cox proportional hazards regression to identify the risk of a cardiovascular event by level of 24-hour urine sodium and/or potassium excretion.

Results: Among the 6,401 Veterans with USD and a 24-hour urine sodium measurement, 715 (11.2%) had a major cardiovascular event. Veterans with a 24-hour urine sodium in the lowest 10th percentile (<113 mEq/day) had a higher risk of a cardiovascular event compared to those with a 24-hour urine sodium between the 10th and 90th percentile (HR 1.55, CI 1.25-1.92). We found no significant association between 24-hour urine potassium excretion and cardiovascular events.

Conclusions: Patients with lower 24-hour urine sodium excretion have a higher risk for cardiovascular events. Patients with higher 24-hour urine sodium excretion or lower 24-hour urine potassium excretion do not have a higher risk of cardiovascular events. These findings differ prior studies that used spot urine samples to identify patients who are at risk for cardiovascular disease, suggesting that direct measurement of 24-hour urine sodium or potassium excretion more accurately identifies patients who are at risk for cardiovascular disease.

PO0607

Indoxyl and Cresyl Sulfate Are Respectively Linked to Phosphocalcic Metabolism Abnormalities and to Cardiovascular Morbidity in Hemodialysed Patients

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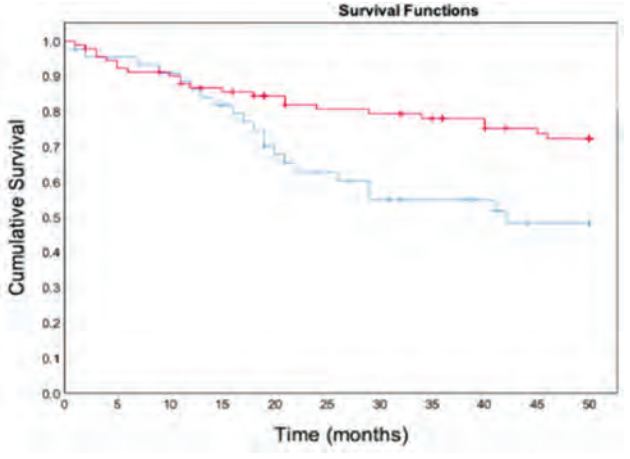
Background: Indoxyl sulfate (IS) and Cresyl sulfate (CS) are uremic toxins generated by the intestinal amino acid catabolism. Blood levels of these toxins increase in patients with CKD and are linked to cardiovascular events.

Methods: Therefore, we studied the relationship between serum levels of free IS and CS and divalent ion metabolism variables and cardiovascular morbidity (stroke, heart failure, angor and myocardial infarction) in 139 hemodialysis patients (age 68±13 yrs, weight 65±13 kg, dialysis vintage 69±71 months). We divided patients according to tertiles of free serum IS and CS.

Results: Patients in the highest tertile of serum free IS showed shorter dialysis vintage and higher body weight gain between dialysis sessions than patients in the other two tertiles. Patients in the highest tertile of IS showed lower body weight and serum concentrations of alkaline phosphatase, 1, 25$(OH)_2$D and PTH compared to the lowest tertile. No relationships of serum free CS concentrations with phosphate and calcium metabolism variables were observed. Kaplan-Meier survival analysis shows an increased cardiovascular morbidity in patients in the CS highest tertile (blue line in the figure) compared to those in the lowest and middle tertiles taken together (red line; p=0.01). This association was not found considering IS tertiles.

Conclusions: Our findings suggest that serum IS could predispose to adynamic bone disease, while CS may have higher cardiovascular toxicity.

	Serum IS lower tertile	Serum IS middle tertile	Serum IS highest tertile
N (M/F)	45 (12/33)	48 (13/35)	46 (19/27)
Free serum IS (µg/ml)	32±14	49±17	56±18
Free serum CS (µg/ml)	2.1±1.9	3.5±2.6	3.6±5.1
Dialysis vintage (months)	74±72	87±81	45±52
Interdialytic body weight gain (kg)	1,2±0,75	1.5±0.91	1.9±1.04
Body weight (kg)	69±12	64±15	62±12
1,25-vit D (ng/ml)	11,7±9,4	10,9±7,1	7,6±4,4
PTH (pg/ml)	106±68	83±89	65±57
Alkaline Phosphatase (U/l)	132±77	116±69	102±42



PO0608

Expression Pattern of the Runt-Related Transcription Factor (RUNX) Family and the Role of RUNX1 During Kidney Development

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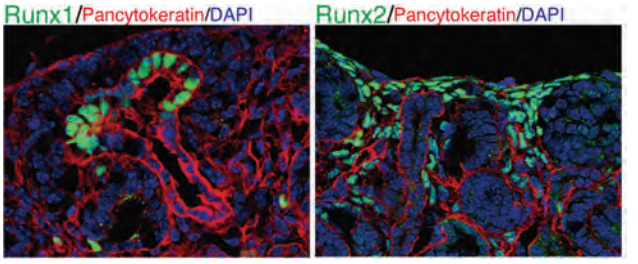
Background: RUNX family plays critical roles during the developmental process in multiple organs. The mammalian RUNX family consist of RUNX1, RUNX2 and RUNX3, each of them has distinct tissue-specific expression and function but also has a redundancy. Here, we examined the distribution of RUNX family in the kidney. We also assessed the involvement of RUNX1 during renal development in the conditional knockout mice using Cre-LoxP strategy.

Methods: We examined the temporal and spatial expression pattern of RUNX family in the kidney by immunostaining and qPCR analysis. In order to analyze the role of RUNX1 in kidney development, we utilized HoxB7-Cre mice and R26CreER^{T2} mice. To induce activation of CreER^{T2}, we administered tamoxifen to pregnant mothers at E12.5 and analyzed the embryos at E16.5. Long-term observation was impossible due to the severe anemia caused by hematological toxicity of the systemic activation of CreER^{T2}.

Results: In the neonatal kidney, RUNX1 was strongly expressed in the uretic bud (UB) tip and also weakly expressed in the distal portion of renal vesicle, comma body, and S shaped body. RUNX1 was also expressed in the pelvic urothelium and immune cells. RUNX1 expression in the UB tips was detectable from E13.5 and disappeared by P7. In contrast, RUNX2 was restricted in the stroma firstly detected from E15.5 and was strongly expressed in both cortical and medullary fibroblasts at P2. RUNX3 was only expressed in the immune cells. There was no difference in the number of UB branching or Six2$^+$ nephron progenitor cells per UB tip in Runx1$^{fl/fl}$: HoxB7-Cre mice, which lack Runx1 expression in UB. Further analysis utilizing Runx1$^{fl/fl}$: R26CreER^{T2} mice showed no obvious abnormality. In addition, neither RUNX2 nor RUNX3 compensated the loss of RUNX1 in deficient embryos.

Conclusions: We precisely analyzed the unique expression pattern of RUNX family during kidney development and identified RUNX1 as the marker of UB tip and RUNX2 as the marker of fibroblasts in the embryonic kidneys, although RUNX1 was dispensable for nephrogenesis.



Expression of RUNX1 and RUNX2 in the developing kidney

PO0609

Rac1 Promotes Kidney Collecting Duct Integrity by Limiting Actomyosin Activity

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Background: A polarized collecting duct (CD) is critical for an intact kidney. The branched kidney collecting system is formed from the ureteric bud (UB). This requires a dynamic actin cytoskeleton and balanced actomyosin activity allowing normal tissue polarization, morphology and function. The small Rho GTPase, Rac1, is a key molecular switch that controls actin polymerization and branching. We investigated the role of Rac1 in kidney collecting system morphogenesis by selectively deleting it in mice at the initiation of UB development.

Methods: We crossed Rac1$^{flox/flox\ (f/f)}$ with Hoxb7-cre deleting Rac1 in the ureteric bud starting at E10.5 and followed kidney development throughout adulthood. We also analyzed the role of Rac1 in regulating signaling, migration, spreading, tubulogenesis and polarity by utilizing primary inner medullary collecting duct Rac1 null cells.

Results: The kidneys of Hoxb7:Rac1$^{f/f}$ exhibited only a mild branching morphogenesis defect as Rac1 is expressed after most UB branching is complete. However, with aging the CD developed a disruption of epithelial integrity, resulting in fibrosis, and a urine concentration defect. Despite intact integrin signaling, Rac1-null CD cells had profound spreading, adhesion and polarity abnormalities that were independent of the major downstream Rac1 effector, Pak1. Instead, Rac1 null cells demonstrated defective WAVE2-Arp2/3 dependent actin cytoskeletal branching which resulted in excessive actomyosin activity and severe abnormalities in epithelial cell shape. The functional and morphological defects caused by Rac1 deficiency were reversed by direct myosin II inhibition using low dose blebbistatin.

Conclusions: Unexpectedly, Rac1 does not play a major role in early branching morphogenesis of the renal collecting system, however it is required for adult CD integrity. Mechanistically, Rac1 controls Arp2/3-dependent cytoskeletal branching which limits actomyosin hyperactivity allowing normal epithelial polarization, function and morphology.

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

PO0610

Stromal Transcription Factor 21 Is Critical for Development of the Interstitium and Nephron Progenitor Cells via Interaction with Wnt/β-Catenin Signaling

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Background: Reciprocal signaling between the collecting duct progenitors and the nephron progenitor cells (NPC) is the primary driver for kidney development. In addition, recent studies implicate input from the interstitial progenitor cells in multiple aspects of kidney development. However, the mode of insterstitial cell action on kidney development is poorly understood. We previously showed that the Transcription factor 21 (Tcf21) in interstitial progenitors is required for normal ureteric bud branching. Here, we examined roles for Tcf21 in renal interstitial progenitors in mediating stromal functions during kidney development.

Methods: Stromal Tcf21 was evaluated with the Foxd1Cre;Tcf21$^{f/f\ or\ +/+}$ mouse kidney by standard immunohistological analyses. MK3 and M15 metanephric mesenchymal cell lines were used for analyses of b-catenin signaling.

Results: In the Foxd1Cre;Tcf21$^{f/f}$ kidney, absence of Tcf21 from Foxd1+ stromal progenitors caused decrease in stromal cell proliferation, leading to marked reduction of the medullary stromal space. Lack of Tcf21 in FoxD1 stromal cells also led to defective differentiation to perivascular cells and mesangial cells. Non-autonomously, absence of stromal Tcf21 led to expansion of the Six2+ NPC, suggestive of delayed NPC differentiation, and to poor development of the Loop of Henle and the collecting ducts. We next examined whether Tcf21 modulates Wnt/ β-catenin signaling. Significantly less β-catenin was observed in stroma of the Foxd1Cre;Tcf21f/f mouse compared to their wild-type littermates. In MK3 and M15 cells, stabilization of β-catenin by Lithium Chloride upregulated Tcf21 expression, while over-expression of Tcf21 enhanced expression of Wnt-target genes upon β-catenin stabilization. Further, Tcf21 enhanced TCF/LEF reporter

activity upon β-catenin stabilization, while mutated-Tcf21 failed to increase TCF/LEF activity. Immunoprecipitation assay showed that Tcf21 is bound to β-catenin at basal and activated states in-vitro.

Conclusions: Together, our findings suggest that Stromal-Tcf21 is essential for medullary stroma development, by enhancing Wnt/β-catenin signaling to promote stromal cell proliferation and differentiation. Stromal Tcf21 is also required for the development of the adjacent nephron epithelia.

Funding: NIDDK Support

PO0611

ZEB2 Is Essential for FOXD1+ Kidney Stromal Progenitor Cell Differentiation During Kidney Development

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Background: FOXD1$^+$ derived stromal cells are essential for normal kidney development. They give rise to pericytes and resident fibroblasts that support the kidney vasculature and also cooperate with cells that give rise to the developing nephron. However, FOXD1$^+$ derived stromal progenitors may also serve as precursors of myofibroblasts in kidney fibrosis. The signals that regulate the differentiation of FOXD1$^+$ stromal progenitors are not well understood. Given that zinc finger E-box-binding homeobox2 (ZEB2), a SMAD-interacting transcription factor, is expressed in developing kidney stromal cells, we examined the role of ZEB2 in kidney stromal cell differentiation in the developing mouse kidney.

Methods: We generated *Zeb2* stromal-specific conditional knockout mice (cKO) by crossing *Zeb2* flox mice with *Foxd1Cre* mice and analyzed the phenotype of homozygous *Zeb2*$^{flox/flox}$;*Foxd1Cre*$^+$ mice (*Zeb2* cKO) and their wild-type littermate controls. Kidney histology, renal function, and lifespan were studied in *Zeb2* cKO mice. Cell fate mapping was performed using tdTomato mice. Protein expression analyses were performed by immunostaining and Western blotting of several markers for stromal progenitors, collagen, pericytes, fibroblasts, myofibroblasts, endothelial cells, renal tubules, and SMAD proteins in *Zeb2* cKO and wild-type controls. Nephrogenesis was analyzed by immunostaining using nephron morphogenesis markers SIX2, WT1, nephrin, and Jagged1.

Results: Deletion of mouse *Zeb2* in FOXD1$^+$ stromal progenitors produced dysplastic and hypovascular kidneys. The *Zeb2* deficient FOXD1$^+$ stromal progenitors in these kidneys took on a myofibroblast cell fate that led to kidney fibrosis and kidney failure. Cell marker studies confirmed that these myofibroblasts expressed pericyte and resident fibroblast markers including PDGFRβ, CSPG4, Desmin, GLI1, and NT5E. Notably, increased interstitial collagen deposition associated with loss of *Zeb2* in FOXD1$^+$ stromal progenitors was accompanied by increased expression of activated SMAD1/5/8, SMAD2/3, and SMAD4.

Conclusions: Our study identifies a key role of ZEB2 in maintaining the cell fate of FOXD1$^+$ stromal progenitors during kidney development and loss of ZEB2 leads to differentiation of FOXD1$^+$ stromal progenitors into myofibroblasts and kidney fibrosis.

Funding: NIDDK Support

PO0612

Uncovering the Podocyte Foot Process Proteome

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Background: Podocyte foot process integrity is vital for kidney function and health. Disruptions to podocyte architecture, or effacement, is one of the most common observations in kidney disease. However, the full complement of players responsible for maintaining podocyte foot process integrity is still unknown. The membranous cellular environment and specialized junctional complexes have previously hindered their isolation and testing.

Methods: The discovery of a proximity-dependent biotin identification (BioID) moiety that utilizes a promiscuous biotin ligase has opened new avenues to generate spatially localized proteomes. Podocin (*Nphs2*) localizes to the slit diaphragm and is one of the most abundant foot process proteins. Therefore, we developed a novel genetic mouse model via knock in of the BioID moiety to the *Nphs2* locus (*podocin-BioID*) to identify the in vivo proteome of the podocyte foot process localized within the vicinity of podocin.

Results: We validated our transgenic *podocin-BioID* model by assessing correct expression and localization of the fusion protein via western blot, immunofluorescence (IF), and electron microscopy (EM). Injection of *podocin-BioID* mice with excess biotin leads to the significant biotinylation of proteins within podocytes. We isolated the biotinylated proteins and performed mass spectrometry analyses (MS) to uncover novel proteins localized to the foot process. In silico analysis of the top proteins uncovered from MS identified 'cell junctions', 'adherence', and 'adhesion' as the top gene ontogeny terms. One novel candidate we uncovered is the Immunoglobulin-like domain-containing receptor 2 (Ildr2) protein. We confirmed Ildr2 is expressed in mouse podocytes by immunofluorescence and utilized publicly available single cell RNA-seq data to confirm its restricted, conserved expression in both mouse and human podocytes.

Conclusions: Current efforts are aimed at knocking out Ildr2 specifically in the podocytes of mice and zebrafish to assess the functional significance of Ildr2 in podocyte foot process integrity. These biorthogonal assays have allowed us to identify and interrogate novel components of the foot process proteome leading to a new set of potential players and biomarkers for kidney disease.

Funding: NIDDK Support, Other NIH Support - NIAMS:5F32AR073649-05 to GFG, Private Foundation Support

PO0613

Autophagy Deficiency in Urothelial Cells Activates Progressive NF-κB Signaling

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Background: The urothelium is a specialized epithelium that functions as a urine permeability barrier along the upper urinary tract and bladder. We have shown that conditional knockout (CKO) of exocyst gene *Exoc5* in ureteric bud cells disrupts the urothelial stratification process during ureter development, which subsequently triggers cell death and ureter obstructions. This *Exoc5* CKO mouse is a novel model of congenital obstructive uropathy (COU) and may be useful for elucidating the underlying pathological mechanisms of COU. Here, we investigated the role of exocyst-mediated autophagy in the stress responses of urothelial cells.

Methods: Cre/loxP *Exoc5* urothelial ablation was accomplished with *Ksp-Cre* and *Upk3-Cre*^{ERT2} mouse driver strains for both embryonic and adult urothelial knockout. An immortalized human urothelial cell line (SV-HUC-1) was used for cellular assays. Autophagic flux and cell stress signaling were measured by immunofluorescence and western blotting.

Results: We report that urothelial *Exoc5* ablation disrupted autophagy and promoted non-canonical NF-κB signaling during ureter development in *Ksp-Cre* mice. Adult urothelial Exoc5-knockout mice also showed disrupted autophagy, with an accumulation of lysosomes in the bladder urothelium. In SV-HUC-1 cells, EXOC4 co-immunoprecipitated with ATG7, and silencing of *Exoc5* led to an accumulation of LC3II/I and p62, indicating poor autophagic flux. Direct inhibition of autophagy with BafA1 or VPS34i induced an early canonical RelA NF-κB response followed by a delayed p52 non-canonical NF-κB response and eventual cell death.

Conclusions: Here, we report that *Exoc5* contributes to autophagy in urothelial cells, and impaired autophagy triggers progressive NF-κB signaling. The initial stress response activates canonical RelA NF-κB signaling, which is associated with survival mechanisms and inflammation. However, when the injury is not resolved, a delayed p52 non-canonical NF-κB signaling follows. Under these conditions, non-canonical NF-κB mediators TWEAK and its receptor Fn14 were highly responsive. Further investigation of this progressive NF-κB signaling series in urothelial cells may be critical for understanding the etiology of COU and any lingering chronic response after COU is resolved.

Funding: NIDDK Support

PO0614

Mechanisms of VEGFR3 Signaling in Glomerular Development

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Background: Dysregulation of Vascular Endothelial Growth Factor Receptor 3 (VEGFR3), known primarily for its role in lymphangiogenesis, is causally linked to the development of kidney diseases, including renal fibrosis and cystogenesis. However, the mechanisms of VEGFR3 signaling in kidney development, how it influences kidney disease, and the vascular beds involved remains uncertain.

Methods: We performed a detailed expression profile of VEGFR3 in the developing mouse kidney from embryonic age (E)13.5 through 3 months. We generated a new transgenic mouse model to investigate the role of *Vegfr3* in the kidney vasculature (*Vegfr3*^{Flx}). Conditional and cell-specific excision of the floxed allele was performed using the Rosa-rtTA-TetOCre, Cdh5-Cre/ERT2, and Prox1-Cre/ERT2 driver strains to evaluate global, pan-endothelial, and lymphatic endothelial cell deletion of Vegfr3 respectively. Additionally, breeding of mice carrying podocyte-specific deletion and overexpression of the VEGFR3 ligand, VEGF-C, are underway to define ligand-dependent and independent function of VEGFR3 in the glomerulus. Mice underwent a detailed phenotypic evaluation and kidney sections were processed for histology.

Results: VEGFR3 undergoes dynamic expression through development in glomerular endothelial cells (GECs), beginning with high expression in the angiogenic sprouts which invade the capillary cleft of the developing nephron. Constitutive deletion of *Vegfr3* during mid-embryonic development resulted in reduced viability, lymphatic vascular defects, a reduction in kidney size, and a reduction in average cross-sectional glomerular count on serial sectioning (mean difference -3.767 ± 1.238, $p < 0.005$). Additionally, deletion of *Vegfr3* at embryonic day 11.5 demonstrated marked disruption of glomerular development with cavernous capillary malformations. Immunofluorescence and electron microscopy revealed glomerular structures surrounded by simplified podocytes, abnormal attachment of endothelial cells with reduced fenestrations, and poor formation of the glomerular basement membrane. VEGF-C mutant mice will be characterized once available.

Conclusions: VEGFR3 is expressed in GECs and is integral to normal glomerular development. The mechanisms of VEGFR3 signaling in GEC crosstalk with podocytes will be essential to define prior to the development of therapeutics targeting this pathway.

Funding: NIDDK Support, Private Foundation Support

PO0615

The ATP-Binding Cassette Protein ABCG2 Marks Kidney Resident Endothelial Colony-Forming Cell Activity in Multiple Endothelial Clusters Identified by Single-Cell RNA Sequencing

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Background: Side-population cells (SP) were originally identified in hematopoietic stem cells based on their ability to efflux the DNA binding dye Hoechst 33342, an activity thought to be mediated by members of the ATP-binding cassette protein family such as ABCG2. We hypothesized that ABCG2-expressing endothelial cells (EC) are enriched in colony forming cell (ECFC) activity, and may contribute to vascular homeostasis in kidney.

Methods: The fate of ABCG2 expressing EC was investigated using adult Abcg2-CreERT X Td-tomato Rosa$^{fl/fl}$ reporter mice (ABCG2-TT). Transgene with tamoxifen (TMX; 50 μg/g, 1X) followed by FACS analysis for TdTomato in EC. For single-cell RNA sequencing, mouse kidney ECs were isolated following digestion with collagenase, and CD45 depleted/CD31+(positive) magnetic selection. Isolated single cells were sequenced using the 10X platform. Data were analyzed with Seurat.

Results: 24 hours following TMX, 2.9% of kidney EC (CD31+/CD45-) expressed TdTomato. The percentage of Td-Tomato+ EC progressively increased to 5.3% (p=0.4) by 1 week and 15.4% (p<0.0001) by 6 weeks post injection. To determine the EC subtypes expressing ABCG2-associated progenitor activity, scRNAseq was conducted on isolated kidney endothelial cells of ABCG2-TT mice 24 hours following TMX injection. A total of 10 endothelial clusters were identified. Analysis of top expressing genes suggested these clusters correspond to different kidney EC populations such as peritubular capillaries, venules, arteries, arterioles, AVR, DVR and lymphatics. The expression of the reporter was based on identification of WPRE response element expressed Rosa mice following Cre activation. Interestingly, no single discrete cluster of ECs expressing WPRE were identified. Rather, a variable percentage (4.3 to 38.7%) of WPRE expressing cells were identified in each cluster.

Conclusions: Taken together these data suggest that ABCG2+ expressing cells contribute to vascular maintenance in adult kidney and that such cells are found in most kidney EC populations. In addition, reporter expressing EC cells do not represent a transcriptionally distinct subset of EC but are transcriptionally similar to the surrounding tissue endothelial cell subsets.

Funding: NIDDK Support

PO0616

Stromal-Derived Ntn1 Influences Renal Vascular Formation and Kidney Development

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Background: Renal vascular networks are critical to maintaining fluid homeostasis. Despite their important roles, formation and patterning of the renal endothelium and its effect on kidney development are poorly understood. Netrin-1 (*Ntn1*) is a secreted ligand critical for vascular guidance during embryogenesis and is highly expressed by renal stromal progenitors (SP). Therefore, netrin-1 is an ideal candidate for regulating endothelial network formation. In turn, the endothelium releases angiocrine factors that may influence the formation of surrounding tissues.

Methods: To investigate the role of netrin signaling during kidney development, we deleted *Ntn1* from SPs and interrogated the embryonic phenotype using immunofluorescence, high-resolution and 3D microscopy, and cellular analyses.

Results: Conditional knock-out (cKO) of *Ntn1* results in hypoplastic kidneys, extended nephrogenesis, and arterial mis-patterning. Using 3D light-sheet microscopy, we quantitated arterial tree defects. At p0 we found significant reductions in branch number (24%), vessel length (20%), end points (27%) and total area (18%) in our *Ntn1* cKOs. Vascular defects persist at 7 months of age but result in significantly increased arterial metrics across most parameters including branch number (17%), vessel length (23%), end points (33%), total area (25%) and branch level (26%). Bulk RNA-seq of E15.5 *Ntn1* cKO kidneys was performed to gain insights into the resulting phenotypes. We found changes in Notch and Bmp pathway components suggesting altered signaling may contribute to the observed defects. Additionally, analysis of scRNA-seq data has identified *Igf1* and *Tgfb1* as potential renal angiocrine factors and we are currently investigating their role in kidney development.

Conclusions: Taken together, our studies provide novel insights into the establishment of vascular networks in the developing kidney, which will help inform strategies to engineer kidneys *de novo*, where establishing proper vascular networks will be critical.

Funding: NIDDK Support, Other NIH Support - 5T32HL069768

PO0617

Three-Dimensional Visualization of Neonatal Glomerulogenesis in the PodoTRAP Model by Simplified Tissue-Clearing Approach

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Background: The process of glomerulogenesis is complex and the dynamics and spatio-temporal coordination involved in the formation of the glomerular architecture are still poorly understood. Conventional histopathological methods and 2D-microscopy techniques allow only a limited visualization and reconstruction of processes in the developing kidney which can only be fully appreciated in a 3-dimensional context.

Methods: To specifically study the organisation, maturation and arrangement of podocytes during glomerulogenesis, we used neonatal kidneys from Podo^{TRAP} transgenic animals (P0, P3, P7) in combination with a modified ethyl cinnamate (ECi)-based clearing approach for immunostaining and subsequent 2-photon microscopy. We used IMARIS for comprehensive morphometric analysis and 3D-reconstruction of podocytes and glomeruli during postnatal kidney development.

Results: Tissue clearing is a technique to render biological samples transparent, thereby allowing for high resolution 3D-microscopic imaging of structures deep within the tissue without the need for conventional tissue-sectioning. We used this technique for 3D-imaging, reconstruction and analysis of different glomerular developmental stages (renal vesicles, S-phase, capillary loop, maturing glomerulus) in transparent kidneys of P0, P3, P7 as well as adult Podo^{TRAP} mice. Eci-clearing followed by 2-photon microscopy achieved significantly higher imaging depth compared to uncleared kidneys (~1600μm vs. ~150μm). GFP^{+} podocytes in ECi-treated Podo^{TRAP} kidneys were readily identified due to robust cellular epifluorescence, with GFP signal intensities increasing as podocyte maturation progressed. Amongst others, we conducted comprehensive quantification of glomerular volume increases during postnatal kidney development.

Conclusions: The combination of Eci-clearing and 2-photon microscopy in the Podo^{TRAP} model is well suited for high-resolution 3D-imaging of renal tissue including detailed morphometry of maturing glomeruli in whole neonatal mouse kidneys. Moreover, this approach could also be useful for holistic histopathological analyses and assessments in various glomerular disease models including FSGS.

PO0618

OSR1 Couples Intermediate Mesoderm Cell Fate with Temporal Dynamics of Vessel Progenitor Cell Differentiation

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Background: Transcriptional regulatory networks refine gene expression boundaries throughout embryonic development to define the precise dimensions of organ progenitor territories. Kidney progenitors originate within the intermediate mesoderm (IM), but the pathways that establish the boundary between the IM and its neighboring vessel progenitors are poorly understood.

Methods: We employ a combination of loss-of-function and gain-of-function genetics, RNA in situ hybridization, immunohistochemisty, and transgensis in the zebrafish model system.

Results: Here, we delineate new roles for the zinc finger transcription factor Osr1 in kidney and vessel progenitor development. Zebrafish *osr1* mutants display decreased IM formation and premature emergence of neighboring lateral vessel progenitors (LVPs). These phenotypes contrast with the increased IM and absent LVPs observed with loss of the bHLH transcription factor Hand2, and loss of *hand2* partially suppresses the *osr1* mutant phenotypes. *hand2* and *osr1* are both expressed in the posterior lateral mesoderm, but *osr1* expression decreases dramatically prior to LVP emergence. Induction of *osr1* expression after gastrulation is sufficient for inhibiting LVP development and rescuing IM and pronephron formation.

Conclusions: Together, our data demonstrate that *osr1* modulates both the extent of IM formation and the temporal dynamics of LVP development, suggesting that a balance between levels of *osr1* and *hand2* expression is essential to demarcate the dimensions of kidney and vessel progenitor territories.

Funding: NIDDK Support, Private Foundation Support

PO0619

Membrane Phosphoinositides and Renal Epithelial Cell Polarity Determination in the Xenopus Pronephros In Vivo

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Background: Though only minor components of cell membranes, phosphoinositide lipids (PIs) participate in numerous signaling processes and in membrane identity determination. Many studies of cultured MDCK cells found that PIs are distributed with polarity among plasma membrane (PM) domains, and that their polarized distributions are required for the delivery of distinct populations of apical and basolateral membrane proteins. The extent to which PIs drive these processes in actual renal epithelial cells *in vivo* has never been examined. We investigate the distribution of PIs *in vivo* in the pronephros of Xenopus Tropicalis tadpoles using MCherry-tagged Pleckstrin Homology (PH) domains that selectively bind different PIs (PH-AKT, PH-PLCD1, which bind to (PI(3,4,5,)P3 and PI(4,5)P2 respectively) with the goal of assessing whether and how PI localizations affect cell polarity determination and the trafficking of proteins to their sites of ultimate functional residence in renal epithelial cells *in situ*.

Methods: mRNA encoding MCherry-PH-AKT or MCherry-PH-PLCD1 was injected into fertilized oocytes and their distributions were assessed in the developed pronephros at stage NF45 via fluorescence microscopy. Knockdown (KD) of PTEN, a lipid 3′ phosphatase that regulates membrane PI composition, was achieved via injection of targeted morpholinos and confirmed by western blotting. The effects of PTEN KD on MCherry-PH-AKT distribution were assessed by fluorescence microscopy.

Results: In MDCK cells PH-AKT and PH-PLCD1 localize to the basolateral and apical PMs, respectively. Their distributions are quite different in the pronephros, with both sensors showing a markedly apical signal in the proximal portion of the tubule and diffuse cytosolic staining in the distal part. PH-AKT staining dramatically re-distributes to the lateral domain of renal cells upon PTEN KD but this treatment does not alter the localization of protein markers of epithelial PM polarity.

Conclusions: These studies constitute the first effort to assess the role of PIs in establishing PM polarity in renal epithelial cells *in vivo*. Our data reveal discrepancies with previous reports from *in vitro* systems. These findings highlight the need to explore the processes that produce renal epithelial cell polarity *in vivo* and in the context of intact renal tubules.

Funding: NIDDK Support

PO0620

Autonomous Calcium Signaling in Human and Zebrafish Podocytes Controls Kidney Filtration Barrier Morphogenesis

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Background: Mutations in nephrotic syndrome genes that lead to elevated cytoplasmic calcium in podocytes cause disruption of filtration barrier function and nephrotic syndrome. Whether calcium signaling plays a role in the initial formation of the filtration barrier is not known. Here we show that calcium signaling is active during podocyte differentiation, occurs independently of neighboring cell types, and is required for foot process and slit diaphragm formation.

Methods: The calcium biosensor GCaMP6s was expressed in zebrafish podocytes during larval development using a podocin:Gal4 x UAS:GCAMPs transgene cross to evaluate calcium signaling during development. Calcium signals in differentiating podocytes in human kidney organoids were detected using Fluo-4. Filtration barrier formation in zebrafish was evaluated by electron microscopy.

Results: Immature zebrafish podocytes generated calcium transients that correlated with interactions with forming glomerular capillaries. Calcium transients persisted until 4 dpf and were absent after glomerular barrier formation was complete. Similar calcium transients were detected in maturing human organoid glomeruli suggesting a conserved mechanism. In both models, inhibitors of SERCA or IP3 receptor calcium-release channels blocked calcium transients in podocytes, while lanthanum was ineffective, indicating the source of calcium is podocyte intracellular stores. Calcium transients were not affected by deficiencies in heartbeat, endothelium or endoderm, and persisted in isolated glomeruli, suggesting that they were generated cell autonomously. Inhibition of phospholipase C gamma 1 (PLCg1), but not Nephrin or phospholipase C epsilon1 (PLCe1), expression lead to a significant decrease in calcium activity. Finally, blocking calcium release impacted glomerular shape and podocyte foot process formation, supporting the critical role of calcium signaling in glomerular morphogenesis.

Conclusions: Our results establish cell autonomous calcium signaling as a prominent and conserved feature of podocyte differentiation and demonstrate the requirement for intracellular calcium elevations for podocyte foot process formation.

Funding: NIDDK Support

PO0621

Zebrafish Kidney Regeneration as a Model for Engraftment of Stem Cell-Derived Kidney Replacement Tissue

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Background: *In vivo* engraftment of iPS cell derived mammalian kidney organoids is a major goal for kidney regenerative medicine. A major challenge in engraftment is in establishing patent tubule conduits between organoid graft and host tubules to allow fluid filtration and excretion. Stem cell-derived nephrons are continuously made during zebrafish kidney growth and regeneration that “plumb into” the pre-existing collecting system, making the zebrafish a viable model of kidney tissue engraftment. Using the zebrafish adult kidney to model synchronous fusion, we investigated the role of growth factor signaling pathways in this process.

Methods: Tg(Lhx1a:eGFP) expression labels distal invading ends of new nephrons. Tg(TCFLef-miniP:dGFP) Wnt reporter expression was used to reveal high Wnt signaling domains in new nephrons. The Wnt inhibitors IWR1 and IWP2 were applied to injured adult zebrafish to test requirements for Wnt signaling. Homozygous adult Crispr/Cas9 indel mutants in *fzd9b* and *wnt9b* were generated.

Results: We find that new nephron aggregates are patterned by canonical Wnt signaling. Cells with high canonical Wnt signaling form a single cell thick dome within cell aggregates and polarize to form rosettes with an apical constriction predicting the site of future tubule lumen. *Tg(Lhx1a:eGFP)* marks cells at the distal end of the new nephron which extend invasive processes or invadopodia into the underlying tubular epithelium. Short term inhibition of Wnt signaling using IWR1 and IWP2 inhibits invadopodia formation and blocks tubule interconnection events. Adult homozygous *fzd9b* mutants exhibit ectopic distal cell proliferation and a failure of convergent extension in new nephrons after injury while *wnt9b* mutants produce fewer new nephrogenic aggregates. A quantitative RT-PCR screen of candidate genes highly upregulated in both zebrafish nephron progenitors after injury and human cancer metastasis implicates invadopodia markers *mmp14a/b, cortactin, tks5*, as well as *cdh11, c-jun*, and *id-1* in the invasion and interconnection process.

Conclusions: Wnt signaling is required for kidney tubule invasion and engraftment and correlates with expression of multiple genes associated with metastatic cell invasiveness. Manipulation of Wnt signaling is an opportunity to engineer kidney tubule interconnections.

Funding: NIDDK Support, Private Foundation Support

PO0622

Evidence for Convergence of NF-κB and Growth Hormone (GH) Signaling on Stem Cell Activation in the Adult Zebrafish Kidney

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Background: Adult progenitor cells in the mesonephric kidneys are required both during neo-nephrogenesis replacing injured tubules but also during overall growth. Single-cell RNA transcriptomes of adult kidney progenitor cells point to at least two receptor systems that may initiate stem cell-based nephrogenesis: growth hormone (GH) and interleukin receptors. Here we present evidence for both injury (NF-κB activation) and growth-related pathways (GH) in stimulating stem cell-based nephrogenesis.

Methods: Adult zebrafish kidneys were injured by gentamicin *i.p.* injection. NF-κB signaling was determined four days post injury (dpi) by NF-κB:GFP detection of the NF-kB reporter line *Tg(NF-κB:EGFP)* and NF-kB-associated gene expression using qRTPCR. Requirement of NF-κB signaling during regeneration was evaluated by pharmacological NF-κB inhibition. GH signaling was evaluated after either GH or gentamicin injection by quantification of progenitor marker lhx1a:GFP in *Tg(lhx1a:GFP)* and stem cell marker expression by qRTPCR. Inhibitors of GH downstream signaling were used to determine GH signaling impact after kidney injury. Bulk RNAseq from positive selected GFP^+ and $mcherry^+$ single cells by FACS was performed from kidneys 7 dpi by gentamicin injection using *Tg(lhx1a:EGFP;cdh17:mCherry)* fish.

Results: Gentamicin-induced kidney injury leads to an increase in tubular NF-κB nuclear translocation at 4 dpi and is associated with an upregulation of NF-κB downstream target gene expression detected by qRTPCR. Gentamicin also causes GH receptors mRNA upregulation at 7 dpi along with the kidney progenitor markers *osr1* and *eya4*. GH injection induced the formation of new nephrons as marked by *Tg(lhx1a:GFP)* expression in new nephron aggregates.

Conclusions: Multiple pathways may converge on adult kidney stem cells to activate new nephron formation. Growth and growth hormone may induce new nephron formation in response to increased body mass and need for osmoregulation. Kidney injury and nephron replacement correlate with nuclear translocation of NF-κB in injured tubules, suggesting the possibility of cytokine-mediated nephrogenesis in response to injury.

Funding: NIDDK Support, Other NIH Support - Maine INBRE grant (GM103423), Government Support - Non-U.S.

PO0623

Dual Tubular Par1a/b cKO Is Protective Against Renal Fibrosis

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Background: Partitioning defective Par1a/b proteins are highly homologous serine threonine kinases and contribute to kidney development. Tubular Par1a/b expression increases following folic acid and unilateral ureteral obstruction (UUO). Loss of Par1a/b expression during development impairs Notch signaling pathway expression. Notch signaling activation contributes to renal fibrosis. We hypothesized that Par1a/b expression is maladaptive following injury and promotes renal fibrosis.

Methods: Using publically available single cell RNA sequencing data, we examined the cell types where Par1a (Mark3) and Par1b (Mark2) were expressed following UUO. Localization was confirmed using immuno-fluorescence with antibodies specific for Par1a and 1b. Conditional Par1a and 1b *flox* mice were generated using CRISPR/Cas9 gene editing. Dual tubular conditional Par1a/b knockout (cKO) mice (Pax8-rtTA:tet-O-Cre:Mark2flox:flox:Mark3flox/flox) mice were generated. Deletion of Par1a (*Mark3*) and Par1b (*Mark2*) was confirmed following doxycycline induction. UUO was performed in adult (10 week old) male tubular Par1a/b cKO mice and controls; phenotype was examined at 7 days. Tubular Par1a/b deletion was induced by feeding mice doxycycline in chow starting 7 days prior to UUO. Controls were uninduced (-dox) transgenic littermates and doxycycline treated *Mark2flox/flox:Mark3flox/flox* mice. 6-8 mice/group were studied. To detect renal fibrosis, Picro-Sirius Red staining of collagen was performed. Polarized light and Image J was utilized to quantify fibrosis on 200 x images.

Results: Single cell analysis demonstrated increased expression of Par1a/b in proliferating and injured proximal tubules following UUO. This was confirmed by co-expression of Par1a in ki67 and Sox9 positive tubules following UUO. Dual tubular Par1a/b deletion was protective against fibrosis, with % fibrosis decreasing from 1.6 to 0.65 percent 7 days following UUO (p=0.0048).

Conclusions: Dual Par1a/b knockout in tubules protected against fibrosis. Ongoing studies are examining optimal timing of deletion to promote repair vs. fibrosis. Par1 kinase inhibitors may be potential promising therapeutics for preventing fibrosis in chronic kidney disease.

Funding: NIDDK Support

PO0624

TRIM72-Containing Exosome for Kidney-Targeted Expression and Protection

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Background: TRIM72 is a myokine and appears to confer protection to the kidney in ischemia-reperfusion (I/R) injury. There are low levels in the kidney. We did experiments to see if TRIM72 could be transferred to the kidney so it could be used therapeutically.

Methods: Exosomes were purified from C2C12 myotubes differentiated from C2C12 myoblasts by differential centrifugation. C2C12 exosomes were given to *TRIM72* null mice twice weekly for 4-weeks by tail-vein injection. Five-days post the last exosome injection, real time PCR and western blotting were used to examine tissue expression. For comparison, samples obtained from *wildtype* littermates served as positive controls.

Results: *TRIM*72 mRNA remained detectable five days post the final C2C12 exosome infusion. Moreover, *TRIM*72 mRNA delivered by exosomes reconstituted *TRIM72* to the same organ distribution as in *wildtype* littermates, with high levels in kidney, skeletal muscle and moderate levels in heart and skin. TRIM72 protein expression was detected in tissues accordingly to TRIM72 mRNA distribution. Compared to a TRIM72-deficient exosome derived from NIH3T3 condition media, treatment with C2C12 exosome mitigated high serum creatinine level of I/R injured *wildtype* mice. This suggested a sustained TRIM72 expression and protection in kidney when delivered in exosome format.

Conclusions: Adoptive transfer of C2C12 exosomes demonstrated TRIM72 could be reconstituted to its native organ distribution and expression in TRIM72-deficient mice. TRIM72-containing exosome mitigated elevated serum creatinine level of I/R injured mice. Pharmacologic administration of TRIM72-containing exosome might be a promising approach for the treatment of kidney disease.

Funding: NIDDK Support, Other NIH Support - NIA

PO0625

Development of Noninvasive Clinically Applicable In Vivo Tracking of Extracellular Vesicles Using MRI

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Background: Extracellular vesicles (EVs) derived from amniotic fluid stem cells (AFSC) hold great potential for the treatment of chronic kidney diseases (CKD). We showned that AFSC-EVs are renoprotective in a mouse model of CKD, Alport syndrome. However, there is an important unmet need for real-time *in vivo* monitoring of these therapeutic EVs to determine biodistribution to inform about safety, targeting, and effectiveness. While current optical imaging solutions like bioluminescence and fluorescence are useful for EV tracking studies in animal models, there is limited utility in clinical applications. Here we present a novel *in vivo* tracking solution for therapeutic EVs in Alport mice, utilizing clinically applicable MRI technology.

Methods: To generate trackable EVs, AFSC were labeled with a novel magnetic agent (VSCM). EVs secreted by the labeled AFSC were isolated by ultracentrifugation. The viability and morphology of labeled-cells were evaluated, and the *in vitro* MR properties of EVs were analyzed by magnetometer. Purity, potency and identity of labeled EV was compared to non-labeled EVs. *In vivo* biodistribution of labeled EVs was evaluated in WT and Alport mice by MRI at 10 min and 3 hr post injection, and retro-orbital and intra-cardiac routes of delivery were compared.

Results: The magnetic label did not affect the physiological characteristics of the cells and did not change identity, purity and potency (therapeutic effect in vivo) of EVs. MRI phantom studies confirmed the in *vitro/ex vivo* detectability of labeled-EVs. Importantly, as expected MRI studies showed that EV homing to the kidney injected intra-cardiacally into Alport mice was more efficient vs the retro-orbital route, and Prussian blue staining of sections confirmed EV homing to the kidney.

Conclusions: We have developed a clinically applicable novel magnetic nanoparticle agent that can be used to label and track the biodistribution of EVs in the kidney and other organs using non-invasive, safe, and effective MRI technology that's widely available. This technology is highly adaptable and can be deployed in both preclinical and clinical settings.

PO0626

Extracellular Vesicles Rescue Alport Glomerular Endothelial Lipid Dysfunction

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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD). We have previously shown that glomerular endothelial cells (GEC) are damaged in Alport syndrome mice (AS, characterized by mutations in collagen IVα3α4α5), manifested by enlarged fenestrations and damaged glycocalix in the early stage of the disease. In the present study we report on the role of altered fatty acid utilization pathways leading to GEC dysfunction in AS, and the role of extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs) in re-establish lipid homeostasis.

Methods: GEC were isolated from tdTomato-reporter AS and WT mice at 4 months of age by FACS and transcriptome was analyzed and compared by bulk RNA-seq. Tissue samples from patients with AS were used to confirm our findings by immunohistochemistry. In vitro, silencing experiments using human primary GEC were performed to study the role of decreased fatty acid synthase (FASN) in GEC dysfunction, and AFSC-EVs (which contain FASN in their cargo) were applied as a rescue strategy to normalize FASN level and restore lipid homeostasis. Data were confirmed using AFSC-EV $^{FASN-/-}$.

Results: AS GEC were highly enriched for differentially expressed genes associated with cellular metabolism, and lipid metabolism in particular. Genes associated with fatty acid transport (CD36, FATP-1, FATP-2, Fabp3) and synthesis (FASN) among others were downregulated, which was further associated with glomerular accumulation of lipid droplets in mice. We observed similar findings in human biopsy samples from AS patients by histology. In vitro, AFSC-EVs were able to rescue FASN deficiency and improve GEC function, unlike AFSC-EV $^{FASN-/-}$.

Conclusions: We report for the first time a lipid metabolic dysfunction in Alport GEC, and the ability of AFSC-EVs to rescue this phenotype. Therefore, better understanding of the functional role of GEC in AS could lead to the development of targeted new therapies for the treatment of this and other forms of CKD.

Funding: Private Foundation Support

PO0627

Administration of Mesenchymal Stromal Cell-Derived Exosomes Is an Effective Rescue Therapy for Progressive AKI in Rats

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Background: Preclinical and clinical studies have shown Mesenchymal Stem Cells (MSCs) to be effective for prevention of AKI [NCT00733876]. Yet studies where MSCs are given 48 hrs. post-insult, a time at which most patients with severe AKI are diagnosed and when no rescue therapy is available, show them to be ineffective or even damaging due to compromised renal blood flow in capillary beds, where introduction of large cells has the potential to cause further deterioration of renal function [NCT01602328]. While MSCs' renoprotection is largely due to their release of beneficial cytokines and exosomes, their potential negative impact on renal blood flow is a concern. Administration of MSC-derived exosomes is known to exert beneficial effects that are similar to those of the parent cells. We hypothesized that since MSC-derived exosomes can prevent AKI, their small size and ability to move through the microvasculature might allow them to also be an effective rescue therapy for late stage AKI where MSCs are ineffective.

Methods: MSCs from Sprague Dawley (SD) rats were used. Their purified exosomes were characterized for size by nanoparticle tracking analysis, protein concentration, gene expression of relevant markers, FACS (CD44 and CD29), and rtPCR. I/R AKI (50-52 min bilateral renal pedicle clamp) was induced in 3 groups of SD rats (6-8/group). SCr was assessed at baseline, Days (D) 1 and 2. If the SCr value on D2 was greater than that on D1, then on D3, rats were given i.a. either 1 ml of Vehicle, 4x10e10, or 2x10e6 ASCs. Studied Endpoints: SCr at Days 0-9; survival and renal injury.

Results: In contrast to what is found when MSCs are administered to rats immediately upon reflow, when administered to rats 48 hrs post-I/R AKI, 2x10e6 MSCs prove ineffective at ameliorating injury, while MSC-derived exosomes significantly and sustainably improve renal function by D5 post-injury.

Conclusions: MSC-derived exosome therapy administered 2 days post-insult, when renal blood flow is compromised, but also when most clinical instances of AKI are diagnosed, is superior to MSC therapy for rescue of AKI, likely due to the mirrored paracrine content, but significantly smaller size of exosomes compared to MSCs. Our results support the hypothesis that MSC-derived exosomes could be used as a rescue therapy for non-spontaneously recovering AKI.

Funding: Commercial Support - SymbioCellTech

PO0628

Human Induced Pluripotent Stem Cell-Derived Kidney Organoids to Model Idiopathic and Congenital Nephrotic Syndrome

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Background: Recent advances in human stem cell-derived kidney organoid models have opened new avenues to accurately model podocytopathies in 3D *in vitro*. The aim of this study is to develop and characterize human induced pluripotent stem cells (iPSC)-derived 3D kidney organoids as a first step in modeling idiopathic and congenital nephrotic syndrome (NS) *in vitro*.

Methods: Human iPSC were successfully cultured into kidney organoids and characterized using scRNA sequencing, immunocytochemistry, TEM and RNAscope. The protamine sulphate (PS) model and FSGS plasma treatment were used to model idiopathic NS. Podocin mutant organoids were used to study congenital NS.

Results: Kidney organoids showed a clear podocyte population expressing, amongst others, podocin, nephrin, PLA2R, WT1, VEGFA and collagen IV alpha 3. The slit diaphragm was confirmed by TEM. To model podocyte injury, organoids were exposed to protamine sulphate (PS) or active FSGS plasma. PS-induced injury in organoids showed clear podocyte cytoskeleton rearrangements and the induction of pNPHS1-1176 protein expression. The induced podocyte injury was rescued by heparin sulphate, illustrating recovery of injury associated mechanisms in 3D podocytes. The PS effect was organoid-podocyte specific as their 2D iPS-derived podocyte counterparts did not express pNPHS1-1176. Organoids exposed to active FSGS plasma for 4h showed increased granule formation, a podocyte stress marker, in NPHS1+ podocytes which was less abundant when treated with remission plasma. To model congenital nephropathy, erythroblasts from a pediatric patient with compound heterozygous mutations p.Arg138Gln (exon 3) and p.Asp160Tyr (exon 4) in the podocin (*NPHS2*) gene, were successfully reprogrammed in iPSC. Aberrant localization and weak podocin expression was shown in organoids. Using CRISPR/Cas9 the exon 3 mutation was repaired and podocin expression was restored.

Conclusions: We successfully developed human iPSC-derived kidney organoids that will serve as a state-of-the-art tool to accurately study podocytopathies in a dish.

Funding: Other NIH Support - The Dutch Research Council

PO0629

Five-Year Outcome in Patients with ESRD Who Received the Bioengineered Human Acellular Vessel for Dialysis Access

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Background: In a previous prospective, phase 2 trial, where 40 Human Acellular Vessels (HAV) were implanted into 40 hemodialysis patients at 3 sites in Poland from 2012 to 2014 (NCT01744418), initial results demonstrated the HAV provided safe and functional hemodialysis access in these subjects at 2 years. This long-term follow-up assessed subject and conduit status in patients who continued routine dialysis with the HAV at 60 months.

Methods: HAVs are bioengineered by culturing human vascular smooth muscle cells (SMC) on a biodegradable polymer matrix within bioreactors that provide pulsatile mechanical strain. After a quantitative decellularization process, the final complete vessel comprises human vascular extracellular matrix constituents and has the mechanical strength of the original vessel without cellular components that might stimulate host immunologic recognition. In this study, subjects with patent HAV implants were followed for subject and functional conduit status every 3 months, starting after the main portion of the study (at Month 27) through at least 5 years post-implantation. This current report contains 5-year follow-up functional and histological data on 29 patients who were previously enrolled in our initial Phase 2 trial.

Results: At Month 60, 1 subject maintained primary patency, two subjects maintained primary-assisted patency, and ten subjects maintained secondary patency. Secondary patency was estimated at 58.2% (95% confidence interval: 39.2 to 73.1%) at 5 years, after censoring for deaths (n=8) and withdrawals (n=1). No infections of HAV conduits reported during follow up period.

Conclusions: This long-term follow up shows that the HAV provides durable and functional hemodialysis access for patients with end-stage renal disease who dialyze three times per week.

PO0630

Mechanistic Elucidation of Nephron Progenitor Cell Expansion Using a Small Molecule, TCS21311, That Replaces BMP7 and Promotes Cell Proliferation

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Background: Nephron progenitor cells (NPCs) give rise to all epithelial components of the nephron, which is the smallest functional unit of the kidney. The development of a stable supply of NPCs is expected to contribute to kidney regeneration research. Although most reports on the development of NPC expansion culture use BMP7, the detailed mechanisms of action of BMP7 are unknown. To elucidate the roles of BMP7 and improve the NPC expansion culture method, we sought small molecules that can replace BMP7 in the culture system.

Methods: We isolated NPCs from Six2-GFP reporter mice and screened 4,395 chemical compounds using a previously reported expansion culture system. The activity of analogous chemicals from the hits was examined. We predicted the molecular targets of the hit compounds by chemoinformatics analyses of molecular structures. Known downstream signaling pathways were examined by immunoblotting, and differentially expressed genes (DEGs) were analyzed by removing BMP7 from the NPC expansion culture. Furthermore, we improved the expansion culture method using mouse embryonic and human induced pluripotent stem cell (iPSC)-derived NPCs by adding the hit compounds to the expansion culture condition including BMP7.

Results: The chemical screening identified a JAK3 inhibitor, CP690550, in the mouse NPC expansion culture. Although several JAK3 inhibitors as well as some JAK2/3, JAK1/2 and JAK2 inhibitors showed similar activity, one JAK3 inhibitor, TCS21311, showed especially potent effects. A structural analysis of TCS21311 confirmed that JAK3 is its primary target. A pathway analysis of the DEGs by the BMP7 removal indicated STAT3 pathway activation. The phosphorylation of Smad1/5 was increased by TCS21311 even in the absence of BMP7, suggesting a mechanism by which TCS21311 replaces BMP7 via JAK3-STAT3. Furthermore, the addition of TCS21311 to the expansion culture containing BMP7 resulted in more efficient proliferation of mouse embryonic and human iPSC-derived NPCs.

Conclusions: These results will contribute to understanding the roles of BMP7 in NPC proliferation and to the stable supply of NPCs.

Funding: Commercial Support - Astellas Pharma Inc., Rege Nephro Co., Ltd., Government Support - Non-U.S.

PO0631

The Transcription Factor GATA3 Regulates Hyaluronan-Mediated Stromal-Cell Responses During Kidney Injury, Repair, and Fibrosis

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Background: Stromal-mediated processes are critical in determining fibrosis progression. Stromal cells are essential for kidney development and homeostasis, but are also myofibroblast precursors and their maladaptive responses tip the balance from tissue repair to scarring. Our work shows that GATA3 is crucial for developing and mature renal stroma and its expression marks a distinct fibroblast subset associated with improved tissue outcomes following injury. Hyaluronan-(HA), a matrix glycosaminoglycan, is a key regulator fibroblast heterogeneity and predominance of distinct HA synthase (HAS) isoform expression separates fibroblasts into subsets which mediate fibrosis progression or resolution. Here, we investigated GATA3$^+$ fibroblasts in relation to factors that regulate HA-matrix synthesis and metabolism during fibrosis progression *versus* prevention.

Methods: Immunohistology was performed on rat kidneys with bilateral ischaemia-reperfusion-injury +/- ischemic pre-conditioning (IPC) or BMP7 administration (prevention models). Primary human fibroblasts were used to test the role of GATA3 in BMP7 antagonism of TGFβ1-driven myofibroblast differentiation. siRNA and plasmids were used for knockdown or over-expression. HA levels were correlated with fibrosis profiles using ELISA, RT-qPCR and immunofluorescence.

Results: GATA3$^+$ fibroblasts increased in abundance during regenerative phase following injury, co-stained for PDGFRβ and surrounded repairing tubules. More GATA3$^+$PDGFRβ$^+$ fibroblasts were observed in prevention models suggesting a protective, anti-fibrotic role. In prevention models, prominent co-localisation was observed between GATA3 and HAS1 in VSMCs, distal tubules and a distinct stromal population. In contrast, GATA3 expression was attenuated in α-SMA+ myofibroblasts in chronic fibrotic lesions where HAS2 was prominent. *In vitro*, BMP7 induced GATA3 expression and GATA3 knockdown attenuated BMP7-driven antagonism of TGFβ1-driven myofibroblast differentiation, in part by increasing HAS2 expression and pericellular HA. HAS2 promoter analysis confirmed enrichment of GATA binding motifs.

Conclusions: GATA3 is critical for maintaining a distinct stromal subset and mediating the reno-protective effects of IPC and BMP7 on IRI-induced renal damage by modulation of HA-matrix and HAS isoform expression.

PO0632

The Regenerative Response to Renal Injury of the African Spiny Mouse Is Epigenetically Regulated Through H3K27 Methylation

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Background: Lysine methylation of histones plays an important role in regulating gene expression. When tri-methylated, chromatin regions marked by H3K27me3 are inaccessible for transcription. EZH2 of the Polycomb group methylates H3K27, with opposing action carried out by histone demethylases JMJD3 & UTX. EZH2 activation and subsequent increase in H3K27me3 has been associated with renal fibrosis. We hypothesize that in the African spiny mouse, a mammalian model of kidney regeneration, demethylation of H3K27 is associated with regenerative wound healing after ischemia-reperfusion kidney injury.

Methods: Experiments were carried out on kidneys of spiny mouse and house mouse in normal kidneys and kidneys 1 & 3 days after unilateral ischemia-reperfusion injury. Mass spectrometry was used to profile histone modifications. Expression of key genes involved in methylation of H3K27 were quantified using RNA-sequencing, and protein concentration was quantified by western blot. H3K27me3 marks were visualized by immunofluorescent staining. Genes marked by H3K27me3 were identified using CUT&RUN ChIP-sequencing.

Results: H3K27me3 is significantly increased in mouse kidney after ischemia reperfusion injury whereas no change in the repressive mark was noted in spiny mouse when quantified by mass spectrometry and western blot. H3K27me3 marks are abundant in fibrotic mouse kidneys and distributed throughout kidney tissue, while H3K27me3 is reduced in repaired kidneys of spiny mouse. RNA-sequencing demonstrated a 4-fold increase in *Ezh2* in mouse after injury vs 2-fold increase in spiny mouse. During the course of injury, *Jmjd3* expression increased in spiny mouse but decreased in expression in mouse. We previously identified nephrogenic progenitor genes potentially associated with regenerative wound healing in spiny mouse, including *Cdh1, Cdh6* and *H19*. CUT&RUN identified these genes as repressively marked by H3K27me3 in mouse but available for transcription in spiny mouse.

Conclusions: This work suggests that the regenerative response to renal injury in spiny mouse is orchestrated at least in part through the methylation of histone H3K27. Modification of the histone methylation landscape through small molecular modulators may redirect the outcome of kidney injury from fibrosis to regeneration.

Funding: NIDDK Support

PO0633

Effect of Hypoxic Preconditioning on Angiogenesis and Senescence in Human Adipose Tissue-Derived Mesenchymal Stem Cells

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Background: Hypertension(HTN) and chronic kidney disease(CKD) alter the angiogenic and immunomodulatory properties of human adipose-derived Mesenchymal Stem Cells(AMSC). Hypoxic conditions modify growth potential, paracrine functions and gene expression of AMSCs. We tested the hypothesis that AMSCs in CKD patients, preconditioned with hypoxia, will have reduced senescence, enhanced migratory, proliferative and angiogenic functions compared to healthy kidney donors.

Methods: We cultured AMSCs(P3-4) from healthy kidney donors(Controls), patients with HTN and CKD(n=6 each group) under normoxia(20%O_2) and hypoxia(1%O_2). We tested AMSC migration and proliferation, quantified angiogenic and inflammatory factors (VEGF,HGF,TNF-α,TGF-β) in cell culture supernatant, and analyzed gene expression(VEGF,HGF,P16,P21) using rt-PCR.

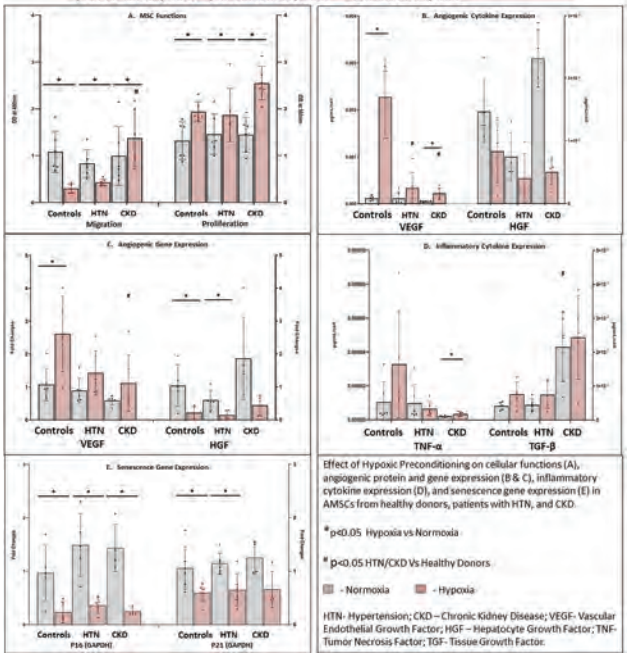
Results: The table shows characteristics of enrolled patients. Hypoxia suppresses AMSC migration in controls and HTN patients while enhancing it in CKD patients and increasing proliferation in all groups. Hypoxia increases VEGF secretion in controls and CKD while downregulating HGF gene expression in controls and HTN group. In CKD patients, TGF-β secretion was higher at baseline and under hypoxia, TNF-α was elevated. Senescence(gene expression of P16/P21) was not different among the groups at baseline but hypoxia attenuated it in all groups.

Conclusions: Hypoxic preconditioning of AMSCs increases migration, proliferation, upregulates VEGF secretion and gene expression, and downregulates pro-senescence genes. These results support hypoxic preconditioning to enhance the regenerative potential and overcome challenges in autologous stem cell therapy for nephropathies.

Funding: NIDDK Support

	Healthy Donors (n=6)	Essential Hypertension (n=6)	Chronic Kidney Disease (n=6)
Age (years)	56 ± 6.9	61.6 ± 15.2	74.3 ± 1.5 *
% of Males	50 %	33.3 %	50%
Systolic Blood pressure (mmHg)	115 ± 11.6	124.6 ± 14.5 **	122 ± 17.2
BMI (kg/m²)	28.2 ± 2.7	27 ± 5.2	25.7 ± 2.5
Serum Creatinine (mg/dL)	0.8 ± 0.1	0.9 ± 0.1	1.9 ± 0.4 ***
Estimated glomerular filtration rate (mL/min/1.73 m²)	88.8 ± 9.3	82.8 ± 12.7	33.8 ± 10.3 ***
Serum Cholesterol (mg/dL)	172 ± 20.3	156.3 ± 19.3	165.6 ± 32.2
Urine Protein/Osmolality Ratio	0.25 ± 0.1	0.18 ± 0.06	0.52 ± 0.4

*p<0.05 CKD vs Healthy Donors **p<0.05 HTN vs Healthy Donors ***CKD vs HTN & Healthy Donors



PO0634

Effect of Hypoxia on the Regenerative Capacity of Adipose Tissue-Derived Mesenchymal Stem Cells in an Experimental Model of Atherosclerotic Renal Artery Stenosis

Naba Farooqui, Arjunmohan Mohan, Xiang yang Zhu, Ishran M. Saadiq, Christopher M. Ferguson, Kyra L. Jordan, Hui Tang, Stephen C. Textor, LaTonya J. Hickson, Alfonso Eirin, Lilach O. Lerman, Sandra Herrmann. *Mayo Clinic Minnesota, Rochester, MN.*

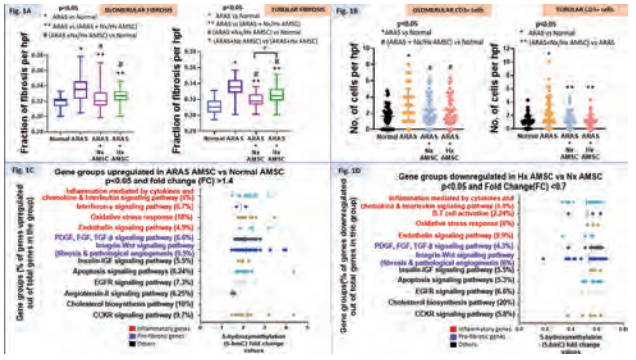
Background: Atherosclerotic renal artery stenosis(ARAS) is a risk factor for parenchymal renal disease. Autologous mesenchymal stem cells(MSC) therapy reduces kidney fibrosis and inflammation in ARAS. Studies have shown that hypoxia preconditioning(Hx) improves MSC function by affecting DNA hydroxymethylation (5-hmC). But the effect of Hx MSCs *in vivo* ARAS model has not been evaluated. We hypothesize that Hx MSCs would improve renal histology better than normoxic (Nx) MSCs and also compare 5-hmC differences between MSC groups.

Methods: MSCs isolated from abdominal fat of ARAS pigs were cultured under normoxia(20%O_2) or hypoxia(1%O_2) till 70-80% confluence. Autologous Nx or Hx MSCs(10^7 cells each) were injected into the swine renal artery 6 wks after induction of ARAS(N=4 each) and compared to Normal and Untreated ARAS pigs(N=5 each). 4 wks later, *ex-vivo* renal trichrome and CD3(T-cell) staining was performed. MSC gene groups with significant 5-hmC fold change levels were grouped on Panther's database.

Results: ARAS pigs treated with either Nx or Hx MSC show reduced renal fibrosis and interstitial inflammation(CD3 cells) versus untreated ARAS pigs(Fig1A,1B). Interstitial fibrosis was less with Nx MSC therapy versus Hx MSC therapy(Fig1A). Interstitial inflammation shows a decreasing trend with Hx MSC therapy versus Nx MSC therapy(p=0.09). Epigenetic analysis showed higher DNA 5-hmC levels of profibrotic and inflammatory genes in ARAS MSC versus Normal Pig MSC(Fig1C). 5-hmC levels of some of these genes were lower in Hx MSC(Fig1D).

Conclusions: In swine model of ARAS, intra-arterial renal delivery of autologous MSCs with or without hypoxia preconditioning reduces kidney fibrosis and interstitial Tcell infiltration. Hx MSCs' effect was not different from Nx MSC. But, enhanced DNA hydroxymethylation of profibrotic and inflammatory genes in ARAS MSC could be mitigated by hypoxia preconditioning.

Funding: NIDDK Support



PO0635

In Vivo Data to Support Induced Pluripotent Stem Cell-Derived Renal Progenitors as Potential Cell Therapy for Kidney Disease

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Background: Novel therapies are needed to deliver life changing medicines to renal patients and cell therapy is a relatively new strategy of kidney therapy. We have developed novel methodology to produce kidney organoids for target validation. Here we have used this learning, to derive human renal progenitor cells (RPC) and examine their differentiation in-vivo using 2 delivery models

Methods: We used iPSC modified to contain a GFP reporter of nephrin expression, to generate human RPC differentiated to day 6 and 10 using a previously described kidney organoid protocol. We then used kidney capsule implantation and intravenous delivery in naïve and Ischemia/Reperfusion Injury (IRI) NOD/SCID background mice respectively. For kidney capsule, we compared RPC implantation number (3 and $5x10^6$) and time (1 and 5 weeks). For IRI, we infused i.v RPC ($5x10^6$) directly after kidney clamping (24mins)/ reperfusion and measured systemic biodistribution of RPC at 2 and 25 days. Other readouts included kidney human RNAseq, renal function, plasma cytokines and histology

Results: We can currently show RPC implanted in kidney capsule continue differentiation towards mature renal cell types. Using histology and hRNA signatures, there is some enrichment towards tubular like cells particular at high dose, using day 10 matured progenitors at 5 weeks after implantation. These include differentiation of tubular transporters, such as nucleoside (ENT1) and water-transporting proteins (AQP1). In IRI experiments, i.v infusion was well tolerated with normal disease course based on increases in plasma creatinine, BUN and urinary KIM-1. Biodistribution and differentiation analysis is underway, focused on anti-human nuclear staining in multiple organs and qPCR. Plasma inflammatory, cardiac and renal biomarkers analysis will examine any RPC infiltrate response

Conclusions: These observations clearly demonstrate the use and differentiation potential of RPC in a pre-clinical setting. These studies may aid design and delivery modality, for any future effort in examining RPC therapy for renal disease

Funding: Commercial Support - AstraZeneca

PO0636

Synthetic Peptide Hydrogels as Support Matrices for the Generation of Distinct Cell Populations Within Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: Kidney organoids that display improved maturity with reduced variability are needed to produce models that faithfully mirror the *in vivo* organ. We propose that organoid development will benefit from the biophysical support provided by a tunable, fully defined microenvironment. Synthetic self-assembling peptide hydrogels are ideal systems to support organoid development that more accurately mimics the *in vivo* environment due to the simplicity of the structure formed at the molecular level, their low immunogenicity, cell-retention, biodegradability, and tuneable mechanical properties.

Methods: Peptide hydrogel properties were investigated via transmission electron microscopy and rheology. Organoids were characterized by immunofluorescence and single cell RNA sequencing using the 10x Genomics platform.

Results: The self-assembling peptide hydrogels (SAPHs) were comprised of a fibrous structural architecture similar to that of natural polymer networks. The mechanical properties of the SAPHs were dynamic with Alpha4 increasing in G' stiffness over time while Alpha5 reached a peak G' on day 3 of media conditioning. Monolayer differentiation saw the loss of pluripotency markers, transient expression of primitive streak marker brachyury, and high levels of intermediate mesoderm markers PAX2 and HOXD11 by day 7. Suspension culture for 48 hours resulted in compacted pellets that allowed for encapsulation on day 9. By day 24 organoids displayed high levels of viability and were shown to have functionality through dextran uptake. Immunostaining confirmed the generation of key cell types of the maturing nephron. Organoids contained WT1+ve podocytes, LTL+ve proximal and ECAD+ve distal tubules, laminin+ve basement membrane and meis1/2/3+ve interstitial cells. scRNA-seq revealed distinct clusters comprising nephron and stromal compartments. Interestingly, growth within the SAPHs resulted in varying proportions between these two cell types particularly with increased stromal cells seen in Alpha4 organoids.

Conclusions: We propose that peptide hydrogels due to their defined and tunable nature provide an alternative to animal-derived support matrices. These results further support the use of designer matrices that will improve iPSC differentiation towards renal cell fate trajectories.

Funding: Commercial Support - Manchester BIOGEL, Government Support - Non-U.S.

PO0637

Gelatin Methacryloyl (GelMA) as a Tuneable Biophysical Environment for the Derivation of Human Induced Pluripotent Stem Cell-Derived Kidney Organoids

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Background: The translational utility of hiPSC-derived kidney organoids relies on our ability to comprehensively mimic both the biochemical and biophysical properties of the cellular milieu *in vitro*. An improved understanding of how the mechanical environment effects the renal progenitor niche during development and how perturbations to such biophysical environments effects cell fate are required. Within this context, Gelatin methacryate (GelMA), a derivative of collagen, represents a mechanically amendable scaffold to probe cell fate dynamics.

Methods: hiPSC-derived kidney organoids were differentiated within photo-crosslinked GelMA hydrogels of defined mechanical strengths. Hydrogels were characterised using rheological analysis and SEM. Enrichment of renal cell types in response to the various mechanical microenvironments was subsequently investigated.

Results: Rheological analysis revealed a diverse stiffness profile range from the formulated hydrogels. Hydrogels comparable to the stiffness of the gastrulation-stage embryo (G′ = 400 Pa), human kidney tissue (G′ = 2.5 kPa) and fibrotic tissue (G′ = 8-10 kPa) were generated. SEM revealed that hydrogel pore size was dependent on starting gelatin concentration in the hydrogel formulations. PCNA and cleaved caspase-3 staining of organoids embedded within scaffolds demonstrated high cell proliferation and viability in all hydrogel constructs by day 26 of differentiation. The formation of glomerular, proximal tubular and distal tubular structures, that were supported by basement membrane and interstitial cells was confirmed in all conditions using qRT-PCR and immunofluorescent analysis. Significant enrichment of MEIS1/2/3^{+ve} interstitial cells was noted in organoids differentiated within stiffer hydrogels. Interstitial expansion and increased extracellular matrix deposition was confirmed using H&E and Masson's trichrome staining within stiff GelMA scaffolds.

Conclusions: We propose the utility of GelMA hydrogels as faithful extracellular supports for the specification of hiPSC-derived kidney organoids. These scaffolds represent a mechanically tuneable microenvironment to investigate the effects of the biophysical milieu on renal development and disease perturbations.

Funding: Government Support - Non-U.S.

PO0638

Generation of Chimeric Nephrons in Newborn Mice for Testing Drug-Induced Nephrotoxicity

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Background: Studies have reported certain limitations of experiments on animals for assessing nephrotoxicity. Due to species differences in tubular transporters, a model for evaluating nephrotoxicity in humans is desirable. Organoids are a novel research method, but the absence of their connection to the urinary tract makes them difficult for use in the evaluation of chronic nephrotoxicity. Therefore, our goal was to develop a new pre-clinical assessment model that is amenable to repeated dose toxicity studies. In particular, this model aimed to produce human nephrons chimerized in the kidneys of host animals. We previously reported "*exo utero*" cell transplantation in which exogenous renal progenitor cells (RPCs) were transplanted into the retroperitoneal cavity of mouse fetuses without lethality. Although transplanted cells differentiated into functional nephrons chimerized with host kidneys, this method requires proficiency. In this report, because continuous nephrogenesis takes place over several days after birth in mice, we used newborn mice as host animals and conducted a proof-of-concept study using mouse RPCs.

Methods: Metanephroi extracted from green fluorescent protein (GFP)-labeled mouse embryos were dissociated into single RPCs and injected into the subcapsular areas of newborn mice at postnatal days 0–1. After 2 weeks, kidneys of host mice containing

exogenous nephrons were extracted for the immunohistochemical evaluation. In addition, cisplatin was administered intraperitoneally to the host mice and the response of exogenous proximal tubular cells (PTCs) was evaluated.

Results: Immunohistochemistry revealed around 10% chimerism in glomeruli, proximal and distal tubules in the injected areas. Exogenous PTCs exhibited dose-dependent expression of Kim-1 in response to cisplatin administration. We aim to subsequently report data from single-cell RNA sequencing.

Conclusions: Mouse exogenous RPCs could form chimeric nephrons in newborn mice that reproduced drug-induced nephrotoxicity seen in native kidneys. The neo-tubules are expected to be a tool that can be applied to long-term repetitive drug administration because of its integration into the host functioning nephrons.

Funding: Government Support - Non-U.S.

PO0639

Interrogating the Contribution of Innervation to Kidney Development and Disease

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Background: Kidney functions range from blood filtration and regulation of body fluid homeostasis to promoting the production of red blood cells and active vitamin D. These functions are regulated by intrinsic cellular mechanisms including signaling through renal nerves. The kidney is innervated by axonal projections from exterior ganglia. These projections can be classified as either afferent sensory fibers which impact cardiovascular function by relaying information from the kidney to the central nervous system (CNS), or efferent sympathetic fibers which impact renal function by relaying information from the CNS to the kidney. While the role of innervation in adult renal pathophysiology is an area of active investigation, there is a significant deficit in our understanding of renal innervation during development. I hypothesize that renal nerves release spatially and temporally regulated signaling factors contributing to proper kidney development.

Methods: To first characterize the process of renal innervation, we generated 3D anatomical maps of renal innervation throughout development using light-sheet imaging of embryonic, neonatal, and adult kidneys. We also utilized confocal microscopy to interrogate the association of renal nerves (synapse formation) with distinct renal structures including tubules, glomeruli, and vasculature. To assess function, we genetically ablated renal innervation utilizing a knockout mouse for the TrkA receptor which is required for neuronal survival.

Results: Our analyses show that renal innervation begins at E13.5 as the renal arterial tree becomes smooth muscle actin (SMA) coated. Innervation continues via multiple branching events following SMA+ vasculature until the main renal nerve branches are established by E16.5. From there, renal nerves grow further via interstitial branching until projections reach renal target structures as early as E17.5. TrkA knockout kidneys assessed postnatally had a significant reduction in renal innervation and presented with abnormal glomerular and tubules phenotypes.

Conclusions: Future efforts will aim to conditionally delete sensory or sympathetic renal nerves independently and investigate the resulting functional phenotypes. Taken together our findings will significantly bridge the gap in knowledge concerning the establishment of renal innervation and the role of nerves in kidney development and disease.

PO0640

Constitutive Activation of Hedgehog Signaling in FOXD1+ Renal Stromal Cells Impairs Ureteric Epithelial Branching via CXCL12

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Background: Renal dysplasia, characterized by disorganization of stromal tissue, malformation of collecting ducts, and decreased nephron number, is a major cause of renal failure in children. Nephrons and collecting ducts develop via reciprocal inductive interactions between two intermediate mesodermal tissue elements - the *Osr1*+ metanephric mesenchyme (MM), within which reside *Six2*+ nephrogenic and *Foxd1*+ stromal cell progenitors, and the *Hoxb7*+ ureteric bud, which gives rise to ureteric branches and their daughter collecting ducts. The key roles of expanded *Foxd1*+ stromal progenitors in the genesis of dysplastic tissue are largely undefined. Here, we identify a novel pathogenic stromal *Hh-Cxcl12* signaling axis driving impaired ureteric epithelial branching.

Methods: Mice with deficiency of *Ptch1* specific to FOXD1+ stromal cells (*Foxd1Cre;Ptch1*$^{loxP/-}$; referred to as stromal *Ptch1*-deficient) were analyzed by immunostaining, single-cell RNA sequencing, and bulk RNA sequencing. To investigate *Cxcl12* as a downstream target of increased stromal Hh signaling, *in vivo* analysis of ureteric branching was assessed in *Cxcl12* compound mutants (*Foxd1Cre; Ptch1*$^{loxP-}$*; Cxcl12*$^{loxP/+}$).

Results: Stromal *Ptch1*-deficient kidneys exhibited renal dysplasia characterized by a 41% reduction in nephron number ($P<0.01$, n=4) at E18.5 and a 26% reduction in ureteric epithelial branch tips at E12.5 ($P<0.01$, n=6). Whole kidney qRT-PCR analysis at E13.5 further demonstrated a reduction in ureteric branching effectors *Gdnf, Wnt11, Etv4,* and *Etv5* in stromal *Ptch1*-deficient mice ($P<0.05$, n=4). Bulk RNA sequencing of stromal *Ptch1*-deficient whole kidneys revealed a significant upregulation in numerous medullary stromal markers including the secreted stromal cell-derived factor *Cxcl12* ($P<0.01$, n=3). Complementary single-cell RNA sequencing analysis further demonstrated upregulation of *Cxcl12* in medullary stromal clusters of *Ptch1*-deficient kidneys relative to control samples. Analysis of branching morphogenesis in compound mutant mice heterozygous for *Cxcl12* in a stromal *Ptch1*-deficient background revealed a complete rescue of ureteric epithelial branching defects ($P<0.001$, n=6).

Conclusions: A pathogenic increase in stromal Hh signaling in mice causes nephron deficiency and impaired ureteric epithelial branching due to increased *Cxcl12* activation.

Funding: Government Support - Non-U.S.

PO0641

Maturation-Enhanced Proximal Tubules Enable Functionality, Toxicity Screening, and Infectious Disease Modeling in Kidney Organoids

Jessica M. Vanslambrouck,[1] Ker sin Tan,[1] Sean Wilson,[1,2] Ella Groenewegen,[1] Jessica A. Neil,[3] Rajeev Rudraraju,[3] Michelle Scurr,[1] Sara E. Howden,[1,2] Kanta Subbarao,[3,4] Melissa H. Little.[1,5] *[1]Murdoch Childrens Research Institute, Parkville, VIC, Australia; [2]The University of Melbourne Department of Paediatrics, Parkville, VIC, Australia; [3]The University of Melbourne Department of Microbiology and Immunology, The University of Melbourne, Peter Doherty Institute for Infection and Immunity, Parkville, VIC, Australia; [4]WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Parkville, VIC, Australia; [5]The University of Melbourne Department of Paediatrics and Department of Anatomy and Neuroscience, The University of Melbourne, Parkville, VIC, Australia.*

Background: The highly specialised proximal tubule (PT) nephron segment is responsible for most kidney functions in mammals and is acutely vulnerable to disease, making it a key objective for toxicity screening and disease research. While induced pluripotent stem cell (iPSC)-derived kidney organoids represent a promising approach, the PT remains immature with limited evidence of functional transporters. Here we report the development of PT-enhanced organoids with nephron functionality, enabling improved modelling of PT-relevant conditions including drug-induced toxicity and infection such as SARS-CoV-2.

Methods: Standard and fluorescent reporter iPSC lines were subjected to prolonged monolayer differentiations (modified from: Howden *et al*. EMBO Rep 2019; Vanslambrouck *et al.* JASN 2019) and precisely-timed morphogens for targets such as WNT, BMP and NOTCH pathways prior to organoid generation (Takasato *et al*,. Nat Protoc 2016). Maturation was analysed via immunofluorescence, live confocal imaging of fluorescent reporters, transcriptional profiling, transporter function assays, and SARS-CoV-2 infectivity.

Results: Prolonged nephron progenitor differentiation with simultaneous prevention of spontaneous nephrogenesis resulted in PT-enhanced kidney organoids with elongated and aligned nephrons. Striking proximo-distal nephron orientation resulted from localised WNT antagonism. Improved upregulation of PT-specific markers compared to standard organoids was strengthened by evidence of transporter functionality, including uptake of albumin, organic cations, and cisplatin (eliciting appropriate KIM1 upregulation). This approach also improved expression of SARS-CoV-2 entry factors, confirmed by susceptibility to infection and viral replication.

Conclusions: We describe enhanced kidney organoids with improved PT maturity arising from alterations to early mesodermal patterning and delayed nephron initiation. The enhanced conditions also provided more stringent control over nephron spatial arrangement. PT-enhanced organoids provide an ideal model to better understand human PT maturation, inherited and acquired PT disease, and drug toxicity implications.

PO0642

Estrogen-Related Receptor Gamma Identified as a Novel Link Between Ciliogenesis and Nephron Development

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Background: Aberrant formation of cilia, hair-like projections that facilitate mechano- and chemo-sensing, has been linked to developmental disorders, kidney dysfunction, and renal cyst formation. Since prostaglandin signaling has been noted as a key regulator of ciliogenesis, we investigated potential upstream factors that could contribute to both kidney and cilia development. One nuclear receptor, *Esrrγ*, was of particular interest, as it interacts with known ciliogenic factors and causes renal cysts in mouse knockout models.

Methods: We confirmed that *Esrrγ* does indeed affect endogenous prostaglandin levels through an ELISA assay of *Esrrγ* deficiency models. We also assessed the effect of *Esrrγ* deficiency using whole mount in situ hybridization to characterize changes in distinct nephron cell populations. We used immunohistochemistry to quantify aberrant cilia formation, cell polarity, and cell turnover in the kidney, ear, and node. We utilized qRT-PCR to measure changes in transcription of potential downstream targets, and used overexpression or chemical treatments to rescue with these targets or their products to further support regulatory relationships.

Results: *Esrrγ* deficient embryos had decreased endogenous PGE2 levels and exhibited nephron composition defects including expanded expression of proximal markers and reduced distal segments. These were likely due to changes in cell fate choice, as no changes in cell death or proliferation were found. The formation of renal cilia was also disrupted, where both cilia length and number of ciliated basal bodies were significantly reduced in ciliated cell populations. Interestingly, *Esrrγ* was required for ciliogenesis in other tissues as well, as cilia length was also decreased in the node and the ear. These phenotypes were consistent with a disruption of prostaglandin signaling,

and we found that expression of the prostaglandin cyclooxygenase enzyme (Cox1) and prostaglandin regulator *Pgc1a* was reduced in *Esrrγ* deficient embryos. Treatment with dmPGE2 or *Cox1* overexpression was sufficient to rescue renal and cilia defects.

Conclusions: These data position *Esrrγ* as a novel link between ciliogenesis and nephrogenesis through regulation of prostaglandin signaling, and highlight *Esrrγ* as a potential new target for future ciliopathic treatments.

PO0643

Single-Cell Analysis of Senescent Epithelia Reveals Targetable Mechanisms Promoting Fibrosis

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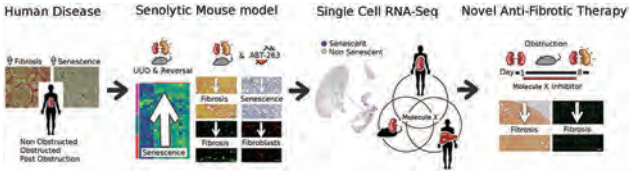
Background: Progressive fibrosis and maladaptive organ repair result in significant morbidity and millions of premature deaths annually. Senescent cells accumulate with ageing and after injury and are implicated in organ fibrosis, but the mechanisms by which senescence influences repair are poorly understood. Here, we address the role of senescence in maladaptive repair and identify new anti-fibrotic targets.

Methods: We analyse human kidney tissue samples post deobstruction and corresponding murine models to test involvment of senescent cells in maladpative repair via pharmacological depletion. We use single cell RNA-Seq to examine these cells in more detail. We validate our findings using in-vitro models of senescence and fibroblast activation. Finally we use murine models of injury to test inhibition of in silico targets as anti-fibrotic.

Results: We demonstrate for the first time in man that senescence and fibrosis persist in kidneys in the aftermath of a resolved obstructive injury. Using a relevant murine model of injury and repair we show senescent epithelia persist after relief of ureteric obstruction and that depletion of senescent epithelia reduces fibrosis and promotes repair. We next characterise senescent epithelia in murine renal repair using single cell RNA-Seq for the first time. We extend our classification to human kidney and liver disease, identifying conserved pro-fibrotic molecules which we validate in vitro and in human disease. Inhibition of one of these molecules is essential for TGFb mediated fibroblast activation in vitro and in vivo. Importantly for translation, inhibition of this molecule in vivo significantly reduces kidney fibrosis after injury.

Conclusions: Our data shed light on the role of senescent epithelia in renal disease and identify a new anti-fibrotic molecule. Analysis of signaling pathways of senescent epithelia connects the important pathways such as the cell stress response to organ fibrosis, permitting rational design of anti-fibrotic therapies.

Funding: Private Foundation Support



Graphical Abstract

PO0644

Treatment of Diabetic NOD/SCID Mice with Human "Neo-Islets," 3D Organoids of Mesenchymal Stromal and Pancreatic Islet Cells, Normalizes Blood Glucose Levels: Significance for Clinical Trials

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Background: We reported that allogeneic "Neo-Islets" (NI) are immune protected and permanently correct autoimmune diabetes in NOD mice by omental engraftment and endocrine cell redifferentiation. This new "endocrine pancreas" delivers islet hormones physiologically into the hepatic portal vein. Further, treatment of insulin-dependent dogs with allogeneic canine NIs (ongoing FDA-approved Pilot Study) consistently improved glycemic control without the need for antirejection drugs. The current preclinical study was undertaken in anticipation of a Phase 1 Clinical Trial with two objectives: to determine (a) whether human NIs (hNIs) can also restore euglycemia, and (b) whether redosing of suboptimally controlled diabetic animals could restore euglycemia in streptozotocin (STZ)-diabetic NOD/SCID mice, as has been previously shown for mouse and dog cell-derived NIs.

Methods: Passaged cells that were to be used to treat diabetic NOD/SCID mice were characterized for gene expression profiles by rtPCR. For *in vivo* testing, NOD/SCID mice were made diabetic with STZ, then randomized based on blood glucose levels into groups of 6 each, treated with insulin pellets, and once blood glucose levels were stabilized near normal animals were treated i.p. either with ~2x10e5 human cell-derived NIs/kg bw (n=6) or vehicle (n=6), then followed for 8 weeks. Once blood glucose levels were determined to be no longer significantly improved compared to controls without administration of exogenous insulin, mice in each group were again treated with either 2x10e5 NIs/kg bw or vehicle, and followed for an additional 6 weeks. Therapeutic efficacy was assessed by survival, 2x weekly blood glucose monitoring, and glucose tolerance tests administered 57 and 41 days post the 1st and 2nd doses, respectively.

Results: Human NI therapy significantly improved glycemic control and survival vs. vehicle. A 2nd dose given to the initial group normalized blood glucose levels long-term.

Conclusions: Despite the limitations of the diabetic NOD/SCID model, these data show that human NIs are curative, and in conjunction with data from the dog study, where allogeneic NI therapy reduces the need for insulin without need for antirejection drugs, have high translational relevance and support the planned conduct of human NI clinical trials.

Funding: Commercial Support - SymbioCellTech

PO0645

IL-33 as a Novel Target for the Treatment of Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) has classically been thought as a microvascular disorder, although inflammation has emerged as a key pathophysiological mechanism involved in the development of diabetic kidney injury. Consequently, inflammatory mediators have aroused as promising therapeutic targets.

Methods: IL-33 is a broad acting cytokine, expressed in endothelial and epithelial barriers, that mediates local tissue inflammation. It exerts its function by binding to a heterodimer formed by its specific receptor ST2 and co-receptor IL-1RAcP. Due to the evidence of the role of IL-33 in kidney injury, we generated MEDI3506, a potent IL-33 blocking mAb for the treatment of DKD.

Results: Transcriptomic analysis showed that expression of IL-33 RNA is upregulated in both the glomeruli and tubulointerstitium of DKD patients in two independent cohorts. Assessment of expression in both human and experimental DKD demonstrated that IL-33 is among the most regulated inflammatory genes. Preliminary data on IL-33 protein levels in human kidney biopsies indicates that IL-33 is increased in DKD versus controls. Preclinically, the db/db uninephrectomy model of DKD showed IL-33 protein levels in kidney lysates positively correlated with histological glomerular damage from week 7 to 21. More importantly, blockade of ST2 signalling by using a mAb, prevented the progression of albuminuria. In vitro mechanistic studies using primary human glomerular endothelial cells (GECs) and mesangial cells (MCs) showed that both cell types expressed ST2 and upregulated IL-33 in response to TNFα and IFNγ, commonly upregulated in diabetic kidney microenvironment. Moreover, GECs and to a lesser extent MCs, displayed a significant IL-33 induced proinflammatory cytokine release (e.g. IL-8, IL-6...) mediated by MAP kinase activation and NF-kB translocation. All these effects were inhibited by MEDI3506.

Conclusions: Upregulation of IL-33 in diabetic kidney, generates localised chronic kidney inflammation through autocrine signalling in GECs and MCs. This data suggest that targeting IL-33 with MEDI3506 arises as a promising therapeutic intervention for DKD, currently in Ph2b trial.

Funding: Commercial Support - AstraZeneca

PO0646

Endogenous Interleukin 33 Contributes to the Progression of Diabetic Nephropathy

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Background: Inflammation and fibrosis play a crucial role throughout the course of Diabetic Nephropathy (DN). Interleukin 33 (IL-33) is an early alarmin for inflammatory damage and also shows a relationship with fibrosis in multiple organs. However, it was little discussed in the field of chronic kidney disease. Here, we try to explore the role of IL-33 in DN.

Methods: 21 patients with DN diagnosed by renal biopsy were retrospectively included; 6 kidney tissue adjacent to carcinomawere were collected as normal kidney samples; 5 healthy controls were included. IL-33 levels in serum and urine were measured and IL-33 of renal tissue were evaluated. db/db mice were used as an animal model to evaluate the IL-33 expression in the early stage of DN. IL-33KO mice with STZ injection combined with unilateral nephrectomy were used as an animal model to explore the regulatory effect of endogenous IL-33.

Results: In human samples, DN group showed a significantly higher level of IL-33 than that in the normal kidney tissue ($P<0.0001$). And the level was positively related to the degree of kidney fibrosis(Spearman's $\rho=0.072$, $P=0.007$). The expression pattern of IL-33 in DN is different from that in normal condition. Further immunofluorescence staining suggested that IL-33 is expressed mainly by fibroblasts in the kidney of DN. And IL-33 level in DN group was also showed a higher level in urine ($P=0.017$). In animal models, IL-33 increased in the kidney of db/db group compared with db/m ($P=0.011$) during the early stage of DN, which was before the decrease of renal function and appearance of pathological lesions. In the IL-33 knockout mouse of STZ-induced diabetes combined with unilateral nephrectomy, the 32 weeks old IL-33KO group had lower blood glucose levels ($P<0.001$), reduced urinary albumin/creatinine level than ($P=0.021$) wild type group with diabetes. Staining of renal tissue also showed severe tubulointerstitial fibrosis, inflammatory cell infiltration, and glomerular mesangial expansion in wild type group, all of which were significantly attenuated in the IL-33KO group.

Conclusions: IL-33 is involved throughout the course of DN. The increase of IL-33 may play as an early warning factor in the disease and may participate in aggravating diabetic nephropathy by mediating the process of fibrosis. Based on our findings, IL-33 may have the potential to be a target for further mechanism research and treatment of DN.

PO0647

Beneficial Effects of Tumor Necrosis Factor α Blockade in a Mouse Model of Diabetic Nephropathy

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Background: Recent studies indicate that immune activation may play a role in pathogenesis of diabetic nephropathy (DN). We have previously described a mouse model exhibiting characteristics of human DN including high-grade albuminuria and glomerulosclerosis. In this model, glomerular immune and inflammatory pathways, including networks associated with tumor necrosis factor (TNF)-α signaling are upregulated. In this study, we examine the functional impact of the TNF-α pathway in DN.

Methods: We used a mouse model combining the *Akita Ins2* mutation, which causes profound type I diabetes, with a renin transgene (*ReninTg*) producing low level activation of the RAS. *Akita-ReninTg* mice on a susceptible 129 strain background exhibit cardinal features of human DN. To examine the role of TNF-α, 16-week old 129 *Akita-ReninTg* mice were injected with 1mg/kg/week etanercept (E) or saline vehicle (V) subcutaneously for 4 weeks while urinary albumin excretion and other parameters were monitored.

Results: At baseline, 16-week old *Akita-ReninTg* mice have substantial albuminuria (1850±207 μg/day), with no significant difference between E and V groups. Levels of albuminuria increased in the V group to 3626±1024 μg/day at 20 weeks. By contrast, etanercept treatment prevented this increase in albuminuria at 20 weeks (1448±236 μg/day; $p<0.01$ vs V). The extent of kidney hypertrophy was also attenuated with E. Blood glucose levels were similar in E and V groups throughout the treatment period. Renal levels of NF-κB, a key mediator activated by TNF-α was significantly reduced after etanercept consistent with effective pharmacological TNF-a blockade. In addition, renal expression of KIM-1 and TGF-β were both significantly suppressed by E, consistent with reduced kidney injury and pro-fibrotic state, respectively.

Conclusions: In a model of DN, TNF-α blockade administered to mice with established macro-albuminuria substantially suppressed the progression of proteinuria. Etanercept also protected against kidney injury and diminished pro-fibrotic signaling. Our findings support a causal role for TNF-a in the pathogenesis of DN and indicate potential utility of TNF-α blockade in the treatment of DN.

PO0648

A Novel Anti-Inflammatory Renoprotective Effect of GLP-1 Receptor Agonists in Type 1 Diabetes: Shifting Macrophage Polarization

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Background: Diabetic kidney disease (DKD) is a serious complication of diabetes. Increased evidence has shown a vital role of the immune system in the pathogenesis of DKD. Macrophages infiltrate the glomeruli and can polarize into an M1 pro-inflammatory phenotype versus an M2 anti-inflammatory one. Moreover, studies from our group and others highlighted the role of NADPH oxidases induced ROS production in the progression of DKD. Several hypoglycemic agents were investigated for their reno-protective effects. Among these agents, Liraglutide, a GLP-1 receptor agonist. However, its role in modulating DKD development still needs to be elucidated, especially in type 1 diabetes mellitus (T1DM). In this study, we aim to investigate the reno-protective effect of Liraglutide in regulating the NADPH oxidases family of enzymes which are well known for their role in ROS production. More importantly we will assess the involvement of Liraglutide with macrophage polarization, a major component of the immune system.

Methods: C57/BL6J adult male mice were allocated into 3 groups: control, STZ induced T1DM, STZ induced T1DM group treated with liraglutide (0.3mg/kg, SC twice daily) for a duration of 13 weeks. Functional, histopathological, biochemical and molecular studies were performed on kidney tissues for all groups.

Results: Liraglutide treatment improves kidney injury as assessed by blood urea nitrogen, serum creatinine levels, and more importantly proteinuria. The reno-protective effect of liraglutide was further validated via histopathological findings; increased M2 macrophage infiltration, reduced collagen deposition and extracellular matrix expansion. Of interest, these results were associated with decreased mRNA expression of M1 inflammatory markers and increased mRNA expression of the M2 anti-inflammatory ones. In addition, liraglutide treatment attenuated ROS overproduction by reducing NADPH oxidase enzymatic activity paralleled by a decrease in DUOX-1 and DUOX-2 isoforms protein expression and mRNA levels.

Conclusions: To the best of our knowledge, this is the first study to show a reno-protective effect of liraglutide in DKD through shifting macrophage polarization towards the M2 anti-inflammatory phenotype possibly via inhibiting NADPH oxidases induced ROS production.

Funding: Private Foundation Support, Clinical Revenue Support

PO0649

Interferon-γ Signaling and the Progression of Early Diabetic Kidney Disease

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Background: Inflammation plays an important role in pathogenesis of diabetic kidney disease (DKD). However, the pathways by which circulating pro-inflammatory factors activate intrarenal signaling and mediate DKD progression remain poorly defined. Using multiscalar data integration we aimed to identify links between circulating factors in early DKD and activation of kidney signaling pathways and DKD progression

Methods: Transcriptomic data from kidney biopsies of Pima Indians with type 2 diabetes and early DKD (n=74) were used to identify differentially expressed genes (DEGs) and their upstream regulators (URs) associated with end-stage kidney disease (ESKD). Plasma proteomics (n=162) was used to identify ESKD-associated circulating proteins. URs were selected if their regulation in plasma was consistent with the prediction based on transcriptomic analysis. Activation scores were computed based on the downstream signaling cascade at the transcriptomic level and then associated with structural lesions and health outcomes in DKD patients. The findings were validated in podocyte-specific JAK2 transgenic $Ins2^{Akita/+}$ mice (Pod-Jak2TG-Akita) which develop progressive DKD and in human kidney organoid cultures.

Results: Five URs of ESKD-associated DEGs in both glomeruli (Glom) and tubulointerstitium (TI) were identified, with interferon gamma (IFNG) exhibiting the most significant association. IFNG receptor expression was detected in multiple kidney cell types by single cell RNAseq analysis. Higher IFNG pathway kidney activation scores in Glom and TI were associated with increased risk of ESKD and faster GFR decline over 10.5 years. Inhibition of the IFNG pathway reduced kidney IFNG score and ameliorated albuminuria and mesangial expansion in Pod-Jak2TG-Akita mice. IFNG significantly increased IFNG activation score in human organoids, which was reduced by baricitinib, an inhibitor of JAK1 and JAK2, which are major IFNG signaling mediators.

Conclusions: Increased circulating IFNG levels and IFNG pathway activation in kidney tissue in early DKD may lead to DKD progression. Therefore, the IFNG pathway may be a target for intervention in early DKD.

Funding: NIDDK Support

PO0650

Nrf2 Activators Induce Inflammasome Attenuation: Possible Role in Diabetic Nephropathy

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Background: Kidney diseases remain a worldwide public health problem characterized by sustained inflammation. Inflammasome has recently emerged as crucial regulators of renal inflammation. In particular, the NLRP3 inflammasome, is involved in the activation of caspase-1 and the maturation of IL-1β and IL-18, which have been strongly associated with diabetic nephropathy. DJ-1 is a redox-sensitive chaperone with reported antioxidant and anti-inflammatory properties in the kidney, in part due to the regulation of transcription factor Nrf2, which regulates the expression of several antioxidant genes. The 20 amino acid (aa) peptide ND-13, is a new experimental treatment that consists of 13 highly conserved aa from the DJ-1 sequence.

Methods: In this study, we determined NLRP3 inflammasome activation in peripheral blood mononuclear cells (PBMCs) of diabetic nephropathy patients and the capacity of Nrf2 inducers to attenuate inflammasome activation. Mouse bone marrow macrophages were treated with Bardoxolone (1μM), an Nrf2 inducer, and ND-13 (1μM) for 24 hours.

Results: The IL-1β concentration in the medium increased by the stimulation of the NLRP3 inflammasome by LPS/ATP, and decreased in macrophages pre-treated with Bardoxolone (65.07±26%,n=4, P<0.05) but not in macrophages pre-treated with ND-13. Concentration-response curve demonstrates the capacity of Bardoxolone to inhibit NLRP3 inflammasome activation by LPS/ATP. Additionally, in presence of H2O2 (100nM), ND-13 (1μM) significantly decreased IL-1β release after NLRP3 activation (88.6±1.2%, n=4, P<0.05), suggesting the capacity of the ND-13 peptide to reduce NLRP3 inflammasome activity under pathological conditions. PBMCs isolated from the blood of controls patients, patients with diabetes, and patients with diabetes and renal disease were cultured in vitro and stimulated with LPS/ATP. Compared to controls and diabetic individuals, patients with diabetic nephropathy presented a trend to increase IL-1β release.

Conclusions: All these data point out that inflammasome pre-activation could have a role in the pathogenesis of diabetic nephropathy, that Nrf2 pathway stimulation is a promising approach to decrease immune cells inflammasome pre-activation, and ND-13 could be a new approach to protect the renal damage associated to inflammasome over-activation in renal diseases.

Funding: Government Support - Non-U.S.

PO0651

Activation of STING Causes Proteinuria in Mice and Contributes to Diabetic Kidney Disease

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Background: Diabetic kidney diseases (DKD) is one of the major health problems worldwide with no current cure. Podocytes express elements of the innate immune system which may contribute to chronic inflammation and glomerular damage. Stimulator of interferon genes (STING) was identified as a crucial regulator of the DNA sensing pathway and the cGAS-STING signaling pathway has been shown to regulate inflammation and energy homeostasis under obesity conditions, kidney fibrosis and acute kidney injury. Whether STING activation contributes to development and progression of DKD remains unknown. We tested the hypothesis that activation of STING causes podocyte damage and proteinuria in DKD.

Methods: c-diAMP treatment to inhibit STING (10μM) in immortalized human podocytes was performed for 24h. 8-week-old C57BL6 mice were IP-injected with a single dose of c-diAMP (25mg/kg) and sacrificed 72h after injection. 16-week-old db/db mice were used ito evaluate activation of STING in experimental DKD. 10-week-old db/db mice were IP-injected with C-176 (750nM), STING-specific antagonist, for 4 weeks daily. STZ injected STING knockout (STING-/-) and C57BL6 mice were also utilized. Blood and kidneys were harvested and processed for in-depth phenotypical analysis, including urinary albumin-to-creatinine ratio, histological analysis, transmission electron microscopy, glomeruli isolation and serum analysis.

Results: Podocytes showed expression all of the cGAS-STING components at mRNA and protein levels under physiological conditions and treatment with c-diAMP lead to activation of the cGAS-STING pathway. Treatment of C57BL6 mice with c-diAMP resulted in an increased expression of STING in kidney cortex and this was associated with increased urine ACR. STING activation is also implicated in glomerular injury in db/db mice at the baseline, which could be ameliorated with pharmacological (C-176) inhibition. In STZ model of DKD, STING-/- mice did not develop albuminuria and had no changes in their BUN, serum creatinine levels or histological abnormalities compared to STZ controls.

Conclusions: Our findings demonstrate an important role of the cGAS-STING signaling pathway in mediating the glomerular injury in DKD and provide an evidence for STING as a potential treatment target in DKD.

Funding: Private Foundation Support

PO0652

Blocking the ACE N-Domain Prevents Salt Sensitivity in Diabetes

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Background: Angiotensin converting enzyme (ACE) can regulate inflammation independently of angiotensin II production. Specifically, blocking the ACE N-domain results in the accumulation of the anti-inflammatory peptide AcSDKP. We showed that interleukin-6 (IL-6) induces salt sensitivity through an upregulation of the epithelial sodium channel (ENaC) in diabetic mice. Here, we hypothesize that blocking the ACE N-domain reduces renal IL-6 levels and prevents salt sensitivity in diabetes.

Methods: 7-mo-old diabetic db/db mice lacking a functional ACE N-domain (db-nko) and db/db controls (db) were exposed to a high salt diet (HS, NaCl 4%w/w) for 4 weeks (n=6).

Results: Despite similar hyperglycemia and body weight, after HS, db-nko displayed lower mean arterial pressure (MAP) (107±5 vs. 123±4 mmHg, P<0.01), less expression of αENaC subunit (0.8±0.3 vs. 1.4±0.3 A.U., P<0.05), and lower renal IL-6 levels (112±16 vs. 270±17 pg/mg kidney, P<0.01) compared to db mice. Flow cytometry analysis of renal macrophages showed that db-nko mice have lower M1 ($CD45^+F4/80^+CD80^+$) to M2 ($CD45^+F4/80^+CD206^+$) ratio compared to db (2.4±0.6 vs. 4.8±0.7, P<0.05). Further, renal macrophages ($3x10^4$) were isolated by flow cytometry cell sorting, cultured for 16h, and IL-6 assessed in the culture media by ELISA. Macrophages from db-nko release significantly less IL-6 compared to db macrophages (2±1 vs. 7±2 pg/ml, P<0.01). To evaluate the role of AcSDKP, an additional group of db-nko were treated for 8 weeks with S17092, an inhibitor of prolyl-oligopeptidase that forms AcSDKP. After HS, MAP, renal αENaC expression, IL-6, and the macrophage M1/M2 ratio of db-nko+S17092 were similar to db mice. Finally, to evaluate whether the absence of the ACE N-domain affects immune or non-immune renal cells, db mice were transplanted with a bone marrow (BM) of db-nko while db-nko received a db BM. Strikingly, db-nko with db BM developed salt sensitivity but db with db-nko BM remained salt resistant (MAP after HS: 121±8 vs. 107±4 mmHg, P<0.05). The absence of salt sensitivity in db with db-nko BM was associated with less IL-6 levels and lower M1/M2 macrophage ratio in the kidney.

Conclusions: Thus, blocking the ACE N-domain and the consequent AcSDKP accumulation in immune cells, polarize macrophages towards an M2 phenotype resulting in less renal inflammation and no salt sensitivity in diabetes.

Funding: Other NIH Support - NHLBI

PO0653

Renal Type 1 Pericytes in the Development of Diabetic Kidney Disease

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Background: Pericytes are described as regulators and keepers of the vascular system. They can recognize and respond to inflammatory stimulus, through secretory and phenotype alterations. So far, the involvement of pericytes during diabetic kidney disease (DKD) has not been demonstrated yet, as well as how they can change its inflammatory and metabolic profile in this condition. In addition, not much is known about how these cells trigger DKD-associated injury and inflammation.

Methods: DKD was induced in NG2-Dsred mice by the combination of unilateral nephrectomy (UNx) and multiple low doses of streptozotocin (50 mg/Kg). UNx controls received only vehicle. All the mice were followed for 12 weeks. Urine glucose, protein/creatinine and albuminuria were evaluated as markers of renal function. NPHS1, KIM-1, IL-6, PKM2, HK2, CPT1a and LDH (qPCR), pericyte frequency/phenotype/secretion profiles (FACS) were assessed in kidney samples.

Results: DKD mice had an increased in protein/creatine ratio, as well as in glucosuria when compared to non-DKD mice (p<0.01). The impaired renal function was accompanied by reduction in NPHS1 gene expression (p<0.05). Moreover, we observed increase in PKM2, HK2 and IL-6 expression (p<0.05). FACS analysis revealed increase in relative and absolute numbers of CD146+NG2+ cells (p<0.05), as well as an increase of type 1 pericytes (NG2+Nestin-), when compared to non-DKD mice (p<0.05). Furthermore, the analysis showed that pericytes from DKD context had increase LAP-1 and IL-6 MFI, and less Nestin MFI (p<0.05).

Conclusions: Type 1 pericytes seems to contribute to DKD progression, through IL-6 secretion and TGF-b conversion from LAP-1. However, it is still necessary to evaluate the metabolic profile of pericyte during the DKD progression and how this cells communicate with other renal cells. FAPESP (2019/ 19/21359-3 and 2017/05264-7), CAPES and CNPq.

Funding: Government Support - Non-U.S.

PO0654

Follistatin, an Activin A Antagonist in an Accelerated Mouse Model of Diabetic Kidney Disease

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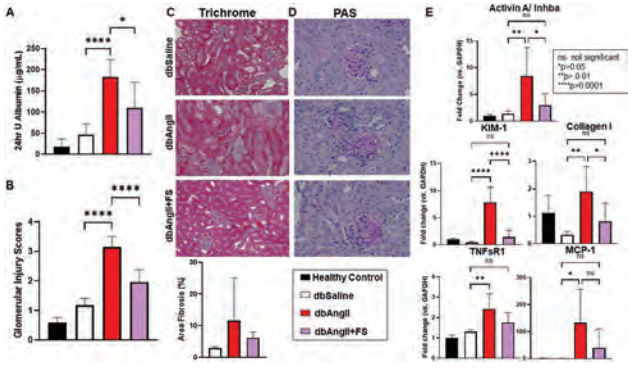
Background: We previously demonstrated that circulating activin A, an inflammatory mediator implicated in cellular senescence-induced adipose tissue dysfunction and profibrotic kidney injury, is increased in human diabetic kidney disease (DKD) and directly correlates with kidney dysfunction. We hypothesized that follistatin, an activin A antagonist, could negate the injurious effects of activin A in DKD.

Methods: An accelerated type 2 diabetes (db/db; 10-week-old) mouse model was generated by implantation of osmotic minipumps loaded with angiotensin (Ang)-II (1000 ng/kg/min, n=14). Mice were randomized to intraperitoneal follistatin (5μg/g) or vehicle at days 15 and 18 post-pump with euthanasia at day 28. Kidney injury markers included: proteinuria, kidney injury marker (KIM)-1, tumor necrosis factor soluble receptor 1 (TNFsR1), collagen I and histological changes were measured. Kidney gene expression of activin A and macrophage chemoattractant protein-1 (MCP-1) were measured by qPCR.

Results: Implantation of AngII (dbAngII) pumps induced proteinuria, mesangial matrix expansion, glomerular sclerosis, and increased fibrosis in db/db mice compared to saline-pump controls (dbSaline; Figure 1A-D). Collagen I, TNFsR1, MCP-1, KIM-1, and activin A gene expression was increased in dbAngII mice (Figure 1E). Follistatin therapy reduced activin A gene expression and other kidney markers in addition to morphology.

Conclusions: Follistatin attenuated diabetic kidney injury, reduced activin A expression and decreased macrophage chemoattractants. Activin A may be a novel therapeutic target for halting DKD progression.

Funding: NIDDK Support, Other NIH Support - DiaComp



PO0655

The Functional Role of Neat1 in Diabetic Kidney Disease

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Background: Long non-coding RNA Nuclear Paraspeckle Assembly Transcript 1 (Neat1) serves as a key structural component of paraspeckle assembly, which has been implicated in a variety of biological processes. Increased Neat1 expression is associated with inflammatory responses and the pathogenesis of acute kidney injury. Yet, it remains unknown whether Neat1 also regulates inflammatory pathways in chronic kidney disease (CKD), especially in diabetic kidney disease (DKD).

Methods: Streptozotocin (STZ)-induced DKD was established in C57B6 mice with a low-dose injection protocol for 5 consecutive days. Neat1 gene was specifically knocked down in the kidney by shRNA gene silencing via ultrasound-mediated microbubble gene transfer. After 10 weeks, all mice were sacrificed for analysis of kidney function, morphology, and expression of inflammatory and fibrotic markers.

Results: Neat1 expression was induced in STZ-induced diabetic kidneys. Overexpression of IL-6 and CCL-2 in diabetic mice was attenuated by Neat1 knockdown in which kidney function was preserved with less kidney tubular injury compared to diabetic control mice. Expression of fibrotic markers, such as fibronectin and collagen-1 was decreased in diabetic mice with Neat1 knockdown.

Conclusions: Neat1 plays a pathogenetic role in DKD and its knock-down could alleviate diabetic kidney injury. *Funding: Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2019.*

PO0656

Cell Surface GRP78 Regulates TGF-β1-Mediated Profibrotic Responses via TSP-1 in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure in North America, characterized by glomerular accumulation of extracellular matrix (ECM) proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses plays a central role in its pathogenesis. We recently showed that the endoplasmic reticulum resident GRP78 translocates to the cell surface in response to HG, where it mediates Akt activation and downstream profibrotic responses in MC. Transforming growth factor β1 (TGFβ1) is recognized as a central mediator of HG-induced profibrotic responses, but whether it is regulated by cell surface GRP78 (csGRP78) is unknown. TGFβ1 is stored in the ECM in a latent form, requiring release for biological activity. The matrix glycoprotein thrombospondin-1 (TSP-1) is an important factor in TGFβ1 activation, known to be increased in DKD and by HG in MC. Here we determined whether csGRP78 regulates the expression of TSP-1 and thereby TGFβ1 activation in HG.

Methods: Primary rat and mouse MC were treated with 30mM HG. TSP-1 upregulation and deposition into the ECM and TGFβ1 activation were assessed using standard molecular biology techniques.

Results: TSP-1 transcript and promoter activity were increased by HG, as were cellular and ECM TSP-1, and these required PI3K/Akt activity. To determine whether csGRP78 was required, its activity was inhibited using vaspin or the C-terminal targeting antibody C38. Alternatively, GRP78 translocation to the cell surface was prevented with siRNA downregulation of its transport chaperone MTJ-1. All of these prevented HG-induced TSP-1 upregulation and deposition into the ECM. The HG-induced increase in active TGFβ1 in the medium was also inhibited, and this was associated with reduced intracellular Smad3 activation and signaling.

Conclusions: These data support an important role for csGRP78 in regulating HG-induced TSP-1 transcriptional induction via PI3K/Akt signaling. Functionally, this enables TGFβ1 activation in response to HG, with consequent increase in ECM proteins. Means of inhibiting csGRP78 signaling represent a novel target for preventing the DKD-associated fibrosis. TGFβ1 is a central mediator of DKD, but its inhibition is not feasible due to adverse effects. Thus, indirect methods of attenuation are of current interest.

Funding: Government Support - Non-U.S.

PO0657

Histone Acetyltransferase p300 Inhibition Attenuates Kidney Fibrosis Under Diabetic Conditions

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Background: Diabetic nephropathy, the major cause of chronic kidney disease, is associated with progressive renal fibrosis. Transforming growth factor (TGF)-β1 plays important roles in extracellular matrix accumulation in diabetic nephropathy. Recently, acetyltransferase p300 has been shown to mediate intracellular TGF-β1 activity through facilitating Smad function. Therefore, in this study, the effect of p300 inhibition on kidney fibrosis under diabetic conditions was investigated to assess the therapeutic potential of p300 modulation.

Methods: Primary tubular epithelial cells (TECs) from C57BL/6 mice were treated with TGF-β1 with or without histone acetyltransferase p300 siRNA transfection of A485, a selective inhibitor for p300. For in vivo experiments, kidney samples were obtained from streptozotocin induced diabetic mice were administered with A485 (1mg/kg) oral gavage for 6 weeks.

Results: In vitro, TGF-β1 (5ng/ml) treatment significantly upregulated p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen mRNA and protein expressions in TECs. These increases were attenuated significantly when TECs were transfected with p300 siRNA. Similar findings were found when the cells were treated with p300 specific inhibitor A485 (100nM). In vivo, the mRNA and protein expression of p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen were significantly increased in kidney samples form DM mice compared to non-diabetic control mice. Oral A485 administration abrogated these increases significantly. In addition, the increased blood urea nitrogen and albuminuria levels were significantly attenuated with oral A485 treatment in the diabetic mice. Immunohistochemistry and Sirius Red staining also revealed that fibronectin expression was significantly higher and tubulointersititial fibrosis was significantly worse in diabetic mice kidneys compared with control mice. These changes were ameliorated by A485 treatment.

Conclusions: These findings suggest that inhibition of histone acetyltransferase p300 could improve diabetic-induced tubular fibrosis and may be a potential therapeutic strategy for diabetic nephropathy.

PO0658

Recombinant Slit2 Attenuates Renal Fibrosis in a Mouse Model of Diabetic Nephropathy

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Background: We recently described Akita$^{+/-}$ Ren$^{+/-}$ mice as a model that replicates many features of human diabetic nephropathy (DN), including hyperglycemia, hypertension, albuminuria, reduced glomerular filtration rate, glomerulosclerosis and interstitial fibrosis. Previously, we showed that recombinant N terminal Slit2 (Slit2) inhibited renal fibrosis in mouse models of postischemic renal fibrosis and obstructive uropathy. To date, however, the anti-fibrotic effects of Slit2 have not been tested in a model of DN. Here we examine the effects of Slit2 therapy in the Akita+/– Ren+/– mouse.

Methods: At 6 weeks of age, Akita+/– Ren+/– and Akita-/– Ren-/– mice were randomized to receive thrice weekly intraperitoneal injections of Slit2 (2 ug) or saline, and followed for a further 20 weeks.

Results: When compared with saline-treated Akita+/– Ren+/–mice, Slit2-treated Akita+/– Ren+/– mice demonstrated improved survival (66.67% vs. 50%) and decreased systolic blood pressure (142±6.1mmHg vs.167±8.5 mmHg). Structurally, Slit2-treated Akita+/– Ren+/– mice displayed decreased glomerulosclerosis (glomerular picrosirius red score: 0.22±0.02 vs. 0.28±0.02) and interstitial fibrosis (picrosirius red staining: 0.08±0.01 vs. 0.10±0.01, a-smooth muscle actin (aSMA) staining: 0.02±0.00 vs. 0.05±0.01, and vimentin staining: 0.11±0.01 vs. 0.15±0.01). Slit2 treatment attenuated the nuclear translocation of the pro-fibrotic proteins YAP (26.44±7.87% vs 66.20±7.63%) and TAZ (28.55±2.99% vs. 71.42±7.90%, a marker of YAP/TAZ activation) in aSMA positive fibroblasts in mouse kidneys. In vitro, Slit2 decreased TGF-b-induced YAP and TAZ activation in cultured NRK49F fibroblasts, as evidenced by a reduction in YAP (55.55±4.67% vs 92.54±1.36%) and TAZ (30.85±7.877.319 % vs 80.2±3.44%) nuclear localization. All p values < 0.05.

Conclusions: Taken together, our results show that Slit2 attenuates diabetic kidney fibrosis, possibly through inhibition of fibroblast YAP and TAZ activity.

PO0659

Impact of Mineralocorticoid Receptor Antagonism in a New Model of Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the most prevalent form of chronic kidney disease and is associated with cardiovascular diseases. Several studies reported beneficial effects of mineralocorticoid receptor (MR) antagonists in DKD, indicating the importance of aldosterone/MR axis in this pathology. To study the metabolic and renal alterations in a new model of DKD and explore the effect of the MR antagonist canrenoate.

Methods: Sham or 5/6 nephrectomy was performed in 6 weeks old C57Bl6J mice. After nephrectomy (Nx) mice were randomly assigned to chow diet (Sham), Nx, 60% fat diet (Nx-HFD) and 60% fat diet + 30 mg/kg/day canrenoate (Nx-HFD-CAN). Glycated hemoglobin (HbA1c) and glucose tolerance (ipGTT) were analyzed after 6 weeks. We evaluated plasma levels of leptin and albuminuria and IL-10 mRNA levels. RNA Nanostring analysis was performed in kidney samples. *In vitro* studies were performed in renal fibroblasts.

Results: HbAc1 was higher in the Nx-HFD group vs Sham or Nx, an effect prevented by canrenoate (see table). The glucose tolerance was impaired in NX-HFD vs Sham or Nx, an effect ameliorated by canrenoate. Kidney fibrosis was increased in Nx HFD group vs Sham or Nx and it was lower in the canrenoate treated group. Nanostring analysis highlighted the impact of canrenoate on inflammation, fibrosis and proliferation pathways. We found high plasma leptin and kidney IL-10 mRNA levels in the Nx-HFD mice which were lower after canrenoate treatment. The profibrotic effect of leptin observed in renal fibroblasts was mediated by IL-10 (Col1 mRNA levels: Ctl: 0.99±0.03, leptin + IgG: 1.19±0.07*#, leptin + anti-IL10 antibody: 0.90±0.05#, n= 6, p<0.05 * vs Ctrl; # vs Leptin+IgG).

Conclusions: MR antagonism improves metabolic and kidney derangements associated with DKD. The upregulation of leptin/IL-10 signalling observed in this DKD model may contribute to the renal fibrosis.

Funding: Commercial Support - Astrazeneca, Government Support - Non-U.S.

	Sham (n=7)	Nx (n=9)	Nx-HFD (n=9)	Nx-HFD-CAN (n=9)
HbAc1 (%)	4.32±0.15	4.2±0.19	4.57±0.06*	4.07±0.14+
GTT AUC	1556±34	1476±72^	2443±198*	1861±75+
Albuminuria (mg/24h)	15.0±0.7	23.3±5.0	34.0±5.5^	22.3±2.7*+
Fibrosis (relative value vs Sham)	1.03±0.28	0.96±0.15	3.06±0.68^	1.15±0.18+
Plasma leptin (log(pg/ml))	2.4±0.33	2.15±0.06	3.59±0.26#	2.89±0.13+
IL10 mRNA levels (relative expression vs Sham)	1.0±0.10	1.12±0.11	4.21±0.35*#	1.03±0.05+

p<0.05 * vs Sham; # vs NX; + vs NX HFD

PO0660

Role of GRP56 in Glomerular Endothelial Cell Injury in Diabetic Kidney Disease

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Background: GEC injury is a key pathogenic event in early Diabetic kidney disease (DKD). However, the mechanisms of GEC injury in DKD remain unclear and the treatments by targeting specifically GEC injury are lacking.

Methods: By taking advantage of transgenic mice expressing enhanced yellow fluorescent protein (EYFP) under the endothelium-specific Flk1 promoter, we were able to sort GECs from both control and diabetic mice for RNA sequencing. We identified G-protein coupled receptor-56 (GPR56) as a highly upregulated gene in diabetic GECs. Then, we confirmed the role of GRP56 in GEC injury in DKD by both in vitro and in vivo studies.

Results: We searched the recent single-cell RNA-seq data and confirmed that GPR56 expresses predominantly in GECs in the glomeruli. We found that both mRNA and protein expression of GPR56 increased in human DKD and correlated negatively with eGFR, suggesting an important role of GPR56 in human DKD. In cultured GECs, GRP56 expression was upregulated by high glucose and advanced glycation endproducts (AGE). Collagen III, a major ligand of GPR56, was able to suppress eNOS phosphorylation and expression through activation of GPR56. We demonstrated that GPR56 reduced eNOS phosphorylation likely through G12/13-mediated RhoA pathway and inhibited eNOS expression via Gi-mediated inhibition of cAMP/PKA/KLF4 pathway in cultured GECs. *In vivo*, knockout of GPR56 attenuated albuminuria and glomerular injury and restored expression of eNOS and KLF4 in GECs in mice with DKD.

Conclusions: Taken together, these findings suggest a critical role of GPR56 and its underlined mechanism in regulation of GEC injury in early DKD.

Funding: NIDDK Support, Veterans Affairs Support

PO0661

Transcriptional Profiling of Renal Endothelial Compartments During Progression of Murine Diabetic Nephropathy

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Background: Kidney endothelial cell (EC) injury and capillary rarefaction are key pathogenic events in diabetic nephropathy (DN). The molecular mechanisms and spatial and temporal patterns of EC responses in DN remain elusive. We hypothesized that single-cell RNA sequencing (scRNASeq) would reveal transcriptional changes in specific kidney EC populations during murine DN progression.

Methods: Kidney EC (n=5,464) collected from 6-, 11-, and 20-week-old BTBR *ob/ob* mice and lean littermates were analyzed by scRNASeq using SmartSeq2. By a combination of established markers, immunofluorescence, and *in situ* hybridization, we ascribed anatomical identity to EC clusters assigned by Pagoda2, assessed their individual transcriptional changes during disease progression, and performed Ingenuity Pathway Analysis.

Results: We identified EC clusters corresponding to afferent and efferent arterioles, glomerular and peritubular capillaries (PTC), ascending and descending vasa recta, veins and lymphatics. BTBR *ob/ob* mice developed progressive PTC rarefaction. Analysis of differentially expressed genes (DEGs) and pathway activity allocated most DN-associated changes to PTC and glomerular EC. Intriguingly, several consistent DEGs showed differential up- and downregulation depending on cell type and disease stage (Fig. 1). E.g., whereas glomerular EC showed DN stage-dependent activation of IGF1 signaling and inflammation, IGF1 signaling and cell cycle progression were inhibited in PTC-EC.

Conclusions: Using high-resolution scRNASeq, our study provides insight into the complexity and diversity of responses in different EC compartments during progression of DN, which may help pinpoint new therapeutic targets.

Funding: Commercial Support - AstraZeneca Gothenburg, Sweden

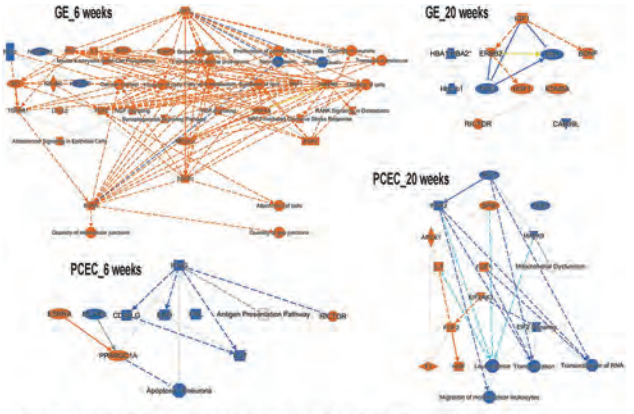

Figure 1. Activated (orange) and inhibited (blue) pathways at 6 and 20 weeks in diabetic glomerular EC and PTC EC.

PO0662

Transcriptomic Alterations of Angiogenesis Activity in Human Mesenchymal Stromal/Stem Cells in Diabetic Kidney Disease

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Background: Therapeutic interventions that optimize angiogenic activities may reduce rates of end-stage kidney failure and extremity amputations in individuals with diabetic kidney disease (DKD). Autologous mesenchymal stromal cells (MSCs) infusion is a promising novel treatment, but DKD-related factors, including hyperglycemia and uremia, might alter MSC angiogenic repair capacity.

Methods: To explore MSC angiogenic dysregulation in DKD, we characterized the transcriptome of adipose tissue-derived MSC obtained from DKD subjects (DKD-MSC) compared to age-matched controls without diabetes or kidney impairment. Next-generation RNA sequencing (RNA-seq) was performed to identify in MSCs differentially expressed (DE; adjusted $p<0.05$, $|\log_2$ fold change$| >1$) mRNA and miRNA involved in angiogenesis (GeneCards). DE miRNAs were further inspected to identify targets involving interactions with angiogenesis genes (miRWalk and Ingenuity pathway analysis).

Results: Mean age in DKD subjects was 65±8 years, 31% were females, and mean eGFR was 38.9±15.4 mL/min/1.73m^2 (n=29), while control subjects (n=9) had higher eGFR (80.5±13.3 mL/min/1.73m^2; $p<0.0001$). RNA-seq analyses revealed 133 DE mRNAs (77 up- and 56 down-regulated) in DKD-MSC compared to Control-MSC. Figure 1A shows the top 30 DE mRNAs. Of 208 DE miRNAs, 14 (Figure 1B) regulated 18 unique DE mRNA targets associated with angiogenesis. Among these miRNAs resulted in pro- and anti-angiogenic regulators including *miR-17-5p, let-7d-5p, miR-125a-5p* and *miR-30c-5p*.

Conclusions: MSC from individuals with DKD may have limited angiogenic potential and reparative capacity, warranting caution in autologous MSC transplantation in DKD.

Funding: NIDDK Support, Private Foundation Support

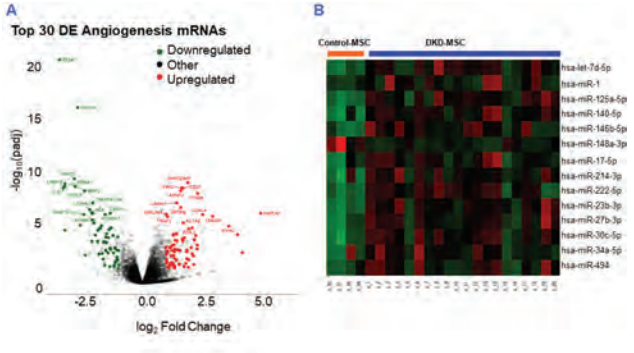

Figure 1.

PO0663

Contribution of Endothelial ADAM17 in a Pre-Diabetic Mouse Model

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Background: ADAM17 activates inflammatory and fibrotic processes through the shedding of various molecules such as TNF-α or TGF-α. In physiological situations, ADAM17 is expressed mainly in the distal tubular cell while, in renal damage, its expression increases throughout the kidney including the endothelium. Galectin 3 (Gal3) is a lectin that is postulated as a biomarker of kidney damage. Its overexpression in diabetic nephropathy could be a compensatory mechanism for damage induced by reactive oxygen species (ROS). To characterize, for the first time, an experimental mice model fed with high-fat diet (HFD) with deletion of ADAM17 in endothelial cells and to describe the expression of kidney Gal3.

Methods: After 25 weeks of HFD, glycaemia, glucose tolerance, body weight, albuminuria, glomerular microscopy (PAS staining) and Gal3 (immunohistochemistry) were analyzed in 15 wildtype (WT) mice and 15 endothelial ADAM17-KO mice.

Results: HFD mice had higher glucose levels, glucose intolerance, and higher body weight compared to standard diet (SD) mice. Moreover, HFD increased albumin/creatinine ratio in WT mice compared to ADAM17-KO mice. At the glomerular level, WT mice with HFD had bigger glomerular size and mesangial matrix expansion. In contrast, the deletion of ADAM17 prevented the increase in glomerular size and decreased the mesangial area and index. Gal3 increased its expression in ADAM17-KO mice on both SD and HFD mice (see table).

Conclusions: The deletion of ADAM17 in endothelium prevents the appearance of glomerular hypertrophy, expansion of the mesangial matrix, albuminuria and increases the expression of Galectin-3 in the renal cortex. The increase in the expression of Galectin-3 could be a compensatory mechanism for the lack of activation of the EGFR/TNFR pathway in the endothelium ADAM17-KO model.

	3h-fasting blood glucose (mg/dL)	Glucose tolerance test (mg/dL)	Body weight (g)	Albuminuria (µg alb/mg crea)	Glomerular tuft Area (µm^2)	Mesangial area (µm^2)	Mesangial index	Galectina-3 expression
ADAM17WT-SD	185,7±6,2	159,6±9,4	36,8±2,6	27,3±4,294	2985,1±135,9	1286,8±63,0	0,42±0,01	11,7±1,0
ADAM17WT-HFD	245,4±12,8*	315,6±20,8*	50,9±1,8*	50,4±4,926*	3344,3±105,1*	1615,7±58,9*	0,48±0,01*	15,6±1,5
ADAM17KO-SD	193,5±5,4	180,7±5,8	40,2±2,0	33,7±13,77	3245,2±100,9$	1392,0±48,05	0,43±0,01	29,7±1,9$
ADAM17KO-HFD	235,4±8,6*	314,6±51,8*	49,7±1,9*	29,7±3,393$	3344,2±105,4	1410,8±48,5$	0,42±0,00$	31,6±1,3$

*p<0,05 HFD vs. SD $p<0,05 KO vs. WT

PO0664

Apolipoprotein C3-Rich Low-Density Lipoprotein Is Elevated in Diabetic Kidney Disease Patients and Enhances Endothelial Cell Injury

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Background: Diabetic dyslipidemia plays a pathogenetic role in the development and perpetuation of diabetic kidney disease (DKD). Apolipoprotein CIII (ApoC3), a component of some triglyceride-rich very-low-density and low-density lipoprotein, expression by glucose may contribute to diabetic dyslipidemia. Early endothelial damage is also associated with progression of DKD. Thus, we want to study the effect of ApoC3-rich low-density lipoprotein (AC3RL) on DKD and its underlying molecular mechanisms.

Methods: Plasma samples were obtained from clinically stable patients with DKD recruited at our outpatient clinic. AC3RL was isolated from plasma low-density lipoprotein with the affinity-purified method.

Results: Level of plasma AC3RL were significantly higher in DKD patients than in control subjects (Figure; $p<0.05$). AC3RL induced endothelial cells (ECs) apoptosis and reduction of the fenestrated endothelium. The level of phosphorylation of IKKa, p53 and Cleaved Caspase-3 (CC3) were markedly increased in AC3RL-induced ECs ($p < 0.05$ vs. control; $n = 4$). The contribution of P-IKKa, p53, and CC3 in AC3RL-mediated apoptosis were blocked in ECs transfected with si-IKKa.

Conclusions: AC3RL elevation may be a risk factor for DKD, and inhibiting IKKa may be novel protect endothelial damage and arrest DKD progression.

Funding: Clinical Revenue Support

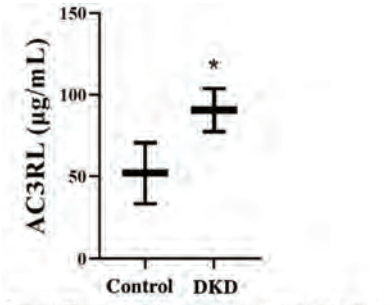

Figure: Plasma AC3RL are increased in patients with DKD. The AC3RL is plotted for the control subjects and the DKD patients (*: p< 0.05 vs. Control; n = 9).

PO0665

Identification of Cell-Specific Transcriptomic Changes and Cross-Talk in Diabetic Mice with Podocyte-Specific Induction of KLF6 Using Single Nuclei RNA Sequencing

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Background: Krüppel-Like Factor 6 (KLF6), a zinc finger transcription factor, is a key regulator of cytochrome c oxidase assembly in the podocytes. We previously reported that podocyte-specific loss of *KLF6* exacerbates diabetic kidney disease (DKD). However, the role of podocyte-specific induction of human *KLF6* in DKD remains unexplored.

Methods: A combination of unilateral nephrectomy and streptozotocin (UNx-STZ) was utilized to induce DKD in mice. Using the "Tet-on" system, mice with podocyte-specific induction of human *KLF6* (*hKLF6^{PODTA}*) were generated by crossing *NPHS2-rtTA* mice with *tre-hKLF6* mice and fed with doxycycline-containing diet. UNx-STZ-*NPHS2-rtTA* and SHAM UNx-Veh mice served as diabetic and non-diabetic controls, respectively. Single nucleus (sn)RNA-seq libraries were prepared from kidney cortex using the 10X Chromium System. Raw sequencing data was aligned to mouse pre-mRNA reference genome using Cell Ranger. Quality control, dimensionality reduction and clustering were performed using the R-package, Seurat.

Results: 23 clusters were generated using unsupervised clustering analysis. Enrichment and pathway analyses showed a downregulation of injury-related pathways such as inflammatory and interleukin signaling in the UNx-STZ-treated *hKLF6^{PODTA}* group across the podocyte, endothelial cell, mesangial cell, and proximal tubular clusters, compared to the UNx-STZ-treated *NPHS2-rtTA* group. Conversely, metabolic pathways such as oxidative phosphorylation and fatty acid metabolism were upregulated. A cross-reference of the differentially expressed genes (DEGs) in the podocyte cluster of the UNx-STZ-treated *hKLF6^{PODTA}* group with a KLF6 ChIP-seq data set revealed the presence of putative KLF6 binding sites in the regulatory regions of several DEGs. A unique proximal tubule (PT) cluster with distinctive gene expression signature was identified in the *hKLF6^{PODTA}* group, suggesting an intercellular communication between podocytes and the PT cells in the *hKLF6^{PODTA}* group that mediates the progression of DKD.

Conclusions: SnRNA-seq demonstrates potential mechanisms by which podocyte-specific induction of *KLF6* attenuates the progression of DKD.

Funding: NIDDK Support

PO0666

Dynein-Driven Pathogenesis of Diabetic Podocytopathy

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Background: Dynein-mediated trafficking of nephrin has been recently identified as a cause of INF2-mediated podocytopathy, where de-sequestrated dynein light chain (Dynll1) by mutant INF2 activated dynein transport complex, which subsequently facilitated nephrin degradation and impared its surface recycling to maintain the glomerular filtration barrier. Transcriptome study revealed upregulated expression of Dynll1 in human diabetic nephropathy (DN), suggesting a potential dynein driven pathogenesis. This work tested the hypothesis whether diabetic stresses cause podocytopathy via dynein-mediated mistrafficking of nephrin.

Methods: The transcription of dynein components in DN was analyzed in Nephroseq and compared to normal kidney, which was validated in cultured podocytes exposed to high glucose (HG, 30 mM), using cells exposed to normal glucose (NG, 5.5 Mm) as controls. The dynein-mediated post-endocytic sorting and recycling of nephrin was examined in an in vitro antibody-mediated trafficking model, with or without interference in the dynein trafficking pathway. The dynein-mediated nephrin trafficking in human DN was evaluated by the Dynll1-nephrin colocalization in kidney biopsy specimen, using normal kidney and other human podocytopathies as controls.

Results: 1. Data analysis in Nephroseq revealed a significant upregulation of Dynll1 in human DN, as compared to other dynein components, and it correlated with the decline of renal function. This upregulated expression was redemonstrated in cultured podocytes exposed to HG at mRNA and protein levels, suggesting Dynll1 is a diabetes-responsive component of dynein transport complex. 2. HG-induced podocytopathy was characterized by enhanced dynein-mediated trafficking reflected by increased recruitment of dynein components to endocytosed nephrin and impaired nephrin recycling, which could be reversed by knock-out of Dynll1 or by direct inhibition of dynein. 3. Immunohistochemistry staining revealed upregulated expression of Dynll1 with a significant colocalization with nephrin in kidney biopsy sections of human DN, as seen in dynein-driven FSGS mediated by INF2 mutations.

Conclusions: Dynein-mediated mistrafficking of slit diaphragm protein is a new mechanism by which high glucose stress causes podocytopathy, where Dynll1 plays a key role as a diabetes-reponsive component. Enhanced Dynll1-nephrin colocalization may be used as a biomarker for dynein-driven pathogenesis in human DN.

Funding: Other NIH Support - 5K12HD027748-28 The University of Iowa Child Health Research Career Development Award (CHRCDA)

PO0667

An Accelerated Method of Podocyte Differentiation from Human Induced Pluripotent Stem Cells for Modeling Diabetic Nephropathy

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Background: Podocytes are highly specialized visceral epithelial cells that maintain glomerular barrier function and play important roles during both kidney development and progression of glomerular disease. Mature podocytes extracted from mammalian kidneys are difficult to culture long-term, hindering research on podocytopathies. Establishing an alternative, inexhaustible source of podocytes would be a valuable tool for understanding the molecular mechanisms underlying specific podocytopathies and developing targeted therapies. The discovery of induced pluripotent stem cells (hiPSCs) led to several protocols for deriving podocytes from hiPSCs, which could potentially serve as an unlimited source of podocytes.

Methods: All the existing effective methods for hiPSC- derived podocytes either require lengthy culture times (~ 30 days) or expensive media. Therefore, we sought to develop a faster and less expensive method. We found a simple and effective method to derive podocytes from hiPSCs in twelve days of culture and at lower cost. Our method followed a stepwise protocol in which the hiPSC were differentiated into primitive streak followed by intermediate mesoderm using activation of Activin A and Wnt signaling. Intermediate mesoderm cells were treated with FGF9 to generate nephron progenitors, followed by a cocktail of established growth factors to finally derive mature podocytes.

Results: The developed podocytes expressed podocyte markers including PODX, synaptopodin, MAFB, Nephrin at protein levels comparable to the existing methods. Flow cytometry analysis revealed that our method results in generation of ~80% mature glomerular podocytes. We confirmed the functionality of the hiPSC-derived podocytes via permeability assay for FITC-albumin uptake. Next, we treated the cells with media containing high glucose (100mM) to generate a hiPSC-derived podocyte model of diabetic nephropathy. The podocytes showed actin rearrangement upon treatment with high glucose, suggesting the ability of these cells to effectively model podocytopathies. In addition, treatment with high glucose resulted in increased cytotoxicity and reduced viability in the podocytes.

Conclusions: Altogether, we have discovered a faster and less expensive method of podocyte differentiation from hiPSCs, as well as a new tissue culture model of diabetic nephropathy for disease modeling.

Funding: Private Foundation Support

PO0668

Contribution of Proximal Tubular ADAM17 in a Pre-Diabetic Mouse Model

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Background: Both acute and chronic kidney lesions induce an increase in ADAM17 that cleaves several transmembrane proteins, among them molecules related to inflammatory and fibrotic pathways. Our group demonstrated that in experimental type 1 diabetes, inhibition of ADAM17 decreases inflammation and renal fibrosis. Indeed, this protease is proposed as a possible therapeutic tool for the treatment of kidney disease. However, its role in pre-diabetic stages has not been fully analyzed.

Methods: In a knockout mouse model for tubular ADAM17 fed with high-fat diet (HFD), we determined glycemia, glucose tolerance, body weight, hypertrophy and mesangial expansion (PAS staining) and the number of podocytes (immunohistochemistry), after 25 weeks of a follow-up (n = 15 WT, n = 15 KO).

Results: Wild-type (WT) mice on HFD had higher body weight and higher glycaemia with dysregulation of glucose homeostasis compared to mice on standard diet (SD). At the glomerular level, WT mice with HFD had greater glomerular size and mesangial expansion. In contrast, the deletion of ADAM17 in the proximal tubular cell improved glucose

tolerance and protected against glomerular injury. The loss of podocytes observed in WT mice with HFD was not observed in HFD-mice with deletion of ADAM17 (see table).

Conclusions: The conditional knockout of ADAM17 at the proximal tubule level improves glucose tolerance and reduces kidney lesions typically observed in diabetes such as glomerular hypertrophy, mesangial expansion and podocytes loss, in a murine model with high-fat diet that mimics pre-diabetes. ADAM17 may therefore have an inducing role in pre-diabetic kidney injury.

	Body Weight (g)	3h-fasting blood glucose (mg/dL)	Glucose tolerance test (mg/dL)	WT-1 staining (podocyte number)	Mesangial Area (µm2)	Glomerular tuft Area (µm2)
ADAM17WT -SD	34,01±0,81	191,91±4,12	155,75±7,20	9,74±0,56	1212,24±83,78	2653,06±198,82
ADAM17WT - HFD	53,18±0,65*	236,63±10,04*	435,25±36,06*	7,25±0,18*	1516,18±115,29*	3332,01±237,49*
ADAM17KO -SD	37,22±1,46	199,13±5,94	221,71±22,21$	10,45±0,63	1323,22±78,6	2996,17±187,55
ADAM17KO -HFD	54,3±3,01*	218,63±13,62	241,17±9,74$	8,6±0,45*$	1403,10±72,36	3274,29±164,66

*p<0,05 HFD vs. SD $p<0,05 KO vs. WT

PO0669

The Role of Cytoskeleton-Associated Protein 4 in the Glomerulus and Diabetic Kidney Disease

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Background: Cytoskeleton-associated protein 4 (CKAP4) was first discovered in the endoplasmic reticulum (ER) where it links the ER to the cytoskeleton. It can also be located in the cell membrane and function as a receptor. CKAP4 has been shown to be involved in various physiological events besides its function in the ER, including cell proliferation and migration. In this study, we explored the function of CKAP4 in the glomerulus and its role in chronic kidney disease (CKD).

Methods: Glomerular CKAP4 gene expression was evaluated in different CKD cohorts. The expression of CKAP4 in human glomeruli was investigated via immunofluorescence and western blot. The CKAP4 homolog in zebra fish was knocked down (KD) *in vivo* and proteinuria and morphology were analyzed. shRNA was used to KD CKAP4 in human podocyte and mesangial cells *in vitro*. Changes in protein expression was analyzed via mass spectrometry and western blot, and the morphology of the actin cytoskeleton via immunofluorescence.

Results: Analysis of different human CKD cohort revealed that CKAP4 was down regulated in glomeruli from patients with diabetic kidney disease (DKD), but not in the other diseases investigated. CKAP4 was expressed by all glomerular cells, but to lesser extent in endothelial cells. KD of the zebra fish CKAP4 homolog rendered the fish proteinuric and led to podocyte effacement. KD of CKAP4 in human podocytes and mesangial cells led to loss of actin stress fibers in both cell types. In addition, the expression of several growth factor receptors was affected, with a prominent loss of PDGF receptors in the mesangial cells reducing their proliferative response to PDGF.

Conclusions: Our results from the *in vivo* and *in vitro* experiments show that reduced expression of CKAP4 leads to glomerular dysfunction and changes in the actin cytoskeleton. In podocytes, this is known to cause foot process effacement which we observed. Less is known about how dysregulation of the actin cytoskeleton affects the mesangial cells, but we found that mesangial cells with CKAP4 KD downregulated their PDGF receptors, and had a reduced proliferative capacity. As patients with DKD have a low expression of CKAP4, we suggest that CKAP4 regulation can be a part of the disease development and progression.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO0670

Store-Operated Ca2+ Entry Contributed to High Glucose-Induced Podocyte Injury

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Background: Diabetic Nephropathy is one of the major microvascular complications of diabetes and the most common cause of end stage renal disease. Hyperglycemia is a known pathogenic stimulus for onset and progression of diabetic nephropathy. Podocyte injury is one of early features of the disease. However, the mechanism of the diabetes-induced podocyte injury is not fully understood. Store operated Ca^{2+} entry (SOCE) has multiple functions in both excitable and non-excitable cells. This ubiquitous Ca^{2+} signaling includes two key components, Orai1 (a plasma membrane protein mediating SOCE) and STIM1 (an ER membrane protein sensing Ca^{2+} level in the ER lumen). Previous studies have demonstrated that alterations in SOCE are involved in cell dysfunction in many cell types. However, whether and how SOCE contributes to podocyte injury in diabetes settings are not known. The present study was aimed to determine that enhanced SOCE mediated high glucose (HG)-induced podocyte injury by upregulating calpain activity.

Methods: All experiments were performed using cultured human podocytes. Western blot was conducted to estimate Orai1, STIM1 and nephrin protein abundance. Ca^{2+} imaging was used to analyze SOCE. Confocal microscopy was used to visualize podocyte actin arrangement. Calpain activity was determined by calpain activity assay kits.

Results: HG (25mM) treatment significantly increased Orai1, but not STIM1 protein abundance for time periods ranging from 2 to 12 hours. The HG-induced Orai1 response was dose dependent. Ca^{2+} imaging experiment showed that HG treatment for 12 hours significantly increased SOCE. In addition, HG treatment significantly decreased nephrin (a podocyte marker) protein abundance and resulted in cytoskeleton rearrangement by formation of cortical F-actin. Both HG responses were significantly blunted by BTP2 (4 μM), an SOCE inhibitor. Furthermore, we found that activation of SOCE by thapsigargin (1 μM) increased calpain activity which was abolished by BTP2. In addition, BTP2 blunted the increased calpain activity induced by HG treatment. Moreover, calpeptin (a calpain inhibitor) attenuated the HG-induced reduction of nephrin protein abundance.

Conclusions: The present study suggests that enhanced SOCE contributes to HG-induced podocyte injury by increasing calpain activity.

Funding: NIDDK Support

PO0671

HDAC6 Inhibition with CAY10603 Alleviates Renal Fibrosis Against Pyroptosis in Tubular Injury

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Background: The essential role of tubular damage has been highlighted during the progression of chronic kidney diseases (CKD), included diabetic nephropathy (DN), but the treatment options are still limited.

Methods: We interrogated the connectivity Map (CMap) with tubular transcriptomic profiles of biopsy-proven DN to identify a drug to reverse the regulated genes in tubulointerstitial component of DN. The effects of potential drug were validated in vivo STZ-induced early and late stage diabetic CD-1 male mice, as well as in non-diabetic mice including adenine-induced CKD and LPS-induced septic kidney injury.

Results: CAY10603, a specific inhibitor of histone deacetylase 6 (HDAC6), was identified as a drug to reverse the signature in both early- and late-stage DN. In patients with DN and mice with DKD, renal tubular expression of HDAC6 was significantly upregulated. In vivo, 5mg/kg dosage of CAY10603 significantly ameliorated tubular injury and tubulointerstitial fibrosis, reduced tubulointerstitial α-SMA and collagen I expression, and infiltration of $F4/80^+$ macrophages in both early and late stage of diabetic kidney disease. In addition, CAY10603 also conferred renoprotection in non-diabetic mice including adenine-induced CKD and LPS-induced septic kidney injury. Mechanically, in vitro HK-2 cells, HDAC6 inhibition with CAY10603 regulated NLRP3 activation and membrane repair upstream and downstream of GSDMD.

Conclusions: Collectively, CAY10603 exhibited therapeutic potential against pyroptosis in tubular injury of CKD

Funding: Government Support - Non-U.S.

PO0672

FRMD3/Protein 4.1O Increases Hippo Signaling in a Glucose-Dependent Manner

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Background: FRMD3 is as a candidate gene for diabetic nephropathy and encodes for protein 4.1O. Different splice variants 207, 204, 201 are expressed in the kidney cortex. Previous data show that protein 4.1O links nephrin to the actin cytoskeleton. In diabetic kidney disease Hippo signaling is increased. Phosphorylated Yes-associated kinase (YAP) and its paralogue TAZ are sequestered into the cytoplasm and degraded (Hippo signaling on). Unphosphorylated YAP/TAZ translocates into the nucleus and activates target genes via different transcription factors (Hippo signaling off).

Methods: Human kidney biopsy samples from healthy and diabetic patients were stained for protein 4.1O with immunohistochemistry. HEK293T cells were stimulated with low (5mmol/l) or high (25 mmol/l) glucose and an osmotic control (mannitol). RNA was isolated and PCR performed. HEK293T cells expressed protein 4.1O 207, 201, 204 or the control vector. Cells were stimulated with low, high glucose or mannitol. After cell lysis, westernblot was performed for phospho-YAP 397 and actin. Co-immunopreciptiation was performed under high, low and osmotic control conditions.

Results: Protein 4.1O expression is detected in healthy human glomeruli. In diabetic patients with CKD stage 3b to 5 and gross proteinuria protein 4.1O expression is increased in podocytes. High glucose leads to enhanced transcription of FRMD3. Under high glucose condition, protein 4.1O 207 and 201 significantly increase YAP phosphorylation. However, protein 4.1O 204 (lacking a c-terminal domain) does not increase YAP phosphorylation under high glucose condition. Functionally, protein 4.1O 207 and nephrin interaction is increased under high glucose conditions.

Conclusions: Expression of protein 4.1O is increased in human diabetic kidney disease and under high glucose conditions. Hippo Signaling is activated under high glucose conditions if protein 4.1O 207 and 201, but not 204, is expressed. The lacking cytoplasmic domain in protein 4.1O 201 may play the essential role in controlling Hippo signaling under high glucose conditions. Identifying the underlying pathomechanism for glucose-dependent regulation of the Hippo pathway by different splice variants of protein 4.1O will help to understand its molecular function in diabetic nephropathy.

PO0673

Human Proximal Tubular Cells in a 3D In Vitro Culture as a Model for Exploring Diabetic Lesions

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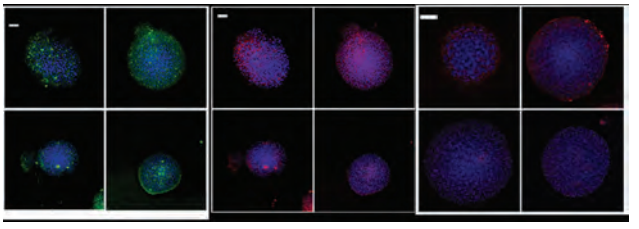
Background: We have previously demonstrated, the beneficial effect of ADAM17 deletion on human proximal tubular kidney cells (HKC-8) in 3D *in vitro* spheroids incubated with high glucose resembling the human kidney diabetic environment. Galectin-3 (Gal-3) is a potent pro-fibrotic protein and modulates the activity of fibroblasts and macrophages in chronically inflamed organs through activation of the TGF-β/Smad3 pathway and it is postulated as regulator of cardiac oxidative stress which can facilitate the development of fibrosis. Also, Dynamin related protein 1 (DRP-1) is a key regulator of the mitochondrial fission and ATP production under stress condition. As ADAM17 has been associated with TGF-β modulation during renal fibrosis, we wanted to evaluate the effect of ADAM17 deletion on Gal-3, Fibronectin and DRP-1 in HKC-8 spheroids incubated under high glucose conditions

Methods: ADAM17 deletion of renal tubular cells was performed using the CRISPR/Cas9 technology. HKC-8 cells grew inside an RGD-functionalized dextran hydrogel to obtain 3D spheroids. 13 days post-seeding, the spheroids were incubated with 35mM of D-glucose (HG), 5mM of D-glucose (LG) or 35mM of mannitol as osmotic control for 72h. Immunofluorescence for Gal-3, pDRP-1 and Fibronectin was performed

Results: HG increased the expression of fibronectin and pDRP-1 and tends to increase Gal-3 in wild-type (WT) spheroids. Interestingly, ADAM17 deletion decreased fibronectin expression in spheroids incubated with HG as compared to WT spheroids. Moreover, ADAM17 deletion abrogates the effect of HG on Gal-3 expression (see table and images, scale bar 50µm). The osmotic control, mannitol, did not affect the expression of the analysed proteins

Conclusions: ADAM17 blockade protects against fibrosis by decreasing fibronectin and Gal-3 and modulated the mitochondrial dynamic in human kidney tubular spheroids under high glucose conditions



PO0674

Animal Models Cannot Well Reflect the Transcriptomic Changes of Human Diabetic Nephropathy: A Comparative Study

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Background: Various mouse models have been developed and widely applied in investigating the pathogenesis of DN. Whether the models share the same underlying molecular changes with human DN is poorly understood. To this end, we performed a systematic analysis of the transcriptomes of the kidney tissues from patients with DN and various mouse models. To our knowledge, this is the largest analysis on this topic

Methods: This study included the bioinformatic analysis and in vivo validation. We comprehensively analyzed the genome-wide mRNA expression of kidney tissues collected from patients with biopsy-proven DN and widely used animal models(n=60). The bioiformatics workflow is shown in figure 1. Then, the expression levels of interested genes were further validated

Results: The transcriptomic profiles of all the animal models had poor correlation with those of patients with DN. However, we observed a much better correlation within species, regardless of the disease stages or modeling methods. In the GSVA analysis, we found the animal models shared similar pathological processes but could not well reflect the real circumstances in human DN. In enrichment analysis, we found the animal models shared the same pathways such as the accumulation of extracellular matrix and MAPK signaling with human DN. However, these models can not well mimic pathways such as cytokine signaling, vitamin D metabolism and SLC transporter disorders. Finally, the expression levels of the interested genes measured by the westernblot method showed good consistency with those generated by high throughput platforms

Conclusions: We found mouse models can not well reflect the transcriptomic changes of human DN in many aspects. We also provided a useful dataset to facilitate the translational research of DN

Funding: Government Support - Non-U.S.

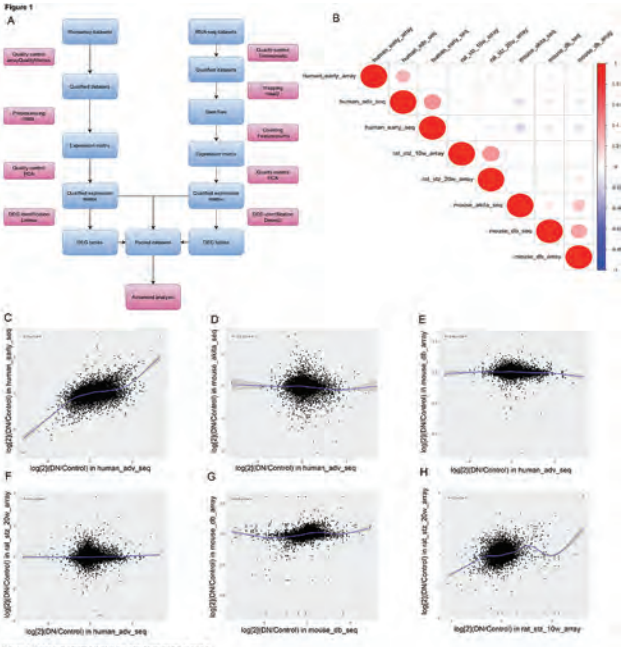

Figure 1 The bioinformatic workflow and correlation analysis
A. The bioinformatic workflow;
B. The correlation plot of the differential expressed genes(DEGs) of all studies. The degrees of correlation were measured using the Spearman' s r and indicated by the color intensities.(red: postive correlation; blue: negative correlation)
C-H. Scatter plots of the DEGs. The axis indicates the log2 fold changes of the DEGs in the DN group as compared to the control group. The generalized additive model was used for curve fitting.
C. the correlation of DEGs between early and advanced human DN. R = 0.4, P < 2.2e-16;
D. the correlation of DEGs between akita mice and advanced human DN. R=-0.11, P < 2.2e-16;
E. the correlation of DEGs between db/db mice and advanced human DN. R = -0.086, P < 2.2e-16
F. the correlation of DEGs between STZ-diabetic rats and advanced human DN. R = 0.027, P = 0.00035
G. the correlation of DEGs obtained by the microarray and RNA-seq in db/db mice. R = 0.29, P < 2.2e-16
H. the correlation of DEGs between STZ-diabetic rats at the age between 10 weeks and 20 weeks. R = 0.23, P < 2.2e-16

Figure 2. The gene set variation analysis(GSVA) and Functional enrichment analysis
A-E. Principal coordinates analysis (PCoA) plots of the GSVA. The PCoA was used to project the original high-dimension space calculated by the GSVA into a 2-dimension space for visualization. Points with smaller distances share more similar biological processes. The red color indicates the control group, while the blue color indicates the DN group. Different symbols represent different species or disease stages.
F-I. Pathway analysis of the dysregulated genes. The x-axis represents the gene-enrichment scores. The size of each dot represents the number of enriched genes, while the colors represent different databases used for enrichment analysis (KEGG or Reactome).
F. Pathway analysis of the down-regulated genes in mouse and down-regulated genes in advanced DN.
G. Pathway analysis of the up-regulated genes in mouse and down-regulated genes in advanced DN.
H. Pathway analysis of the down-regulated genes in mouse and up-regulated genes in advanced DN.
I. Pathway analysis of the up-regulated genes in mouse and up-regulated genes in advanced DN.

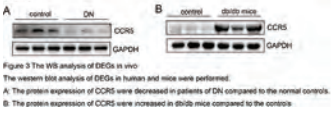

Figure 3 The WB analysis of DEGs in vivo
The western blot analysis of DEGs in human and mice were performed.
A: The protein expression of CCR5 were decreased in patients of DN compared to the normal controls.
B: The protein expression of CCR5 were increased in db/db mice compared to the controls

PO0675

Integrative Transcriptome Analysis Reveals Involvement of Spermatogenesis-Related Genes in Diabetic Nephropathy

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Background: Cell heterogeneity has impeded the accurate interpretation of the bulk transcriptome data from patients with diabetic nephropathy (DN). We performed an analysis by integrating bulk and single-cell transcriptome datasets to uncover novel mechanism leading to DN, especially in the podocytes.

Methods: Microdissected glomeruli and tubules transcriptome datasets were selected from Gene Expression Omnibus (GEO). Then the consistency between datasets was evaluated. The analysis of bulk dataset and single-nucleus RNA dataset was integrated to reveal the cell type-specific responses to DN. The candidate genes were validated in kidney tissues from DN patients and diabetic mice.

Results: We compared 4 glomerular and 4 tubular datasets and found considerable discrepancies among datasets regarding the differentially expressed genes (DEGs), involved signaling pathways and the hallmark enrichment profiles. Deconvolution of the bulk data revealed that the variations in cell-type proportion contributed greatly to this discrepancy. Integrative analysis uncovered that the dysregulation of spermatogenesis-related genes, including *TEKT2* and *PIAS2* was involved in development of DN. Importantly, the mRNA level of *TEKT2* was negatively correlated with the mRNA levels of nephrin (r= -0.66, p<0.0001) and podocin (r= -0.85, p<0.0001) in human diabetic glomeruli. Immunostaining confirmed that the expression of TEKT2 and PIAS2 were up-regulated in podocytes of DN patients and diabetic mice.

Conclusions: The integrative strategy can help us to efficiently use the publicly available transcriptomics resources. Using this approach, we identified *TEKT2* and *PIAS2*, two spermatogenesis-related genes involved in the pathogenesis of DN.

PO0676

Understanding Genetic Mechanisms of Diabetic Nephropathy at the Single-Cell Level

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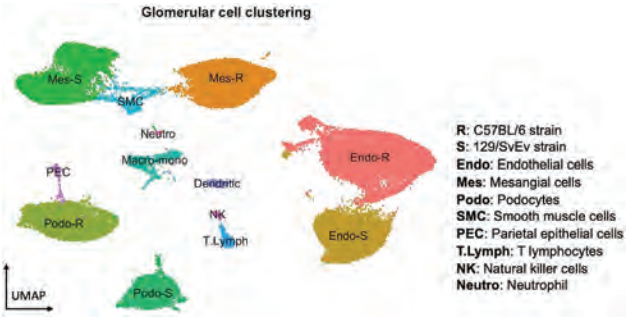
Background: Diabetic nephropathy (DN) is a leading cause of end-stage kidney disease worldwide. Susceptibility to DN is inherited but genetic determinants have not been clearly defined. We have previously described a mouse model combining *Akita-Renin* transgene (AR) that exhibits human DN features including albuminuria, glomerulosclerosis, and genetic predisposition. Susceptible (S) 129 strain AR mice develop overt DN whereas resistant (R) C57BL/6 AR mice are largely free of kidney damage.

Methods: We performed single-cell sequencing of glomerular cell obtained from the wildtype (WT) and AR mice from both S and R strains at 10 weeks of age before overt pathological abnormalities are present in S mice.

Results: A total of 60,682 cells were sequenced from the four conditions. Within the main glomerular cell lineages: podocytes, mesangial and endothelial cells, there were distinct functional clusters corresponding to the S and R strains (see figure). Within the S but not R strain, well-defined cell clusters derived from AR and WT were identifiable within podocytes and mesangial cells, while in other cell types, the impact of strain was much greater than diabetes and renin-angiotensin activation in driving differential gene expression. Gene networks defining the strain differences have potential functional relevance in the development of glomerular diseases. For example, in podocytes, gene networks related to cytoskeleton are activated in the R strain, whereas the S strain shows upregulated oxidative stress responses. A number of candidate genes identified in human DN and other inherited nephropathies are also differentially expressed on the S and R backgrounds.

Conclusions: Single-cell sequencing analysis of glomerular cells from a DN mouse model has identified cell-specific transcriptomic profiles linked to genetic susceptibility and resistance to DN, suggesting causal mechanisms. Substantial overlap with pathways and candidate genes linked to human DN suggest that this model can be useful for understanding genetic pathophysiology of DN in humans.

Funding: Government Support - Non-U.S.



PO0677

Altered Cellular Signaling Pathways Identified by Proteomics and Phosphor-Proteomics in a Rat Model of Diabetic Kidney Disease

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Background: Alterations of cellular signaling are associated with onset and deterioration of various types of disorders, which could be the targets for new drug development and discovery. Currently, post-translational protein modification and glycosylation are identified by comprehensive proteomic analyses. Since diabetic kidney disease (DKD) is the leading cause of chronic end stage renal disease, exploring novel signaling pathways involved in the initiation and progression of DKD may have therapeutic potential. In the present study, we probed renal tissue in a DKD rat model for altered signaling cascades using proteomics and phosphor-proteomics analyses.

Methods: The animal model of type 2 diabetes mellitus, Spontaneously Diabetic Torii Fatty (SDT Fatty) rats were uninephrectomized at 9 weeks of age, and then from 10 weeks of age, 0.3% NaCl was added to drinking water to exacerbate DKD progression for additional 5 weeks (Group A) or 10 weeks (Group B). After the treatment period, blood was collected for biological measurements and kidney tissue was obtained for histology and proteomics and phosphor-proteomics analyses.

Results: In SDT Fatty rats, the stage of DKD was classified as 'early' (Group A) or 'advanced' (Group B) by SUN levels and expansion of mesangial matrix and glomerular sclerosis observed by PAS staining. 25 signaling cascades including the PPAR signaling pathway were activated at early stage DKD, and 41 cascades including the proximal tubule bicarbonate reclamation cascade were activated at advanced stage DKD, detected by proteomics analysis in the KEGG database (P<0.05). Further, 33 annotation clusters including the 'serpin family' as serine protease inhibitors and the 'S100 family' as RAGE ligands were newly detected by functional annotation clustering determination (P<0.05). In addition, five cascades including pathways of 'microRNA in cancer' indicated by Crk, Hnrnpk and Marcks at early stage and two cascades including 'RNA transport' indicated by Casc3, Eif3b and Eif3c at advanced stage were detected by phosphor-proteomics analysis in KEGG database (P<0.05).

Conclusions: These findings demonstrate that several groups of known and new signaling cascades may have important roles for the initiation and/or progression of DKD.

Funding: Government Support - Non-U.S.

PO0678

NETosis Contributes to the Pathogenesis of Diabetic Kidney Disease: A Proposed Mechanistic Pathway

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Background: Diabetic kidney disease (DKD) is one of the most debilitating complications of diabetes. Considerable research has focused on the key role of NADPH oxidases (NOXs) in DKD. Of note, our group has demonstrated the role of mTOR signaling pathway in mediating NOX-derived reactive oxygen species (ROS) production in DKD. Inflammation and an overactive immune response are known to be major risk factors for the development and progression of DKD. Recently, NETosis, a novel neutrophil-specific cell death process, was described to be associated with inflammation and diabetes. However, the effect of NETosis on DKD remains uninvestigated. Interestingly, increasing evidence highlights a pivotal role for the mTORC1 pathway and NOXs in regulating NETosis. Herein, we hypothesize that hyperglycemia activates the mTOR/NOX signaling pathway, leading to excess neutrophil extracellular traps (NETs) formation and eventual kidney injury.

Methods: Control mice, mice treated with phorbol 12-myristate 13-acetate (PMA) to induce NETosis, and mice models of type 1 and type 2 diabetes treated either with Cl-amidine to inhibit NETosis or with Cl-amidine's vehicle were used. Functional, histological, and molecular parameters of the kidneys were determined. Human transcriptomics datasets from GEO were further used for validation.

Results: Our data show that increased NETs formation mediates renal dysfunction and histopathological alterations associated with DKD. Of note, treatment with PMA mimicked diabetes-associated renal injury, as assessed by UAE, UACR, BUN and serum

cystatin C, and induced glomerular hypertrophy, glomerulosclerosis, extracellular matrix expansion and podocyte depletion. Treatment with Cl-amidine attenuated diabetes-induced glomerular and podocyte injury. Increased NETs formation in diabetes was paralleled by an increase in NOX-dependent ROS production and mTOR signaling pathway activation. Our findings were further confirmed in transcriptomic analysis of human DKD, where a positive correlation between NETs and DKD was observed. Querying protein-protein interaction databases also revealed an association between NETs markers, mTOR signaling proteins, and NOXs.

Conclusions: To our knowledge, this study is the first to describe the role of NETosis in DKD, identifying NETosis as one of the final mechanistic drivers of DKD.

Funding: Private Foundation Support, Clinical Revenue Support

PO0679

Alteration of Autophagy-Related Protein 5 (ATG5) Levels and Atg5 Gene Expression in Diabetes Mellitus with and Without Complications

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Background: Autophagy is a catabolic mechanism that involves lysosomal-dependent degradation of unnecessary or ineffective intracellular components. Autophagy is the process responsible for normal cellular homeostasis, by recycling organelles and proteins. Autophagy pathway and its key participant ATG5 are associated with several pathologies such as diabetes mellitus and its complications.

Methods: Levels and expression of autophagy key components ATG5 and LC3B were analyzed in both human model and murine tissues. One hundred and twenty human subjects were divided into four groups: Healthy (control), diabetic without complications, diabetic nephropathy and diabetic retinopathy. Additionally, we used kidneys from diabetic mice model (WT healthy mice and DN mice, Lysate derived from human peripheral blood mononuclear cells, and murine renal cortex lysates were subjected to western blot analyses of ATG5 and LC3B and immunohistochemical analysis was performed on mice renal tissues.

Results: Western blot and immunohistochemical analysis demonstrate that ATG5 protein levels were significantly decreased in DM, DN and DR patients (0.59±0.07; 0.67±0.06; 0.72±0.06 A.U. units respectively), vs. healthy controls (0.96±0.16 A.U. units), and in DN mice compared to healthy mice (0.65±0.04; 1.15±0.13 A.U. units respectively). Quantification of staining area (%) of ATG5 mice tissue expression also decreased in DN vs. healthy mice (4.42±1.08%; 10.87±1.01% respectively). LC3B levels and expression correlates with ATG5 results: significant reduction in peripheral blood mononuclear cells diabetic patients (with or without complications) vs. healthy controls (0.44±0.05; 0.42±0.035; 0.48±0.06 compared with 0.81±0.05 A.U. units). Renal LC3B levels were lower in DN vs. healthy mice (0.36±0.03; 0.68±0.07 A.U. units). Renal LC3B staining quantification revealed significant reduction in DN vs. healthy mice (1.7±0.23%; 8.56±1.7%).

Conclusions: We conclude that ATG5, as well as LC3B, are down regulated in diabetic patients with or without complications. This diminution contributes to deficiencies in the autophagy process. Our observations show a novel association between autophagy-related protein 5 (ATG5) and diabetic kidney and retinal diseases, with ATG5 as a candidate protein for diabetic nephropathy and retinopathy.

PO0680

The Emerging Role of the mTORC2/Rictor Signaling Complex in Autophagy Dysregulation-Associated Diabetic Kidney Disease

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Background: Podocyte injury has been implicated in the pathogenesis of many renal diseases including diabetic kidney disease (DKD). Dysregulation of podocyte autophagy has been positively correlated with podocyte loss and progression of proteinuria in patients with diabetes. Yet, the exact mechanisms behind diabetes-induced autophagy dysregulation remain to be elucidated. Various signaling pathways including the mTORC1 complex have been implicated in maintaining podocyte integrity in DKD. However, the role of mTORC2 in autophagy and its interaction with key mechanistic pathways involved in DKD, including the ROS-producing enzymes, are still unknown. Herein, we investigated the role of mTORC2, its crosstalk with the NADPH oxidases 4 (Nox4)-induced ROS, its effect on autophagy, and the possible link to podocyte integrity in animal models of type 1 and type 2 diabetes.

Methods: Type1 diabetes was induced in mice by streptozotocin (STZ) injections, and type 2 diabetes was initiated by a 'western' diet followed by low-dose STZ injections. Mice were divided into control, diabetic, and diabetic treated with a selective mTORC2 inhibitor (JR-AB2-011). Functional, pathological, and biochemical studies were performed.

Results: Diabetes-induced podocyte injury is reflected by alterations of the slit-diaphragm protein nephrin, paralleled by podocyte depletion as assessed by decreased WT1 staining and accompanied by autophagy dysregulation. The effect of autophagy was further highlighted in control mice treated with the autophagy inhibitor hydroxychloroquine, that mirrored the effect of diabetes on functional, phenotypic, histological, and molecular changes in the kidney. These observations were concomitant with an observed activation of the mTORC2/Rictor protein expression and increased levels of superoxide generation through Nox4. Of interest, these results were paralleled by activation of the mTORC1/p70S6K pathway. Moreover, specific inhibition of mTORC2 curbed the homeostatic function of the kidneys and restored the histological and phenotypical changes, concomitant with regulating the Nox4/mTORC1 signaling axis. More importantly, JR treatment regulated diabetes-induced autophagy protein dysregulation (Beclin, Atg3, and LC3).

Conclusions: Our data suggest that targeting mTORC2 signaling could be a potential therapeutic target for DKD.

Funding: Private Foundation Support, Clinical Revenue Support

PO0681

Mitophagy-Related Renal and Proximal Tubular Protection During the Normoalbuminuric Stage of Diabetes Mellitus

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Background: Oxidative stress during the normoalbuminuric stage of type 1 diabetes mellitus (DM) damages renal cortical mitochondria. Because accumulation of damaged mitochondria can contribute to renal dysfunction, we aimed to determine a) if oxidative stress in DM triggers mitophagy as a mitochondrial quality control mechanism, and b) the renal cortical structures in which these events occur.

Methods: Rats receiving i.p. injection of streptozotocin (STZ, 65 mg/kg) or vehicle (Sham) were either left untreated or treated with telmisartan (TLM, an angiotensin receptor blocker; 10 mg/kg/d). Two weeks later, blood glucose levels (BG), blood pressure (BP), glomerular filtration rate, and urinary excretion of albumin and *N*-acetyl-β-D-glucosaminidase (NAG) were measured. The oxidative stress marker, 3-nitrotyrosine (3-NT), was detected by HPLC. Mitophagy-related proteins (LC3-II, p62, PINK1, BNIP3) were quantified by Western blot and localized by immunoreactivity based on percent of cells staining with various intensities (HistoScore).

Results: STZ rats displayed hyperglycemia and hyperfiltration that were unaffected by TLM. BP, albumin excretion, and NAG excretion were similar in all groups. Renal cortical 3-NT levels were increased in STZ rats, a change that was prevented by TLM (STZ+TLM). Renal cortex from STZ rats displayed TLM-sensitive increases in LC3-II and PINK1 (all $P<0.05$), although BNIP3 and p62 levels did not differ among groups. HistoScore data failed to reveal mitophagy-related proteins in glomeruli. In contrast, immunoreactivity for all 4 proteins was readily evident in proximal tubules, with increased HistoScores in STZ rats; this effect was blunted in STZ+TLM rats. Mitophagy-related protein immunostaining was also apparent in distal tubules, but the Histoscores tended to be less than that of proximal tubules and were unaffected by STZ or TLM.

Conclusions: During the normoalbuminuric stage of DM, renal cortical mitophagy is most prominent in the proximal tubule. This effect is blunted by TLM in association with its antioxidant effect, suggesting a mitophagy-related proximal tubular protection mechanism triggered by oxidative damage.

PO0682

The Molecular Effect of the Sodium-Glucose Transporter 2 (SGLT-2) Inhibitor Empagliflozin on the Autophagy Pathway in Diabetes Mellitus and Its Vascular Complications

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Background: Diabetes mellitus (DM) is a severe metabolic disorder characterized by chronic hyperglycemia. DM is associated with increased oxidative stress that can lead to irreversible kidney damage and kidney failure. Empagliflozin (EMPA) is a novel anti-diabetic drug, known as SGLT2i in T2DM patients. Autophagy is a catabolic mechanism that involves lysosomal-dependent degradation of unnecessary or dysfunctional intracellular components, and is known to have an important role in DM complication (Diabetic Nephropathy-DN). We aim to investigate the protective role of EMPA treatment on DN via the autophagic proteins ATG5 & LC3B.

Methods: We used T2DM animal model-mouse strain BTBR with the ob/ob leptin-deficiency mutation that develops severe type II DM which is presented with hyperglycemia and DN. EMPA will be administrated to the diabetic mice via drinking water for a period of 12 weeks. Routine monitoring of blood and urine standard DM parameters will be carried through experiment duration. At the end of the experiment, mice kidneys will be removed and subjected to further biochemical and histological analysis: Western blot analyses, Immunohistochemistry staining will be performed to evaluate ATG5, LC3B, level and expression.

Results: Blood glucose concentration was normal in control mice (C57) throughout the experiment. In DM mice (BTBR) without EMPA, blood glucose concentration was higher than control, and lower in diabetic mice treated with EMPA compared to DM. Urine volume of BTBR mice treated with EMPA increased throughout the experiment and was higher in comparison to DM mice without EMPA treatment. Renal cortical

expression of ATG5 were 6.83±0.52%, 2.59±0.54% and 6.29±.74% for the C57, DM and DM+EMPA, respectively (P<0.001 vs. DM for both) and LC3B were 9.60±2.14%, 3.19±0.66% 7.39±1.74% in the C57, DM mice and DM+EMPA, respictevely (P<0.001 between all groups.

Conclusions: 1. EMPA Treatment induces glucosuria and body weight reduction in diabetic mice model 2. Chronic Hyperglycemia down regulates the expression of LC3 & ATG5, the two main proteins in the autophagy process. 3. Treatment EMPA for 12 weeks restore the the expression of these proteins in the kidney 4. EMPA can be first line treatment in type II DM patients to slow the progression of DN.

PO0683

Ferroptosis Is Involved in the Process of Diabetic Kidney Disease

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Background: Diabetic kidney disease(DKD) is a major public health problem that threatens human health and causes substantial economic burden. DKD is accompanied by accumulation of ROS and iron in the kidney, a hallmark of ferroptosis. Ferroptosis is a condition that causes cell death by accumulation of lipid reactive oxygen species (ROS), in an iron-dependent mechanism that is different from apoptosis, necroptosis and autophagy. That ferroptosis is involved in DKD has been shown recently, but its role is still unknown.

Methods: We induced diabetic kidney disease in 8-week-old male rats with streptozotocin (STZ) and treated with ferroptosis inhibitor Fer-1 to analyze the degree of renal injury and the related indexes of ferroptosis.

Results: 1. Diabetic renal injury involves ferroptosis. Accumulation of iron was also confirmed by Prussian blue staining and presented morphological changes linked to ferroptosis in DKD group: reduced mitochondrial volume, ruptured mitochondrial membrane and missing mitochondrial cristae. 2. Blocking ferroptosis can alleviate proteinuria and renal tubular injury in STZ-induced DKD. Fer-1 treatment clearly decreased the urine protein-creatinine ratio, both α-1 microglobulin and N-acetyl-β-D-glucosaminosidase in DKD group and the levels of both MDA and Fe^{2+}. In addition, treating DKD rats with Fer-1 reduced iron in the kidney and alleviated kidney fibrosis.

Conclusions: Ferroptosis is involved in the process of diabetic kidney disease.

Markers of renal tubular injury α 1-microglobulin and N-acetyl-β-D-glucosaminosidase measured in urine

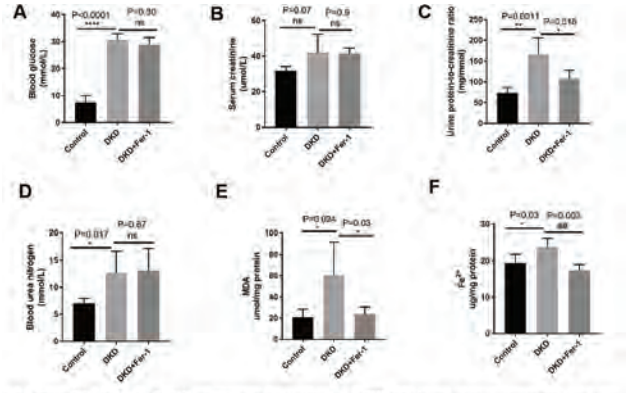

Fig 1. Ferrostatin-1 (Fer-1) alleviates proteinuria and renal injury in DKD rats. Levels of serum glucose (A), blood urea nitrogen (B), urine protein-to-creatinine ratio (C), serum creatinine (D), renal MDA (E) and renal non-heme iron (F) measured for 10 weeks after rats were injected with STZ (n=5).

Group (n=5)	α1-microglobulin (mg/L)	N-acetyl-β-D-glucosaminosidase (U/mmol creatinine)
Control	< 6.35	0.736±0.12
DN	7.54±1.19	2.24±0.96**
DN+Fer-1	< 6.35	0.94±0.67 *

PO0684

Effect of Lisinopril and Pioglitazone in a Mouse Model of Diabetic Kidney Disease

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Background: Diabetic nephropathy affects up to one third of all diabetes mellitus patients, and is the major cause of end stage renal disease. The current study evaluated the uninephrectomized (UNx) obese and diabetic db/db mouse as a model of diabetic kidney disease (DKD), benchmarking a glycemic control agent (Pioglitazone) and an angiotensin-converting enzyme inhibitor (Lisinopril) to affect kidney structure and function.

Methods: Female lean control mice (Db/+, 2 kidneys), sham operated obese mice (db/db, 2 kidneys), and UNx db/db mice (1 kidney) were grouped based on body weight, blood glucose, %HbA1c, and urine albumin:creatinine ratio (UACR). Inclusion criteria were defined as blood glucose >350mg/dl and UACR >250ug/mg. Following grouping, animals were provided a diet admixture of Pioglitazone (169mg/Kg diet) or Lisinopril (0.1mg/mL) in drinking water. Compounds were administered for 8 weeks, during which body weight, food intake, water intake and blood glucose was measured.

Results: Control UNx-db/db animals showed progressive decline in renal function (UACR: 497±62mg/ug at baseline to 1054±159mg/ug at 8wks), whereas sham operated animals remained near baseline levels (284±40mg/ug). Pioglitazone treated mice had significantly lower UACR than control UNx-db/db after 2 weeks whereas lisinopril treated animals had significantly lower UACR after 4 weeks of treatment, primarily by limiting the progression of UACR increase. Increased mesangial matrix deposition in the glomeruli was the primary lesion observed (high incidence and high severity); tubular and interstitial structural findings were very limited; little to no fibrosis was observed. Pioglitazone and lisinopril both showed a comparable effect in decreasing the severity of mesangial matrix deposition.

Conclusions: Hence, the UNx-db/db animal model of diabetic kidney disease is a progressive model of renal function decline and limited histopathological damage which responds to both anti-diabetic and anti-hypertensive control agents, and is a valuable model for the assessment of new therapeutic targets for DKD.

Funding: Commercial Support - Janssen Research & Development

PO0685

miR299a-5p Is a Novel Mediator of Fibrosis in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of kidney failure in North America, characterized by glomerular accumulation of extracellular matrix (ECM) proteins. High glucose (HG) induction of glomerular mesangial cell (MC) profibrotic responses, mediated by the cytokines TGFβ1 and activins, plays a central role in its pathogenesis. We recently showed that TGFβ1 upregulation of microRNA (miR) 299a-5p promoted its profibrotic responses in MC. Here we studied the role of this miR in DKD.

Methods: Primary mouse MC were treated with HG at 30 mM. miR299a-5p was detected by qPCR or ISH. miR overexpression and inhibition plasmids were transfected by electroporation. TGFβ1 and activin signaling was assessed by activity of their downstream mediator Smad3 using the $CAGA_{12}$ reporter. ECM production was assessed using immunoblotting and activity of the COL1α1 promoter luciferase reporter.

Results: HG increased the expression of miR299a-5p in MC. This was also increased in type 1 Akita diabetic kidneys in both glomeruli and tubules, as assessed by ISH. In MC, miR299a-5p overexpression increased Smad3 activation and COL1α1 promoter activity. Conversely, miR299a-5p inhibition attenuated HG-induced COL1α1 promoter and Smad3 activation, as well as upregulation of ECM proteins. miR299a-5p is predicted to target the TGFβ1 inhibitor Cripto-1 (CR-1), and we previously showed that it targeted the activin inhibitor follistatin (FST). Here we show that HG decreased expression of both CR-1 and FST. This was similarly seen with miR299a-5p overexpression. CR-1 or FST treatment individually attenuated the increased COL1α1 promoter and Smad3 activity seen with miR299a-5p overexpression, and together showed an additive inhibitory effect.

Conclusions: These data support an important role for miR299a-5p in regulation of the profibrotic response to HG. Through suppression of two important antifibrotic proteins, CR-1 and FST, miR299a-5p potentiates the action of TGFβ family profibrotic cytokines. Future studies will determine whether inhibition of this miR can attenuate DKD.

Funding: Government Support - Non-U.S.

PO0686

Abstract Withdrawn

PO0687

The Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Improves Left Ventricular Function in Preclinical Diabetic CKD

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Background: The steroidal MR antagonist (MRA) spironolactone and eplerenone reduce mortality in patients with heart failure with reduced ejection fraction (HFrEF) but their use in patients with CKD is not indicated due to the associated risk of hyperkalemia. Finerenone is a non-steroidal MRA which recently reduced the composite kidney and cardiovascular outcomes in the phase III study FIDELIO in CKD patients with T2D. Purpose: To test whether finerenone improves renal and cardiac function in preclinical CKD rat models with T2D.

Methods: 12 weeks old male Zucker Diabetic rats (ZSF1) were used as model of diabetic CKD. Finerenone was administered at the dose of 10 mg/kg/d po. GFR (transcutaneous FITC-sinistrin) and cardiac LV function/hemodynamics (LV catheterization) and LV tissue perfusion (MRI) were assessed *in vivo* at the age of 24 weeks.

Results: 24-week old ZSF1 rats showed classical signs of CKD, with reduced GFR (1.44±0.11 ml/min/100g body weight for non-diabetic rats vs 1.04±0.16 ml/min/100g body weight for ZSF1, $p<0.05$). This was associated with LV diastolic dysfunction, illustrated by the increases in LV end-diastolic pressure (LVEDP; 5.58±0.57 vs. 8.04±0.81 mmHg, $p<0.05$), and LV end-diastolic pressure volume-relation (LVEDPVR; 1.10±0.23 vs. 5.63±0.54 mmHg/relative volume unit, $p<0.05$) without significant changes in LV end-systolic pressure (LVESP; 173±10 vs 197±5 mmHg) or LV end-systolic pressure volume-relation (LVESPVR; 32.7±4.2 vs 28.2±1.09 mmHg/relative volume unit). LV perfusion was reduced (5.21±0.37 vs 4.11±0.21 ml/min/g LV tissue; $p<0.05$). Finerenone treatment did not impact GFR in ZSF1 rats (0.93±0.17 ml/min/100g body weight) but reduced significantly LVEDP (5.72±0.76 mmHg, $p<0.05$) and LV end-diastolic pressure volume-relation (LVEDPVR; 2.73±0.33 mmHg/relative LV volume unit; $p<0.05$). Finerenone increased LV tissue perfusion (6.90±0.34 ml/min/g LV tissue).

Conclusions: Finerenone treatment improves CKD related LV diastolic function in diabetic CKD rats, independently from changes in GFR.

Funding: Commercial Support - Bayer Grant

PO0688

Development and Benchmarking of a Non-Human Primate Model of Diabetic Kidney Disease

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Background: Diabetic Kidney Disease (DKD) is the largest cause of end stage renal disease and is responsible for 40% of new patients that require dialysis. To test novel therapies for DKD, we sought to develop a non-human primate (NHP) model of DKD that would be more representative of the etiology of human disease than genetically modified mouse models and support human dose prediction and biomarker development.

Methods: Cynomologus monkeys were fed a high fat/cholesterol diet for 5.1±2.5 (mean±SD) years and became obese (9.1±1.6 kg), hyperglycemic (267±78 mg/dL), hypertensive (systolic blood pressure [SBP] 141±11 mmHg), and macroalbuminuric (urine albumin/creatinine ratio [UACR] 562±346 mg/g). The responsiveness of the monkeys to pharmacological intervention was benchmarked using irbesartan, an angiotensin II receptor blocker (ARB), which is clinically used to treat DKD. Animals were orally dosed daily for 8 weeks with either vehicle (n=8) or irbesartan (n=14, 3 mg/kg).

Results: Exposures 24-hours after dosing were 165±111 ng/mL, similar to exposure in humans with therapeutic doses. Treatment effects on SBP (-23±8 vs. +2±15 mmHg, irbesartan vs. vehicle), urinary albumin excretion (UAE; -23% vs. +55%, irbesartan vs. vehicle) and UACR (-42% vs. +43%, irbesartan vs. vehicle) were consistent with effects seen in humans with DKD treated with irbesartan for 12 weeks. Pharmacokinetic/pharmacodynamic modeling of the observed NHP UAE response at 8 weeks suggested a similar exposure-response relationship in the NHP model as in human DKD with the magnitude of reductions being somewhat larger in the monkeys than in humans.

Conclusions: Together, these data demonstrate that we have developed and benchmarked a novel NHP model for DKD that has characteristics similar to human pathology and responds to a treatment known to improve DKD in clinical trials. This model is expected to be a valuable translational model for testing novel interventions for DKD.

Funding: Commercial Support - Janssen Pharmaceutical Companies of Johnson and Johnson

PO0689

Insulin Receptor Signaling Is Necessary for NFκB-Activated Host Defense Responses in Murine Intercalated Cells

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Background: Urinary tract infection (UTI) disproportionately affects select groups, especially those with insulin resistance and diabetes mellitus. Kidney intercalated cells (IC) play a key role in preventing UTI by regulating urine pH and secreting cytokines and antimicrobial peptides (AMP). Our data show that insulin receptor (IR) deletion in murine IC causes insulin resistance and increases UTI risk *in vivo* while having no impact on glucose homeostasis or urine acidification. Here, we profile the transcriptomes of IC isolated from IR knockout (IRKO) mice and controls (WT) to identify IR-mediated host defenses.

Methods: *Insr* gene was deleted in murine IC by breeding *Atp6v1b1*-Cre transgenic mice with IR-floxed mice. A tdT reporter was added to aid fluorescence-assisted cell sorting (FACS) of IC. RNAseq was performed on IC and read count data were analyzed for differentially expressed genes (DEG) using edgeR. DEG were defined with FDR adjusted *p*-value < 0.05. Canonical pathway analysis of DEG was performed using Ingenuity Pathway Analysis. Sorted IC were cultured and challenged *in vitro* with uropathogenic *E.coli* (UPEC) to assess response and susceptibility to infection. To define the contributions of NFκB to UTI defense, *NFKB1* was silenced in human medullary cells using siRNA. UPEC attachment and invasion assays were performed.

Results: FACS-enriched IC express IC-specific genes like *Aqp6* and *Atp6v0d2*. Differential expression analysis reveals suppression of 138 genes and upregulation of 232 genes in IRKO vs WT IC. In IRKO IC, a decrease in *Insr* as well as downstream IR-regulated targets and host defense genes such as AMPs were observed. While diverse pathways implicated in innate immunity are suppressed in IRKO IC, many converge on one target: NFκB. When cultured IC from these mice are challenged with UPEC, IRKO IC exhibit suppressed NFκB activation and UPEC were more likely to invade them. Silencing *NFKB1* results in decreased AMP expression and increased UPEC attachment and invasion of human medullary cells.

Conclusions: These data suggest IR signaling impacts the IC host defense transcriptome and identifies IR-sensitive pathways that aid in UPEC defense by activating NFκB signaling and expressing AMPs. A greater understanding of the factors that predispose diabetics to UTI may reveal novel, targeted therapies to prevent/treat diabetes-associated UTI.

Funding: NIDDK Support

PO0690

Differences in Kidney Integrin Alpha-2 Expression Between Humans and Preclinical Models

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Background: Integrin α2 (ITGA2) forms heterodimers with integrin β1 and is one of the four collagen binding integrins with preference for collagen I. Published results implicate α2 in the regulation of kidney injury. Whole body deletion of integrin α2 protects mice from kidney injury in the 5/6 nephrectomy and adriamycin models of nephropathy, and α2 expression in mesangial cells has been proposed to contribute to kidney pathology through regulation of matrix production. We assessed the distribution of α2 protein in human DKD kidney and in multiple preclinical species to get a better understanding of the cell types expressing α2.

Methods: Human kidneys from normal and DKD subjects, as well as kidneys from diabetic mice, rats and cynomolgus monkeys were evaluated by immunohistochemistry (IHC) for α2 expression. Staining antibody was validated with kidneys from α2-KO mice. Identification of α2-positive kidney cell types and scoring was performed by a trained pathologist. Protein expression was compared with RNA expression in snRNAseq datasets from human DKD kidneys and kidneys from db/db mice.

Results: All species showed strong staining in the medulla, but significant differences were noted in the cortical α2 expression between humans and other species. Mainly mesangial, endothelial and distal tubular staining was seen in human kidney cortex. Podocytes were negative while proximal tubules stained weakly. Consistent with IHC data, strong a2 expression in human distal tubules and weaker expression in proximal tubules and glomerular cell types is seen in snRNAseq data. In contrast, mice showed mainly podocyte and endothelial staining. Mesangial cells and mouse proximal tubules were negative for α2, and distal tubules in the cortex stained weakly. Rat kidneys were negative for glomerular α2 expression with medium to strong positivity in the distal tubules of the cortex. Finally, cynomolgus monkeys showed α2 expression in all glomerular cell types: podocytes, endothelial and mesangial, weak staining in proximal and medium to strong staining in distal tubules. Decreased α2 glomerular staining was observed in DKD kidneys compared to normal kidneys.

Conclusions: Differences in integrin α2 cellular expression pattern must be considered when extrapolating function from lower to higher species.

Funding: Commercial Support - Janssen

PO0691

The HIV Protease Inhibitor Darunavir Protects Against Diabetic Kidney Injury in Mice and Alters Stress Granule-Associated Signaling

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Background: Despite the success of antiretroviral therapy (ART) in improving mortality, persons living with HIV (PLWH) still have increased risk of death and kidney disease and diabetes mellitus are important contributors to this excess mortality. Previously published studies in our laboratory demonstrated that the HIV protease inhibitor darunavir (DRV) prevents kidney injury via mechanisms that are independent of HIV protease but the mechanisms by which DRV protects against renal injury remain unclear. Studies in our lab found that DRV binds to several stress granule (SG) associated proteins, including G3BP1. SG are membraneless organelles composed of translationally arrested mRNAs and ribonucleoproteins and have important roles in stress and injury responses.

Methods: Diabetes was induced in 9-week-old eNOS-/- C57BL/6 mice by administration of 5 daily 50 mg/kg doses of streptozotocin (STZ). 14 weeks later, mice were treated with either DRV (100mg/kg) or control by daily oral gavage for 4 weeks. Urinary albumin-to-creatinine ratio (UACR) assay, immunofluorescence (IF) microscopy, western blotting and real-time PCR were performed according to routine protocols in our laboratory. For in vitro studies, human proximal tubular cells (HPT1b) at 40-60% confluence were transfected with Accell siRNA for G3BP1 in Accell Delivery Media.

Results: STZ induced severe hyperglycemia and kidney injury in eNOS-/- mice, which resulted in marked increase in UACR. DRV treatment markedly reduced UACR, attenuated tubulointerstitial fibrosis as detected by type 1 collagen and fibronectin, and prevented loss of podocyte synaptopodin and endothelial CD31 expression in glomeruli as detected by IF. IF studies also demonstrated that G3BP1 and phosphorylation of Stat3,

Src, and Erk were increased in the kidneys of diabetic eNOS-/- mice and these changes were reduced by DRV treatment. To directly test the role of G3BP1 in promoting Stat3, Src, and Erk phosphorylation, we used siRNA to knock down G3BP1 expression in human tubular cells, which reduced phosphorylation of Stat3, Src and Erk.

Conclusions: These data suggest that DRV prevents diabetes-induced kidney injury in mice in part, via interactions with the SG protein G3BP1. Additional studies are needed to further delineate the effects of targeting SG function upon diabetic kidney injury.

Funding: NIDDK Support

PO0692

The Role of Intestinal Flora in Cinnamaldehyde Alleviating Early Proteinuria in Diabetic Nephropathy

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Background: Intestinal dysbiosis played a crucial role in chronic inflammation of diabetic nephropathy (DN). Cinnamaldehyde (CIN) is a traditional natural food addictive from a Chinese herb, recognized as antidiabetic and antibacterial medicine recently. This study was to observe the effects of CIN on renal injury and intestinal flora in DN.

Methods: A total of four groups of rats included DN group induced by streptozotocin (70mg/kg), treated with CIN (DNC), control (NC), and NC treated with CIN (NCC). CIN was given daily for 8 weeks. Blood glucose, bodyweight, 24h urinary volume (24hV), protein (24hUP), the pathology changes of kidney, and the protein expression of Megalin, Fibronectin, TGF-β were measured. We also sequenced 16S rDNA of the intestinal flora of the rats.

Results: Compared with DN, DNC showed significant improvement with lower 24hUP, decreased TBM thickness, Fibronectin, TGF-β, and increased Megalin. Simpson's diversity index of the intestinal flora significantly decreased in the DNC group. PCoA (Fig. A) showed different patterns of clustering between the 4 groups ($p<0.01$). At genera, compared with NC, *g__Lactobacillus* decreased significantly in DN, but recoverd in DNC, and it was also confirmed as significant biomarkers by LEfSe (Fig. B). Besides *g__Lactobacillus*, there were 12 other differentially enriched genera in DNC, such as *g__Alloprevotella*, and *g__Oscillospira*. At species, 3 species decreased in DN and recovered in DNC, including *s__Bacteroides_massiliensis*, *s__Oscillibacter_sp_ER4*, and *s__Lachnospiraceae_ bacterium_ A2*. They were anti-inflammatory probiotics that produce short-chain fatty acids. The abundance of 6 genera correlated well with 24hUP ($p<0.05$, Fig.C). Tax4fun (Fig.D) showed significant differentially enriched functional categories.

Conclusions: Cinnamaldehyde could alleviate renal injury in DN, which was associated with the recovery of the reduced intestinal *g__Lactobacillus.*

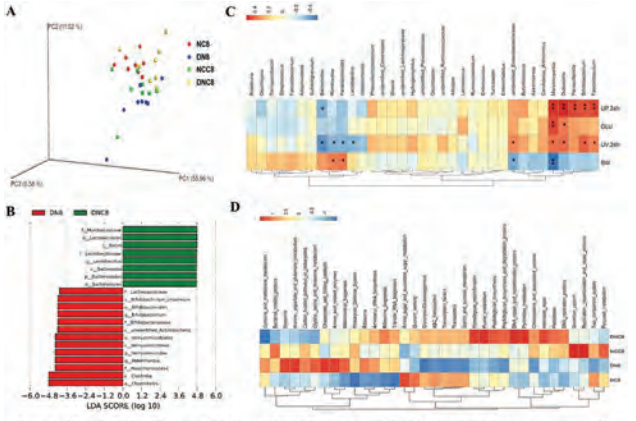

Figure 1. Altered intestinal flora. A: PCoA (weighted UniFrac distance). **B: LEfSe** (LDA>4). **C: Spearman** correlation analysis. **D. Tax4fun** function prediction (KEGG database). NC8: normal control 8W; DN8: diabetic nephropathy 8W; NCC8: normal control treated with CIN 8W; DNC8: diabetic nephropathy treated with CIN 8W. BW: bodyweight. GLU: blood glucose. 24hUP: 24-hour urinary protein. 24hUV: 24-hour urinary volume.

PO0693

Hyperglycemia-Induced Mitochondrial Dysfunction in Kidney and Brain Are Protected by β-Hydroxybutyrate Treatment

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Background: The immediate effects of hyperglycemia on mitochondrial and organ dysfunction are poorly understood. Acute hyperglycemia could reveal key initiating events to determine how organ dysfunction ensues, particularly in response to repeated hyperglycemia exposures as occurs with poorly controlled diabetes. The potential protective benefit of ketone bodies on mitochondrial function across organs during hypergylcemia has also not been well characterized. Here, we evaluated effects of hyperglycemia and β-hydroxybutyrate (BHB) on ATP production in the mouse using a novel *in vivo* brain imaging approach in combination with MALDI-MSI.

Methods: GFAP-fLuc dual-glo transgenic mice were used to test the effect of BHB on brain luciferin-luciferase biolumenescence using a Xenogen IVIS spectrum live-imaging system. Transgenic dual-glo mice expressed the luciferase in astrocytes under the gfap promoter. MALDI-MSI analysis was used to detect the acute impact of BHB on small molecule metabolites in the kidneys and brains of C57BL/6J mice. For *in vivo* experiments, mice were administered either 2.5 g/kg of BHB, 2 g/kg of glucose, a combination of BHB and glucose, or 0.9% NaCl (vehicle control). We determined the timing effect of 20 mM BHB on mitochondria function and glycolysis in HK2 cells, in fresh mice kidney, and in brain tissue using pH and OCR measurements with the Agilent Seahorse instrument.

Results: We found reduced levels of ATP in both brain and kidney tissue slices of mice acutely treated with 25 mM glucose with MALDI-MSI. BHB treatments increased ATP levels in the brain and kidney tissues and cells. Acute glucose exposure in HK2 cells reduced OCR and increased ECAR, which was blocked by BHB treatment. *In vivo*, brain bioluminescence was significantly decreased when mice were injected with 25 mM glucose (4 minutes after luciferin injections), consistent with a loss in ATP production. In contrast BHB injections increased biolumenscence and blocked the loss of signal in the presence of high glucose.

Conclusions: These data indicate that acute glucose exposure reduces ATP production in the kidney and brain, and that BHB can reverse this effect. Together, these studies suggest the acute detrimental effects of hyperglycemia on metabolism and mitochondrial dysfunction can be reversed with ketone bodies treatment.

Funding: Private Foundation Support

PO0694

Dysfunction of the Renal Tubular Circadian Clock Leads to Enhanced Renal Gluconeogenesis and Exacerbated Hyperglycemia in Diabetes

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Background: The circadian rhythms define all biological process cycling with a periodicity of about 24 hours. They are believed to be an evolutionary adaptation that allows biological functions to anticipate variations of environmental conditions imposed by Earth rotation. These rhythms are driven by the circadian clock, a molecular system of interconnecting loops present in virtually each cell of the body. Disturbance of the circadian rhythms or its misalignment with external environment is a risk factor for development of numerous diseases, such as depression, obesity, diabetes or cancers. However, the pathophysiological role of intrinsic renal circadian clocks in the diabetic kidney remains unknown.

Methods: To address this question, we used mice with streptozotocin-induced type I diabetes, and carrying *Bmal1* deletion either in the podocytes (pcKO mice) or in whole renal tubular cells (tcKO mice).

Results: Although diabetic pcKO mice did not show any additional alterations compared to diabetic Control mice, diabetic tcKO mice showed exacerbated hyperglycemia, increased fractional excretion of glucose, enhanced polyuria and a more severe renal hypertrophy compared to diabetic Control mice. Interestingly, renal gluconeogenic pathway was enhanced in diabetic tcKO mice, as demonstrated by increased protein and mRNA expression levels of key enzymes. Moreover, deep sequencing transcriptome and functional analysis of diabetic cKOt mice showed alterations in several mechanisms affecting the gluconeogenic pathway.

Conclusions: Altogether, our data demonstrate that disturbance of renal tubular circadian clock enhances gluconeogenesis in proximal tubule, leading to the aggravation of the hyperglycemia of diabetic mice. These results highlight importance of circadian behaviour in diabetic patients.

Funding: Other NIH Support - Swiss National Science Fundation (SNSF)

PO0695

Dysregulation of Thiosulfate Thiotransferase Pathway Contributes to Tubulointerstitial Injury of Diabetic Nephropathy

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Background: Tubulointerstitial injury plays an important role in the progression of diabetic nephropathy (DN), and its severity is closely related to the prognosis of DN. Thiosulfate thiotransferase (TST) is a key enzyme that mediates protein S-sulfhydrylation and maintains mitochondrial metabolic homeostasis. This study aimed to investigate the role of TST in tubulointerstitial injury of DN and to explore its potential mechanisms.

Methods: Sodium thiosulfate (STS)-treated diabetic mice, adeno-associated virus with TST overexpression transfected diabetic mice, and cell culture model of HK-2 cells transfected by lentivirus with TST overexpression were used for experiments. The protein S-sulfhydration of very long-chain acyl-CoA dehydrogenase (VLCAD) was checked by Western blotting and mass spectrometry analysis. Tubular mitochondrial mitochondrial fatty acid β oxidation (FAO) was checked by ^{13}C labeling combined with mass spectrometry and Seahorse assay. Epithelial mesenchymal transition (EMT) related molecules of tubular epithelial cells were evaluated by immunofluorescent staining and Western blotting.

Results: Our results showed that the expression of TST was decreased in kidneys of diabetic mice and in high glucose-stimulated HK-2 cells, which was significantly correlated with decreased E-cadherin and increased protein expression of collagen I, fibronectin, and α-SMA. Furthermore, the down-regulation of TST expression led to the FAO dysfunction in kidneys of diabetic mice and in high glucose-stimulated HK-cells. On the contrary, STS treatment or overexpression of TST alleviated albuminuria and tubulointerstitial injury. The expression of collagen I, fibronectin, and α-SMA in TST transfected diabetic mice or HK-2cells were significantly decreased, while E-cadherin expression was increased. Further analysis showed that pharmacological inhibition of STS

or overexpression of TST improved mitochondrial FAO dysfunction and tubulointerstitial injury in diabetic mice and in high glucose-stimulated HK-2 cells, which was mainly through the increased S-sulfhydrylation modification of VLCAD.

Conclusions: These findings demonstrated that down-regulation of TST expression mediated the decrease of S-sulfhydrylation modification of VLCAD, which led to mitochondrial FAO dysfunction and then exacerbated the progression of tubulointerstitial injury in DN.

PO0696

CYP450: Protagonists in the Story of Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is a grave complication and a major contributor to all-cause mortality in patients with diabetes. Cytochrome P450 (CYPs) epoxygenases metabolize arachidonic acid into the vasoactive and renal-active HETEs and EETs. Our group, among others, advanced the discovery implicating CYPs and their metabolites in the pathogenesis of DKD by regulating reactive oxygen species. Of interest, CYPs-encoding genes possess different polymorphisms which alter the expression of these key enzymes, affecting the prognosis of patients with DKD. Noteworthy, the CYPs polymorphisms and their correlation with the production of 20-HETE and EETs in DKD remain poorly investigated. In the same spirit, extensive research has highlighted the role of different miRNAs in DKD. To our knowledge, the regulatory effect of miRNAs on the expression of different CYPs in DKD is not yet established. In this study, we aim to elucidate the role of CYPs polymorphism, their metabolites, and miRNAs regulating their expression in the disease onset and progression of DKD.

Methods: Blood and urine were collected from patients with type 2 diabetes (T2D) with or without clinical manifestation of DKD. Levels of 20-HETE and EETs were assessed in the urine samples of the patients alongside with the renal CYPs enzymatic activities in human kidney biopsies. Besides, miRNA analysis was performed on the plasma collected from these patients to study CYP enzymes regulation using the Target Scan online tool.

Results: Our data show that the circulating levels of 11,12-EETs were decreased in patients with DKD when compared to T2D patients with no clinical signs of DKD, concomitant with an increase in the 20-HETE levels. Our results show that in patients with DKD, the expression of miRNA was altered ultimately leading to the downregulation of CYP2B6, CYP4A11 and CYP4F8 enzymes. Furthermore, patients with DKD carry CYPs polymorph with the minor allele frequency resulting in an alteration in their enzymatic activity and subsequently increasing 20-HETE and decreasing EETs production concomitant with a positive correlation with the expression of the corresponding CYPs in human kidney biopsies.

Conclusions: This study yields crucial findings about novel genetic and epigenetic pathways involved in DKD and identifies biomarkers related to CYPs pathways that could be of diagnostic, prognostic, and therapeutic value.

Funding: Private Foundation Support, Clinical Revenue Support

PO0697

Metabolic Images Using Fluorescence Lifetime Imaging Reveals Metabolic Alteration in Proximal Tubular Epithelial Cells in Type 2 Diabetes

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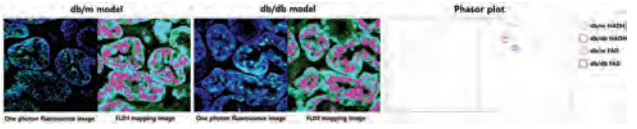
Background: Although there is a massive metabolic alteration of the kidney in diabetes, it is difficult to detect and measure the single-cell nicotinamide adenine dinucleotide hydrogen (NADH), flavin adenine dinucleotide (FAD) production, and redox potential. In particular, proximal tubular epithelial cells (PTECs) are the most laborious and affected cells under high glucose environments. We investigated this study to evaluate quantitative PTECs-specific metabolic images in the diabetic kidney using fluorescence lifetime imaging (FLIM).

Methods: Kidney sections of 20 week-old db/db and db/m mice were used for FLIM. FLIM images are analyzed using the phasor approach. The FLIM image and phasor plot representing FLIM data in vector space were measured through Leica TCS SP8 SMD and LAS-X software. The NADH, FAD, and ATP levels in diabetic kidneys were measured using LC-MS analysis by Q-trap 5500.

Results: NADH and FAD located at the different subcellular levels in PTECs. The NADH phasor analysis of PTECs revealed a right-ward shift toward shorter lifetimes from the db/m to the db/db, while there was no significant alteration of FAD between the two groups. It could be indicative of an increase in the NADH-to-FAD ratio that alters metabolic flux. In addition, the levels of NADH in diabetic kidneys were significantly increased than db/m, while the levels of FAD were reduced in diabetic kidneys. Finally, ATP level decreased in the diabetic kidney compared to db/m.

Conclusions: NADH and FAD FLIM in PTECs is an optimal approach to characterize and monitor metabolism in diabetic kidneys. Quantitative metabolic imaging using FLIM enables to measure and analyze metabolic alteration with spatial information.



PO0698

Female Protection Against Diabetes-Induced Kidney Injury Is Eliminated in Kidney Tubule-Specific AMPK Gamma-2 Knockout Mice

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Background: Reduction in renal AMPK activity is associated with obesity- and diabetes-induced kidney injury which is ameliorated by AMPK stimulation in male mice. Female mice resist obesity-induced kidney injury; this protection is abolished in kidney tubule specific α1 and α2 KO female mice. We tested if interruption of AMPK activity abolishes renal protection against diabetes in AMPK γ2 KO female mice. We also tested if diabetes worsens kidney injury in AMPK γ2 KO male mice.

Methods: 3-4 month-old tubule-specific AMPK γ2 KO male and female mice (n= 6-9 per group) were employed. To generate diabetic animal model, the mice were placed on high fat diet (HFD) for one month, then they received streptozotocin (STZ) 50mg/kg body weight by IP daily for 5 days. After 1 month STZ injection, urine was collected for analyzing urinary KIM-1 and ACR.

Results: Renal cortical expression of AMPK γ2 mRNA as well as protein was reduced in AMPK γ2 KO mice. There were no changes in body weight and random blood glucose level between control and AMPK γ2 KO male and female mice at the baseline. Body weight gain in control and AMPK γ2 KO mice in both genders was increased by HFD compared to normal fat diet fed groups. Random blood glucose level was increased in HFD and STZ-treated control and AMPK γ2 KO mice in both genders. As expected control female mice resisted HFD and STZ-induced kidney injury, whereas urinary KIM-1 excretion and albuminuria were increased in AMPK γ2 KO female mice. Urinary KIM-1 excretion and albuminuria were induced by diabetes in control and γ2 KO male mice with no statistical difference between two groups.

Conclusions: Renal protection against diabetes is abolished in kidney tubule specific AMPK γ2 KO female mice. Therefore, regulation of AMPK as well as its activity contributes to the protective mechanism against diabetes in female mice, and it could be used for a therapeutic target of diabetes.

PO0699

Mitochondrial Fission and Fusion Dynamics Are Regulated by Multiple Pathways in Renal Proximal Tubule Cells Treated with High Glucose

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Background: In type 2 diabetes, hyperglycemia leads to proximal tubular dysfunction, which is accompanied by altered mitochondrial homeostasis. We previously demonstrated that in renal proximal tubule cells (RPTC) grown in high glucose, as well as in diabetic db/db mice, mitochondrial dynamics proteins were altered. Phosphorylation of the mitochondrial fission protein Drp1 increased and the mitochondrial fusion protein Mfn1 decreased. Studies have shown that Drp1 is activated by the RhoA/ROCK1 signaling cascade in the presence of high glucose, leading to increased mitochondrial fission. Conversely, Mfn1 can be activated by MEK/ERK signaling. However, these pathways have not been investigated in the proximal tubule. Therefore, we determined the signaling pathways responsible for altered Drp1 phosphorylation and Mfn1 expression in RPTC.

Methods: Primary cultures of RPTC were grown in the presence of high glucose (17mM), mannitol (17mM) or no glucose for 96hr and were co-treated with either RhoA (CCG-1423), ROCK1 (Y-27632) or MEK 1/2 (GSK 1120212) inhibitors 24 hr prior harvesting. Cells were subjected to GTPase assays to measure Drp1, RhoA and Mfn1 activity and maximal mitochondrial respiration was measured using Seahorse XF96e analyzer.

Results: RPTC treated with glucose for 96 hr exhibited an increase in RhoA and pDrp1 at 96 hr. This increase corresponded with an increase in GTP-bound RhoA and Drp1. Co-treatment with CCG-1423 or Y-27632 prevented the glucose-induced increase in RhoA and Drp1, respectively. Inhibition of RhoA and ROCK1 restored maximal mitochondrial respiration. Co-treatment with GSK 1120212 prevented the glucose-induced decrease in Mfn1.

Conclusions: Together, these results demonstrate that treatment of RPTC with glucose increases RhoA and Drp1 activity and maximal respiration. Pharmacological inhibition of RhoA and ROCK1 prevented increased activity of RhoA and Drp1 and restored respiration, indicating that the RhoA/ROCK1/Drp1 signaling pathway is responsible for increased mitochondrial fission and respiration in high glucose in RPTC. In contrast, we show that inhibition of the MEK/ERK signaling cascade prevents the decrease in Mfn1 observed in the presence of high glucose. These data indicate that the alteration of mitochondrial dynamics in high glucose in RPTC, are regulated by two independent signaling pathways.

Funding: Veterans Affairs Support

PO0700

Medications Targeting the Activation of Tubular Fatty Acid Oxidation Enhance the Renoprotective Effects of Roux-en-Y Gastric Bypass Surgery

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Background: Roux-en-Y gastric bypass surgery (RYGB) improves biochemical and histological parameters of diabetic kidney disease (DKD). Targeted adjunct medical therapy may enhance renoprotection following RYGB.

Methods: The effects of RYGB (n=10) and RYGB plus fenofibrate 100mg/kg, metformin 300mg/kg, ramipril 1mg/kg, and rosuvastatin 10mg/kg (RYGB-FMRR; n=9) on metabolic control and histological and ultrastructural indices of renal injury were compared after 8 weeks of treatment in the Zucker Diabetic Sprague Dawley (ZDSD) rat model of DKD. Sham-operated ZDSD rats (n=9) and healthy Sprague Dawley rats (n=6) served as controls. Renal cortical transcriptomic (RNA-sequencing) and urinary metabolomic (^{1}H-NMR spectroscopy) responses were profiled and integrated. Omic correlates of improvements in structural and ultrastructural indices of renal injury were defined using a molecular morphometric approach.

Results: RYGB-FMRR was superior to RYGB alone with respect to metabolic control, albuminuria, and histological and ultrastructural indices of glomerular injury. RYGB-FMRR reversed DKD-associated changes in mitochondrial morphology in the proximal tubule to a greater extent than RYGB. Attenuation of transcriptomic pathway level activation of pro-fibrotic responses was greater after RYGB-FMRR than RYGB. Transcriptional induction of PPARα-regulated genes, expressed in the proximal tubule and governing fatty acid oxidation (FAO), was a unique feature of the RYGB-FMRR transcriptome associated with increased urinary PPARα-responsive nicotinamide metabolites and reduced urinary tricarboxylic acid (TCA) cycle intermediates. Multi-omic integration identified a strongly positively correlated network of FAO transcripts and nicotinamide metabolites as being distinctive to RYGB-FMRR. Changes in FAO transcripts, nicotinamide metabolites, and TCA cycle intermediates correlated strongly with improvements in glomerular and proximal tubular injury following RYGB-FMRR.

Conclusions: The renoprotective effects of RYGB can be enhanced through the deployment of medications targeting PPARα-mediated activation of tubular FAO responses.

Funding: Government Support - Non-U.S.

PO0701

Polyamine Catabolism Is Enhanced in Streptozotocin-Treated Mice and in Cultured Proximal Tubule Cells Exposed to High Glucose Levels: A Possible Role in Tubular Injury in Diabetic Nephropathy

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Background: Polyamines are indispensable to cell growth and survival. Their cellular levels are regulated via import, export and metabolism. Their catabolism is mediated via the activities of spermine oxidase (SMOX) and spermine spermidine-N1-acetyltransferase (SAT1)/Acetylpolyamine oxidase (PAOX) cascade. Enhanced polyamine catabolism mediates cellular injury by induction of DNA and mitochondrial damage, activation of the endoplasmic reticulum stress/unfolded protein response (ERS/UPR) pathway, and innate immunity. Studies indicate that mitochondrial dysfunction, innate immune response and ERS/UPR are important mediators of tubular injury in diabetic nephropathy. We posit that polyamine catabolism is activated in diabetes mellitus and plays an important role in tubular injury.

Methods: The expression of polyamine catabolic enzymes was examined in streptozotocin (STZ)-induced diabetes in mice and HK-2 proximal tubule cells exposed to high glucose (30mM) levels. The expression levels of SAT1 and SMOX were determined by northern and western blot analyses. Nephron segment expression and localization of SAT1 and SMOX in STZ-treated mice was determined by immunohistochemistry and immunofluorescence microscopy.

Results: Expression of SAT1 and SMOX were elevated in the kidneys of STZ-treated mice compared to their vehicle-treated counterparts. Immunohistochemical and immunofluorescence microscopic studies revealed that SAT1 and SMOX expression are increased the proximal tubule, distal convoluted tubule and collecting duct epithelial cells. *In vitro* studies using HK-2 cells demonstrated that the expression of both SAT1 and SMOX increases in response to exposure to 30mM glucose.

Conclusions: Expression of polyamine catabolic enzymes, SAT1 and SMOX, is increased in proximal tubules, distal convoluted tubules and collecting ducts of mice with diabetes mellitus. Similarly, exposure of HK-2 cells to 30mM glucose increased the expression of both SAT1 and SMOX transcripts. Based on these studies and their known injurious effects, we propose that SAT1 and SMOX play a significant role in the mediation of renal injury in diabetes mellitus likely through the induction of oxidative injury, mitochondrial damage, elevated ERS/UPR and activation of innate immune response.

Funding: Veterans Affairs Support, Private Foundation Support

PO0702

An Interplay of Glucose, IL-1β, and PDGF-B Trigger cPLA2 Activation, Prostaglandin Secretion, and Proliferation in Human Mesangial Cells

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Background: Diabetic kidney disease (DKD) is commonly thought to be originated from diabetic hyperglycemia. DKD development is driven by early glomerular hemodynamic changes and characterized by progressive expansion of the mesangium. A connection between these findings is yet to be elucidated. We speculate that, after hyperglycemia priming, autocrine inflammatory and proliferative stimuli alter mesangial lipid metabolism activating the secretion of vasodilator hormones. Subsequently, this affects glomerular functions. Phospholipase cPLA2 was identified as the central enzyme of the metabolic cascade.

Methods: Human mesangial cells were stimulated with Glucose (30 mM), IL-1β (1 nM), PDGF-B (25 ng/ml). Their synergic counter activation was investigated by western blots and qPCR. Lipidomics was used to analyze lipid variations. Cox-2 induction and prostaglandin secretion were measured via western blot and ELISA. Activation of cPLA2, upstream of Cox-2, was studied using western blot, qPCR, activity assays. ELISA, migration, and proliferation assays were used to evaluate cPLA2 inhibition. Data were validated using the Nephroseq database.

Results: After stimulation with Glucose, NLRP3 and pro-IL-1β were upregulated. IL-1β stimulation increased PDGF-B mRNA levels. In turn, PDGF-B stimulation increased NLRP3 and pro-IL-1β protein levels. Lipidomics analysis after IL-1β and PDGF-B stimulations showed an increase of sphingosine 1 phosphate, a known activator of Cox-2. Cox-2 was induced and prostaglandins secreted accordingly. cPLA2 releases arachidonic acid, the substrate of Cox-2. cPLA2 was upregulated at gene and protein level and activated by phosphorylation. Upregulation of the pathway was confirmed in silico in DKD patients. Since cPLA2 reaction is the rate-limiting step in prostaglandin synthesis, its inhibition with AACOCF3 was studied. Inhibition of cPLA2 reduced migration, proliferation, secretion of prostaglandins in cells treated with IL-1β and PDGF-B.

Conclusions: External stimuli (hyperglycemia from the diabetic environment) and glomerular inflammatory and proliferative stimuli prime DKD early events. The upregulation of cPLA2 was found to be critical in these events. cPLA2 inhibition reduced mesangial secretion of prostaglandins, proliferation, and migration, making it a potential target for therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO0703

CHOP-ASO Ameliorates Glomerular and Tubular Damage on Top of ACE Inhibition in Diabetic Nephropathy

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Background: Maladaptive ER stress signaling in diabetic nephropathy (dNP) is linked to increased glomerular and tubular expression of the cell death-promoting transcription factor C/EBP homologous protein (CHOP). We determined whether therapy with locked nucleic acid (LNA)-modified antisense oligonucleotides (ASOs) targeting CHOP ameliorates experimental dNP.

Methods: Following an *in vivo* dose-escalation study, we determined the efficacy of CHOP-ASO in the early and later stages of experimental dNP (8- or 16-week-old db/db mice, respectively) alone or in combination with an angiotensin-converting enzyme inhibitor (ACEi). Renal functional parameters and morphological analyses were used to determine the effects. Renal gene expression profiling was conducted to determine differentially regulated genes and pathways. Several human CHOP-ASOs were tested in hyperglycemia-exposed human kidney cells.

Results: CHOP-ASOs efficiently reduced renal CHOP expression in diabetic mice and reduced markers of dNP at early and late stages. Early combined intervention (CHOP-ASO and ACEi) efficiently prevented interstitial damage. At the later timepoint, the combined treatment reduced indices of both glomerular and tubular damage more efficiently than either intervention alone. A significantly larger number of genes and disease pathways were affected by CHOP-ASO, including reduced Slc5a2 (sodium-glucose transport protein 2). Human CHOP-ASOs efficiently reduced glucose-induced CHOP and SGLT2 expression and prevented cell death of human kidney cells *in vitro*.

Conclusions: The ASO-based approach efficiently reduced renal CHOP expression in a diabetic mouse model, providing an additional benefit to an ACEi in particular at later timepoints. These studies demonstrate that ASO-based therapies efficiently reduce maladaptive CHOP expression and ameliorate experimental dNP.

PO0704

Suppression of Endoplasmic Reticulum-Associated Degradation Process by Intraglomerular Cross-Talk Between Podocytes and Mesangial Cells Causes Podocyte Injury in Diabetic Kidney Disease

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Background: Mesangial lesion and podocyte injury are essential for the progression of diabetic kidney disease (DKD). Although crosstalk between mesangial cells (MCs) and podocytes is recently suggested by single nucleus RNA-sequence analyses, its molecular mechanisms and role on disease progression still remain elusive.

Methods: We evaluated the ER stress responses of podocytes stimulated with mesangial cell-cultured medium (MC-sup) under high-glucose condition (HG) *in vitro*. Then, the effects of an ER-associated protein degradation (ERAD) inhibitor eeyarestatin I (EerI) in cultured podocytes and glomeruli of *db/db* (type 2 diabetic) mice were also examined by western blotting, immunofluorescence and TUNEL staining. Furthermore, we evaluated the effect of ERAD inhibitor on nephrin phosphorylation of podocytes by flowcytometric analysis and western blotting.

Results: *In vitro* experiments revealed the suppression of the ER-associated degradation (ERAD) pathway and induction of apoptosis in podocytes that were stimulated with the supernatant of mesangial cells cultured in high glucose conditions. In diabetic mice, ERAD inhibition resulted in exacerbated albuminuria, increased apoptosis in podocytes, and reduced nephrin expression associated with the downregulation of ERAD-related biomolecules. Flowcytometry analysis of podocytes isolated from MafB (a transcription factor known to be expressed in macrophages and podocytes)-GFP knock-in mice revealed that ERAD inhibition resulted in decreased nephrin phosphorylation. Decreased nephrin phosphorylation was also confirmed in *in vitro* experiments.

Conclusions: ERAD process has been reported to be important for avoiding ER stress and cellular damages. Our findings suggest that an intraglomerular crosstalk between MCs and podocytes can inhibit physiological ERAD processes and suppress the phosphorylation of nephrin in podocytes, which thereby lead to podocyte injury under diabetic conditions. Therapeutic intervention of the ERAD pathway through the crosstalk between these cells is potentially a novel strategy for DKD.

PO0705

DPP4 Inhibitors Ameliorates Endoplasmic Reticulum Stress in Diabetic Kidney Disease Through Upregulation of SIRT1

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Background: Endoplasmic Reticulum (ER) stress plays vital roles in the progression of diabetic kidney disease (DKD), and Dipeptidyl peptidase-4 (DPP4) inhibitors are widely used antihyperglycemic agents, further exerting renal beneficial effects in DKD, but the precise mechanism underlying the disruption of these processes remains unclear. We examined whether SIRT1/STAT3 pathway regulated ER stress in the progression of DKD.

Methods: *In vivo*, male DBA2/J mice were injected by streptozotoxin to form diabetic mice models, then sitagliptin(Sita) was gavaged to inhibit DPP4. We collected and analyzed kidney samples, urine and serum. *In vitro*, human HK-2 cells were exposed to human serum albumin (HSA), then regulated DPP4, SIRT1 with inhibitors, siRNAs and mutant plasmids. Outcome measures included ER stress, expression of GRP78, CHOP, phosphorylation of PERK (p-PERK), cleaved caspase3 (c-CASP3), SIRT1 and STAT3.

Results: ER stress were observed both in diabetic mice and in HSA-induced human HK-2 cells, as reflected by notably increased GRP78, CHOP, highly phosphorylation of PERK (p-PERK) and elevated cleaved caspase3 (c-CASP3), whereas Sita effectively attenuated these disorders. Meanwhile, Inhibited DPP4 increased the expression of SIRT1 both *in vivo* and *in vitro*, which has a protective effect on diabetic ER homeostasis, whereas decreased SIRT1 accentuated ER stress. Moreover, partly through elevated SIRT1, Sita regulated mitochondrial STAT3 and phosphorylation of STAT3 at ser727, which is required for STAT3 to import into mitochondria. Our work found that the inhibition of DPP4 ameliorated ER stress in DKD partly through SIRT1/STAT3 signaling pathway.

Conclusions: The results suggested a novel mechanism links the DPP4 enzyme to ER stress during tubular injury in DKD and highlight that SIRT1/STAT3 pathway may become a potential target for managing DKD.

Funding: Government Support - Non-U.S.

PO0706

Wnt5a-Ca2+ Non-Canonical Pathway Mediates Mitochondrial Dysfunction in the Progression of Diabetic Nephropathy via Mitochondrial Calcium Uniporter

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Background: Mitochondrial abnormalities play crucial roles in diabetic tubular injury progression. Abnormal expression of Wnt5a has been detected in many metabolic diseases. However, the association of Wnt5a and mitochondrial dysfunction in diabetic nephropathy (DN) progression remains unknown.

Methods: Diabetic DBA2/J mice induced by streptozotocin were assigned to amlodipine (5mg/kg/d) and losartan (10mg/kg/d) for eight weeks. The expression of Wnt5a, mitochondrial dynamics associated proteins (Drp1 and Mfn2), mitochondrial calcium uniporter (MCU) were examined through Western blot and immunohistochemistry in kidney of STZ-induced diabetic and high glucose stimulated HK-2 cells. Calcium concentration in cells and mitochondria was detected through specific ELISA kit.

Results: In this study, upregulation of Wnt5a, increase of both cellular and mitochondrial Ca^{2+}, mitochondrial fragmentation and altered mitochondrial dynamics-associated protein expression were detected in the tubules of diabetic mice and in high glucose stimulated HK-2 cells. In vitro, Wnt5a overexpression induced the Ca^{2+} influx and aggravated mitochondrial fusion-fission disorder. After amlodipine treatment, this Wnt5a-Ca^{2+} pathway was restored, mitochondrial dynamics and morphological changes was improved. Additionally, increase of MCU was also observed in the mitochondrial of tubular cells in DN, suggesting a possible link between Wnt5a-Ca^{2+} pathway and mitochondrial dysfunction.

Conclusions: Our study presented that Wnt5a-Ca2+ signaling pathway might be involved in mitochondrial dysfunction in the progression of DN, and MCU was possibly recognized as the important link during the regulation.

PO0707

The Potential Roles of NAD(P)H:Quinone Oxidoreductase 1 in the Development of Diabetic Nephropathy and Actin Polymerization

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Background: Diabetic nephropathy (DN) is a major complication of diabetes mellitus. NAD(P)H:quinone oxidoreductase 1 (NQO1) is an antioxidant enzyme that has been involved in the progression of several kidney injuries. However, the roles of NQO1 in DN are still unclear. We investigated the effects of NQO1 deficiency in streptozotocin (STZ)-induced DN mice.

Methods: Wild-type (WT) and NQO1 KO male mice on C57BL/6N genetic background were used. For the diabetic nephropathy model, STZ was dissolved in citrate buffer (0.1 M; pH 4.5) and prepared immediately before use. Age-matched 8-week-old WT and NKO male mice were administered STZ (50 mg/kg body weight, intraperitoneal injection) after 4 h fasting, for five consecutive days. ACR were measued. Renal histology and molecular evaluation were done.

Results: NQO1 was upregulated in the glomerulus and podocytes under hyperglycemic conditions. NQO1 knockout (NKO) mice showed more severe changes in blood glucose and body weight than WT mice after STZ treatment. Furthermore, STZ-mediated pathological parameters including glomerular injury, blood urea nitrogen levels, and foot process width were more severe in NKO mice than WT mice. Importantly, urine albumin-to-creatinine ratio (ACR) was higher in healthy, non-treated NKO mice than WT mice. ACR response to STZ or LPS was dramatically increased in the urine of NKO mice compared to vehicle controls, while it maintained a normal range following treatment of WT mice. More importantly, we found that NQO1 can stimulate actin polymerization in an in vitro biochemical assay without directly the accumulation on F-actin.

Conclusions: NQO1 has an important role against the development of DN pathogenesis and is a novel contributor in actin reorganization via stimulating actin polymerization.

PO0708

The Renoprotective Effects of the Soluble Guanylate Cyclase (sGC) Activator Runcaciguat Are Associated with Distinct Changes in Renal Gene Expression Profiles

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Background: Chronic kidney disease (CKD) progression is associated with impaired NO-sGC-cGMP-signaling, low cGMP production and increased oxidative stress. Oxidative stress modifies the native sGC to oxidized, heme-free apo-sGC which cannot be activated by NO anymore. Runcaciguat is a novel potent and selective sGC activator that binds and activates heme-free sGC independently of NO and, thereby, restores cGMP signaling. In the ZSF-1 rat CKD-model, runcaciguat displays renoprotective effects (pronounced decrease in proteinuria and lowering of HbA1c and triglycerides). To understand the underlying mode of action of the renoprotective and metabolic effects of runcaciguat, we investigated the renal gene expression profile.

Methods: The renal expression profile of genes affected by 3mg/kg/bid runcaciguat in obese ZSF1 rats treated between 16 to 27 weeks of age was analyzed with a microarray (all known rat genes) and compared to gene expression changes of lean relative to obese ZSF1 rats aged 14 to 26 weeks to show deregulation over the course of the disease progression.

Results: With the selected deregulation thresholds, 45 and 82 genes were expressed at higher and lower levels after runcaciguat treatment, respectively. Thresholds were set as 1.6-fold differences between vehicle and treatment group with $p<0.05$. Most of the genes decreased by runcaciguat also show decreased expression in lean vs. obese ZSF1 rat kidney, suggesting that runcaciguat converts the kidney expression profile of obese ZSF1 rats partly to the lean pattern. Most of these genes encode proteins involved in fibrosis (e.g. collagens), inflammation (e.g. cytokines), and degeneration/regeneration (e.g. cell cycle progression genes, lipocalin 2) which is supported by the Ingenuity pathway analysis (IPA)

Conclusions: The runcaciguat-induced gene expression changes clearly indicate an at least partial reversal of the fibrotic phenotype and enhanced vascular-endothelial functions in the ZSF-1 CKD rat model. These changes could contribute to the renoprotective effect of runcaciguat. Runcaciguat is currently evaluated in a Ph2a clinical trial (CONCORD) for CKD.

Funding: Commercial Support - Bayer AG

PO0709

Exogenous Hydrogen Sulfide Protects Kidneys of Diabetic Mice from Oxidative Injuries

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Background: Exogenous hydrogen sulfide (H2S) protects kidneys from diabetic injuries in animal models. In order to explore its mechanisms, we determined the effects of H2S donor on renal reactive oxygen species (ROS) related enzymes in diabetic mice.

Methods: Male C57Bl/6J mice (8 weeks old) were intraperitoneally injected with STZ at 50mg/kg/day for 6 days. GYY4137 (20 mg/kg/day in 6 ml of drinking water, GYY+DM group, n=5) or vehicle (6 ml of drinking water, DM group, n=4) plus 60% fat diet were fed the mice 2 weeks after the initial STZ injection when blood glucose remained high relative to background mice. The 2 groups of diabetic mice were injected with long-acting insulin (10U/kg) weekly at week 3.

Results: GYY4137 ameliorated albuminuria and hyperglycemia at weeks 8 & 10. Serum insulin and creatinine were similar in the diabetic mice. Renal morphologic structures (HE, Massson, PAS) were improved by GYY4137 at week 10 when the mice were sacrificed. Renal nitrotyrosine (protein oxidative injury marker) was decreased along with the decrease of laminin (early fibrosis marker) in GYY+DM mice relative to DM mice (western blotting). NOX2, NOX4 were lower but NOS1, HO2, PON1, PON2 were higher in GYY+DM than those in DM group. NOS2, NOS3, NOX1, HO1, SOD1-3 and COX1 were similar between groups. The levels of mRNA were not in agreement with the changes in proteins with all enzymes but HO2.

Conclusions: Our findings suggest that exogenous H2S may decrease ROS production and increase ROS cleavage in kidney via the affected enzymes, thus improve the renal oxidative damage in diabetic nephropathy.

PO0710

Downregulation of Ehhadh and Tubular Dysfunction in Diabetic Nephropathy

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Background: As a peroxisomal protein, enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase (Ehhadh) catalyzes the second and third committed steps in the peroxisomal beta-oxidation pathway. Ehhadh also interacts with catalase and peroxisomal biogenesis factor 5 (PEX5), which decomposes hydrogen peroxide and regulates peroxisomal biogenesis, respectively. Previously we detected reduced tubular Ehhadh expression in human and mouse diabetic nephropathy. This study aims to investigate the potential impact of Ehhadh on peroxisomal/mitochondria functional change in response to high glucose in vitro.

Methods: Primary cultured proximal tubular epithelial cells (PTC) were exposed to high glucose, mannitol or control medium. Ehhadh subcellular localization and peroxisome quantitation (area per cell) were analyzed by confocal microscopy. Ehhadh, catalase, PEX5, ACOX1, Hsd17d4, scp2, ACAA1, cpt1a, Acadm, AHDHB, Acat1 and ACAA2 mRNA expression were assessed by qPCR. Peroxidase activity and oxidase stress were also analyzed.

Results: Ehhadh transcription and protein were significantly downregulated in PTC under high glucose conditions. Ehhadh was localized mostly to peroxisomes and rarely in mitochondria. Key enzymes for beta-oxidation in peroxisomes (ACOX1, Hsd17d4, scp2 and ACAA1) and mitochondria (cpt1a, Acadm, AHDHB, Acat1 and ACAA2) were not changed under high glucose conditions. Catalase transcription and peroxidase activity were reduced in high glucose vs control. PEX5 was also reduced, but peroxisome quantitation was increased 39.6% under high glucose conditions. Oxidative stress was also increased 7.6% in high glucose vs control.

Conclusions: Ehhadh downregulation is associated with reduced peroxidase activity, increased peroxisomal biogenesis and oxidative stress in PTC. Whether altering Ehhadh can impact such dysfunction awaits further study.

Funding: NIDDK Support

PO0711

Oxidative Stress on the Kidney and Heart of Rats with Diabetic Nephropathy Treated with Esculin

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Background: Diabetes mellitus is a chronic disease which progresses with complications such as diabetic nephropathy (DN) and diabetic cardiomyopathy. Esculin (ESC) and its metabolite, esculetin, are coumarin derivatives, belonging to the Oleaceae family, found also in some more known species in the southern hemisphere, such as the pink lemon (Citrus limonia). ESC has been related to antioxidant (AO), anti-inflammatory and anti-apoptotic actions. The aim of the present study was to verify the role of oxidative stress (OS) on the kidney and the heart of rats with DN, and the ESC effect on them.

Methods: We used adult male Wistar rats (N=20), Ethics Committee # 3511260318. Normal rats (CTL) or with blood glucose> 200mg/dL, diabetic (DM, treated with streptozotocin 60 mg/kg, IV, single dose), received ESC (50 mg/ kg, via gavage, for 8 weeks). After this period, we collected blood, 24-hr urine, the kidney and heart of these animals. The organs were homogenized for TBARS (OS marker) and Western blotting of OS and apoptosis markers.

Results: Renal function assessed by urea and creatinine was reduced in DM x CTL. Proteinuria and TBARS increased in plasma and urine in DM rats, with a reduction in DM+ESC group ($p< 0.05$). In DM heart, there were no alterations in TBARS; glutathione, a pro-oxidant, was elevated. In the heart, Nrf-2, responsible for the transcription of several AO, was elevated in the DM, both in its cytoplasmic form and in its active, phosphorylated form. Catalase, an enzymatic AO, and caspase-3 were elevated in DM ($p< 0.05$).

Conclusions: ESC protected the diabetic kidneys reducing proteinuria and OS. Unlike the kidney, the hearts of DM did not present OS, although glutathione and apoptosis were increased. It is important to note, however, that the increase in AO proteins such as Nrf2 and catalase, suggests that at this early stage of DN, they are still able to protect the cardiac tissue against OS. We believe that the monitoring of this disease evolution can better clarify the role of Redox balance/ imbalance in the heart of diabetic rats. This would be very useful in the approach of prevention and treatment of cardiomyopathy, including the possible use of esculin, with its important antioxidant, anti-inflammatory and anti-apoptotic effects, as an adjuvant therapy.

Funding: Government Support - Non-U.S.

PO0712

Targeting Nox with Pan-Nox Inhibitor in Aging Diabetic Kidney

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Background: Aging process is a risk factor for altered glucose metabolism and insulin resistance. Moreover, diabetes with serious complications has been steadily increasing in older patients. Chronic inflammation and increased oxidative stress are commonly shared features of aging and diabetes mellitus. Therefore, we investigated the effect of pan-nox inhibitor on aging diabetic mice.

Methods: Diabetes was induced by intraperitoneal injection of streptozotocin at a 50mg/kg/day for 5 days in 52-week-old week C57BL/6J mice. An orally active pan-nox inhibitor from Aptabio was administered by oral gavage at a dose of 60mg/kg/day for 12 weeks in aging mice and diabetes induced aging mice.

Results: Nox inhibition significantly improved insulin resistance in both aging and diabetic aging mice. Additionally, fasting glucose and HbA1c level were significantly improved with Nox inhibition in diabetic aging group. Interestingly, oxidative stress measured by 8-isoprostane was significantly increased in both aging and diabetic mice. Pan-nox inhibitor significantly reduced plasma 8-isoprostane level in aging group, and urinary 8-isoprostane level in diabetic group. In diabetic aging condition, there was trend to decrease in urinary albumin and nephrin excretion with nox inhibition. Simply aging did not significantly altered PAI-1 and collagen IV expressions in the kidney compared to diabetic condition. However, nox 1 and 4 expressions was as well as increased in aging mice and diabetic mice. Pan-nox inhibitor significantly reduced renal PAI-1, collagen IV expressions in diabetic aging mice. Klotho level was significantly reduced in both aging and diabetic mice and nox inhibition restored klotho level in aging mice, but not in diabetic mice.

Conclusions: Our results provide evidence that pan-nox inhibition may improve systemic insulin resistance and oxidative stress in aging diabetic status, and therefore may have potential protective effects on aging diabetic kidney.

PO0713

NOX5 Promotes Diabetic Kidney Disease by Modulating Redox-Sensitive Pathways

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Background: Enhanced level of reactive oxygen species (ROS) in diabetes is considered a major contributor in aggravating renal injury. We aimed to examine the the role of pro-oxidant enzyme NOX5 and associated redox-sensitive pathways in diabetic kidney disease (DKD).

Methods: We examined the expression of NOX5 and associated redox-sensitive factors including NOX4, thioredoxin-interacting protein (TXNIP), a transcription factor, EGR1 (early growth response 1) and a protein kinase, PKC-α as well as ROS production in human kidney biopsies and in human renal cell lines as well as in human kidney organoids. We also assessed the effect of NOX5 expression independent of NOX4 in Nox5 transgenic mice in the presence or absence of diabetes.

Results: We identified increased expression of renal NOX5 in diabetic patients in association with upregulation of ROS-sensitive factors including EGR-1, PKC-α and TXNIP. We also observed upregulation of human NOX5 and TXNIP in renal organoids exposed to high glucose. Silencing of Nox5 attenuated high glucose induced gene expression of markers of fibrosis and inflammation as well as downregulation of EGR-1, PKC-α and TXNIP. Our data also suggest that Nox5 is upstream of Nox4 and that Nox5 inhibition also downregulates Nox4, but not vice versa. In vivo, overexpression of Nox5 independent of NOX4 pathways demonstrated an increase in albuminuria, renal fibrosis and inflammation in association with upregulation of EGR-1, PKC-α and TXNIP and enhanced ROS production in comparison to diabetic mice not expressing Nox5.

Conclusions: These findings suggest that NOX5 plays a key pathogenic role in renal inflammation and fibrosis, thereby providing impetus for the development of NOX5 specific inhibitor to combat DKD.

PO0714

Hyperpolarized MRI Detection of Dapagliflozin Effect on Gluconeogenesis in Live Animals: Proof of Principle

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Background: SGLT2 inhibitors including dapagliflozin (dapa) ameliorate hyperglycemia by inducing glucosuria but also induce gluconeogenesis (GNG), thus blunting efficacy. The lack of insight into the relative contributions of kidney and liver to GNG in different states is due at least in part to limitations in the technology to separately assess liver and kidney GNG in live animals. Our study exploits a powerful technology, Hyperpolarized Magnetic Resonance Imaging (HP-MRI), which can detect metabolic conversions non-invasively in specific organs in animals and humans, in real-time, in vivo. Notably, the chemicals based on stable isotopes of carbon (13-C) used here are approved for multiple diagnostic uses in humans, for example in monitoring metabolism in cancers.

Methods: Metabolic features of healthy WT (male, age ~12 weeks) rats were studied *in vivo* using hyperpolarized (HP) ^{13}C magnetic resonance imaging (MRI) is based on ~50,000-fold nuclear magnetic resonance (NMR) signal enhancements of ^{13}C-labeled substrates via dissolution dynamic nuclear polarization (DNP). To account for potential metabolic effects of infusion of pyruvate, we also performed [1- ^{13}C] pyruvate tolerance tests (PTT).

Results: We successfully detected the conversion of [1-^{13}C]pyruvate to [1-^{13}C]lactate and [1-^{13}C]alanine in the liver and kidneys of rats. We found that Intravenously injected HP [1- ^{13}C]pyruvate was rapidly metabolized to [1- ^{13}C]lactate and [1- ^{13}C]alanine in the liver and kidneys of rats. The PTT data show that there is a clear trend toward an increase in blood glucose following [1- ^{13}C]pyruvate injection. Dapa increased glycosuria, as expected. Furthermore, an effect of dapa was on the conversion of [1-^{13}C]pyruvate to [1-^{13}C]lactate and [1-^{13}C]alanine in the kidney but not the liver. This effect, however, was variable and appeared to be influenced by baseline GNG in the rats.

Conclusions: We establish here for the first time that HP-MRI technology can detect SGLT2i effects on metabolism in live rats, and can distinguish metabolic markers of GNG in kidney vs. liver in this context. Although the methodology requires further development to be useful as a consistent marker of SGLT2i effects on GNG, it could be useful in humans both for characterizing sub-categories of T2DM and detecting risk factors for SGLT2i resistance and/or side effects.

Funding: NIDDK Support, Commercial Support - Astra Zeneca, Private Foundation Support

PO0715

Investigation of the Renoprotective Effect of SGLT-2 Inhibitors Focused on Glomerular Hyperfiltration and Oxidative Stress in Mice with Diabetic Kidney Disease

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Background: In recent clinical trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors slowed the progression of DKD compared with placebo. One of the main mechanisms for the renoprotective effect of SGLT2 inhibitors in DKD is the improvement of glomerular hyperfiltration. We previously demonstrated that the adenosine/adenosine A1 receptor pathway played a pivotal role in the tubulo-glomerular feedback system in type 1 diabetic model mice (Circulation, 2019). We also reported that increased glomerular oxidative stress was involved in the progression of albuminuria in DKD (Diabetologia, 2010). Loss of tetrahydrobiopterin (BH4), which is a cofactor of eNOS, causes uncoupling of endothelial nitric oxide (NO) synthase (eNOS), resulting in increased superoxide production in DKD (AJPRP, 2005; JASN, 2013). In this study, we explored the renal protective effects of SGLT2 inhibition, with a focus on glomerular hemodynamics and glomerular oxidative stress.

Methods: We used db/db mice as a model for type 2 diabetes. Mice were treated with canagliflozin (CANA; 10mg/kg) for 8 weeks. We evaluated the change of single nephron glomerular filtration rate (SNGFR) and glomerular permeability of albumin using in vivo multiphoton microscopy imaging. Glomerular reactive oxygen species (ROS) and NO production were evaluated by ex vivo study. Low temperature sulfate-polyacrylamide gel electrophoresis was performed for detection of eNOS uncoupling. In addition, tomato lectin staining was carried out to estimate the vascular endothelial damage.

Results: Glomerular hyperfiltration and urinary albumin excretion in db/db mice was ameliorated by CANA treatment. Accelerated ROS production and diminished bioavailable NO caused by eNOS uncoupling in glomeruli were observed in db/db mice. CANA suppressed eNOS uncoupling and improved ROS/NO imbalance via maintenance of BH4. CANA inhibited degradation of endothelial surface layer due to increased glomerular oxidative stress.

Conclusions: SGLT2 inhibitor restore glomerular hyperfiltration in DKD. Simultaneously, intraglomerular ROS/NO imbalance via eNOS uncoupling was improved by SGLT2 inhibitor.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

PO0716

Empagliflozin (SGLT-2 Inhibitor) Ameliorates Early Features of Diabetic Retinopathy and Nephropathy in Type 2 Diabetic Mice Model via the Klotho Protein

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Background: The diabetic nephropathy (DN) and diabetic retinopathy (DR) are the most common serious vascular complications of diabetes Chronic hyperglycemia in DM triggers different processes that leads to Diabetic Retinopathy (DR) and Nephropathy (DN) development. α-Klotho (KL) is an anti-aging gene encoding a protein with multiple pleiotropic effects, involved in suppression oxidative stress and inflammation processes. We investigate the protective effect of Empagliflozin (EMPA) on the expression of KL on DN&DR in DM mice model.

Methods: BTBR mice with ob/ob leptin-deficiency develops severe type II DM with DN and DR. 8 weeks-old male mice were randomly divided into 3 groups: C57BL/6J Wild Type, BTBR ob/ob vehicle and BTBR ob/ob treated with EMPA. Mice were sacrificed after 13 weeks of treatment. Mice retinas were removed and fixed by immersion in 2% paraformaldehyde overnight at 4°C. After PBS rinses eyes were immersed in increased concentrations of sucrose-PBS solutions at 4°C and finally frozen in O.C.T. Cryostat sections (16 µm) were incubated overnight at 4°C with primary anti-KL antibody, then for 1 h with secondary antibody. We assessed immunohisto-fluorescence intensity of each experimental group, using an Olympus BX53 fluorescent microscope, and identical exposure for each image. Finally, the data is presented as percent area of the inner plexiform layer (IPL), especially the ganglionic cells, covered with positive signal to KL. Concomitantly, kidneys were removed and subjected to similar immunostaining for the KL protein.

Results: KL expression in the IPL (ganglionic cells) was 48.3±2.7 % in control mice, 11.9±2.% in DM mice ($P<0.001$ *vs.* control) and 20.4±2.% in DM mice treated with EMPA ($P<0.05$ *vs.* un treated DM mice). In control mice KL expression was 6.8% of the renal tissue area, expression was attenuated in the DM mice occupying 0.065 %, in DM mice treated with EMPA, the KL expression reached 4%.

Conclusions: The data suggested that KL protein can play a potential protective factor against retinopathy and nephropathy in DM mice. Early therapy with EMPA that targets the early pathogenesis of DR and DN, is wildly needed to prevent the onset & slow the progression of those pathologies to to vision loss and dialysis, respectively.

PO0717

SGLT-2 Inhibition Ameliorates Tubular Injury with Metabolic Suppression in Very Early Phase of Diet-Induced Diabetic Kidney Disease

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Background: Therapies that target the sodium glucose cotransporter 2 (SGLT2) are known to benefit diabetic patients via both metabolic and hemodynamic effects, however, mechanisms promoting renal protection are incompletely known. Here, we investigated the mechanism of reno-protective effects by SGLT2 inhibition in diabetic kidney disease (DKD), focusing on kidney metabolism.

Methods: 10 week-old male SGLT2 mutant (Sweet Pee) and wildtype (WT) mice, fed with normal or high fat diet (HFD, 60% calories from fat) for eight weeks, were analyzed. Weekly changes in body weight, food intake, insulin and glucose tolerance were determined. Renal injury was evaluated by transdermal measurement of GFR, urinary

albumin creatinine ratio (uACR), KIM-1, NGAL and cleaved caspase 3 expression in the renal cortex and TUNEL staining of the kidney. Metabolic changes of the kidney were examined by qPCR of genes related to glycolysis, TCA cycle and fatty acid oxidation.

Results: Similar degree of HFD-induced obesity occurred in both SGLT2 mutant and WT mice while compensatory hyperphagia was observed only in mutant mice. HFD led to elevation of post-prandial blood glucose level, glucose intolerance and insulin resistance. Increases in postprandial blood glucose and glucose intolerance were blunted in SGLT2 mutant mice. Although changes of GFR and urinary albumin excretion were not observed, KIM1 and NGAL expression were upregulated by HFD feeding, indicating that this model represents an early phase of DKD. KIM1 and NGAL upregulation was abrogated in SGLT2 mutant mice. Furthermore, HFD feeding induced apoptosis in the cortex of WT mice, but not in SGLT2 mutants. Kidney/ body weight ratio was decreased by HFD in WT but increased in SGLT2 mutant mice, suggesting metabolic differences in the kidney. Genes related to glycolysis (PGK and PKM), TCA cycle (IDH2) and fatty acid oxidation (CPT1a, CPT2, PPARα and PGC1α) were suppressed in SGLT2 mutant vs WT HFD groups.

Conclusions: SGLT2 inhibition ameliorates tubular injury associated with renal hypertrophy and metabolic suppression in very early phase of diet-induced DKD.

Funding: NIDDK Support

PO0718

mTORC2 Is Essential for Sodium-Glucose Cotransporter 2

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Background: The role of mammalian target of rapamycin (mTOR) complexes mTORC1 and mTORC2 in renal tubule ion transport has been well characterized. We and others have shown that mTORC2 is a key regulatory kinase for serum and glucocorticoid kinase 1 (SGK1) and that its activity is required for epithelial Na^+ channel (ENaC)-dependent sodium reabsorption in the aldosterone-sensitive distal nephron (ASDN). Also, it has been shown that mTORC1 activity is increased in renal proximal tubule cells (RPTCs) in diabetes, which was prevented by the inhibition of sodium-glucose co-transporter 2 (SGLT2), and that mTORC1 KO in mice causes a Fanconi's syndrome-like phenotype. However, the roles of mTORC2 in the regulation of RPTC transporters, particularly as it pertains to glucose reabsorption remain obscure. In this study we explored the relationship between mTORC2 and SGLT2 in CRISPR-modified HEK-293Tcells and in mice, using patch clamp and membrane expression studies

Methods: We used CRISPR-Cas9 to generate Sin1 (an essential component of mTORC2)-deficient HEK-293T cells, which were compared with wild-type cells. The cells were transiently transfected with SGLT2. We recorded in WT HEK-293T cells the Dapa-sensitive SGLT2 sodium current. We used an inducible Cre-Lox system (Pax8-LC1) to KO Rictor (another key component of mTORC2) in mice. Dapagliflozin-sensitive whole-cell SGLT2 sodium current was measured in the microdissected proximal tubules and HEK-293T cells

Results: Strikingly, in mTORC2-knockout HEK-293T cells the Dapa-sensitive SGLT2 sodium current was significantly reduced versus WT HEK-293T cells. In mice, mTORC2 KO caused glycosuria without hyperglycemia, and patch-clamp studies showed decreased glucose-induced, dapagliflozin-inhibited Na^+ current.

Conclusions: Knockout of mTORC2 in the HEK-293T cells or in mice inhibits SGLT2-sodium current. Our study delineates the essential role of mTORC2 in SGLT2 function. These observations may explain the broad role of SGLT2 inhibition therapy and variable resistance to their effects.

Funding: NIDDK Support

PO0719

MAP17 and D-AKAP-2, Two Major Scaffolder Proteins, Are Upregulated in Experimental Diabetic Nephropathy in Response to Empagliflozin on Top of RAS Blockade

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have proven to delay diabetic nephropathy (DN) progression on top of the standard of care renin-angiotensin system (RAS) blockade. This protection is mostly attributed to improvement in renal hemodynamics although direct effects on the kidney cannot be ruled out. Further, the molecular mechanisms underlying the synergic effect of SGLT2i and RAS blockers is unknown.

Methods: 12 weeks old diabetic db/db mice were given empagliflozin (10mg/Kg/day), ramipril (8 mg/Kg/day) or the combination of both drugs during 8 weeks. Vehicle treated db/db and db/m mice were used as controls. Serum glucose, blood pressure, GFR and albuminuria were measured at baseline and at the end of study. At the end of the experiment, mice were euthanized and the kidneys were saved to perform a differential high-throughput proteomic analysis by mass spectrometry using isobaric tandem mass tags (TMT labelling).

Results: Vehicle db/db mice showed increased glycaemia during the whole experiment and empagliflozin normalized blood glucose. Ramipril treatment decreased blood pressure. Diabetic vehicle mice showed incipient DN, mesangial expansion and albuminuria were significantly increased when compared to their non-diabetic littermates. All the treatments reduced mesangial expansion and albuminuria. The differential proteomic analysis revealed 207 proteins differentially expressed in one or more experimental groups (FDR < 0.05 and Log FC>1); among them MAP17 and D-AKAP-2 were upregulated in the kidney of the db/db treated with empagliflozin with ramipril. We validated these findings by western blot.

Conclusions: The combined therapy of empagliflozin with ramipril upregulated both MAP17 and D-AKAP-2 in the kidney of a diabetic mice model. MAP17 and D-AKAP-2 are two major scaffolding proteins found in the proximal tubular cells that place transporters together such as SGLT2 and NHE3 and also regulate the function of protein kinase A (PKA) which in turns inactivates NHE3 by phosphorylation. Our results suggest that SGLT2i on top of RAS blockade may protect the kidney by boosting the inactivation of NHE3 via the upregulation of key scaffolder proteins such as MAP17 and D-AKAP-2.

Funding: Commercial Support - Boehringer Ingelheim, Government Support - Non-U.S.

PO0720

Added Benefit of SGLT-2 Inhibitor with ACE Inhibition in a Mouse Model of Severe Diabetic Nephropathy

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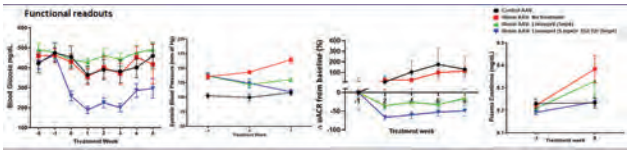
Background: The clinical success of sodium glucose cotransporter 2 inhibitor (SGLT2i) for the treatment of diabetic kidney disease (DKD) has ushered in a new phase in the discovery and development of novel drugs for DKD. As the development of SGLT2i did not follow the traditional drug discovery paradigm exemplified by testing efficacy in a relevant preclinical model, here we present the evaluation of combinatorial therapy of SGLT2i and standard of care in the hypertensive Renin AAV db/db uninephrectomy mouse model of severe DKD.

Methods: Severe DKD was established by AAV mediated hepatic overexpression of renin in uninephrectomized db/db mice. Mice were treated with Lisinopril (ACEi) in drinking water and SGLT2i (JNJ39933673) in diet, at a dose of 5 mpk for 8 weeks. Study groups included untreated DKD control (N=11), Lisinopril treated (N=11), Lisinopril + SGLT2i treated (N=11) and LacZ AAV control (N=10).

Results: SGLT2i significantly reduced blood glucose levels upon treatment inception (Day-3 vs. Day 4; 465.1±33.1 vs. 258.7±24.8; mean ± sem, mg/dl, p=0.001). ACEi reduced systolic blood pressure by 21 mm of Hg within 2 weeks of treatment (p=0.02), which was further reduced by 20 mm of Hg by SGLT2i co-treatment on week 7 (p=0.03). While ACEi treatment alone reduced UACR by 15% to 35% below baseline, dual treatment with SGLT2i led to a reduction of UACR by 49% to 67% during the 8 weeks treatment phase (p= n.s), leaving a residual albuminuria of 5561 ug/mg. Plasma creatinine doubled during the study period and was blunted only by ACEi+SGLT2i (No treatment vs. ACEi+SGLT2i; 0.38±0.06 vs. 0.24±0.02; mean ± sem; mg/dl, p=n.s). Histological assessments revealed additive benefits of ACEi+SGLT2i, in measures of glomerular, vascular and tubulointerstitial lesions. Reduced plasma levels of sTnfr1 reflected therapeutic benefits of SGLT2i on top of ACEi.

Conclusions: Our study demonstrates the possibility of testing combinatorial therapies in this translational preclinical model of severe DKD. Residual injury in ACEi+SGLT2i animals should enable testing of novel agents in this model on this new standard of care for CKD.

Funding: Commercial Support - Janssen R&D



PO0721

Assessment of Candidate Renal Protective Drug-Induced Biomarkers in Diabetic Kidney Disease Using Targeted Proteomic Profiling

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Background: The sodium-glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin slows the progression of kidney function decline in type 2 diabetes in addition to lowering blood glucose levels. However, the underlying molecular mechanisms of SGLT2i for renoprotection are not yet completely understood. We assessed non-invasive biomarkers associated with empagliflozin or enalapril treatment in a rat model of diabetic kidney disease (DKD).

Methods: Obese diabetic and hypertensive ZSF1 rats were treated with vehicle, enalapril (10 mg/kg/d, p.o.), or empagliflozin (30 mg/kg/d, p.o.) for 8 weeks. Along with phenotypic parameters, Olink Mouse Exploratory panel was used to simultaneously detect the levels of 92 proteins in plasma and urine samples using the proximity extension assay.

Results: Compared to vehicle and enalapril**,** empagliflozin reduced blood glucose, HbA1c, total cholesterol, and triglyceride levels while increasing HDL levels in ZSF1 rats. Empagliflozin significantly affected the levels of 16 proteins in plasma samples. Lower plasma concentrations after empagliflozin-treatment were detected for Notch3, tenascin-R, glial cell line-derived neurotrophic factor, and erythropoietin. In urine, we found 23 proteins responding to empagliflozin, 6 of which overlapped with plasma markers. Of these, compared with enalapril, empagliflozin restored the levels of dihydropteridine reductase and dimethylarginine dimethylaminohydrolase 1, proteins known for their role in decreasing ROS activity and oxidative stress. Eight plasma proteins and one urinary protein were found to be differentially expressed after enalapril treatment. Plasma tenascin-R was the only protein associated with both enalapril and empagliflozin treatment.

Conclusions: We identified biomarkers that are associated with SGLT2i and ACEi treatment. Our results may additionally provide mechanistic insights into the beneficial effects of renoprotective drugs. Translation and validation of these preclinical findings in human patient samples is the proposed next step. *This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115974. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA with JDRF.*

Funding: Commercial Support - Pharmaceuticals, Bayer AG, Wuppertal Germany

PO0722

Elucidation of Glomerular Hemodynamic Changes by SGLT-2 Inhibitors and ARBs in a Type 2 Diabetic Animal Model Using In Vivo Imaging

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Background: In recent clinical trials have shown that SGLT2 inhibitor (SGLT2i) inhibit the progression of diabetic kidney disease (DKD). We established the method for measuring single-nephron GFR (SNGFR) in mice by in vivo imaging and found that the adenosine / adenosine A1 receptor (A1aR) pathway in tubuloglomerular feedback (TGF) is involved in the pathogenesis of glomerular hyperfiltration (GH) in DKD using type1 diabetic animal model (Kidokoro K. et al. Circulation 2019). The mechanism of development of GH, and improvement of GH by SGLT2i is considered to be different in type 1 and type 2 DKD. However, the detailed regulatory mechanism of GFR has not been elucidated in type 2 DKD. We conducted experiments to elucidate the glomerular hemodynamic changes in type 2 diabetic animal model, using SGLT2i alone and in combination with RAAS inhibitor.

Methods: Zucker Lean (ZL) and Zucker Diabetic Fatty (ZDF) rats were used. Multi photon microscope was used to evaluate SNGFR, afferent arteriole (AA) and efferent arteriole (EA). The change in AA, EA, and SNGFR were observed every 30 minutes after SGLT2i administration. Furthermore, we investigated the involvement of the adenosine / A1aR pathway in type 2 diabetic animals using an A1aR antagonist (A1aRant). We made a SGLT2i + ARB combination group and measured AA, EA, and glomerular volume.

Results: ZDF showed a significant increase in blood glucose and urinary protein levels compared to ZL. SNGFR, AA and EA were significantly increased in ZDF compared to ZL, indicating GH. SGLT2i administration resulted in correction of AA hyperdilation and inhibition of GH. The inhibitory effect on hyperfiltration by SGLT2i was abolished by the concomitant use of A1aRant. There was no significant change about blood pressure, but urinary protein excretion was significantly suppressed by ARB treatment in ZDF. Glomerular volume was significantly increased, while there were no significant changes in AA and EA. SGLT2i ameliorated abnormal expansion of AA also in the presence of ARB, and no change in EA.

Conclusions: Our results showed that the regulation of AA vascular tonus by the adenosine/ A1aR pathway in TGF was involved in the GH in type 2 DKD.

Funding: Commercial Support - TAISHO PHARMACEUTICAL CO., LTD.

PO0723

GLP-1's Effect on Renal Perfusion and Oxygenation Measured with Quantitative MRI: A Potential Renoprotective Pathway in the Human GLP-1-Renal Axis

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Background: GLP-1 receptor agonism has shown significant beneficial cardiovascular effects that may be related to renoprotection. In the human kidney, a high GLP-1 extraction and its natriuretic effect are fully dependent on the GLP-1 receptor and associated with suppression of angiotensin II. Preclinical data showed that angiotensin II constricts vasa recta and lowers medullary blood flow. The current randomized and controlled study was designed to test the hypothesis that GLP-1 increases renal medullary perfusion.

Methods: Under fixed sodium intake (2 mmol NaCl/kg body weight/day) for 4 days before each study day, 10 lean healthy male participants were examined twice in random order during a 1-hour infusion of either GLP-1 (1.5 pmol/kg/min) or vehicle (0.9% NaCl) together with an intravenous infusion of 0.9% NaCl (750 mL/h). Interleaved measurements of renal artery flow, oxygenation (R2*), and perfusion (arterial spin labeling) were acquired in the renal cortex and medulla, using Magnetic Resonance Imaging (MRI) during infusions.

Results: During GLP-1 infusion, medullary perfusion increased 32 ± 7% ($p<0.001$) and cortical perfusion increased 13 ± 4% ($p<0.001$) compared to vehicle where medullary perfusion decreased -5 ± 2% ($p=0.007$) and cortical perfusion remained unchanged. R2* values increased 3 ± 2% ($p=0.025$) in the medulla and 4 ± 1% ($p=0.008$) in the cortex during vehicle infusion (indicative of decreased oxygenation) but remained unchanged during GLP-1 infusion. Renal arterial blood flow was not altered significantly by either intervention.

Conclusions: GLP-1 increases mainly medullary but also renal cortical perfusion and oxygenation during NaCl loading. In perspective, GLP-1 may promote Na excretion through this mechanism and exert long-term protective effects against hypoperfusion and ischemia.

Funding: Commercial Support - Novo Nordisk

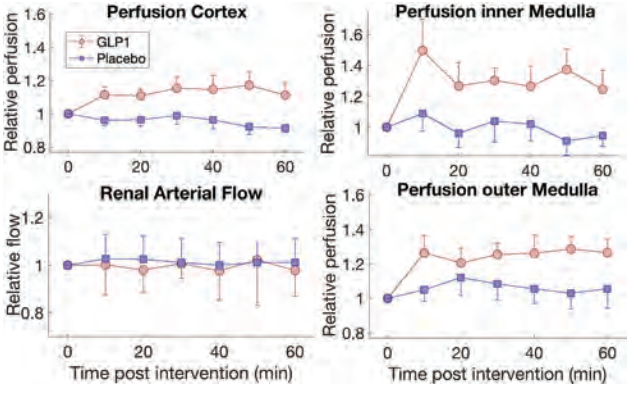

Figure 2. Relative changes in renal hemodynamics during GLP-1 and placebo intervention.

PO0724

Circulating SIRPα Is Upregulated in Type 2 Diabetes, Impairing Insulin Signaling in Skeletal Muscles and Adipose Tissues

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Background: A major etiology of chronic kidney disease (CKD) is diabetes mellitus. Even at early stages of CKD with near normal GFR, impaired insulin signaling is present, suggesting an early trigger of insulin resistance. We have discovered a potential driver of insulin resistance, signal regulatory protein alpha (SIRPα) which adversely influences skeletal muscles and adipose tissues in a model of type 2 diabetes.

Methods: Control mice vs. global SIRPα knockout (KO) mice were subjected to HFD >12 weeks. Glucose (GTT) and insulin tolerance tests (ITT), immunoblots, and treatment of myotubes with recombinant SIRPα were performed. n=4-6 mice/group, results are presented as mean ± SD.

Results: Control mice with HFD displayed impaired insulin signaling with reduced levels of tyrosine phosphorylation of the IGF1R, PI3 kinases and pAKT (ser473) in skeletal muscles. However, in SIRPα KO mice with HFD there was no downregulation of these insulin signaling proteins. Next, we examined adipose tissues of these mice and found impaired pAKT in control mice fed a HFD. In SIRPα KO mice pAKT signaling remained intact despite exposure to HFD. Next, control mice exposed to HFD displayed impaired GTT/ITT. However, KO mice had preserved GTT/ITT despite the presence of HFD. Finally, we identified a high level of serum SIRPα in control mice exposed to HFD. Therefore, we treated myotubes with exogenous recombinant SIRPα which led to downregulation of pAKT signaling.

Conclusions: Suppression of SIRPα in a HFD model of type 2 diabetes improves insulin resistance and is a potential therapeutic target for the treatment of type 2 diabetes.

Funding: Other NIH Support - NHLBI

PO0725

Metabolic Acidosis Does Not Impair Insulin Sensitivity in Rats with CKD

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Background: Insulin resistance is common in patients with chronic kidney disease (CKD) without diabetes, however, the factors driving this remain unclear. Metabolic acidosis has been implicated in the development of insulin resistance. The current study was designed to quantify the effect of changes in blood pH on insulin sensitivity using a rodent model of CKD.

Methods: We hypothesized that alkali or acid loading would promote varying levels of acid-base disturbances and consequently decreased insulin sensitivity in rats with graded renal mass reduction. Male Sprague Dawley rats (12 wks, SD) underwent either

2/3 nephrectomy (n=7; Nx) or 5/6 Nx (n=4). Rats recovered for 4 weeks, then underwent insulin tolerance testing (ITT; 0.75 U/kg i.v.) before and after alkali (2 weeks 0.1M $NaHCO_3$) and acid loading (1 week 0.1M NH_4Cl) in the drinking water. Male Zucker obese rats (10 wks) underwent 5/6 Nx (n=4) and were also given 4 weeks of recovery before being placed on 0.1M NH_4Cl for 4 days.

Results: In Nx SD rats, 0.1M $NaHCO_3$ did not produce metabolic alkalosis (Table 1) or reduce insulin sensitivity (P_{Rx}=0.67). 0.1M NH_4Cl in Nx SD rats produced a mild metabolic acidosis (Table 1). However, this did not alter the response to insulin (P_{Rx}=0.56). 0.1M NH_4Cl produced a severe metabolic acidosis in Zucker rats with 5/6 Nx (Table 1). Again however, this was not associated with an impaired insulin response. Rather, following NH_4Cl loading, Zucker rats had a greater response to insulin (P_{Rx}=0.01). Unexpectedly, we observed a negative relationship between the magnitude of change in blood glucose (inverse area under the curve) and plasma pH (*r*=-0.27, P=0.03) and plasma HCO_3^- (*r*=-0.33, P=0.0098) in remnant kidney rats.

Conclusions: These data demonstrate that metabolic acidosis does not impair insulin sensitivity in rats. Our data suggest that the direct effects of metabolic acidosis are unlikely to underlie significant impairments in insulin sensitivity in CKD.

Funding: Other NIH Support - P01HL134604 (to PMO), R21AI150723 (to PMO)

Table 1.

Group	Treatment	pH	HCO3- (mmol/L)
SD 2/3 & 5/6	Baseline	7.35 ± 0.02	22.6 ± 0.84
	0.1M NaHCO3	7.35 ± 0.02	23.0 ± 0.77
	Baseline	7.34 ± 0.01	23.7 ± 0.44
	0.1M NH4Cl	7.25 ± 0.03*	18.6 ± 1.45**
Zucker obese 5/6	Baseline	7.29 ± 0.01	21.7 ± 0.83
	0.1M NH4Cl	7.03 ± 0.02**	10.4 ± 0.37***

PO0726

Understanding Mechanisms Underlying Diabetic Kidney Disease Using Integrative Transcriptome and Proteome Profiling of Insulin-Resistant Human Cell Lines

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Background: One of the strongest metabolic features of diabetic kidney disease (DKD), in both type 1 and type 2 diabetes, is insulin resistance and it is increasingly clear that disruptions to renal cellular insulin responses can drive DKD development. The present study aims to generate a comprehensive network of molecular changes occurring in the kidney in response to insulin resistance using cell models

Methods: Conditionally immortalised human podocytes (Pod), glomerular endothelial cells (GEC), mesangial cells (MC) and proximal tubular cells (PTC) were studied. A diabetic, insulin resistant, environment was established using a combination of TNFα, IL-6, high glucose and high insulin. The cellular proteome and transcriptome were studied simultaneously using Tandem-Mass-tagged mass spectrometry and RNA sequencing. To explore the changes occurring in insulin resistance, integrated transcriptome and proteome data were analysed using univariate and multivariate statistical models and gene set enrichment analysis (GSEA) was performed to identify significantly regulated cellular processes

Results: Initial results revealed that exposure to a diabetic environment induced differential insulin resistance between human kidney cell lines. Differential expression analysis of both transcriptome and proteome found that insulin resistance had the most pronounced effect on expression in Pod and PTC and highlighted 45 consistently regulated genes/proteins. GSEA identified consistent increases in the inflammatory response, ER stress and glycoprotein metabolism and a consistent decrease in hippo signalling across all insulin resistant cells. In contrast, mitochondrial-related signatures were significantly reduced at the protein level in Pod and PTC but increased in GEC. Investigation of these gene/protein signatures in human DKD cohorts is currently ongoing

Conclusions: By performing integrated omics profiling on renal cell models, we identified conserved and cell-specific changes occurring in insulin resistance. Integration with human cohort data will highlight conserved pathways and the utility of cell models in pre-clinical investigations, aiding the identification of molecular processes underlying the development and progression of DKD

PO0727

Insulin Resistance Is Associated with Decreased Renal Insulin Receptor Beta in Aged D4 Null Mice

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Background: Insulin resistance is a major concern in metabolic disorders related to diabetes.

Methods: In order to explore the hypothesis that D4 dopamine receptor (D4R) increases insulin sensitivity through its activation of insulin receptor beta (IR-beta), we demonstrated the functional role of D4R in the prevention of insulin resistance by studying Drd4 null ($Drd4^{-/-}$) mice and wild-type ($Drd4^{+/+}$) littermates.

Results: We found that $Drd4^{-/-}$ mice (14 mos) had increased fasting blood glucose regardless of sex but their urines were negative for glucose and ketones, suggesting that the mice fed normal salt/normal fat diet were pre-diabetic. Serum insulin levels were increased in male $Drd4^{-/-}$ mice but not altered in female $Drd4^{-/-}$ mice after an 8 hr fast indicating that these mice have resistance or insensitivity to endogenous insulin. The aged male and female $Drd4^{-/-}$ mice had similar body weights, fasting serum total and free cholesterols, triglycerides, to their age and sex -matched $Drd4^{+/+}$ littermates, suggesting that the old $Drd4^{-/-}$ mice were not obese and had no dyslipidemia. Relative to $Drd4^{+/+}$ littermates (100±7 %, n=6), $Drd4^{-/-}$ mice had decreased IR-beta (19±4%, n=4) but normal protein expressions of IR-alpha, insulin degrading enzyme, insulin substrate 1, sodium glucose transporter 2 and glucose transporters in renal cortex homogenates, indicating that the decreased protein expression of IR-beta contributed to the insulin resistance in the aged $Drd4^{-/-}$ mice. $Drd4^{-/-}$ mice had decreased phosphorylated IR-beta at Tyr1631&1345, not Tyr972. Renal expression of insulin receptor beta was located in mouse renal glomeruli and tubules and co-localized n the apical membrane with NCC in the distal convoluted tubules in cortex and NKCC2 in the thick ascending limbs of loop of Henle in the outer medulla. D4R and IR-beta were co-immunoprecipitated in immortalized mouse renal distal convoluted tubule cells and the co-immunoprecipitation was increased by D4R agonist and not altered by D4R antagonist.

Conclusions: Our results suggest that disruption of D4R may play an important role in the insulin resistance via interactions with IR-beta in kidney.

PO0728

Renal Mass Reduction Enhances the Blood Glucose Response to Exogenous Insulin in Rats

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Background: The effect of chronic kidney disease (CKD) on responses to exogenous insulin are complex and may vary depending on the level of underlying insulin resistance. The kidneys play an important role in the catabolism of insulin, and progression of CKD in patients with diabetes mellitus is often associated with reducing insulin needs. Conversely, impairments in insulin sensitivity are observed in CKD patients absent diabetes, indicating that CKD itself may drive insulin resistance.

Methods: In order to clarify the roles of CKD and underlying insulin resistance on the response to exogenous insulin, in the current study we investigated the effect of graded renal mass reduction on the blood glucose response to insulin in healthy Sprague Dawley (SD) and insulin resistant Zucker obese rats. Male SD (12 wks) and Zucker obese (10 wks) rats underwent either sham (n=6 SD, 3 Zucker), 2/3 nephrectomy (n=7 SD; Nx), or 5/6 Nx (n=8 SD, 4 Zucker). Rats recovered for 4 weeks, then underwent insulin tolerance testing (ITT; 0.75 U/kg i.v.).

Results: There was a graded response in the blood glucose curves for SD rats ($P_{LevelofNx}$<0.0001; Fig 1A) with sham rats having the smallest blood glucose response to insulin, and 5/6 Nx rats having the greatest response to insulin. Similarly, the blood glucose response to insulin was about 5x greater for Zucker 5/6 Nx rats than for shams ($P_{LevelofNx}$=0.0019; Fig 1B). There were no significant differences in plasma insulin levels during the ITT between Nx and sham SD rats, while sham Zucker rats had greater plasma insulin levels than Nx rats ($P_{LevelofNx}$=0.0001).

Conclusions: These data indicate that renal mass reduction increases the response to exogenous insulin independent of the level of underlying insulin resistance, and that this is not mediated by an increased half-life of circulating insulin. Further investigation into the factors that contribute to greater insulin responses in CKD may identify novel targets for the treatment of insulin resistance.

Funding: Other NIH Support - P01HL134604 (to PMO), R21AI150723 (to PMO)

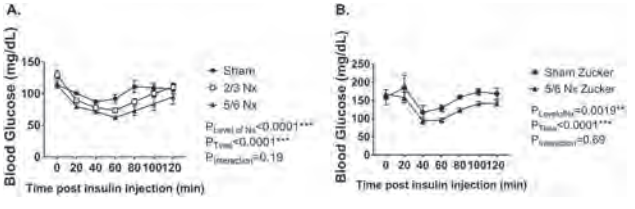

Figure 1.

PO0729

The Essential Role of Intact Mitochondrial Substrate Balance in Preventing Renal Injury

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Background: Alterations in mitochondrial function are linked to the development of chronic/diabetic kidney diseases. Proximal tubular cells (PTCs) are highly energy demanding, covering this need mostly from mitochondrial fatty acid oxidation. It is suggested, but not entirely clear whether derailments in mitochondrial metabolism and function are forerunners of tubular damage. In our previous studies we modeled mitochondrial substrate overload - an important aspect of metabolic disease - by creating mice lacking the enzyme carnitine acetyl-transferase (CrAT) in the PTC. These studies revealed that mitochondrial substrate overload in proximal tubules causes tubular injury and secondary glomerulosclerosis.

Methods: Here we demonstrate the importance of intact mitochondrial substrate efflux by titrating the amount of overload through the generation of a heterozygous CrAT knockout mouse model ("PT-CrAT^{HET}" mouse). We used an integrated approach of imaging, electron microscopy, functional studies (mitochondrial/cell respiration) and Next Generation RNA Sequencing combined with Ingenuity Pathway Analysis.

Results: PT-CrAT^{HET} mice developed tubular and glomerular injury similarly to their homozygous counterparts (N=5-7 mice examined, at least three separate cohorts). Mitochondria were structurally and functionally impaired in both sexes. Transcriptomic analyses, however, revealed striking differences in the pathways leading to renal injury in males vs females (evaluated using NextGenSeq and IPA with a threshold of $P<0.1$). In response to CrAT haploinsufficiency, males almost completely shut down fatty acid oxidation and related pathways. Females had a much weaker transcriptional response in metabolism-related pathways but activation of inflammation was more prominent when compared to males. Proximal tubular cells from these animals exhibited a shift in metabolism towards a more glycolytic phenotype (N=8 biological replicates, $P<0.05$ in at least three independent experiments), which was also more pronounced in males.

Conclusions: Our findings demonstrate that maintaining an intact mitochondrial substrate metabolism balance is crucial for the PTC. Potentially broad implications are: the metabolic shift and the sexual dimorphisms discovered herein offer new intervention points for the future and novel approaches to consider for treating kidney disease.

Funding: NIDDK Support

PO0730

Spexin-Based Galanin Receptor 2 Agonist (NS200) Improves Diabetic Nephropathy in Type 2 Diabetes

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Background: Spexin is a novel neuropeptide having an emerging role in metabolic diseases such as obesity and diabetes and involved in energy homeostasis and food intake. Spexin-based galanin receptor 2 agonist (NS200) has anti-depressive action and anxiolytic effect. The aim of this study is to investigate the effect of NS200 on insulin resistance and diabetic nephropathy in type 2 diabetic animal.

Methods: 8 to 10 week old *db/m* and *db/db* mice were treated with NS200 for 12weeks. NS 200 was administered by intraperitoneal injection at a dose of 1.0 mg/kg/day as reported in the previous study.

Results: There were no changes in body weight, food and water intake, urinary volume, fasting glucose level and HbA1c level by NS200 treatment in diabetic mice. Insulin tolerance test and glucose tolerance test were not also changed by treatment. NS200 lowered systolic blood pressure. Interestingly, NS200 improved urinary albumin excretion significantly in diabetic mice. Renal histology showed reduced glomerulosclerosis and tubulointerstitial fibrosis in treatment groups. Renal TGFβ and type IV collagen expressions were decreased in NS200 treated group, whereas PAI-1 and F4/80 expression were increased in treatment group. Insulin signaling pathway such as PI3K, p-AKT, and p-ERK protein expression were significantly suppressed by treatment in diabetic nephropathy. Despite there were no beneficial effects in basal metabolic parameters and insulin resistance, NS200 treatment in diabetic mice showed renoprotective effects in urinary albumin excretion and renal structural changes.

Conclusions: Our results provide the evidence that spexin-based galanin receptor 2 agonist by NS200 has renoprotective effect in diabetic nephropathy. These findings suggest the mechanism via its inhibition of renal insulin signaling pathway therefore provide a considerable promise as a new agent in diabetic nephropathy.

PO0731

Cell Sex and Sex Hormones Regulate Kidney Metabolism of Glucose and Glutamine: Implications for Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the major cause of end-stage kidney disease. Male sex is a risk factor for DKD, but the reasons for this predilection are unclear. We demonstrated that androgens accentuate DKD *in vivo*, and increase enzymes involved in glucose and glutamine metabolism, in male proximal tubular epithelial cells (PTECs). We aimed to determine the effect of cell sex and sex hormones on kidney metabolism.

Methods: Male and female PTECs were stimulated with control, dihydrotestosterone (DHT), or estradiol. Sex differences in key metabolites were validated in diabetic mice, and in type 2 diabetic patients and their age- and weight-matched healthy controls (n=180, iCARE cohort).

Results: Male PTECs showed significantly higher glycolysis, oxygen consumption (OCR), glucose consumption, oxidative stress, and apoptosis, compared to female PTECs, especially in the presence of DHT. Higher OCR in male PTECs was further enhanced in the presence of glucose and glutamine, but not observed in the presence of pyruvate. Under high glucose, male PTECs showed a decline in OCR and ATP levels over time, and increased lactate production. Male PTECs had significantly higher intracellular levels of TCA cycle metabolites (glutamate, citrate, malate, aspartate) and glutathione metabolites. In turn, female cells had higher levels of pyruvate. *In vivo*, male sex was linked to increased circulating levels of glucose, lactate, and glutamate in healthy and diabetic mice. Male sex was also independently associated with increased serum levels of glutamate, succinate, fumarate, and 9 metabolites of the glutathione cycle, in healthy and diabetic individuals.

Conclusions: This is the first study to demonstrate that the kidney metabolism of glucose and glutamine is modulated by cell sex and sex hormones. Male sex was linked to increased oxidative stress, cell injury, glucose- and glutamine-related enzymes, lactate secretion, and levels of TCA cycle and glutathione metabolites. Our key findings were validated in the blood metabolome of healthy and diabetic humans. Our work has uncovered physiological sex differences that are important for DKD and may lead to new therapeutic paradigms based on patient sex.

PO0732

Circulating Fibroblast Growth Factor 20 (FGF-20) as a Novel Protein Protective Against Progression to ESKD in Diabetes

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Background: Growing evidence from animal, cellular and targeted biomarker studies supports an involvement of fibroblast growth factor (FGF) family members (FGF23, FGF21) in diabetic kidney disease (DKD) progression. However, the majority of the studies were cross-sectional and performed in a targeted manner focusing on individual proteins. Therefore, we aimed to comprehensively evaluate the profiles of circulating FGF proteins in progressive DKD leading to end-stage kidney disease (ESKD) in individuals with diabetes.

Methods: This was a prospective cohort study of individuals with type 1 (n=214) and type 2 (n=144) diabetes, persistent proteinuria and CKD Stage 3 followed for progression to ESKD within 10 years. Measurement of circulating FGF proteins (n=17) were performed in baseline plasma samples using aptamer-based (SOMAscan) proteomic profiling.

Results: One hundred eight (50%) and 35 (24%) individuals with T1D and T2D, respectively, developed ESKD within 10 years. Six out of 17 FGF proteins were protective against progression to ESKD in the univariable Cox regression model. The strongest protection was observed for FGF20 (HR (95% CI): 0.68 (0.59, 0.79), $p=7.0x10^{-7}$). The cumulative 10-year risk of ESKD was about 2 times lower in individuals with high versus low levels of FGF20. Three proteins remained significant after further adjustment by clinical covariates, however, only the protective effect of FGF20 was confirmed in a third cohort of T1D individuals (n=294) with early DKD (CKD Stage 1 and 2); (OR (95% CI): 0.48 (0.37, 0.61), $p=6.1x10^{-9}$). Interestingly, non-diabetic parents of T1D children with ESKD or Proteinuria had lower FGF20 concentrations than those parents with T1D children without kidney complications.

Conclusions: This study identified circulating FGF20 as protective against progression to ESKD in three independent cohorts of individuals with T1D and T2D and varying stages of DKD. The protective effect was independent from the clinical legacy measures of DKD. Identification of proteins that protect individuals from ESKD may be useful targets for the development of therapeutics for preventing or delaying the onset of ESKD.

Funding: NIDDK Support

PO0733

Proteome Analysis of Glomerular Formalin-Fixed Paraffin Embedded Kidney Samples Distinguishes Diabetic Nephropathy from Controls

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Background: Liquid chromatography tandem-mass spectrometry (LC-MS/MS) is a sensitive technique for in depth proteome analysis but its usage as a diagnostic tool for kidney diseases is still in development. We investigated the potential use of LC-MS/MS in diagnosing diabetic nephropathy (DN) in renal biopsies.

Methods: Biopsies from 10 DN patients without renal comorbidity were compared to 10 pretransplantation biopsies. Glomerular cross-sections were collected using laser capture microdissection and tryptic peptides were analysed using LC-MS/MS. Resulting spectra were used for protein identification and further analysis.

Results: Based on all identified proteins, DN patients and controls clustered separately (Figure 1). Moreover, we identified 47 significant differentially expressed proteins after adjusting for multiple testing. In DN proteins with increased expression included collagens IV, VI and XVIII, fibronectin, vitronectin, fibulin, complement component C3, C4 and C9, complement factor H, clusterin, fibrinogen and apolipoprotein E. Proteins with decreased expression in DN included nephrin, chloride intracellular channel protein 5, Rab GDP dissociation inhibitor alpha and complement receptor 1.

Conclusions: Proteins identified by LC-MS/MS from glomerular cross-sections successfully distinguished kidney biopsies with DN from normal kidneys. Moreover, a set of differentially expressed proteins were identified, most of which were previously suggested to play a role in the development of DN, which further emphasizes the applicability of LC-MS/MS as a diagnostic tool.

Funding: Private Foundation Support, Government Support - Non-U.S.

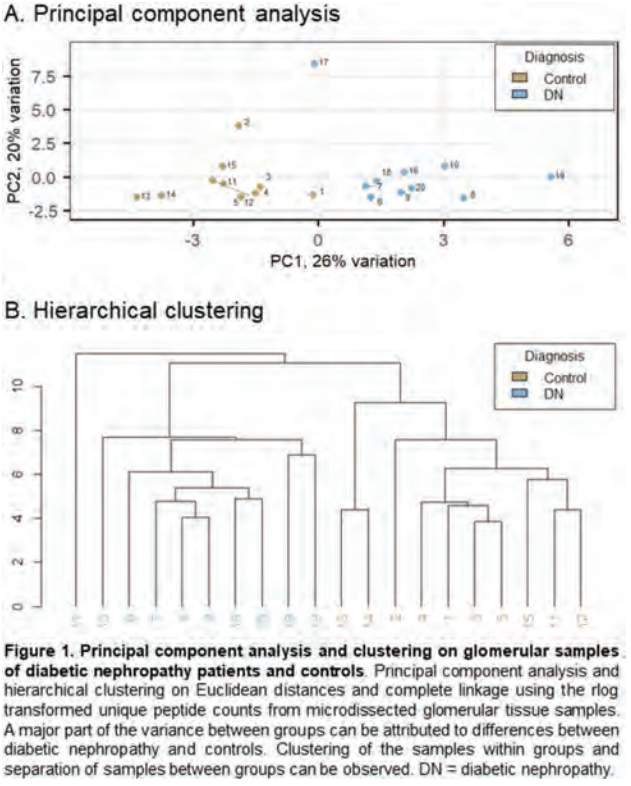

Figure 1. Principal component analysis and clustering on glomerular samples of diabetic nephropathy patients and controls. Principal component analysis and hierarchical clustering on Euclidean distances and complete linkage using the rlog transformed unique peptide counts from microdissected glomerular tissue samples. A major part of the variance between groups can be attributed to differences between diabetic nephropathy and controls. Clustering of the samples within groups and separation of samples between groups can be observed. DN = diabetic nephropathy.

PO0734

The Extracellular Matrix Signaling Molecule Endotrophin Is Associated with Diabetic Complications in Type 1 Diabetes

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Background: Persons with diabetes have a high risk of late complications related to both the micro- and macrovascular circulation. Early intervention targeting several risk factors is implemented, but tools to predict complications before clinical manifestations are still lacking. The PRO-C6 assay reflects collagen (COL) type VI formation and levels of endotrophin (ETP), a bioactive molecule derived from COL VI. In this study, we investigated the cross-sectional association between ETP and microvascular complications. Follow-up data is currently being collected to investigate the potential of ETP to predict development of complications and mortality.

Methods: We measured ETP in 1444 serum (S-ETP) and 1249 urine (U-ETP) samples (collected from 2012 to 2016), using the PRO-C6 ELISA (Nordic Bioscience) in persons with type 1 diabetes recruited from Steno Diabetes Center Copenhagen. All urine samples were normalized to urinary creatinine levels.

Results: In crude analyses, S-ETP levels increased significantly with CKD stage and albuminuria stage, and presence of retinopathy and neuropathy (all P<0.0001). S-ETP could discriminate patients with eGFR < 60 ml/min/1.73 m² with an AUC of 0.83 (P<0.001). In multiple linear regression analyses including age, sex, SBP, smoking, BMI, LDL cholesterol, HbA1c, albumin excretion and eGFR, lower age (r=-0.16, P<0.0001), higher albumin excretion (r=0.35, P<0.0001) and lower eGFR (r=-0.30, P<0.0001) were associated with higher S-ETP levels. U-ETP levels were not associated with disease severity or any of the investigated parameters. Following multiple linear regression, none of the parameters were associated with U-ETP. There was no correlation between S-ETP and U-ETP.

Conclusions: In conclusion, we demonstrate that ETP released during COL VI formation was associated with kidney disease severity, retinopathy, and neuropathy in patients with type 1 diabetes. These findings may indicate that ETP identifies diabetic patients with active fibrogenesis, and tissue injury. The potential of ETP to predict complications and mortality will be investigated once follow-up data has been collected.

PO0735

Urinary Sphingolipids in Youth-Onset Diabetes

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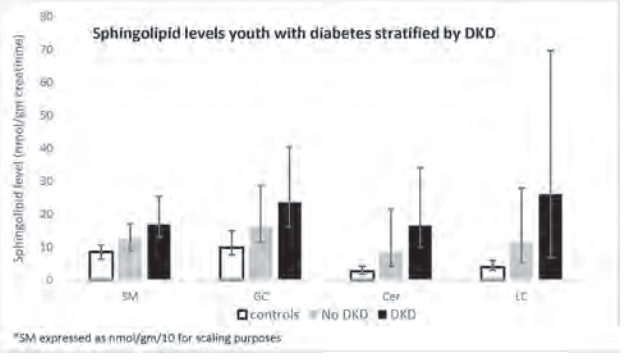
Background: Sphingolipid metabolism is altered in diabetes has been implicated as a mediator of diabetic kidney disease (DKD). The purpose of this study was to evaluate urinary sphingolipids as an early marker of kidney injury in youth with type 1 (T1) and type 2 diabetes (T2DM).

Methods: A comprehensive panel of urinary sphingolipids, including sphingomyelin (SM), glucosylceramide (GC), ceramide (Cer), and lactoslyceramide (LC) species, was performed in patients with youth-onset diabetes from the Treatment Options for Diabetes in Youth (TODAY) cohort. Sphingolipid levels, normalized to urine creatinine, were compared in 57 youth with T1DM, 59 with T2DM, and 44 healthy control subjects. The association of sphingolipids with early markers of DKD (albumin-to-creatinine [ACR] ratio and estimated glomerular filtration rate [eGFR]) was evaluated.

Results: The median age (IQR) of youth with diabetes was 22.2 years (19.9, 23.6) and the median duration of diabetes was 9.3 (8.5, 10.2) years. Urinary sphingolipid concentrations in youth with and without DKD (ACR ≥ 30) were significantly elevated compared to healthy subjects (all p<0.001). There were no significant differences between youth with type 1 and type 2 diabetes. All sphingolipid species were positively correlated with eGFR (all p < 0.001) and negatively with albumin-to-creatinine ratio (p < 0.001 for SM, Cer, GC; p = 0.0015 for LC). In multivariable analysis that adjusted for BMI and HgbA1c, all urinary sphingolipid species remained significantly associated with eGFR (all p < 0.01). SM, GC, and Cer species remained independently associated with ACR (all p < 0.05).

Conclusions: Urinary sphingolipids are elevated in youth with diabetes and correlate with eGFR and albuminuria. Urinary sphingolipids may therefore represent an early marker of DKD.



PO0736

Long Non-Coding RNA Profiles and Declining Kidney Function in Patients with Diabetes and CKD

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Background: Long non-coding RNAs (lncRNAs) are endogenous molecules that are involved in gene regulation and play important roles in the pathogenesis of various renal diseases, including diabetic kidney disease (DKD). lncRNA signatures associated with DKD, however, have not been fully established. The objective of this study was to determine the whole blood lncRNA signature that is associated with increased risk of DKD progression.

Methods: Eighty-eight lncRNAs that were previously reported to be related to DKD were measured by quantitative PCR (qPCR) in RNA from whole blood (PAXgene RNA tubes) from 22 patients with type 1 diabetes and chronic kidney disease (12 of whom progressed to ESKD during 7-10 years of follow-up). GAPDH was used for sample normalization. We assessed declining kidney function as eGFR slope (ml/min/1.73m²/year).

Results: Seventy-two of the 88 lncRNAs were detectable in more than half of the samples included in this study (n>11). Using Pearson's test, eGFR slope was found to be significantly correlated with lncRNAs H19 (r=-0.56, P=0.0073) and CRNDE (r=-0.42, P<0.05). H19 and CRNDE were not correlated with HbA1c (r=0.22, P=0.32 and r=-0.15, P=0.52 respectively), suggesting that these lncRNAs are associated with progression of DKD mediated by distinct pathway(s) independent of hyperglycemic condition.

Conclusions: We investigated plasma lncRNA profiles associated with declining kidney function in patients with diabetes. Although we need to confirm the results in an independent validation panel, our findings suggest that H19 and CRNDE are associated with declining kidney function and have potential to serve as circulating biomarkers for progression of DKD.

Funding: Commercial Support - Novo Nordisk

PO0737

A Comparison of PromarkerD to Standard-of-Care Tests for Predicting Renal Decline in Type 2 Diabetes

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Background: Diabetic kidney disease (DKD) can progress to end stage renal disease with associated increased morbidity and mortality. Current standard of care (SoC) for assessing DKD includes measurement of estimated glomerular filtration rate (eGFR) and urinary albumin:creatinine ratio (ACR), but both tests have limitations. This study compared the biomarker-based PromarkerD test with SoC for predicting renal decline in community-based patients with T2D.

Methods: Baseline plasma biomarkers (CD5L, ApoA4, IGFBP3) measured by mass spectrometry were combined with clinical data (age, serum HDL-cholesterol, eGFR) using a validated algorithm to provide PromarkerD scores categorized as low, moderate or high risk in 857 participants with T2D from the Fremantle Diabetes Study Phase II. The 1° endpoint was incident DKD (reduction in eGFR to <60 mL/min/1.73m^2 during follow-up) or eGFR decline ≥30% in participants with baseline eGFR <60 mL/min/1.73m^2. Logistic regression was used to compare the association of i) PromarkerD, ii) eGFR, iii) ACR, and iv) eGFR+ACR, with outcomes during 4 years of follow-up. Model performance was assessed by the ROC area under the curve (AUC).

Results: At baseline, participants (mean age 65 years, 54% males, median diabetes duration 7 years) had mean eGFR 82 mL/min/1.73m^2, geometric mean ACR 26 mg/g and were classified by PromarkerD as low (63%), moderate (13%) or high risk (24%) for renal decline. During 4.2±0.3 years of follow-up, 107 (13%) participants reached the 1° endpoint. PromarkerD had significantly higher predictive performance (AUC=0.88) compared to eGFR (0.82), ACR (0.63) and eGFR+ACR (0.82) (all P<0.001). Higher PromarkerD scores had a stronger association with the 1° outcome (odds ratio (OR) 3.26, 95% CI 2.67-3.99 per 1 standard deviation (SD) increase) compared to lower eGFR and higher ACR (OR=2.63 (2.13-3.23) and 1.21 (1.04-1.40) per 1 SD increase, respectively). PromarkerD remained significantly associated with the 1° outcome after adjusting for eGFR and ACR (OR=2.78 (2.19-3.53) per 1 SD increase). PromarkerD moderate and high-risk scores were increasingly prognostic for the 1° outcome (OR 8.11 and 21.34 versus low risk, respectively; both P<0.001).

Conclusions: PromarkerD outperformed the standard of care tests eGFR and ACR for predicting future renal decline in T2D.

Funding: Commercial Support - Proteomics International

PO0738

Urinary Interleukin 9 in Youth with Type 1 Diabetes Mellitus

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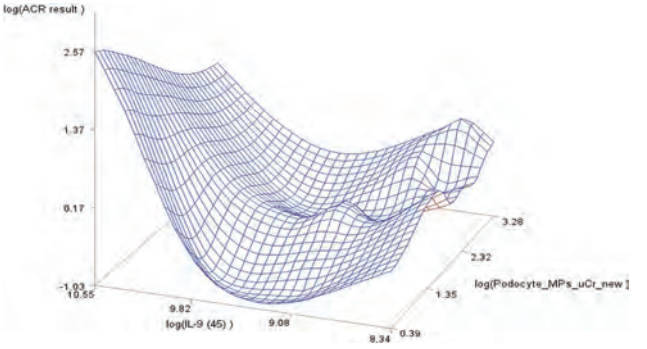
Background: Interleukin-9 (IL9) is a cytokine that promotes podocyte health in mice with Adriamycin-induced nephrotoxicity but its role in human kidney disease is uncertain. Glomerular podocyte stress leads to the release of microparticles (MP) into the urine and we have reported that urinary Podocyte-derived MPs correlate with both eGFR and blood glucose (BG) in youth with type 1 diabetes (T1D). We first sought to relate urinary IL9 levels to Podocyte-derived MPs in youth with T1D. We then studied the impact of cytokines implicated in diabetic nephropathy, including VEGF, TNFα and IL6, on the relationship between IL9 and ACR, a functional measure of podocyte health.

Methods: We performed an analysis of urine samples and clinical data from youth with T1D (n = 53). We measured ACR and used flow cytometry to count urinary podocyte-derived MPs and a Luminex platform (Eve Technologies) to measure a panel of urinary cytokines.

Results: Mean age was 14.7±1.6 years and the duration of diabetes was 6.7±2.9 yrs. Mean HbA1c was 70.3± 13.9 mmol/mmol. The mean ACR was1.3±1.9 mg/mmol with a mean eGFR of 140.3±32.6 ml/min/1.73 m^2. MPs normalised to urinary creatinine (MP/UCr) were inversely related to IL9 (r= -0.56, p< 0.001) in males and females. BG and eGFR values were associated with IL9 (r=-0.44, p<0.001; r=-0.49, p<0.001; respectively) but the relationship between IL9 and ACR was modest (r=-0.26, p=0.06). There was a significant interaction between IL9, MPs, and ACR (p=0.0066). Urinary IL9 and VEGF levels were positively correlated (r= 0.72, p< 0.001) and the relationship of IL9 with ACR depended on VEGF levels (p=0.0032). The relationship between IL9 and ACR was strongly determined by TNFα levels (p=0.014) and IL6 (p=0.0096).

Conclusions: Our analyses show that IL9 is a determinant of podocyte health in early T1D, and that there are complex interactions between urinary IL9, inflammatory cytokines, and ACR.



A three-dimensional representation of the relationships between IL-9, MPs, and ACR.

PO0739

Human Kidney Proteomics Identifies Biomarkers Associated with Kidney Function in Patients with Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the most common cause of chronic kidney disease (CKD) and end stage kidney disease, worldwide. However, the pathogenesis of DKD is poorly understood. While RNA sequencing emerged as an important tool to understand gene expression changes, protein level changes are poorly understood. SOMAscan is an emerging method that can robustly measure the level of thousands of proteins.

Methods: We have performed unbiased SOMAscan proteomics and quantified the amount of 1317 proteins in 24 snap frozen kidney tissues collected from nephrectomies. Our samples included 10 control healthy samples, 10 from subjects with overt DKD (CKD stage 3a), and 14 from subjects with late DKD (CKD stages 3b or 4). Demographic and clinical characteristics of the subjects were collected.

Results: The mean of age was 61 ± 16 and 65 % of the subjects were male. The median glomerular filtration rate (eGFR) was 108 (33) in control, 54 (5) in overt DKD, and 32 (28) in late DKD. We identified 279 proteins showing differences at overt DKD samples, and 381 proteins in late DKD samples compared to controls. Gene ontology analysis indicated enrichment for immune system and metabolic processes. The protein level of matrix metalloproteinase-7 (MMP-7) showed the strongest differences between control and DKD. Linear regression, adjusted for key co-variates identified 96 proteins those levels correlated with eGFR including cystatins C and MMP-7. We observed a moderate correlation between transcript and protein levels (r = 0.43, p < 2.2e-16).

Conclusions: SOMAscan proteomics identified important changes in protein expression in overt and late DKD, these could serve as important biomarkers or therapeutic targets.

Funding: NIDDK Support

PO0740

Diabetes Mellitus Associates with Differences in the Metabolome of Patients with CKD

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Background: Diabetic Mellitus (DM), the most common cause of chronic kidney disease (CKD), is associated with increased risk of death, cardiovascular disease, and kidney failure even if the DM is well-controlled. We hypothesized that significant differences exist in the metabolome of CKD patients with well-controlled DM as compared to CKD patients without DM.

Methods: Gas chromatography mass spectrometry (GC-MS) was used to perform serum metabolomic analysis of 46 subjects (28 CKD with DM and 18 CKD without DM). Unpaired t-tests were performed to compare metabolites between the 2 groups and Spearman correlation was utilized to evaluate the potential correlation between the metabolites and measures of kidney function. MetaboAnalyst (V5.0) was utilized to identify metabolic pathways that differed between those with or without DM.

Results: In the subjects with CKD and DM, the mean(SD) hemoglobin A_{1C} was 7.11(1.8) vs 5.5(1.4) in those with CKD but without DM. Of the 90 metabolites detected by GC-MS, 17 differential metabolites were significantly altered in the CKD with DM vs CKD without DM groups (p≤0.10). MetaboAnalyst indicated galactose metabolism, glycerolipid metabolism, starch and sucrose metabolism, fructose and mannose degradation, and fatty acid biosynthesis are the top differential pathways between both groups. In those with CKD and DM, citrate correlated with estimated glomerular filtration rate (GFR) (r=0.42, p=0.031) and homoserine and glycerol correlated with ACR (r=0.42, p=0.048 and r=0.42, p=0.044, respectively).

Conclusions: We have identified significant differences in the metabolome of CKD patients with well-controlled DM compared to those without DM. Further research is needed to evaluate the potential role of these metabolic pathways and if they contribute to the high morbidity and mortality burden in CKD patients with DM.

Funding: NIDDK Support, Veterans Affairs Support

PO0741

Urine Biomarkers and ESKD Risk in Persons with Diabetes and CKD

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Background: Tubulointerstitial damage is a feature of diabetic CKD, but correlates poorly with eGFR and albuminuria. Urine biomarkers of kidney tubule health may be independently associated with risk of ESKD in diabetic CKD.

Methods: We identified 1,145 participants from the REGARDS study with baseline eGFR≤60 mL/min/1.73m^2 and diabetes. Per case-cohort design, we randomly selected a subcohort of 560. Within the subcohort there were 93 ESKD cases; we further sampled all remaining ESKD cases not included in the subcohort (N=68). These 161 ESKD cases were identified by USRDS linkage over mean follow-up of 4.3±2.7 years. In baseline urine samples, we measured biomarkers of kidney tubule injury (kidney injury molecule-1 [KIM-1]), inflammation and fibrosis (monocyte chemoattractant protein-1 [MCP-1]; chitinase-3-like protein [YKL-40]), function (alpha-1-microglobulin [α1m]; uromodulin [UMOD]), and cell repair (epidermal growth factor [EGF]). Using weighted Cox models, we calculated hazard ratios (HR) of ESKD by baseline biomarkers. LASSO regression identified a subset of biomarkers most strongly associated with ESKD.

Results: Subcohort participants had mean age 70±9 years, 47% male, 53% Black, mean eGFR=40±13 mL/min/1.73m^2 and median UACR 33 (IQR 10-213) mg/g. Adjusting for baseline eGFR and albuminuria, higher KIM-1, α1m, and MCP-1 were each associated with higher ESKD risk. Strengths of association were of comparable magnitude to urine albumin (**Table**). LASSO regression retained KIM-1 (HR per doubling=1.31 [1.06-1.62]) and α1m (HR per doubling=1.36 [1.08-1.70]) as most strongly associated with ESKD.

Conclusions: Among persons with eGFR≤60 mL/min/1.73m^2 and diabetes, urine KIM-1 and α1m captured the influence of kidney tubule health on longitudinal risk of ESKD. These biomarkers may facilitate identification of persons with kidney disease and diabetes at greatest risk of ESKD.

Funding: NIDDK Support

Urine Biomarker	*Adjusted Hazard Ratio (95% CI)†*	
	Model 1	*Model 2*
KIM-1	**1.61 (1.38, 1.86)**	**1.43 (1.17, 1.75)***
MCP-1	**1.60 (1.37, 1.88)**	**1.27 (1.06, 1.53)***
YKL-40	**1.33 (1.24, 1.43)**	1.08 (0.99, 1.19)
EGF	**0.36 (0.28, 0.46)**	0.80 (0.57, 1.12)
α1m	**2.12 (1.83, 2.47)**	**1.47 (1.19, 1.82)***
UMOD	**0.71 (0.65, 0.78)**	1.00 (0.83, 1.20)
Albumin	**1.49 (1.40, 1.58)**	**1.34 (1.23, 1.47)**

†Per doubling of urine biomarker concentration (each modeled individually)
Model 1: adjusted for urine creatinine; Model 2: additionally adjusted for age, sex, race, systolic blood pressure, body mass index, antihypertensive medication use, cardiovascular disease, baseline eGFR, and urine albumin.
KIM-1: kidney injury molecule-1; MCP-1: monocyte chemoattractant protein-1; YKL-40: chitinase-3-like protein; EGF: epidermal growth factor; α1m: alpha-1-microglobulin; UMOD: uromodulin.

Adjusted HR per doubling of individually-modeled urine biomarkers with ESKD

PO0742

The Potential Value of Urinary Extracellular Vesicles VEGF-A165b in Diagnosis of Diabetic Kidney Disease

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Background: Novel biomarkers are needed for management of diabetic kidney disease (DKD). Urinary extracellular vesicles (uEVs) were served as an ideal resource of biomarkers in kidney disease. VEGF-A165b is a angiogenic factor secreted from podocytes correlated with DKD. The study was aimed to evaluate the diagnostic value of uEVs-VEGF-A165b in DKD.

Methods: Urine samples were collected from 36 patients with T2DM and 12 controls. Subjects with T2DM were stratified into three groups according to UACR, eGFR, and T2DM duration. To isolate exosomes, 25 ml urine was ultracentrifuged to obtain exosomes. Protein was extracted from uEVs and subjected to western blot (Wb) for detecting VEGF-A165b. Immunohistochemistry (IHC) staining of VEGF-A165b was performed in kidney paraffin sections from STZ-induced DM rats. ROC curve was used to evaluate the diagnostic value of uEVs-VEGF-A165b in DKD.

Results: Urinary MVs and exosomal VEGF-A165b were higher in T2DM with ACR>300mg/g than those with ACR<30mg/g. In addition, urinary MVs VEGF-A165b were higher in patients with ACR30-300mg/g than those with ACR<30mg/g, and exosomal VEGF-A165b levels were lower in patients with ACR30-300mg/g than whose ACR>300 mg/g. Furthermore, VEGF-A165b in uEVs increased with the DM duration. VEGF-A165b in patients with duration longer than 10 years were higher than whose duration less than 5 years. Correlation analysis revealed eGFR was negatively correlated with urinary MVs and exosomal VEGF-A165b. ROC curve showed that AUC of urinary MVs and exosomal VEGF-A165b for the diagnosis of DKD were 0.9091 and 0.8269. IHC revealed that VEGF-A165b was elevated in renal tubules in STZ-induced DM rats.

Conclusions: A increased level of uEVs-VEGF-A165b was observed in DKD patients and was correlated with decline of eGFR. uEVs-VEGF-A165b may be used as a promising biomarker reflecting the severity of DKD and may suggest a pathological role in the development of the disease.

Figure1

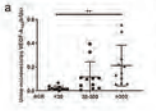
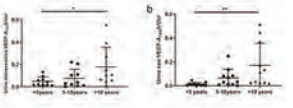


Figure2



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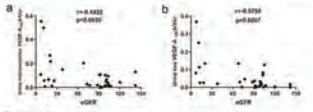


Figure4

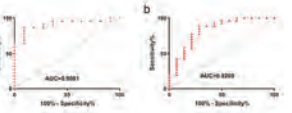
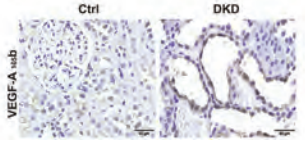


Figure5



PO0743

Independent Predictive Factors of Estimated GFR Decline in Type 2 Diabetes Patients with Preserved Kidney Function

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Background: We examined predictors of annual decline in estimated glomerular filtration (eGFR) in patients with type 2 diabetes and preserved kidney function.

Methods: In a prospective, observational cohort study, 392 Japanese patients with type 2 diabetes and baseline eGFR ≥ 60 ml/min/1.73m^2 were followed over one year (mean period 5.5 years; IQR 3.9-7.3). Linear regression was used to estimate participants' annual decline rate in eGFR over time. We defined subjects with an annual eGFR decline ≥ 5% per year as rapid progression and the eGFR decline < 5% as slow progression. In addition, time-averaged values of each laboratory data were calculated and used for sensitivity analysis.

Results: The study population had a median age of 59.0 years (IQR, 53.0–64.0) and 75% were male. The median duration of diabetes was 15.9 years (IQR, 11.2–20.4). During the follow-up period, 46 (11.7%) patients had a rapid decline in eGFR (median decline -6.51%; IQR, -8.59 – -5.60). Compared to patients with a slow decline in eGFR (N = 346), those with a rapid decline in eGFR had significantly higher HbA1c levels and lower HDL-cholesterol (HDL-c) levels at baseline. Multivariable logistic regression models revealed

that lower baseline hemoglobin and HDL-c levels were independent predictors of annual decline in eGFR (OR, 0.69, 95% CI, 0.53–0.89, *P* = 0.005; OR, 0.97, 95% CI 0.94–0.99, *P* = 0.007, respectively). Furthermore, time-averaged hemoglobin and HDL-c levels were also independent predictors of annual decline in eGFR (OR, 0.62, 95% CI, 0.46–0.82, *P* = 001; OR, 0.97, 95% CI 0.94–0.99, *P* = 0.007, respectively).

Conclusions: Our findings highlight the important effect of lower hemoglobin and HDL-c levels as independent predictors of rapid decline in eGFR in patients with type 2 diabetes and preserved kidney function.

PO0744

Post-Hospitalization Blood Pressure (BP) and Diabetes (DM) Control and Outcomes in Patients with Diabetic Kidney Disease (DKD)

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Background: DKD is the most common cause of ESKD in the US but because the course of progression is prolonged, research to elucidate risks and effective interventions are difficult. In a high-risk cohort with DKD, do post-hospitalization BP and DM control act as good surrogate markers for outcomes?

Methods: Using Looking Glass, Montefiore Medical Center's clinical database, we created a cohort of patients with a first discharge in 2016 who met the following criteria: CKD stage 3b or 4 and Proteinuria >300 and <5000mg/gm. Follow up data regarding CKD outcomes up to 2 years, clinic visits, RAASi prescriptions, mean systolic BP (SBP) and HgbA1c levels within 1 year of discharge were collected. Cox proportional hazards was used in adjusted analyses, to estimate the HR of mean SBP and HgbA1c levels, both dichotomized at the 75th percentile, with ESKD incidence or death over 2 years of follow-up.

Results: A total of 572 individuals met DKD criteria and had a first discharge in 2016. The mean age for the cohort was 66.8 years (SD 11.5), 244 (42.7%) were male, 224 (39.3%) were Black, 210 (36.8%) were Hispanic and 33 (5.8%) were White. Sixty-eight percent had a readmission within 1 year of discharge with median time to readmission at 63 days (IQR 22-184). Ninety-three percent of individuals had an outpatient clinic visit and the median number of clinic visits was 30 (IQR 16-47) over 1 year, with median time from discharge to an outpatient visit of 8 days (IQR 4-18). Mean SBP was 138mmHg (SD 22.2) with 26.9% of individuals with a mean SBP >150mmHg during 1 year of follow up. Mean HgbA1c was 8.6 (SD 2.1) with 192 (33.6%) who had HgbA1c >9.7 over 1 year of follow up. Eighty-eight (15.4%) patients died and 99 (17.3%) progressed to ESKD over 2 years of follow up. In models adjusting for age, sex and race/ethnicity there was a positive association between SBP >150 (HR 1.53, 95% CI: 1.12-2.09) and HgbA1c>9.7 (HR 1.58 95% CI: 1.16-2.15) and time to ESKD or death.

Conclusions: High mean BP and HgbA1c levels during 1 year post-discharge are associated with adverse outcomes in a cohort of hospitalized patients with DKD. These measures serve as useful surrogate biomarkers to study DKD interventions in a high-risk population.

PO0745

Finerenone Dose-Exposure-UACR Response Analyses of FIDELIO-DKD Phase 3 and the Effect of SGLT-2 Inhibitor Co-Medication

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Background: The mineralocorticoid receptor antagonist finerenone and sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce albuminuria and the risk of kidney failure. The combination of these therapies holds promise to augment nephroprotection through activation of different pathways. Model-based approaches considering individual dosing and exposure and correcting for covariates can support stronger conclusions than stratification for baseline comedication. We developed a population pharmacokinetic/pharmacodynamics (popPKPD) model to assess the finerenone dose-exposure-response relationship for urine albumin-to-creatinine ratio (UACR) and the impact of combined SGLT2i-finerenone use on UACR.

Methods: We analysed 37296 UACR measurements in 5674 patients (549 patients with any recorded SGLT2i use) using nonlinear mixed-effects popPKPD modelling considering individual drug exposure. The model was used to characterize the trajectory of UACR progression over time, the exposure-response relationship of finerenone on UACR and the effect of SGLT2i.

Results: The popPKPD model described the observed UACR data well, with a proportional UACR progression over time, an indirect power model for the exposure-response relationship of finerenone and a constant effect of SGLT2i use. SGLT2i use did not modify finerenone efficacy (p=0.25) and indicated with 95% confidence that finerenone is at least 94.1% as efficacious in reducing UACR in patients using SGLT2i (Figure 1).

Conclusions: We successfully developed a popPKPD model that adequately described the dose-exposure-response of finerenone on UACR. The results demonstrate additive effects of SGLT2i on top of finerenone.

Funding: Commercial Support - Bayer AG

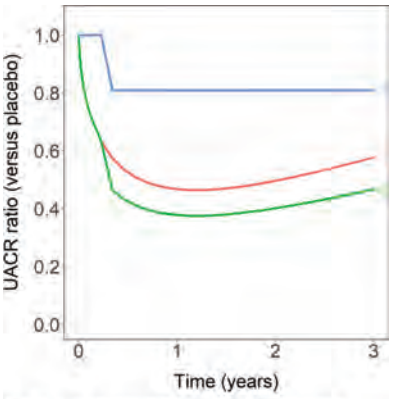


Figure 1. Illustrative simulation of UACR relative to placebo over time in a typical individual taking finerenone 20 mg once daily starting at day 1 (red line), SGLT2 inhibitors starting at day 125 (blue line), or both (green line).

PO0746

Effects of Ertugliflozin on Kidney End Points in Patients with Non-Albuminuric Diabetic Kidney Disease in VERTIS CV

David Cherney,[1] Samuel Dagogo-Jack,[2] Francesco Cosentino,[3] Darren K. Mcguire,[4,5] Richard E. Pratley,[6] Robert Frederich,[7] Mario Maldonado,[8] Chih-Chin Liu,[9] Christopher P. Cannon.[10] VERTIS CV investigators *[1]University of Toronto, Toronto, ON, Canada; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]Unit of Cardiology, Karolinska Institute & Karolinska University Hospital, Stockholm, Sweden; [4]The University of Texas Southwestern Medical Center, Dallas, TX; [5]Parkland Health and Hospital System, Dallas, TX; [6]AdventHealth Translational Research Institute, Orlando, FL; [7]Pfizer Inc., Collegeville, PA; [8]MSD Limited, London, United Kingdom; [9]Merck & Co., Inc., Kenilworth, NJ; [10]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: Non-albuminuric diabetic kidney disease (NA-DKD) is an increasingly recognised condition. Data from VERTIS CV (NCT01986881) were analyzed to study the impact of ertugliflozin on kidney outcomes in patients with NA-DKD.

Methods: Patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease were randomized (1:1:1) to ertugliflozin 5 mg, 15 mg (both doses were pooled for analyses) and placebo. Subgroups were defined by baseline eGFR (mL/min/1.73 m^2) and UACR (mg/g): No DKD (N-DKD), eGFR ≥60 + UACR <30 (n=3916); NA-DKD, eGFR <60 + UACR <30 (n=867); albuminuric-DKD (A-DKD), UACR ≥30 (n=3247). eGFR slopes (chronic from week [W]6 to W260 and total from W0 to W260) and Cox proportional hazards for the time to first event of a kidney composite were assessed.

Results: The NA-DKD subgroup had the slowest rate of total eGFR decline and the A-DKD subgroup the fastest rate of decline (Figure). The effect of ertugliflozin to slow the rate of eGFR decline vs placebo did not significantly differ across the subgroups. The hazard ratio for ertugliflozin showing reduction in the risk of the composite kidney outcome vs placebo was consistent across subgroups, $P_{interaction}$ = 0.26 (Table).

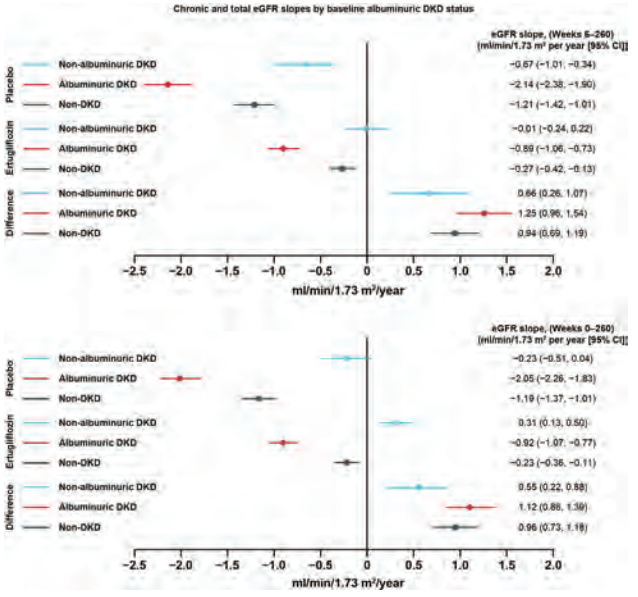
Conclusions: In VERTIS CV, participants with NA-DKD had the slowest rate of eGFR decline over time and lower kidney composite outcome event rates.

Funding: Commercial Support - The study and this analysis were funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, in collaboration with Pfizer Inc. Medical writing and/or editorial assistance was provided by Moamen Hammad, PhD, and Ian Norton, PhD, both of Scion, London, UK. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Pfizer Inc., New York, NY, USA.

Table

Cox proportional hazards model for time to first kidney composite comprising sustained 40% decrease from baseline in eGFR, chronic kidney replacement therapy, or kidney death

	Treatment	Number of participants	Number of participants with event (%)	Event rate/ 100 person-years	Hazard ratio (95% confidence interval)	
Overall population	Placebo	2747	85 (3.09)	0.90	0.66 (0.50, 0.88)	P-value <0.01
	Ertugliflozin	5499	113 (2.05)	0.60		
N-DKD	Placebo	1307	31 (2.37)	0.68	0.44 (0.26, 0.74)	P-interaction = 0.26
	Ertugliflozin	2609	27 (1.03)	0.30		
A-DKD	Placebo	1087	51 (4.69)	1.41	0.73 (0.51, 1.04)	
	Ertugliflozin	2160	75 (3.47)	1.03		
NA-DKD	Placebo	290	3 (1.03)	0.30	0.82 (0.20, 3.44)	
	Ertugliflozin	577	5 (0.87)	0.25		



Figure

PO0747

KidneyIntelX as an Enrichment Tool for Clinical Trials in Early Diabetic Kidney Disease

George Vasquez-Rios,[1] Girish N. Nadkarni,[1] Bruce Neal,[2] Kenneth W. Mahaffey,[3] Michael K. Hansen,[4] Fergus Fleming,[5] Hiddo J. L Heerspink,[6] Steven G. Coca.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]University of New South Wales, Sydney, NSW, Australia; [3]Stanford University, Stanford, CA; [4]Janssen Research and Development LLC, Raritan, NJ; [5]Renalytix, New York, NY; [6]Rijksuniversiteit Groningen, Groningen, Netherlands.*

Background: Clinical trials in nephrology are often enriched for patients with high levels of albuminuria to increase event rates. KidneyIntelX is a composite risk score that incorporates plasma biomarkers and clinical data to predict progression of diabetic kidney disease. We sought to assess the value of KidneyIntelX for future clinical trials in patients with type 2 diabetes and normo- or microalbuminuria.

Methods: Plasma TNFR-1, TNFR-2, and KIM-1 were measured on the Renalytix KidneyIntelX platform in participants in the CANVAS trial with UACR <300 mg/g (n=3277). A logistic regression model incorporating the 3 biomarkers and clinical variables was applied to obtain the predicted probabilities for a composite kidney outcome of eGFR decline ≥5 ml/min/1.73 m², sustained 40% eGFR decline, or kidney failure. We assessed the potential utility of KidneyIntelX for enrichment in a hypothetical trial using BioPET (http://prognosticenrichment.com).

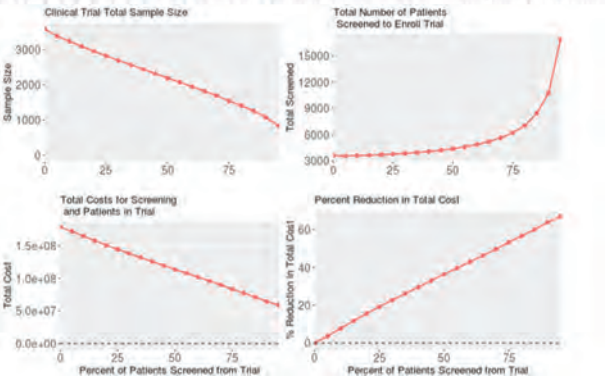
Results: 176 kidney outcomes occurred over a median of 6.1 years follow-up (5.6% incidence). The composite kidney endpoint occurred in 0.6% in the 1st decile and increased to 16.8% in the 10th decile of KidneyIntelX risk strata (**Figure 1a**). Application of an enrollment threshold at the top 20%-25% of KidneyIntelX score, assuming a 40% RRR of therapy, alpha 0.05, $1000 for screening and $50,000 for full trial run-through, would reduce the sample size needed by approximately 39-43%, and reduce trial costs by 53-57% (**Figure 1b**).

Conclusions: The KidneyIntelX platform facilitated a significant enrichment of kidney events in CANVAS participants that are typically excluded from kidney-specific randomized controlled trials due to low levels of albuminuria. KidneyIntelX has the potential to be an effective tool for trial enrichment.

Funding: Commercial Support - Janssen

Figure 1a. Composite Kidney Outcome by KidneyIntelX Risk Score

Figure 1b. Sample size, number of patients needed to screen, total costs and percent reduction in total costs for various thresholds of KidneyIntelX cutoffs



PO0748

Effects of Canagliflozin (CANA) on Kidney Outcomes: Pooled Analyses from the CANVAS Program and CREDENCE

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Background: CANA reduced the risk of sustained loss of kidney function in patients with type 2 diabetes mellitus (T2DM) and high cardiovascular (CV) risk or nephropathy. We analyzed the effects of CANA on time to first occurrence of doubling of serum creatinine (SCr) and end-stage kidney disease (ESKD) events using pooled data from the CANVAS Program and CREDENCE.

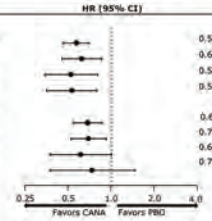
Methods: This *post hoc* analysis included integrated data from the CANVAS Program and CREDENCE trials. The effects of CANA compared with placebo (PBO) on doubling of SCr and ESKD were examined in subgroups by baseline estimated glomerular filtration rate (eGFR; <45, 45-60, and >60 mL/min/1.73 m²). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model, stratified by trial.

Results: A total of 14,543 participants from the CANVAS Program (N = 10,142) and CREDENCE (N = 4,401) were included. Among participants with baseline eGFR measurements, 1919 (13.2%) had eGFR <45 mL/min/1.73 m², 2972 (20.4%) had eGFR 45-60 mL/min/1.73 m², and 9649 (66.3%) had eGFR >60 mL/min/1.73 m². CANA delayed the time to first doubling of SCr event and first ESKD event relative to PBO. Compared with PBO, CANA reduced the risk of doubling SCr (HR, 0.58; 95% CI, 0.47–0.71) consistently across eGFR subgroups (interaction P = 0.78; **Figure**). Reduced risk of ESKD was also seen with CANA versus PBO (HR, 0.69; 95% CI, 0.55–0.87), irrespective of baseline eGFR (interaction P = 0.86).

Conclusions: In patients with T2DM and high CV risk or nephropathy, CANA reduced the risk of doubling of SCr and ESKD, with consistent benefits observed across baseline chronic kidney disease stage, including those with preserved eGFR >60 mL/min/1.73 m².

Figure. Effects of CANA on Doubling of SCr and ESKD.

	Number of participants with an event (n/N)		HR (95% CI)	Interaction P value
	CANA	PBO		
First occurrence of doubling of SCr				
Overall	145/7995	221/6545	0.58 (0.47, 0.71)	0.78
eGFR <45 mL/min/1.73 m²	66/976	98/943	0.63 (0.46, 0.86)	
eGFR 45-60 mL/min/1.73 m²	35/1559	63/1413	0.53 (0.35, 0.81)	
eGFR >60 mL/min/1.73 m²	44/5460	60/4189	0.54 (0.36, 0.80)	
First occurrence of ESKD				
Overall	126/7995	173/6545	0.69 (0.55,0.87)	0.86
eGFR <45 mL/min/1.73 m²	84/976	113/943	0.70 (0.53, 0.93)	
eGFR 45-60 mL/min/1.73 m²	26/1559	42/1413	0.62 (0.38, 1.01)	
eGFR >60 mL/min/1.73 m²	16/5460	18/4189	0.74 (0.38, 1.46)	



CANA, canagliflozin; SCr, serum creatinine; ESKD, end-stage kidney disease; PBO, placebo; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

PO0749

Phase Ib Study of the Soluble Guanylate Cyclase Activator BI 685509 in Patients with Diabetic Kidney Disease

David Cherney,[1] Dick de Zeeuw,[2] Hiddo J. L Heerspink,[2] Marc Desch,[3] Arne Wenz,[3] Friedrich Schulze,[3] Masaomi Nangaku.[4] *[1]University of Toronto, Toronto, ON, Canada; [2]University Medical Center Groningen, Groningen, Netherlands; [3]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [4]The University of Tokyo Graduate School of Medicine, Tokyo, Japan.*

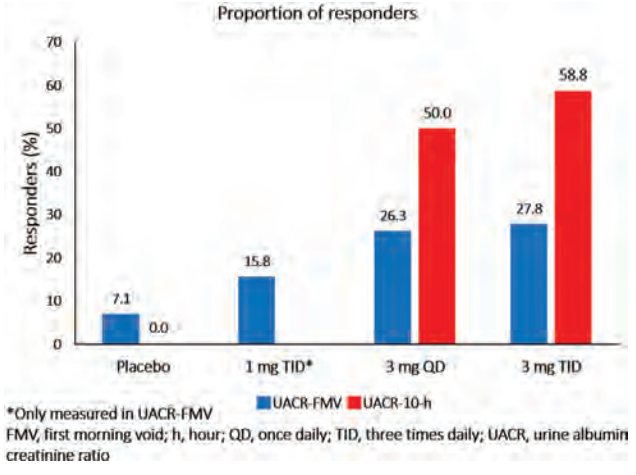
Background: Soluble guanylate cyclase (sGC) plays a key role in the kidney nitric oxide–cyclic guanosine monophosphate (NO-cGMP) pathway. Increased albuminuria is associated with kidney function loss. The NO-independent sGC activator BI 685509 lowers albuminuria in experimental models. This Phase Ib study (NCT03165227) assessed the safety and efficacy of BI 685509 in patients with diabetic kidney disease and albuminuria.

Methods: This placebo (PBO)-controlled, multiple dose study enrolled patients with type 1 or 2 diabetes, estimated glomerular filtration rate (eGFR) 20–75 mL/min/1.73m² and urinary albumin creatinine ratio (UACR) 200–3500 mg/g. Patients (N=74) were randomised to three active dose groups receiving oral BI 685509 (tested doses after titration: 1 mg three times daily [TID], n=20; 3 mg once daily [QD], n=19; 3 mg TID, n=20) or PBO (n=15) for 28 days. Efficacy was assessed by the proportion of responders, defined as patients with ≥20% decrease from baseline in UACR measured in first morning void ($UACR_{FMV}$) and 10-h ($UACR_{10h}$) (PBO, 3 mg QD and 3 mg TID only) urine.

Results: At baseline, median eGFR was 47.0 mL/min/1.73m² and median UACR was 641.5 mg/g, although this varied between groups. Drug-related adverse events (AEs) occurred in 12 patients (16.2%; BI 685509 15.3%, PBO 20.0%); the most frequent were hypotension (4.1%) and diarrhoea (2.7%). AEs leading to study discontinuation occurred in 4 patients (5.4%; BI 685509 5.1%, PBO 6.7%). Compared with PBO, the proportion of patients receiving BI 685509 classed as responders was higher (Figure).

Conclusions: BI 685509 treatment was generally well-tolerated with over 50% of patients in the 3 mg QD and 3 mg TID dose groups appearing to show a response in $UACR_{10h}$.

Funding: Commercial Support - Boehringer Ingelheim



Proportion of responders (≥20% decrease from baseline in UACR)

PO0750

Comparative Effectiveness of SGLT-2 Inhibitors, DPP-4 Inhibitors, and GLP-1 Agonists in US Veterans with and Without CKD

Yoko Narasaki,[1] Csaba P. Kovesdy,[2] Amy S. You,[1] Praveen Kumar Potukuchi,[2] Ankur A. Dashputre,[2] Keiichi Sumida,[2] Fridtjof Thomas,[2] Elani Streja,[1] Kamyar Kalantar-Zadeh,[1] Connie Rhee.[1] *[1]University of California Irvine, Irvine, CA; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN.*

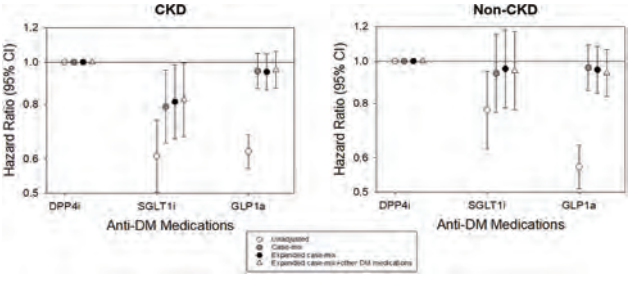
Background: Recent clinical trials have shown that SGLT2 inhibitors (SGLT2i) vs. placebo substantially reduce the risk of eGFR decline, ESRD, and renal-/CV-related mortality in CKD patients. However, little is known about the comparative effectiveness of SGLT2i vs. other newer anti-diabetic medications (DPP-4 inhibitors [DPP4i], GLP1 agonists [GLP1a]) on CKD outcomes using real-world data in patients with and without CKD.

Methods: In US Veterans with diabetes receiving care from the VA healthcare system over 2004-18, we identified incident (new) users of SGLT2i vs. DPP4i vs. GLP1a therapy, excluding combined users of the examined classes. In analyses stratified by presence vs. absence of CKD defined by eGFR and albuminuria levels, we examined associations of SGLT2i vs. DPP4i vs. GLP1a use with the composite outcome of incident ESRD+all-cause death using multivariable Cox models.

Results: In 64,564 patients who met eligibility criteria, 51% patients had CKD, and 8%, 77%, vs. 15% were new users of SGLT2i, DPP4i, vs. GLP1a, respectively. Patients contributed a total of 182,177 person-years of follow up, during which 10,861 incident ESRD/death events were observed (crude rate 59.6 events/1000 person-years). Median (IQR) at-risk time was 2.1 (0.9, 4.0) years. Compared to DPP4i, use of SGLT2i was associated with lower risk of the composite outcome across all Cox models (adjusted HR [95%CI] 0.86 [0.75-1.00]). The beneficial association of SGLT2i use with the composite outcome was limited to patients with pre-existing CKD. Across all cohorts (overall, CKD, non-CKD), GLP1a had comparable risk of the composite outcome when compared to DPP4i in adjusted analyses.

Conclusions: In a national cohort of US Veterans with diabetes, SGLT2i use was associated with lower risk of the composite outcome of ESRD+mortality in CKD patients, yet had comparable risk to DPP4i in those without CKD. Further studies are needed to determine the long-term safety and effectiveness of novel anti-diabetic medications using real-world data.

Funding: Veterans Affairs Support



PO0751

Phase 1c Study of the Aldosterone Synthase Inhibitor BI 690517 in Diabetic Patients with Kidney Disease

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Background: Preclinical studies showed aldosterone synthase inhibitors (ASis) to be beneficial in diabetic nephropathy. This placebo (PBO)-controlled, multiple dose, Phase Ic study (NCT03165240) assessed the safety and efficacy of the selective ASi BI 690517 in diabetic patients with kidney disease and albuminuria.

Methods: Patients with type 1 or type 2 diabetes, estimated glomerular filtration rate (eGFR) 20–75 mL/min/1.73m² and urine albumin creatinine ratio (UACR) 200–3500 mg/g, receiving stable angiotensin receptor blocker/angiotensin-converting enzyme inhibitor treatment were randomised to receive daily oral BI 690517 (3/10/40 mg), eplerenone (25–50 mg) or PBO for 28 days. Drug related adverse events (DRAEs) and seated systolic blood pressure (SBP) were recorded to assess safety. Efficacy was assessed by the proportion of responders, defined as patients with ≥20% decrease from baseline UACR (measured in first morning void [$UACR_{FMV}$] and 10-h urine [$UACR_{10h}$] [10/40 mg only]). Due to COVID-19, eplerenone and BI 690517 40 mg group enrolment were stopped early; BI 690517 doses were compared with matching PBO pooled from all dose groups.

Results: IIn total, 58 patients (3 mg n=18; 10 mg n=13; 40 mg n=14; eplerenone n=4; PBO n=9) with median baseline UACR of 873.5 mg/g and eGFR of 41.0 mL/min/1.73m² were treated. DRAEs occurred in 8 patients (14.8%), all receiving BI 690517; the most frequent were constipation and hyperkaliaemia (both 3.7%, n=2). Treatment was prematurely discontinued in 5 patients (9.3%: BI 690517 n=4; PBO n=1), 2 cases (3.7%)

due to DRAEs. Changes seen in SBP did not differ between PBO and BI 685509 dose groups. Compared with PBO, the proportion of patients receiving BI 690517 classed as responders was higher for $UACR_{FMV}$ (PBO 37.5% vs 3 mg 61.1%; 10 mg 53.8%; 40 mg 80.0%) but similar for $UACR_{10h}$ (PBO 50.0% vs 10 mg 50.0%; 40 mg 60.0%).

Conclusions: BI 690517 was generally well tolerated and appears to have an early effect on UACR, with over 50% of treated patients being classed as responders. These data need to be confirmed in larger studies.

Funding: Commercial Support - Boehringer Ingelheim

PO0752

A Comparison of the Renal Composite Outcome Between Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide 1 Receptor Agonists in Japanese Diabetes Patients

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Background: The renal outcome benefit in some large-scale clinical trials has been most pronounced for not only sodium-glucose co-transporter 2 inhibitors (SGLT2i), but also glucagon-like peptide 1 receptor agonists (GLP1Ra) in patients with type 2 diabetes mellitus (T2DM). However, there is not enough evidence of direct comparison between these drugs in clinical practice.

Methods: We retrospectively built two databases of T2DM patients who were visiting members of the Kanagawa Physicians Association. One database consisted of T2DM patients who were administered SGLT2i and the other of T2DM patients who were administered GLP1Ra for more than a year. We compared the renal composite outcome of 541 SGLT2i-treated patients without the concomitant use of GLP1Ra and 265 GLP1Ra-treated patients without the concomitant use of SGLT2i. We have set the renal composite endpoint as the progression of the stage of albuminuria or the decrease of estimated glomerular filtration rate (eGFR) by ≥15% per year. For comparative analyses, we built the cohort model of patients treated with SGLT2i or GLP1Ra, using a propensity score–matching method with the following algorithm: 1:1 nearest neighbor match with a ±0.063 caliper and no replacement.

Results: The comparison of 134 propensity-matched patients in each group was performed. The median values of the age, body mass index, eGFR, ACR, and duration of treatment when both groups were combined were 64.0 years, 26.9, 71.1 mL/min/1.73 m^2, 29.8 mg/gCr, and 36 months, respectively. The incidence of renal composite outcome was significantly lower in SGLT2i treated patients than in GLP1Ra treated patients (n = 15 [11%] and n = 27 [20%], respectively, $p = 0.001$ by McNemar's test). The estimate hazard ratios and robust 95% confidence intervals (CI) for the renal composite outcome by the analysis of cox proportional hazards models were 0.69(95% CI, 0.53, 0.90; $p = 0.006$) in SGLT2i treated patients. There was a significant difference in the annual change in eGFR between the two groups: -1.8 ± 5.1 % in SGLT2i treated patients and -3.4 ± 7.0 % in GLP1Ra treated patients ($p = 0.0049$).

Conclusions: By this retrospective study, SGLT2i treatment had shown more preferable influence on the change of eGFR than GLP1Ra treatment in Japanese T2DM patients.

PO0753

Role of β2-Adrenergic Receptor Agonists in the Treatment of Diabetic Nephropathy

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Background: Diabetes is the leading cause of end stage kidney disease (ESKD) and affects podocytes. We previously showed in cells and mice that pharmacological activation of mitochondrial biogenesis by the long-acting β_2-AR agonist formoterol contributes to podocyte recovery from injury.

Methods: We examined the association between COPD, in which the vast majority of patients receive β_2-AR agonists, and CKD progression in a national cohort created from patient records within the Veterans Health Administration (VHA). Cohort members were limited to age 65 to 85 years with stage 3 CKD defined based upon ICD-9 codes (ICD-9: 585.3, N18.3) or two eGFR values of 30-59 mL/min/1.73m^2 at least 90 days apart. COPD was defined based upon ICD-9 codes (ICD-9: 416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8). Veterans entered the cohort in 2010 and were followed through 2016. We are also currently testing the efficacy of formoterol in restoring glomerular function in type I (streptozotocin) and type 2 (high fat diet) diabetic murine models.

Results: Of 194,119 Veterans with stage 3 CKD in 2010, 4,727 progressed to stage 5 CKD by 2016. The age- and sex-adjusted odds ratio for the association between baseline COPD and progression to stage 5 CKD was 0.89 (95% CI: 0.83, 0.96), indicating that Veterans with COPD at baseline had lower odds of progression to stage 5 CKD than Veterans without COPD at baseline.

Conclusions: Our large retrospective cohort study suggests that β_2-AR agonists slow the progression of CKD. Given that diabetes is the most common cause of ESKD, the effect of β_2-AR agonists on progression of CKD is likely driven by the effect on diabetic nephropathy. Animal studies to directly test this hypothesis are underway.

Funding: NIDDK Support, Veterans Affairs Support

PO0754

Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Serum Electrolyte Levels in Patients with Type 2 Diabetes: A Network Meta-Analysis of Randomized Controlled Trials

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Background: Previous studies have reported that sodium-glucose co-transporter 2 (SGLT2) inhibitors(SGLT2is) affect serum electrolytes levels, especially magnesium. This study aimed to integrate direct and indirect trial evidence to maximize statistical power to clarify their overall and comparative effects of all SGLT2is on electrolyte levels in patients with type 2 diabetes (T2D).

Methods: We systematically searched PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov up to through January 2021 to identify eligible randomized controlled trials (RCTs) that reported the mean changes in serum electrolytes, including magnesium, sodium, potassium, phosphate, and calcium. We performed both random-effects pairwise and network meta-analyses to calculate the weighted mean difference (WMD) and 95% confidence intervals (CI).

Results: In total, we included 26 RCTs involving 28,943 T2D patients with 6 SGLT2is. Compared with the placebo, SGLT2is were significantly associated with elevations in serum magnesium by 0.7mmol/L (95% CI,0.06, to 0.08 mmol/L) and serum phosphate by 0.02 mmol/L (95% CI, 0.01 to 0.03 mmol/L). Our network meta-analysis showed no evidence of significantly superior efficacy of any specific SGLT2 inhibitor over the others, although dapagliflozin was associated with a larger magnitude in significant increment ases in serum magnesium associated with dapagliflozin (WMD = 0.16 mmol/L), compared to other SGLT2is. Similarly, no statistically detectable differences were evident between any two of SGLT2 inhibitors on serum levels of other electrolytes.

Conclusions: SGLT2is could significantly increased serum magnesium and phosphate levels, consistent with a class effect of SGLT2 inhibition. However, further investigation on more data for long-term efficacy and safety in T2D patients with different clinical phenotypes are needed for further investigation.

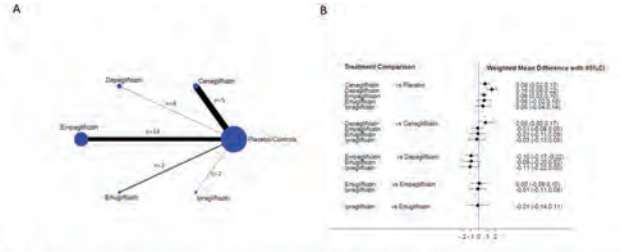

Figure A. Network of eligible comparisons for the multiple-SGLT2 inhibitors meta-analysis for effects on blood magnesium levels. Each node represents one treatment. The directly compared treatments are linked with a solid line, the width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomized participants (sample size). B. Network meta-analysis combining direct and indirect evidence within a network of eligible trials for the effects of SGLT2 inhibitors on blood magnesium levels (μmol/L). The black solid lines represent the confidence intervals for weighted mean differences of blood magnesium levels for each comparison and the blue line is the line of no effect (WMD equal to 0).

PO0755

Association of Fibrate Use with Cardiovascular Disease Mortality Across CKD Stages

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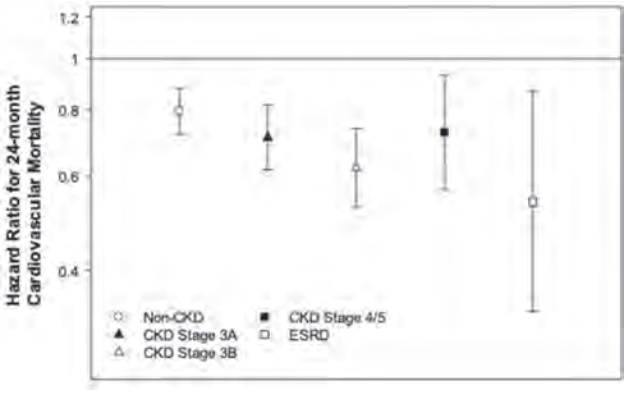
Background: Elevated serum lipids are risk factors for cardiovascular disease (CVD) in the general population and common first-line treatment includes fenofibrates for those with high triglycerides (TG) or low high-density lipoproteins (HDL). Recent studies have suggested that fibrates may be beneficial for CVD death outcomes in those with chronic kidney disease (CKD). Yet how the relationship between fibrates and early CVD death differs across CKD stages remains uncertain.

Methods: In male Veterans with adverse lipid levels (TG≥150 mg/dL or HDL ≤40 mg/dL), initial fibrate users and non-users were matched on CKD stage, TG and HDL levels. The cohort of 233,082 patients were followed until 2014. We used inverse probability weighting in the fitting of marginal structural models to adjust for time-varying confounding and informative censoring in investigating the average direct effect of fibrate use (reference: non-use), with 24-month cardiovascular mortality. Models were stratified by CKD stage at baseline.

Results: Patients were a mean±SD age of 62±12 years, and 26% of patients had CKD or end-stage renal disease (ESRD). The median[IQR] of baseline TG and HDL were 310 [220,436], and 34 [30, 40] mg/dL, respectively. Across all baseline CKD stages, the use of fibrates were associated with lower risks of 24-month CVD mortality, compared with non-users. These associations gradually declined across advancing CKD stages, where patients with ESRD on renal replacement therapy had the lowest observed risks (Hazard Ratio[95%CI]: 0.54[0.34, 0.87]) [Figure 1].

Conclusions: Fibrate use was associated with lower CVD mortality. These risks varied across CKD stage, but those with ESRD tended to have better CVD death outcomes. Additional studies are imperative to better tailor lipid therapy and management against adverse outcomes among the late-stage CKD and ESRD patients.

Funding: Veterans Affairs Support



PO0756

Effect of CKD Stage on Myocardial Infarction Risk with Niacin Use in Male Veterans

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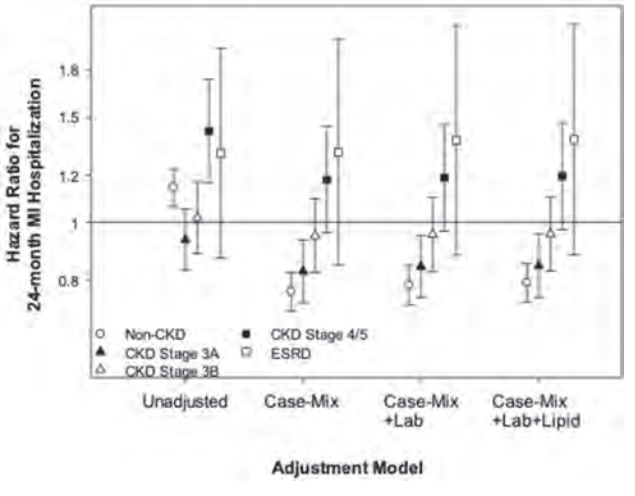
Background: Niacin is a lipid therapy shown to have cardio-protective effects, particularly in those with high triglyceride (TG) and low high-density lipoprotein (HDL) levels. But, in chronic kidney disease (CKD) patients who have elevated risk of cardiovascular risk and altered lipid levels, it remains unclear if CKD stage impacts these associations.

Methods: In males with worse lipid levels (TG≥150 mg/dL or HDL ≤40 mg/dL), we matched patients with an incident niacin prescription to non-niacin users on CKD stage, TG and HDL levels. In this study of 336,178 niacin users and non-users, we evaluated the relationship of time-varying niacin use with 24-month myocardial infarction (MI) hospitalization. Cox models included adjustment for time-varying covariates and were stratified by baseline CKD stage.

Results: Patients were a mean 64 years old, with a median[IQR] of TG and HDL of 203[143, 297] and 34[29, 39] mg/dL, respectively. In unadjusted models, non-CKD, CKD 4/5 and end-stage renal disease (ESRD) niacin users had higher risks of a MI hospitalization, yet CKD 3A-3B patients had null risks, compared with non-users. With adjustment for case-mix variables, including comorbidities, we observed a linear relationship across baseline CKD stages, where risks progressively increased with worse stage. Non-CKD niacin users had lowest risks of 24-month MI hospitalization, while both CKD 4/5 and ESRD patients trended towards elevated risks of event. The relationships between niacin use and MI hospitalization remained the same with adjustment for laboratory and other lipids.

Conclusions: In time-varying analyses, niacin use was associated with lower risks of 24-month MI hospitalization in non-CKD and CKD 3A patients. The risks of MI hospitalization were progressively elevated with worse CKD stages. Additional studies are needed to further examine the relationship between lipid modulating therapies in the context of CKD patients.

Funding: Veterans Affairs Support



PO0757

Advantages of Metformin for the Prevention and Mitigation of Diabetic Foot Ulcer in Diabetic Kidney Disease from a Large-Scale, Real-World Cohort

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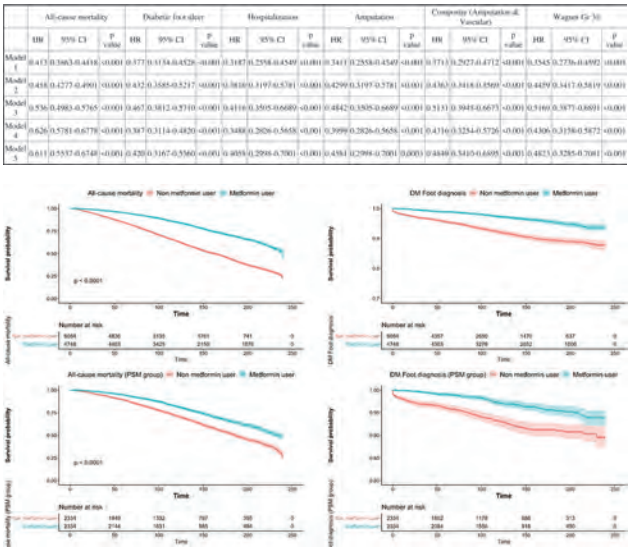
Background: Diabetic foot ulcer(DFU) and diabetic kidney disease (DKD) are diabetes-related microvascular complications strongly correlated with high morbidity and mortality. Metformin potentially confers a wound-healing advantage, although there are no well-established evidence. We first time investigated the effect of metformin on DFU among large retrospective cohort of DKD.

Methods: This retrospective cohort study enrolled DKD patients from two South Korean tertiary-referral centers. Primary outcomes were all-cause mortality and DFU events; secondary outcomes included hospitalization, amputation, composite of amputation or vascular intervention, and Wagner Grade >3. Multivariate cox analysis and Propensity score matching (PSM) was used to balance baseline intergroup differences between metformin users and metformin non-users.

Results: Among 10,832 patients (4,748 metformin users; 6,084 metformin non-users), the 117.5±66.9 months follow-up period, all-cause mortality rate and DFU incidence were, 37.1%, and 5.2%, respectively. Fully adjusted multivariate Cox analysis showed that metformin users had a lower all-cause mortality (adjusted hazard ratio 0.63; 95% confidence interval 0.58–0.68; p<0.001) and DFU events (0.39; 0.31–0.8; p<0.001, Table). After PSM, metformin users showed lower all-cause mortality (0.61; 0.55–0.67; p<0.001), DFU events (0.42; 0.32 –0.56; p<0.001), and secondary outcomes (hospitalization, amputation, composite of amputation or vascular intervention, and DFU with Wagner Grade >3. Table).

Conclusions: Metformin therapy in DKD patient can lower all-cause mortality, DFU incidence, and DFU progression.

Survival analysis of primary and secondary outcomes



PO0758

Gaps in CKD Awareness Among People with Type 2 Diabetes

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Background: Diabetes is one of the most common causes of chronic kidney disease (CKD) in adults, with around 1 in 3 people with diabetes also living with CKD. Clinical guidelines recommend annual screenings of urinary albumin and glomerular filtration rate for people with type 2 diabetes (T2D). Previous studies have identified low awareness, testing and diagnosis of CKD among people with T2D and their healthcare providers (HCP). By drawing comparisons to cardiovascular disease (CVD), the present study aimed to assess awareness of CKD, renoprotective diabetes therapies, and kidney health metrics among people with T2D.

Methods: In February 2021, 1021 people with T2D from the dQ&A Patient Panel responded to an online survey assessing perceptions, knowledge, HCP engagement, and lifestyle behaviors related to CKD and CVD. Respondents received $10 USD for completing the survey. Data was collected with Qualtrics, prepared with IBM SPSS, and analyzed in MarketSight.

Results: Awareness of the link between T2D and CKD was lower than awareness of the link between T2D and CVD; 57% of respondents strongly agreed that having T2D increases the risk of CKD, compared to 63% who strongly agreed that T2D increases the risk of CVD. The percentage of respondents who often consider their personal risk of CKD (19%) was also lower than for CVD (26%). Awareness of renoprotective and cardioprotective therapies was low overall. While 37% were aware that some T2D drugs are cardioprotective, only 22% were aware of renoprotective benefits. Respondents on SGLT-2 inhibitors or GLP-1 agonists were more likely to be highly aware of their cardioprotective benefits than their renoprotective benefits (52% vs. 30% for SGLT-2 users, 45% vs. 31% for GLP-1 users). Knowledge of personal metrics for renal health indicators, eGFR (38%), and uACR (26%), lagged behind knowledge of diabetes and CVD metrics: weight (100%), A1C (98%), blood pressure (94%), and cholesterol (75%). Only 41% of respondents had discussed their CKD risk with a diabetes-related HCP, but those who had were more likely to be aware of CKD risks and therapies.

Conclusions: This data highlights a gap between T2D patients' awareness of CKD risks and protective therapies and those of CVD. To prevent CKD and improve outcomes, this study emphasizes the need for better patient education on CKD's connection to T2D.

Funding: Commercial Support - AstraZeneca

PO0759

Feature Selection and Machine Learning Model for Predicting Diabetic Kidney Disease Risk in Asians

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Background: Machine learning (ML) techniques may improve disease prediction and interpretability of regression models by identifying the most relevant features in multi-dimensional data. We evaluated the ability of various ML classifiers for feature identification and improving the prediction accuracy of diabetic kidney disease (DKD).

Methods: We utilized longitudinal data from 1364 Chinese, Malay and Indian participants aged 40-80 years with diabetes but free of DKD who attended the baseline visit of the Singapore epidemiology of Eye Diseases Study in 2004-2011 and were followed up for 6 years (2011-2017). Incident DKD (n=162) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2+25% decrease in eGFR at follow-up. We evaluated 339 features including demographic/clinical, retinal imaging, genetic and serum metabolomics profile and tested nine ML algorithms along with feature selection (gradient boosting decision tree, elastic net, random forest, support vector machine, neural network, LASSO etc.). The performance of the best ML model based on optimum features was compared to that of logistic regression (LR) with traditional risk factors using the area under the receiver operating characteristic curve (AUC), sensitivity and specificity.

Results: The best performing model was a combination of Recursive feature elimination (RFE) for variable selection and Elastic Net (EN) using 15 predictors from demographic/clinical +metabolite set with AUC, sensitivity and specificity of 0.852, 83.0% and 73.5% compared to 0.796, 83.0% and 61.8% by LR. The top-15 predictors of DKD risk included seven risk factors and eight metabolites: age, antidiabetic medication use, presence of hypertension, diabetic retinopathy, higher levels of systolic blood pressure, HbA1c, lower levels of eGFR; higher levels of triglycerides in IDL, phospholipids in chylomicrons and medium VLDL, total cholesterol in chylomicrons and very small VLDL, medium LDL, cholesterol esters in very large HDL and lower levels of DHA, lactate and acetate.

Conclusions: ML together with feature selection improved prediction accuracy of DKD risk in the general population with diabetes and identified novel risk factors including metabolites.

Funding: Government Support - Non-U.S.

PO0760

Risk Score to Predict CKD Among Mexican Individuals with Diabetes Mellitus

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Background: The two major causes of CKD are type 2 diabetes (T2D) & hypertension, which are responsible for up to two-thirds of the cases. More than half of patients in Mexico with incident ESRD have an underlying diagnosis of T2D. Some prediction models have been developed for the purposes of screening CKD & its progression. However, their generalizability to the Mexican population is not known, & few have been validated in different populations & rarely in LMIC. We aimed to develop & validate a lab and office-based risk prediction scores for CKD among Mexican patients with T2D

Methods: The prospective cohort consisted of 105,310 patients enrolled in the Integral Management of Diabetes by Stages program. 18,148 patients were randomly assigned to the training & testing sets on an 80-20 ratio. Logistic regression models were used to assess risk factors for CKD. A stepwise selection process was performed to determine the best predictive equations

Results: A total of 1,617 patients developed CKD (mean follow up of 1.1 years). Age, BMI, duration of T2D, treatment with insulin & oral hypoglycemics, treatment with nephroprotective agents, retinopathy & alcohol use were predictors in both models. Triglyceride levels & eGFR proved to be important predictors in the lab model. The lab score had a C statistic of 0.77 & a calibration slope of 1, whereas the office score had 0.67 & 0.89, respectively

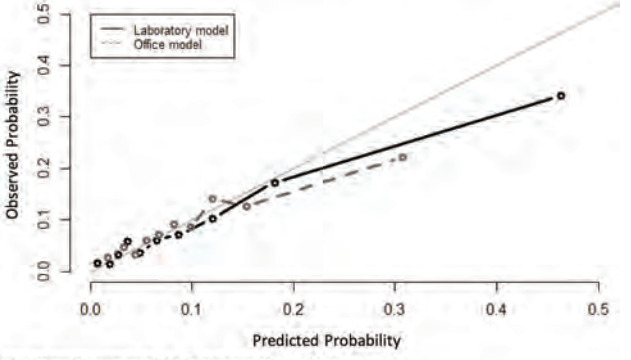
Conclusions: These models can be used to identify individual patients with T2D who are at risk of developing CKD. This can facilitate early detection to intensify T2D treatment in a timely manner

Table 1. Laboratory and office risk scores for the development of chronic kidney disease, defined as eGFR < 60 ml/min/1.73m².

	Laboratory Model	Office Model
	OR (95% CI)	OR (95% CI)
Age	1.03 (1.02, 1.04)	1.16 (1.08, 1.24)
Age²		1.00 (1.00, 1.00)
BMI [kg/m²]	1.01 (1.00, 1.02)	1.02 (1.01, 1.03)
Years of evolution of T2D	1.01 (1.00, 1.02)	1.02 (1.01, 1.02)
Treatment with oral hypoglycemics	1.10 (0.81, 1.53)	1.07 (0.79, 1.48)
Treatment with insulin	0.99 (0.57, 1.70)	1.01 (0.59, 1.69)
Treatment with OH & insulin	1.51 (1.09, 2.12)	1.46 (1.06, 2.04)
Treatment with ARB or ACEi	1.26 (1.11, 1.42)	1.37 (1.21, 1.54)
Retinopathy	1.29 (1.05, 1.57)	1.33 (1.09, 1.62)
Diabetic foot	1.43 (0.97, 2.05)	1.35 (0.92, 1.90)
Neuropathy		1.11 (0.97, 1.28)
Alcohol intake	1.41 (1.09, 1.84)	1.42 (1.11, 1.85)
GFR [mL/min/1.73m²]	0.94 (0.94, 0.95)	
Triglycerides [mg/dL]	1.00 (1.00, 1.00)	
Intercept	0.37 (0.13, 1.00)	0.00 (0.00, 0.00)

Selected from a Stepwise Selection based on AIC.
BMI: body mass index; T2D: type 2 diabetes mellitus; OH: oral hypoglycemic agents; ARB: Angiotensin II receptor blocker; ACEi: Angiotensin-convertor enzyme inhibitor; HTN: hypertension; FPG: fasting plasma glucose; GFR: glomerular filtration rate.

Fig. 1. Observed and predicted risk of chronic kidney disease events by decile.



Line of equality represented by the light gray diagonal line.

PO0761

Changes in Kidney Disease: Improving Global Outcomes (KDIGO) Risk Categories in Patients with Type 2 Diabetes and CKD

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Background: UACR is an important measure of kidney damage, but it is under-utilized in clinical practice. To comprehensively characterize the course of CKD in patients with T2D and CKD, this study evaluated changes in KDIGO risk categories based on both eGFR and UACR.

Methods: A prevalent cohort of adult patients with T2D and both eGFR and UACR measures indicating CKD of moderate or high risk based on KDIGO risk categories were identified from the Optum electronic health records database (2007 - 2019). The index date was defined as the first record indicating CKD of moderate or high risk after T2D diagnosis. The proportion of patients moving to a higher risk category in 5 years was estimated using Kaplan-Meier analysis. Average eGFR and UACR were also calculated over time.

Results: The index risk categories among the 269,187 patients with T2D and CKD were 81% moderate risk and 19% high risk. The majority of high-risk patients with impaired eGFR moved to very high risk within 5 years (G2-A3: 72%; G3a-A2: 88%; G3b-A1: 87%). Patients with index moderate risk and impaired eGFR also had high risk of moving to a higher risk category (G2-A2: 54%; G3a-A1: 84%). (Table) Patients with comparable eGFR had faster eGFR decline if their UACR level was elevated. (Figure)

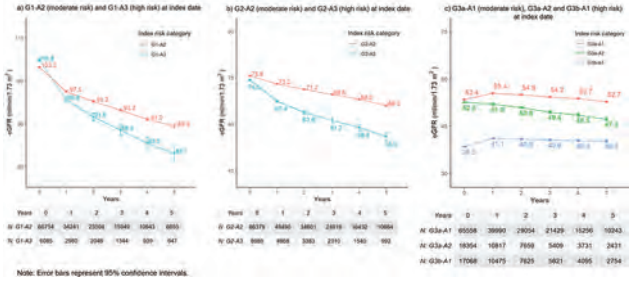
Conclusions: The majority of T2D patients with CKD of moderate or high risk moved to a higher risk category within 5 years, even with mildly decreased eGFR. Those with more impaired UACR had faster decline in eGFR, which confirms the value of UACR in CKD management.

Funding: Commercial Support - Bayer U.S. LLC

Table. Changes in KDIGO risk categories in 5 years

	Moderate Risk at Index Date			High Risk at Index Date			
	G1-A2 n=66,754	G2-A2 n=86,379	G3a-A1 n=65,558	G1-A3 n=6,085	G2-A3 n=8,989	G3a-A2 n=18,354	G3b-A1 n=17,068
Moved to high/very high risk (%)	18.8	53.9	83.7	12.8	71.6	88.0	87.1
Moved to high risk (%)	16.7	37.8	56.3	–	–	–	–
Moved to very high risk (%)	2.1	16.1	27.4	12.8	71.6	88.0	87.1

Figure. 5-year eGFR trajectories by index KDIGO risk category



PO0762

Using Machine Learning to Predict CKD upon Type 2 Diabetes Mellitus Diagnosis

Angier O. Allen, Zohora Iqbal, Abigail Green-Saxena, Ritankar Das. *Dascena Inc., Houston, TX.*

Background: Chronic kidney disease (CKD) accounts for the majority of increased risk of mortality for diabetic patients, manifesting in approximately half of patients diagnosed with type 2 diabetes mellitus (T2DM). Although increased screening frequency can avoid missed diagnoses, this is not implemented uniformly. We developed and retrospectively validated a machine learning algorithm (MLA) to predict CKD within 5 years upon T2DM diagnosis.

Methods: Electronic health records (EHR) data of 171,201 recently diagnosed T2DM patients (age ≥ 18) was extracted from a proprietary database of >700 healthcare sites across the US between 2007-2020. A random forest MLA was developed to assess risk of Stage 3+ CKD (CKD 3+) in T2DM patients using EHR data collected in the year prior to T2DM diagnosis. International Classification of Diseases codes (ICD-9 and ICD-10) were used to identify T2DM and CKD 3+ patients. The MLA was tested on a hold-out test set of 42,801 patients as well as a separate external validation dataset. The Centers for Disease Control and Prevention (CDC) CKD risk score was used as a comparator. Performance of the MLA and CDC CKD risk score was assessed on the hold-out test set and the external validation dataset via area under the receiver operating characteristic curve (AUROC).

Results: On a hold-out test set and an external validation dataset, the MLA outperformed the CDC CKD risk score when analyzed for prediction of CKD 3+ in recently diagnosed T2DM patients (Fig 1).

Conclusions: This retrospective study shows that a MLA can provide timely predictions of CKD among recently-diagnosed T2DM patients. Early detection of CKD in diabetic patients may enable therapeutic interventions, lifestyle changes, prevention of progression, and reduction of dialysis dependency, as well as healthcare costs.

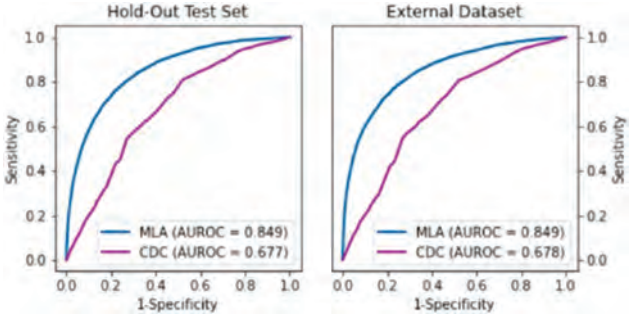


Figure 1. Area under receiving operating characteristic curves for the machine learning algorithm (MLA) and CDC CKD risk model (CDC) for Stage 3+ diabetic CKD predictions performed on the hold-out test set and external validation dataset.

PO0763

Contemporary CKD Incidence Rates in Diabetes by Race/Ethnicity, Sex, and Age

Katherine R. Tuttle,[1,2] Cami R. Jones,[1] Kenn B. Daratha,[1,2] Alain Koyama,[3] Susanne B. Nicholas,[4] Radica Z. Alicic,[1,2] Keith C. Norris,[4] Nilka Rios Burrows,[3] Meda E. Pavkov.[3] CURE-CKD *[1]Providence St Joseph Health, Renton, WA; [2]University of Washington, Seattle, WA; [3]Centers for Disease Control and Prevention, Atlanta, GA; [4]University of California Los Angeles, Los Angeles, CA.*

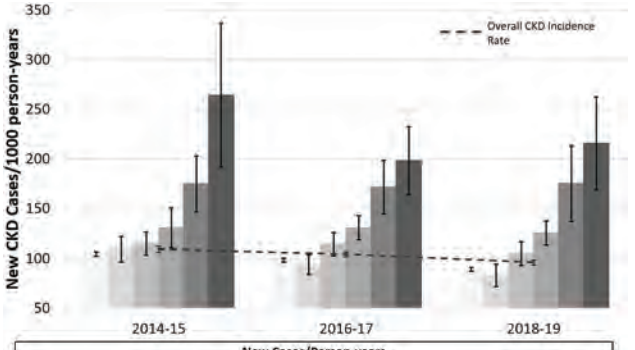
Background: Diabetes is the most common cause of chronic kidney disease (CKD), yet little is known about current CKD incidence rates and demographic predictors in these patients. The study aim was to estimate CKD incidence over time in adults with diabetes treated in two large healthcare systems.

Methods: The Center for Kidney Disease Research, Education, and Hope registry data is curated from electronic health records at Providence St. Joseph Health and University of California Los Angeles Health. Age, sex, and race/ethnicity adjusted CKD incidence rates were calculated over two-year time periods covering 2014–2019. CKD was identified by ≥2 laboratory measures (estimated glomerular filtration rate <60 mL/min/1.73m^2, urine albumin/creatinine ratio ≥30 mg/g, urine protein/creatinine ratio ≥150 mg/g) ≥90 days apart or administrative codes. Diabetes was identified by laboratory measures (HbA1c, blood glucose), use of glucose-lowering medication, or administrative codes.

Results: The overall CKD incidence (95% CI) rate in diabetes declined from 109.1 cases/1000 person-years (106.1–112.1) in 2014-15, to 104.2 cases/1000 person-years (101.7–106.8) in 2016–17, to 96.0 cases/1000 person-years (93.5–98.5) in 2018–19 (p<0.001 for trend, Figure). CKD incidence only declined in Whites over these time periods. CKD incidence rates were lowest in Whites and Asians and highest in American Indians/Alaska Natives (AI/AN) and Native Hawaiians/Pacific Islanders (NH/PI). CKD incidence rates were higher in men than women and increased with age.

Conclusions: CKD incidence has recently declined in patients with diabetes overall, and specifically among Whites. AI/AN and NH/PI patients with diabetes had the highest rates of CKD incidence. Studies of targeted strategies in high-risk populations will be important to prevent CKD.

Funding: Other U.S. Government Support



	New Cases/Person-years		
White	15,799/113,490	17,349/138,220	18,224/155,357
Asian	1,514/11,498	1,846/15,553	2,041/18,756
LatinX	576/4,511	939/6,526	1,200/9,183
Black	1,217/7,786	1,478/9,498	1,462/10,138
AI/AN	271/1,460	282/1,699	290/1,874
NH/PI	216/952	234/1,231	300/1,505

Figure.

PO0764

Renal Oxygenation, Perfusion, and Blood Flow in Type 1 Diabetes with Albuminuria Compared with Healthy Controls

Jens christian Laursen,[1,2] Ida Rasmussen,[1] Joana Melo,[1] Bryan Haddock,[3] Farzaneh Safavimanesh,[1] Joachim Størling,[1] Christian S. Hansen,[1] Henrik Bo W. Larsson,[3] Per-Henrik Groop,[4] Marie Frimodt-Moller,[1] Ulrik B. Andersen,[3] Peter Rossing.[1,2] Complications Research *[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [2]Kobenhavns Universitet, Kobenhavn, Denmark; [3]Rigshospitalet, Kobenhavn, Denmark; [4]Folkhalsanin tutkimuskeskus, Helsinki, Finland.*

Background: The mechanisms behind the progression of diabetic kidney disease in type 1 diabetes (T1D) are poorly understood. We aimed to evaluate the renal oxygenation, perfusion and blood flow using magnetic resonance imaging (MRI) in persons with T1D and albuminuria and in healthy controls (CONs).

Methods: Cross-sectional study in 15 persons with T1D and albuminuria compared with 15 CONs. MRI (3 Tesla Philips Scanner) was used to assess renal R_2* (a low value corresponds to a high tissue oxygenation), renal perfusion (arterial spin labelling) and renal artery flow (phase contrast imaging). Differences in outcomes between groups and associations were adjusted for age and sex.

Results: There was no difference between groups in the mean (SD) age (T1D: 58 (14) years; CONs: 56 (15) years; p=0.82) or in the gender distribution (33% female in both groups, p=1). Participants with T1D had a mean duration of diabetes of 38 (18) years, a higher median urine albumin creatinine ratio (UACR) (T1D: 46 (IQR 21-58) mg/g; CONs: 4 (3-6) mg/g; p<0.0001) and a lower mean estimated glomerular filtration rate (eGFR) (T1D: 73 (32) ml/min/1.73m^2; CONs: 88 (15) ml/min/1.73m^2; p=0.12), although not significantly for the latter. There were no significant differences between groups in renal cortical R_2* (T1D: 22.2 (5.0) s^{-1}; CONs: 22.1 (2.6); p=0.92) or medullary R_2* (T1D: 33.9 (6.1) s^{-1}; CONs: 37.7 (4.6); p=0.14). Renal cortical perfusion was lower in T1D than in CONs (T1D: 163 (40) ml/100g/min; CONs: 224 (49) ml/100g/min; <0.01), but there was no difference in the medullary perfusion (T1D: 43 (11) ml/100g/min; CONs: 44 (15) ml/100g/min; p=0.92). Renal artery blood flow was lower in T1D than in CONs (T1D: 360 (130) ml/min; CONs: 430 (113) ml/min; p=0.01). A lower renal cortical perfusion was associated with a higher UACR (p<0.01) but not with eGFR (p=0.25). A lower renal artery blood flow was associated with a higher UACR (p<0.01) and with a lower eGFR (p=0.01).

Conclusions: Renal cortical perfusion and artery blood flow were lower in persons with T1D and albuminuria than in healthy controls, confirming findings from previous studies. Impaired renal cortical perfusion and blood flow were associated with impaired renal function.

Funding: Private Foundation Support

PO0765

CKD-Associated Frailty Risk Trajectory over Time Among Patients with Newly Diagnosed Diabetes Mellitus: A Population-Based Cohort Analysis

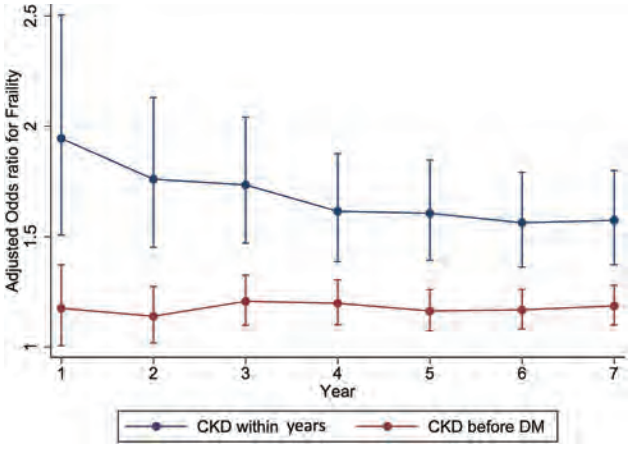
Chia-Ter Chao. *National Taiwan University Hospital Beihu Branch, Taipei, Taiwan.*

Background: Patients with chronic kidney disease (CKD) and diabetes mellitus (DM) are at high risk of frailty and adverse functional outcomes. CKD likely further aggravates the risk of frailty among patients with DM. However, whether the timing of CKD onset relative to incident DM affects the subsequent risk of frailty over time remains unclear.

Methods: We recruited patients with newly diagnosed DM but without frailty from a population-based cohort (n=488,458), dividing them into those without CKD throughout study period (7 years), with CKD prior to DM diagnosis, and with CKD years after incident DM. Their risk of frailty, based on a modified FRAIL scale, were examined. We used Cox proportional hazard regression to calculate CKD-associated risk of frailty, accounting for demographic, morbidities, medication, and prior hospitalization, followed by multiple regression analyses to calculate the annual probability of developing frailty starting immediately after DM occurrence.

Results: Among the enrolled patients with newly diagnosed DM, 80.8% (n=394,673) had no CKD throughout study period, while 3.3% (n=16,037) and 15.9% (n=77,748) had CKD prior to and after DM, respectively. Cox proportional hazard regression showed that newly diagnosed diabetic patients with CKD after DM had a significantly higher risk of developing frailty than those without CKD throughout study period (hazard ratio [HR] 1.649, 95% confidence interval [CI] 1.45 – 1.88), while those with CKD before DM had a higher but rather modest risk (HR 1.200, 95% CI 1.11 - 1.29). The annual probability of frailty occurrence was highest early during the course of DM and decreased slowly but gradually among CKD after DM group, while that of frailty remained stable throughout the study period among CKD prior to DM group (Figure).

Conclusions: The risk of CKD-related frailty exhibited temporal changes in patients with newly diagnosed DM. It would be prudent to carefully select the timing of providing frailty-oriented care in these patients.



PO0766

Understanding Patient Receptivity Towards Receipt of Prognostic Risk Score for Diabetic Kidney Disease

Tamara S. Muller, Nidhi Naik, Shivani Rathi, Sharlene Martin, Azadeh Zabetian. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Few studies examined the attitudes of patients with diabetic kidney disease (DKD) on risk stratification tools. An intrinsic barrier to undertake a risk stratification test is knowledge, awareness, and desire to know the risk of kidney disease. This study aimed at exploring the baseline knowledge about kidney disease and type 2 diabetes mellitus (T2DM) as a major contributing factor, alongside possible motivators, and the patient's receptivity towards risk score delivery of KidneyIntelX, a novel prognostic test that assesses the risk of kidney disease progression over the next 5 years in patients with DKD stages 1-3.

Methods: In May 2021, we contacted a subset of patients with stages 1-3 DKD and T2DM at one primary care site at the Mount Sinai Health System to communicate results obtained on their KidneyIntelX test and we administered a survey. We assessed patient knowledge about the test, their receptivity, and attitude on the usefulness of the test to improve their kidney health.

Results: A subset of patients (n=37) tested with KidneyIntelX in May 2021 were successfully contacted by the APRN on the DKD Care Navigation Team at Mount Sinai and completed the post-test survey. The majority of patients (70%) were aware diabetes is a contributing factor to kidney disease. 73% were unfamiliar with the prognostic test goals, while 27% were provided with an explanation by their physician. 89% were appreciative of the post-test call, and receiving risk scores through a post-test call were helpful for all patients (60% helpful, 40% very helpful) in improving their understanding of kidney health. Additionally, all patients were motivated to implement lifestyle changes to improve kidney health, and 63% desired educational content on diabetes, kidney disease and diet **(Table)**.

Conclusions: Dedicated phone calls from the Care Navigation Team after KidneyIntelX testing enhanced patient understanding about kidney disease and revealed substantial motivation to take appropriate actions and receive further education for their kidney health.

Funding: Commercial Support - Renalytix, Clinical Revenue Support

Table: Patient Responses on Post KidneyIntelX Test Survey Questions Categorized by Predefined Themes

Predefined themes	Questions	Patient response (%)
Prior Knowledge	Diabetes can affect the kidneys	Yes (70) No (30)
Prior Knowledge	Information received from physician about goal of the test	No information (57) Recognize just the name of test (16) Received information from physician (27)
Receptivity	Appreciative to receive calls from the DKD Care Navigation team	Yes (89) No (11)
Receptivity	Helpfulness of the KidneyIntelX test score in understanding patients' kidney health	Helpful (60) Very helpful (40) No (0)
Activation	Motivated to take appropriate actions to improve kidney health	Yes (100) No (0)
Activation	Desired educational materials on T2DM, CKD, diet/nutrition	Yes (63) No (37)

PO0767

Adequacy of Laboratory Monitoring of CKD for Diabetic Patients Empaneled with Primary Care

Bjoerg Thorsteinsdottir, LaTonya J. Hickson, Rachel Giblon, Joel A. Hickman, Suzanne M. Norby, Andrew D. Rule, Robert C. Albright. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Studies have shown poor adherence to chronic kidney disease (CKD) guideline adherence in primary care, contributing to late referral to nephrology and suboptimal clinical outcomes. We sought to assess the performance of our health system in adhering to laboratory monitoring guidelines for diabetic patients with laboratory confirmed CKD.

Methods: We identified all adult patients empaneled in a regional health system who had creatinine and urinary albumin measurements between 2014-2016 excluding pregnant patients, as well as those transplanted or already on dialysis or hospice and crossed this cohort with our existing diabetic patient registry. CKD defined based on calculated GFR and CKD risk defined per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. We defined laboratory monitoring compliance as meeting the number of creatinine measurements recommended by KDIGO per year with at least 3 months between measurement.

Results: 27943 diabetic patients had laboratory measurements allowing us to assess their CKD status. Of those 18466 (57%) had low risk/no CKD. Of those meeting CKD criteria, 13966 (50%) were missing a measure of albuminuria, 8030 (28.7%) had moderate, 3563 (12.8%) high and 2384 (8.5%) CKD risk. Compliance with laboratory monitoring was 82.7% for moderate risk, 59.9% for high risk and 44.8% of very high risk patients. Limitations include potential for access to disease monitoring outside of our health system.

Conclusions: Diabetic patients with CKD empaneled in our health system were often not adequately risk stratified for their CKD due to lack of attention to the need for albuminuria measures. For those who could be risk stratified, monitoring for low and moderate risk patients was adequate but the patients in the higher risk categories had worse guideline adherence. Better decision support systems are needed to improve kidney care for this high risk population.

Funding: NIDDK Support, Other NIH Support - NIA k23 AG051679

PO0768

Characteristics of Patients with CKD and Diabetes by Use of ACE Inhibitors or ARBs

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Background: The Center for Kidney Disease Research, Education and Hope (CURE-CKD) registry is curated from electronic health records (EHR) of >3.4 million patients with or at-risk of chronic kidney disease (CKD) at two, large healthcare systems. The study aim was to compare demographic and clinical characteristics of patients with CKD and diabetes (DM) by use of angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor II blockers (ARBs).

Methods: Demographic and clinical characteristics of adults (≥20 years) with CKD and DM (guideline-based laboratory criteria, use of glucose-lowering agents, administrative codes) were described for the time periods of 2015-17 and 2018-20. Pearson's chi-squared (categorical), Student's t-test (normal, continuous), or Mann-Whitney U (non-normal, continuous) analyses determined differences between users and non-users of ACEi or ARB defined by prescriptions in the EHR.

Results: ACEis/ARBs were used in 59% and 58% of patients with CKD and DM in 2015-17 and 2018-20, respectively. Adults >60 years old, men, and White/non-LatinX individuals more commonly used ACEis/ARBs (Table). In both time periods estimated glomerular filtration rate (eGFR) was significantly lower and systolic blood pressure was significantly higher in ACEi/ARB users versus non-users. The urine albumin-to-creatinine ratio did not differ by ACEi/ARB use. SGLT2 inhibitors and GLP-1 receptor agonists were more commonly given to ACEi/ARB users but prescribing of these agents was rare overall.

Conclusions: ACEi/ARB use remains sub-optimal in patients with CKD and DM and is more common in those who are older, men, and White/non-LatinX. Use of glucose-lowering agents recommended for kidney and heart protection remains very low. Further studies are needed to elucidate reasons for under-use of recommended therapies in patients with CKD and DM.

Funding: Commercial Support - Bayer

Table: Characteristics of adults with CKD and DM prescribed or not prescribed an ACEi or ARB (N=391,056; all comparisons significant p<0.001 except UACR p=0.09 in 2015-17, p=0.10 in 2018-20).

	2015-2017 N=132,576		2018-2020 N=114,607	
	Prescribed n=78,432 (59%)	Not Prescribed n=54,144 (41%)	Prescribed n=66,311 (58%)	Not Prescribed n=48,386 (42%)
Demographics				
Age, n (%), y				
20-59	16,553 (21)	17,300 (32)	13,562 (21)	15,933 (33)
60+	61,879 (79)	36,844 (68)	52,749 (79)	32,453 (67)
Sex, n (%)				
Men	41,251 (53)	26,500 (49)	35,620 (54)	23,723 (49)
Women	37,179 (47)	27,644 (51)	30,690 (46)	24,661 (51)
Race/ethnicity, n (%)				
White non-LatinX	53,994 (69)	35,768 (66)	45,278 (68)	31,153 (64)
All Others[a]	22,401 (29)	16,236 (30)	19,004 (29)	15,044 (31)
Urban/Rural[b], n (%)				
Urban	68,050 (87)	47,351 (87)	57,811 (87)	42,606 (88)
Rural	9,845 (13)	6,331 (12)	8,070 (12)	5,441 (11)
Baseline Clinical Characteristics				
eGFR, mean, SD (n), mL/min/1.73m²	56.9, 23.2 (69,624)	60.0, 28.6 (47,197)	57.5, 22.7 (57,699)	60.8, 28.9 (41,023)
eGFR w/o race, mean, SD (n) mL/min/1.73m²	56.4, 22.9 (69,624)	58.5, 28.3 (47,197)	57.1, 22.5 (57,699)	60.4, 28.6 (41,023)
SBP, mean, SD (n), mm Hg	131, 17 (75,230)	127, 17 (50,770)	130, 17 (62,708)	126, 17 (44,372)
HbA1c, median, IQR (n), %	6.7, 6.0-7.8 (28,606)	6.5, 5.8-7.7 (18,721)	6.7, 6.0-7.7 (20,140)	6.5, 5.8-7.7 (13,772)
UACR, median, IQR (n), mg/g	42, 17-116 (6,489)	40, 15-111 (3,514)	47, 21-134 (4,801)	44, 18-142 (2,372)
Medication, n (%)				
GLP-1 receptor agonist	1,477 (2)	410 (1)	2,467 (4)	686 (1)
SGLT2 inhibitor	2,275 (3)	610 (1)	3,177 (5)	97 (<1)

CKD-chronic kidney disease, DM-diabetes mellitus, ACEi-angiotensin converting enzyme inhibitor, ARB-angiotensin receptor II blocker, SD-standard deviation, IQR-interquartile range, eGFR-estimated glomerular filtration rate, SBP-systolic blood pressure, Hb-hemoglobin, UPCR-urine protein-to-creatinine, GLP-glucagon-like peptide, SGLT-sodium glucose co-transporter, [a] Includes White LatinX, Black/African American, Asian, American Indian/Alaska Native, Hawaiian Native/Pacific Islander, [b] Census Division Rural-Urban Commuting Area Codes Categorization C

PO0769

Impact of Non-Pharmacological Interventions in Indigenous Populations with Diabetes Mellitus on Cardiovascular and Kidney Disease: A Scoping Review Using the REAIM Framework

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Background: Diabetes mellitus is a common cause of mortality from cardiovascular (CV) and kidney diseases. This scoping review utilized the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework to assess the impact of non-pharmacological interventions on CV and kidney health outcomes (KHO) in Indigenous populations

Methods: We searched Medline, Embase, Cochrane Library, CINAHL, Web of Science, PsycINFO and other grey literature to identify studies that used non-pharmacological interventions (exercise, nutrition, telehealth, educational, health worker, and cultural) to achieve improved glycaemic control, and reduction of clinical or laboratory markers of CV or KHO in Indigenous communities

Results: Our search yielded 7,692 studies, from which 35 studies were selected. Culturally appropriate interventions were mostly utilized (77.1%); telehealth programs were least utilized (8.6%). Clinical and laboratory indices of CV and KHO were infrequently assessed (KHO assessed in 40%); improved kidney function was reported in 10.5% of health worker interventions. (Table 1). Reporting of items of the RE-AIM framework showed that internal validity items were more frequently reported than those of external validity: reach (60%), efficacy (52.1%), adoption (46.1%), implementation (41.9%), and maintenance (37.2%) (Table 2)

Conclusions: Due to the high prevalence of CV and kidney diseases in diabetic patients of Indigenous groups, studies using diabetes interventions need to report more items of external validity to allow the findings of such interventions to be translatable into practice

Table 1: Summary of outcomes by intervention type

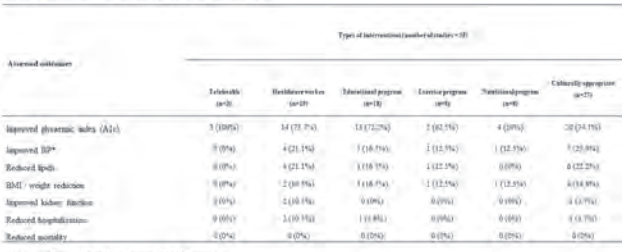

Table 1

Table 2: Proportion of diabetes interventions in Indigenous populations reporting the 21-item RE-AIM dimensions and components

RE-AIM dimensions and components	Total (n= 35; [%])
Reach	
• Method to identify target population	35 (100%)
• Inclusion criteria	26 (74.3%)
• Exclusion criteria	13 (37.1%)
• Participation rate	17 (48.6%)
• Representativeness	14 (40%)
Average across Reach components	60%
Efficacy / effectiveness	
• Results for at least one follow-up	35 (100%)
• Intent-to-treat analysis utilized	8 (22.9%)
• Quality-of-life or potential negative outcomes	9 (25.6%)
• Patient attrition	21 (60%)
Average across Efficacy/Effectiveness Components	52.1%
Adoption	
• Description of intervention location	24 (68.6%)
• Description of staff who delivered intervention	24 (68.6%)
• Method to identify staff who delivered intervention (target delivery agent)	13 (37.1%)
• Level of expertise of delivery agent	27 (77.1%)
• Inclusion/exclusion criteria of delivery agent or setting	9 (25.7)
• Adoption rate of delivery agent or setting	0 (0%)
Average across Adoption Components	46.1%
Implementation	
• Intervention duration and frequency	32 (91.4%)
• Extent protocol (program) delivered as intended	7 (20%)
• Measures of cost of implementation	5 (14.3%)
Average across Implementation Components	41.9%
Maintenance	
• Assessed outcomes ≥ 6 months post intervention	31 (88.6%)
• Qualitative measure of individual-level maintenance	7 (20%)
• Measures of cost of maintenance	1 (2.9%)
Average across Maintenance Components	37.2%

Table 2

PO0770

Cause-Specific Death Differs Based on HbA1c Levels in Hemodialysis Patients with Diabetes

Soo-Young Yoon, Dae Kyu Kim, Jongho Kim, Shinyeong Kang, Jin sug Kim, Kyung hwan Jeong, Sangho Lee, Ju young Moon, Hyeon Seok Hwang. *Kyung Hee University Medical Center, Seoul, Republic of Korea*.

Background: Adequate glycemic control with achieving target HbA1c is critical in hemodialysis (HD) patients with diabetes and HbA1c level is closely associated with mortality risk. However, it is unclear whether different HbA1c levels affect mortality risk of cause-specific deaths or not.

Methods: A total 24,620 maintenance HD patients with diabetes were enrolled from the electronic health record-based registry data of Korean Society of Nephrology. Plasma HbA1c level was measured at the time of the study data entry, and patients were classified into six categories according to the HbA1c level (≤5.5%, 5.6-6.5%, 6.6-7.5%, 7.6-8.5%, 8.6%-9.5%, and >9.5%). In multivariable Cox regression analysis, we examined the relationship between HbA1c level and the risk of cause-specific death (cardiovascular, infection, non-cardiovascular/non-infection).

Results: Compared with the group with HbA1c 6.6-7.5%, the risk of all-cause mortality in each group tended to increase as HbA1c level rose; 0.99-fold (95% confidence interval [CI], 0.91-1.07) in HbA1c 5.6-6.5%, 1.08-fold (95% CI, 0.99-1.19) in HbA1c 7.6-8.5%, (95% CI, 0.99-1.19), 1.26-fold in HbA1c 8.6-9.5% (95% CI, 1.12-1.42), and 1.57-fold in HbA1c >9.5% (95% CI, 1.39-1.78). In cause-specific death analysis, cardiovascular-related mortality risk showed similar hazard ratio pattern like all-cause mortality risk and the adjusted risk for each group were 0.96 (95% CI, 0.84-1.09), 1.17 (95% CI, 1.01-1.35), 1.53 (95% CI, 1.29-1.82) and 1.57-fold (95% CI, 1.30-1.91) for HbA1c 5.6-6.5%, HbA1c 7.6-8.5%, HbA1c 8.6-9.5% and HbA1c >9.5%, respectively. However, infection-related mortality risk did not significantly increase across HbA1c strata except the risk in HbA1c >9.5% group (HR, 1.71; 95% CI, 1.29-2.26). Non-cardiovascular related/non-infection related mortality risk did not increase in all six HbA1c categories.

Conclusions: All-cause mortality and cause-specific mortality risk were different according to HbA1c levels in the patients who were undergoing HD with diabetes. Furthermore, this study showed that cardiovascular mortality risk needs to be assessed in priority than infection or non-cardiovascular related/non-infection mortality risk when HbA1c level is increased in HD patients with diabetes.

PO0771

In-Hospital Outcomes in Diabetic Ketoacidosis and Impaired Kidney Function

Karthik Gangu, Aniesh Bobba. *University of Missouri System, Columbia, MO.*

Background: Diabetes Mellitus is one of the most common causes of End-Stage Renal Disease (ESRD) in the United States. In this study, we used the National Inpatient Sample (NIS) database to compare the outcomes of Diabetic Ketoacidosis (DKA) admissions in Chronic Kidney Disease (CKD) and ESRD to DKA with normal creatinine.

Methods: We performed a retrospective study by utilizing the 2016 NIS, which comprises 20% of hospital discharges for that year. We included patients aged 18 or older admitted to the hospital with a principal diagnosis of DKA. Diagnosis data were obtained by utilizing ICD 10 CM codes. A multivariate logistic regression model was used to analyze the effect of ESRD on mortality and intubation rate. Linear regression was used to analyze the impact of ESRD on length of stay. All outcomes were adjusted to age, sex, race, insurance status, Elixhauser Comorbidity index, hospital location, and characteristics.

Results: A total of 184,050 patients were included in the study, of which 12,605 had CKD and 6025 had ESRD. The mean age was 44.1 years (SD 12.8), and 51.9 % of patients were female in ESRD. The mean length of stay was 5.2 days for the ESRD group and 3.1 for DKA with the normal creatinine group. The adjusted length of stay was 0.9 day longer (p<0.001), and the adjusted cost of hospitalization was 13,684 US dollars more expensive in the ESRD group. Adjusted Odds Ratio for mortality 1.2 (CI 0.58-2.4, p = 0.61), and intubation 0.95 (CI 0.64-1.4, p = 0.81) were not statistically significant. Outcomes for CKD patients were similar to patients with normal creatinine. (Table 1)

Conclusions: DKA in ESRD patients was associated with increased length of stay and cost of hospitalization. Further studies looking into factors contributing to the longer length of stay in the ESRD population will help in improving outcomes and significant cost reduction in taking care of these patients.

Table 1

Outcomes	DKA with normal creatinine(n=16960)	Stage 1 CKD(n=320)	Stage 2 CKD(n=1466)	Stage 3 CKD(n=7790)	Stage 4 CKD(n=2055)	Stage 5 CKD(n=440)	ESRD(n=6025)
In-hospital mortality(%)	647(0.39%)	5(1.5%)	0	78(0.96%)	15(0.73%)	0	50(0.83%)
OR*(CI)		1.9(0.26-13.8,p=0.52)		0.73(0.4-1.3,p=0.31)	0.68(0.21-2.21,p=0.53)		1.2(0.58-2.4,p=0.61)
Intubation %	1.3%	1.5%	1.03%	3.2%	3.1%	4.5%	3%
OR*(CI)		0.44(0.05-3.2, p=0.43)	0.28(0.09-0.89, p=0.03)	0.72(0.33-1.03, p=0.73)	0.68(0.36-1.29, p=0.24)	1.42(0.5-4, p=0.5)	0.95(0.64-1.4, p=0.81)
Mean Los*	3.1	4.3	4.1	4.9	5.1	5	5.2
Adjusted Los*		0.35(p=0.75)	-0.3(p=0.25)	0.34(p=0.29)	0.4(p=0.12)	0.59(p=0.1)	0.9(p<0.001)
Mean $*	2876)	40084	35567	41603	42073	462068	52735

*Adjusted for Age, sex, race, elixhauser comorbidity index, insurance status hospital location and characteristics.

PO0772

Hypoglycemia and Glycemic Status Ascertained by Continuous Glucose Monitoring vs. Blood Glucose in a Prospective Hemodialysis Cohort

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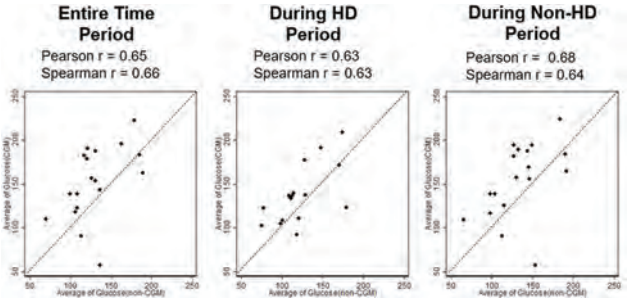
Background: In non-CKD patients, evidence shows continuous glucose monitoring (CGM) provides convenient, automated, and less invasive measurements vs. conventional self-monitored blood glucose, and leads to reduced hypo-/hyperglycemia and glycemic variability (hypoglycemia risk factor), as well as increased time in goal glucose range and quality of life. However, accuracy of CGM interstitial glucose vs. gold-standard blood glucose measures has not been well-studied in dialysis patients.

Methods: In 18 HD patients with diabetes hospitalized during 10/2020-5/2021, we conducted simultaneous protocolized glucose measurements using 1) Dexcom G6 CGM devices vs. 2) blood glucose levels using capillary fingerstick or venous blood glucose, with the latter measured ≥4 times per day (before each meal and at night), plus every 30 minutes during HD. We examined the correlation of averaged CGM and blood glucose levels, and compared the prevalence of hypoglycemia detected by these methods.

Results: During the overall assessment period, Pearson and Spearman correlations for averaged CGM vs. blood glucose were 0.65 and 0.66; similar correlations were observed when stratified by HD vs. non-HD periods. A similar proportion of patients were identified as having American Diabetes Association (ADA) Level 1 Hypoglycemia (<70mg/dl) using CGM and blood glucose (33%). In contrast, a higher proportion of patients were identified as having ADA Level 2 Hypoglycemia (<54mg/dl) by CGM (33%) vs. blood glucose (11%). A similar proportion of patients were identified as having high glucose variability (%CV >36%) using CGM vs. blood glucose (11%).

Conclusions: In a prospective cohort of hospitalized HD patients with diabetes, CGM interstitial glucose via the Dexcom G6 remote access system showed similar correlation with blood glucose levels. Whereas CGM vs. blood glucose had similar detection of Level 1 Hypoglycemia, CGM had greater detection of Level 2 Hypoglycemia vs. conventional approaches.

Funding: Commercial Support - Dexcom, Inc.



PO0773

Effectiveness of Intradialytic Plantar Electrical Nerve Stimulation During Hemodialysis to Improve the Gait in Adults with Diabetes and Renal Failure: A Randomized Double-Blinded Controlled Trial

Abdullah I. Hamad,[1] Ram kinker Mishra,[2] Rania A. Ibrahim,[1] Mincy Mathew,[1] Mohamed Yahya Abdelhai Mohamed,[1] Heba M. Ateya,[1] Saifatullah Khan,[1] Talal Talal,[3] Bijan Najafi,[2] Fadwa M. Al-Ali.[1] *[1]Hamad Medical Corporation, Doha, Qatar; [2]Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Houston, TX; [3]Diabetic Foot and Wound Clinic, Hamad Medical Corporation, Doha, Qatar.*

Background: Impaired mobility is a persistent problem among patients undergoing hemodialysis (HD). Although exercise could be beneficial, factors such as post-dialysis fatigue, time limitation, and severe frailty to travel may result in poor adherence to conventional exercise programs. To address this gap, we are exploring an alternative therapy using intradialytic plantar electrical nerve stimulation (IPENS) provided during the routine hemodialysis process.

Methods: Participants were randomized into either an intervention group (IG: n=21, age=55±2.7 years, BMI=30.6±1.3 kg/m^2, female=31%) or a control group (CG: n=24, age=56±2.2 years, BMI=32.2±1.2 kg/m^2, female=41%). The IG received 1-hour IPENS during the routine HD process (3 sessions/week) for 12 weeks. The CG received an identical but non-functional device for the same period. Participants and therapy-providers were blinded to the group allocation. Gait performance was assessed under single-task (ST) and dual-task (DT) conditions at the baseline, 6 week, and 12-week under supervised condition. To determine the effect of intervention, we estimated Cohen's effect size d. In addition, time effect, group, and time×group effects were estimated using general linear model.

Results: All participants in the IG tolerated the IPENS and completed all therapy sessions, indicating the feasibility. While, under DT condition, cadence (steps/min) and stride time (sec) increased significantly in both groups over the time, we observed a trend towards higher improvement in IG group (Cohen's d=0.54, p=0.086 for cadence and d=0.52, p=0.09 for stride time) with a medium effect size compared to CG. We observed significant time effect on other gait parameters under ST and DT conditions with the similar trends towards group effect.

Conclusions: This pilot trial provides earlier results on IPENS therapy's feasibility and effectiveness as an alternative to exercise programs to improve gait in HD patients. Even though, the improvement didn't reach statistical significance in our current sample size. However, the effect size was medium, which is very promising.

Funding: Government Support - Non-U.S.

PO0774

Economic Burden Associated with CKD Progression Based on Kidney Disease: Improving Global Outcomes (KDIGO) Risk Categories in Type 2 Diabetes

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Background: CKD progression adds substantial economic burden in T2D. This study evaluated the medical costs associated with CKD progression defined by KDIGO risk categories in patients with T2D and CKD.

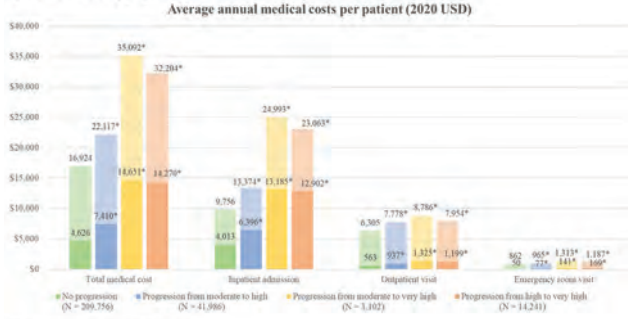
Methods: A prevalent cohort of adult patients with T2D and CKD who had measures of eGFR and UACR indicating moderate or high KDIGO risk categories were identified from the Optum electronic health records database (Jan 2007- Dec 2019). CKD progression was defined as an increase in KDIGO risk category. Annualized costs for inpatient admissions, emergency room visits, and outpatient visits were evaluated for up to 2 years after the index date (i.e., the first record indicating CKD progression for progressors; the later of the first record indicating the patient's risk category or two years before the end of follow-up for non-progressors).

Results: Among 218,624 patients with baseline moderate risk, 41,986 (19%) progressed to high risk and 3,102 (1%) progressed to very high risk; among 50,461 patients with baseline high risk, 14,241 (28%) progressed to very high risk. Compared to non-progressors, the annual incremental costs were $5,193 for patients progressed from moderate risk to high risk, $18,168 for moderate risk to very high risk, and $15,280 for high risk to very high risk (Figure 1). Inpatient costs were the major driver of incremental costs. CKD-related medical costs contributed to 28%, 34%, 42%, and 44% of total medical costs in the 4 groups, highest in patients who progressed to very high risk.

Conclusions: Patients with T2D and CKD in KDIGO moderate or high risk categories had significantly higher medical costs when they progressed to a higher KDIGO risk category compared to those without progression. Preventing progression could bend the cost curve in patients with T2D and CKD.

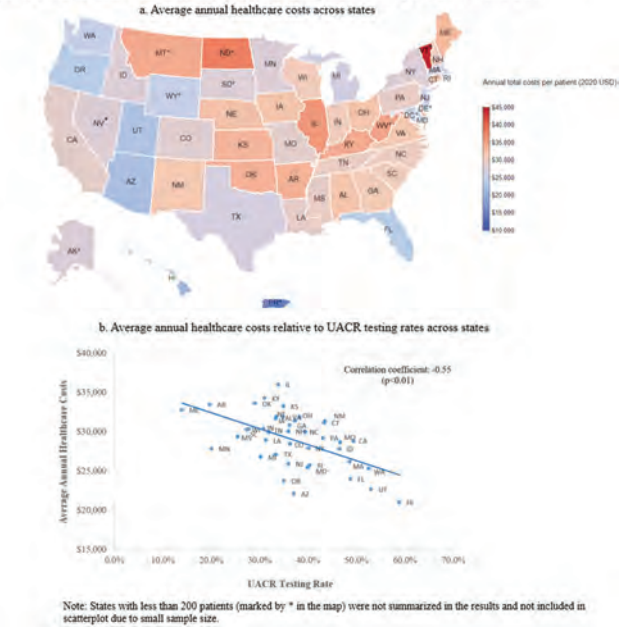
Funding: Commercial Support - Bayer

Figure 1. Medical costs by progression status[1,2]



[1] Solid areas represent CKD-related medical costs
[2] * denotes significance compared with patients with no progression

Figure 1. Average annual healthcare costs across states among patients with T2D and CKD (2020 USD)



Note: States with less than 200 patients (marked by * in the map) were not summarized in the results and not included in scatterplot due to small sample size.

PO0775

Geographic Variations in Healthcare Resource Utilization (HRU) and Costs and Their Associations with Albuminuria Testing in Patients with CKD and Type 2 Diabetes (T2D)

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Background: Albuminuria monitoring is critical for CKD management. The study evaluated the geographical urine albumin-to-creatinine ratio (UACR) monitoring patterns in the US along with the associated economic outcomes in patients with CKD and T2D.

Methods: Adult patients with T2D and CKD were identified from the Optum Clinformatics® claims data (Jan 2015-Dec 2019). HRU, healthcare costs (in 2020 USD), and percentage of patients receiving at least one UACR test were summarized by state during the one-year after T2D and CKD diagnoses. Patients who had dialysis or kidney transplantation before or during the study period were excluded.

Results: Among the 101,057 patients with T2D and CKD, the average annual healthcare costs were $28,636 and increased with CKD severity, from $20,122 (stage I, n = 4,070) to $38,072 (stage V, n = 242). Large variation exists across states ranging from $21,003 [HI] to $35,995 [IL] (Figure 1a). The average number of inpatient visits (range: 0.3 [AZ] to 0.7 [AR]), outpatient visits (18.3 [CO] to 29.8 [CT]), and emergency room visits (0.4 [MI] to 1.0 [KS]) also varied substantially. The average UACR testing rate was 38.7%, consistently low across states (14.0% [ME] to 58.9% [HI]). States with lower UACR testing rates tended to have higher healthcare costs (Figure 1b).

Conclusions: Patients with CKD and T2D had high HRU and healthcare costs with large variations across states. Lower UACR testing rates were associated with higher economic burden.

Funding: Commercial Support - Bayer U.S. LLC

PO0776

Cardiovascular and CKD-Related Healthcare Costs for Patients with Type 2 Diabetes and CKD

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Background: Cardiovascular (CV) events and chronic kidney disease (CKD) management incur high medical costs in patients with type 2 diabetes (T2D) and CKD. This study aimed to provide reliable regression-based cost estimates of these events among patients with T2D and CKD.

Methods: This study used Optum Clinformatics® claims data from 52,599 adults with T2D and CKD identified during 2015-2019 and followed until disenrollment, death, or end of data availability. Medical costs (2020 USD) associated with CV events and CKD management were estimated using a generalized estimating equation model adjusting for age, sex, as well as CV complications and medical costs at baseline. Costs were assessed in 4-month cycles as commonly evaluated in clinical trials in this population, with acute event costs assessed in the first 4 months after the incident CV events and renal replacement therapies (RRT). Mortality costs were assessed in the last month prior to death.

Results: The estimated 4-month CKD management costs were $7,725 for stage 1 or 2, $8,928 for stage 3, $10,809 for stage 4, and $11,879 for stage 5 (without RRT). The estimated acute event costs for dialysis and kidney transplantation were $87,538 and $124,271, respectively. The costs decreased to $49,573 and $7,079 in subsequent 4-month cycles following dialysis initiation and kidney transplantation. The estimated costs for acute CV events were $31,063 for heart failure, $21,087 for stroke, $21,016 for myocardial infarction, and $19,954 for atrial fibrillation ($30,500 with hospitalization and $5,162 without). In subsequent 4-month cycles, costs were $4,931 for heart failure, $2,327 for stroke, and $1,941 for myocardial infarction. The acute cost of hyperkalemia was $15,149 ($31,212 with hospitalization and $1,782 without). In the month before death, the costs associated with CV-related death, renal-related death, and death from other causes were $17,031, $12,605, and $9,900, respectively.

Conclusions: CV events and CKD management incur significant healthcare costs for patients with T2D and CKD. The cost estimates from this study may support the parametrization of economic models and help clinicians determine the cost-effectiveness of interventions.

Funding: Commercial Support - Bayer

PO0777

Clinical and Histological Predictors of Renal Survival in Patients with Biopsy-Proven Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of the most important complications of diabetes and has become the leading cause of end stage renal disease (ESRD). However, clinical and pathological factors alone can't reliably predict renal survival in patients with biopsy-proven DN, potentially resulting in the delayed treatment of patients at a high risk of renal failure. Therefore, this study sought to develop and validate a predictive model incorporating both clinical and pathological markers to predict renal outcomes in patients with biopsy-proven DN.

Methods: A predictive nomogram was developed based upon data pertaining to 194 patients with biopsy-proven DN. The prognostic relevance of individual clinicopathological variables was assessed through univariate and multivariate Cox regression analyses. A prognostic nomogram was then developed and validated based upon concordance (C)-index values, area under curve (AUC) and calibration curves. Internal validation was conducted through bootstrap resampling, while the clinical utility of this model was assessed via a decision curve analysis (DCA) approach.

Results: Nephrotic-range 24-hour proteinuria, late-stage chronic kidney disease (CKD stage 3-4), glomerular classification III-IV, and an IFTA score 2-3 were all identified as independent predictors of poor renal outcomes in DN patients and were incorporated into our final nomogram. Calibration curves revealed good agreement between predicted and actual 3- and 5-year renal survival in DN patients, while the C-index value for this nomogram was 0.845 (95% CI 0.826–0.864) and the 3- and 5-Year AUC were 0.933 (95%CI 0.898-0.968), 0.923 (95%CI 0.886-0.960). DCA analysis revealed that our nomogram was superior to models based solely upon clinical indicators.

Conclusions: A predictive nomogram incorporating clinical and pathological indicators was developed and validated for the prediction of renal survival outcomes in patients with biopsy-proven DN. This tool will be of value to clinicians, as it can serve as an easy-to-use and reliable tool for physicians to guide patient management based on individualized risk in order to improve patient outcomes.

PO0778

Histological Diabetic Nephropathy in Autopsied Diabetic Cases with Normoalbuminuria from a Japanese Community-Based Study: The Hisayama Study

Takaya Sasaki,[1,2] Kaneyasu Nakagawa,[3] Jun Hata,[1,3] Yoichiro Hirakawa,[1,3] Mao Shibata,[1,4] Toshiaki Nakano,[3] Nobuo Tsuboi,[2] Yoshinao Oda,[5] Takanari Kitazono,[1,6] Takashi Yokoo,[2] Toshiharu Ninomiya.[1,6] *[1]Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [3]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [4]Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [5]Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [6]Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.*

Background: Albuminuria is a clinical indicator of diabetic nephropathy (DN). However, it is controversial whether pathological DN lesions are present in diabetic individuals with normal albuminuria. We investigated the association between albuminuria levels and the frequency of DN lesions in autopsied diabetic cases from a Japanese community.

Methods: Autopsied specimens obtained from deceased people in the town of Hisayama from 2002 to 2017 were used in the present study. During this period, 131 deceased individuals with diabetes underwent autopsy examinations. A total of 106 autopsied cases with diabetes mellitus (mean age 76 years, 43.4% male) who died within 6 years since the last health examination were included in the study. Urinary albumin-creatinine ratio (UACR) levels were divided into three groups: <30.0, 30.0–299.9, and ≥300.0 mg/g. The kidney specimens were evaluated with light microscopy, and were categorized into class 0–I, IIa, IIb, and III glomerular DN lesions according to the Renal Pathology Society's criteria. A Cochrane-Armitage test was used to examine the association between the UACR levels and the presence of class IIa or higher glomerular DN lesions.

Results: In the overall cases, the frequency of class IIa or higher glomerular DN lesions was 63.2% (IIa, 36.8%; IIb, 3.8%; and III, 22.6%). Its frequencies increased significantly with higher UACR levels (P for trend = 0.02, **Figure**). Even in individuals with UACR of <30 mg/g, the frequency of class IIa or higher glomerular DN lesions was 51.2%.

Conclusions: The present study showed a positive association of the UACR levels with the presence of class IIa or higher glomerular DN lesions, which were also frequently found even in the normoalbuminuric range, among autopsied diabetic cases from a Japanese community.

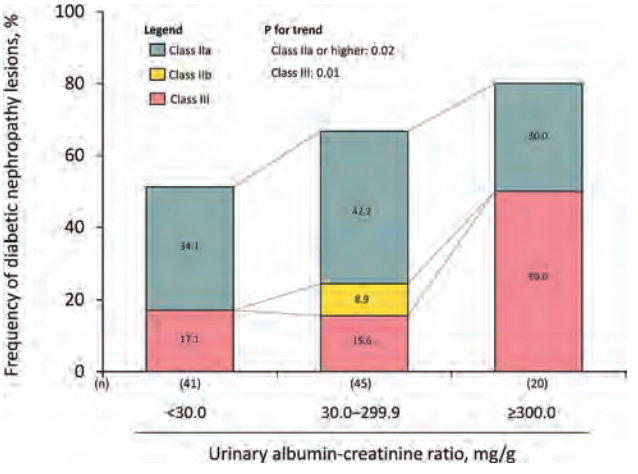


Figure.

PO0779

Clinical and Pathological Significance of Orai1 Expression in Human Diabetic Nephropathy

Yoojin Kwak, Hanwul Shin, Jun Young Lee, Jae seok Kim, Jae Won Yang, Seung-Kuy Cha, Minseob Eom. *Yonsei University Wonju College of Medicine, Wonju, Republic of Korea.*

Background: Diabetic nephropathy (DN) causes about half of ESRD. The attempts for targeted therapy for DN have been lacking to date. Store-operated Ca entry (SOCE) is a primary Ca influx mechanism in non-excitable cells that is mediated by pore-forming subunit Orai1. Currently, it has been argued whether Orai1 overexpression protects against renal pathologies. Here, we investigate the significance of Orai1 expression in human DN.

Methods: Ninety-three DN patients from 2009 to 2019 were enrolled. The paraffin blocks were used to perform immunohistochemical staining for Orai1 (figure). Renal Pathology Society DN classification (RPS) and clinical parameters were compared with Orai1 expression. The results were compared by dividing them into a glomerulus (G) and tubulo-interstitium (T-I).

Results: In T-I, Orai1 was overexpressed in DN, and Orai1 expression was significantly correlated with the higher RPS and interstitial fibrosis & tubular atrophy score ($p < 0.001$). While Orai1 expression was correlated with serum Cr and CKD stages, eGFR and HbA1c were inversely associated with Orai1 expression ($p < 0.001$). By logistic regression, Orai1 expression was significantly correlated with the higher RPS and the advanced CKD stage. Moreover, Orai1 expression was strongly associated with the advanced CKD stage by the multivariate logistic regression ($p = 0.002$) (table). The result of G was similar to that of T-I.

Conclusions: It is suggested that Orai1 is a valuable biomarker for predicting the progression and prognosis of DN, that provides new perspectives on therapeutic targets for DN.

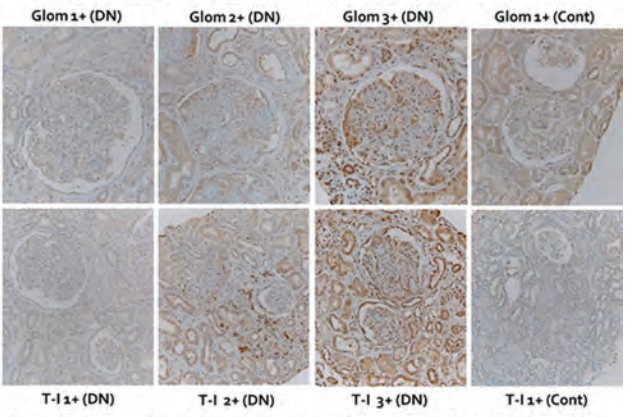
Funding: Government Support - Non-U.S.

The correlation between Orai-1 expression and CKD stage in DN (Multivariate logistic regression)

Adjustments	Parameters	Odds ratio	95% Confidence interval		p-value
			Lower limit	Upper limit	
Age, Sex, BMI, HbA1c, DM duration, and HTN	Orai-1 (G)	11.208	2.590	48.497	0.001
	Orai-1 (T-I)	13.876	2.694	71.476	0.002

BMI, body mass index; HTN, hypertension; G, glomerulus; T-I, tubulo-interstitium

Figure. The result of immunohistochemical stain for Orai-1 in DN



Glom, glomerulus; DN, diabetic nephropathy; Cont, control; T-I, tubulo-interstitium

PO0780

Prevalence and Risk Factors Associated with Diabetic Nephropathy in Patients with Diabetes Undergoing Nephrectomy

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Background: Diabetic kidney disease (DKD) affects about 40% of patients with diabetes and is the most common cause of end-stage renal disease in the US. The prevalence of morphologic features of DKD, known as diabetic nephropathy (DN), is likely underestimated since kidney biopsies are performed when other diseases are clinically suspected. The availability of non-neoplastic kidney tissue from nephrectomies offers us the opportunity to evaluate the prevalence and risk factors associated with morphologic evidence of DKD.

Methods: A total of 198 nephrectomies of diabetic patients, where the status of the non-neoplastic kidney tissue was reported, were included. Clinical, demographic, and histological data were collected retrospectively. Logistic regression models were used to examine the association between clinical and demographic characteristics as primary exposure and morphologic evidence of DKD as the dependent variable.

Results: The mean age across all diabetic patients undergoing nephrectomy was 64±11 years, 59% were male, 9% African-American (AA), and 39% Hispanics. Clinical DKD was found in 47% of patients, 60% had hypertension, 66% had a GFR ≥ 60mL/min/1.73m^2 and 62% had no proteinuria. Morphologic features of DKD were observed in 56 (28%) patients. In multivariable-adjusted logistic regression analyses, the presence of morphologic features of DKD was significantly associated with older age (odds ratio [OR] per 10-year increase, 1.64 [95% confidence interval (CI), 1.08-2.48]), proteinuria (OR, 2.27 [95% CI, 0.99-5.17]), and neuropathy (OR, 4.92 [95% CI, 1.76-13.75]). The presence of morphologic features of DKD was associated with retinopathy only in univariate analysis (OR, 8.47 [95% CI, 1.65-43.47]). No association ((p>0.05) with AA race, hypertension, clinical DKD, and eGFR was noted.

Conclusions: Morphologic features of DKD are highly prevalent in patients undergoing nephrectomy. Older age, proteinuria, and neuropathy were independently associated with significantly greater odds of morphologic evidence of DKD. Future studies should evaluate the prevalence of non-diabetic renal disease in patients with diabetes undergoing nephrectomy.

PO0781

Biopsy Results in a Diverse Diabetic Cohort

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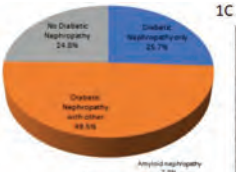
Background: Diabetes is the most common cause of kidney failure in the US. However, many of these patients never receive a biopsy, and therefore diabetic nephropathy (DN) is presumed based on clinical features. Therefore, we sought to determine the prevalence and outcomes of non-diabetic renal disease (NDRD) in a diverse cohort of diabetic patients referred for biopsy.

Methods: Patients were included if they had a biopsy performed at The Mount Sinai Hospital from 2018-2019, and if they had a hemoglobin A1c > 6.5% or diabetes was mentioned in their past medical history. Charts were excluded if no data existed after biopsy, dialysis-dependence occurred prior to biopsy, and if insufficient amounts of glomeruli were observed. Baseline characteristics including age, gender, race/ethnicity, blood pressure, creatinine, and urine protein/creatinine ratio (UPCR) were recorded. Outcomes measured were 1 year UPCR, 1 year creatinine, need for dialysis, and death.

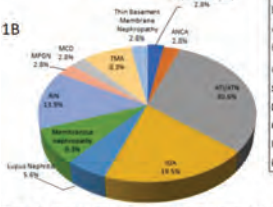
Results: In total, 81 charts were included for analysis, of which 21 biopsies had DN alone, 26 had DN + NDRD, and 27 had NDRD alone (Figure 1A). In patients with NDRD, a broad range of pathology was seen (Figure 1B). There were no significant differences in characteristics of patients with DN alone and any NDRD (Figure 1C). There was a non-statistically significant difference in median one year creatinine and one year UPCR between patients with DN and NDRD (1.67 vs. 3.07 (p=0.1) and 2490 vs. 3540 (p=0.2)). Additionally, there was a non-statistically significant difference in death and dialysis treatment between DN and NDRD patients, 4 (14%) vs. 3 (6%) (p=0.2) and 5 patients (18%) vs. 19 (36%) (p=0.09), respectively. DN had lower odds of requiring dialysis at 1 year from biopsy OR 0.39 (95% CI 0.13-1.19).

Conclusions: In our selected diverse population of diabetic patients with kidney biopsies, the majority of patients had NDRD on pathology. While not statistically significant, DN patients had lower follow up creatinine and UPCR, and less patients on dialysis at 1 year.

1A



1B



1C

Characteristics of patients with DN alone vs any NDRD at time of biopsy			
	DN alone (n=28)	Any NDRD (n=53)	p-value
Sex (%)			
Female	11 (39%)	17 (32%)	0.5164
Age (median(IQR))	61.5 (56-72)	61 (53-65)	0.1
Race/Ethnicity (%)			
White	5 (18%)	5 (9%)	0.3026
Black	7 (25%)	19 (36%)	0.3199
Asian	1 (4%)	3 (6%)	1
Hispanic/Latino	4 (14%)	18 (34%)	0.052
Other/Unknown	11 (39%)	8 (15%)	
SBP (median)	129	140	0.7
DBP (median)	72.5	72	0.8
Creatinine (median)	1.92	2.51	0.8
UPCR (median) (mg/g)	2870.5	3456	0.09
Hemoglobin A1C (median)	6.8	6.8	0.3

Figure 1: Figure 1A breaks down overall prevalence of DN alone, DN with NDRD, and NDRD alone, Figure 1B breaks down the different NDRD pathologies seen on biopsies, Figure 1C displays baseline characteristics of patient with DN alone vs any NDRD at time of biopsy

PO0782

Identification of Kidney Disease Diagnoses in Patients with Diabetes by Biopsies and Electronic Health Records

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Background: Diabetic kidney disease (DKD) refers to chronic kidney disease in diabetes, but not a specific diagnosis. This report describes a patient cohort with electronic health record (EHR) data linked to manual data abstraction for kidney histopathology.

Methods: Patients were selected from the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) registry which contains curated EHR clinical and administrative data from two large healthcare systems. Inclusion criteria consisted of a native kidney biopsy, diagnoses of diabetes and CKD but not on dialysis. Clinical investigators manually abstracted health history, laboratory data, and histological features from kidney biopsy reports. DKD was classified as: diabetic nephropathy (DN), DN mixed with nondiabetic lesions (Mixed), and nondiabetic lesions only (Other).

Results: In 523 patients with diabetes who underwent kidney biopsy in the years 2015-2017 (Table), diagnostic frequencies were DN 39.8% (n=208), Mixed 36.9% (n=193), Other 23.3% (n=122). Patients with DN were younger, displayed higher albuminuria, increased nodular glomerulosclerosis and arteriolar hyalinosis than the Mixed group. Those with DN more commonly had diabetes duration >10 years and higher albuminuria compared to the Other group, while lesions characteristic of DN (mesangial expansion, nodular glomerulosclerosis, GBM thickening, arteriolar hyalinosis, tubular basement membrane thickening) were uncommon in Other.

Conclusions: Higher levels of albuminuria, nodular glomerulosclerosis and arteriolar hyalinosis were distinctly more common in DN compared to Mixed and Other groups, and nodular glomerulosclerosis was rarely observed in the Other group. Future work will use machine learning models of the EHR data to predict DN and select precision therapies.

Funding: Commercial Support - Goldfinch Bio

Table. Clinical and histological characteristics of the DKD cohort (N=523)

Diagnosis	DN	Mixed	Other	P-value[a] DN vs Mixed	P-value[a] DN vs Other
Number (%)	208 (39.8)	193 (36.9)	122 (23.3)	-	-
Age (years, mean ± SD)	57.8 (± 11.7)	61.9 (± 11.9)	60.7 (± 13.6)	**0.022**[a]	1[a]
Female (%)	46.2	44.6	47.5	1[b]	1[b]
Non-white race or LatinX (%)	45.2	46.1	36.9	1[b]	1[b]
Diabetes duration >10 years (%)	55.8	46.6	26.2	1[b]	**<0.001**[b]
eGFR CKD-EPI mL/min/1.73 m^2 (median, IQR)	30.3 (20.4 – 46.1)	25.5 (18.1 – 41.6)	34.2 (19.4 – 67.7)	0.88[c]	0.37[c]
UACR (mg/g, median, IQR)	2124.0 (551.5 – 4401.0)	2011.0 (535.0 – 3402.5)	342.5 (40.0 – 2241.2)	**<0.001**[c]	**<0.001**[c]
UPCR (g/g, median, IQR)	5.3 (2.2 – 8.7)	4.0 (1.5 – 6.8)	2.1 (0.7 – 5.7)	1[c]	1[c]
Mesangial expansion (%)	99.0	95.9	42.6	1[b]	**<0.001**[b]
Nodular glomerulosclerosis (%)	87.0	50.8	6.6	**<0.001**[b]	**<0.001**[b]
GBM thickening (%)	91.3	86.5	20.5	1[b]	**<0.001**[b]
Arteriolar hyalinosis (%)	94.7	81.9	37.7	**0.0042**[b]	**<0.001**[b]
TBM thickening (%)	46.6	43.5	4.1	1[b]	**<0.001**[b]
Interstitial inflammation (%)	88.9	87.0	68.9	1[b]	**<0.001**[b]
Interstitial fibrosis (%)	98.1	97.4	80.3	1[b]	**<0.001**[b]

[a]Student's t-test, [b]Chi-squared/Fisher's exact test, [c]Mann-Whitney-U test, [d]Bonferroni corrected p-values,
DKD – diabetic kidney disease, SD – standard deviation, IQR – interquartile range, eGFR CKD-EPI - estimated glomerular filtration rate (GFR) from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, UACR- urinary albumin-to-creatinine ratio, UPCR - urinary protein-to-creatinine ratio, GBM - glomerular basement membrane, TBM - tubular basement membrane

PO0783

Triglyceride-Glucose Index Is Associated with Renal Dysfunction in Stage 2 CKD Patients

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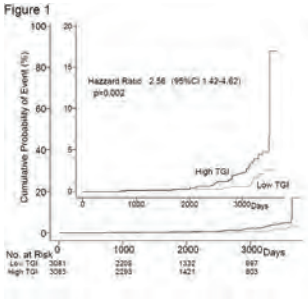
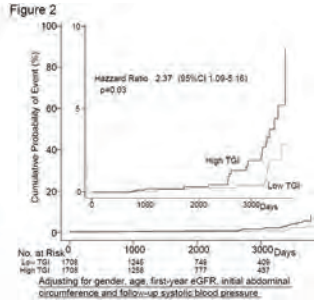
Background: SGLT2i, nephroprotective agent, are known to improve hyperinsulinemia and hyperlipidemia, especially triglyceride metabolism. However, their effects on renal function have not been clearly elucidated. Triglyceride-Glucose Index (TGI) has gathered attention as a new marker of metabolic syndrome. Since it reflects both lipotoxicity and glucotoxicity, we investigated the relationship between TGI and renal function.

Methods: In this single-institutional observational study, we screened subjects whose blood (triglyceride, creatinine, and blood glucose) and body profile (abdominal circumference, height, and weight) assessment on the same day at annual health examinations between 2008 to 2018. Among these individuals, those with an estimated glomerular filtration rate (eGFR) value of 60–90 ml/min/1.73 m^2, which indicates stage 2 chronic kidney disease (CKD) in the first year, were included in the study. The subjects were divided into two groups based on high and low mean TGI values during the course of the study. The changes in their renal function were compared. We evaluated both groups by time-to-event analysis in terms of a 30% eGFR decline.

Results: Of the 19,940 individuals (73,084 tests) who were assessed initially, only 8,203 individuals had health records beyond one year. Among these, we examined 6,164 patients with stage 2 CKD (mean age: 49.2 ± 11.1 years, observation period: 1,906.1 ± 1,084.3 days, mean eGFR 75.5 ± 7.8 ml/min/1.73 m2). Univariate analysis by the Lon-rank test showed that the renal function as significantly more deteriorated among individuals with a high TGI (P = 0.001). The difference remained significant after adjusting for gender, age, first-year eGFR, abdominal circumference, and follow-up systolic blood pressure using the propensity score matching method (p = 0.02).

Conclusions: In conclusion, among patients with mild renal dysfunction (stage 2 CKD), High TGI was associated with decreased renal function, and this did not change after adjusting for background factors.





PO0784

Effect of Dapagliflozin on Soluble Urokinase-Type Plasminogen Activator Receptor in Type 2 Diabetes with Albuminuria

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Background: Given the documented protective effect of the sodium-glucose co-transporter 2 inhibitor, dapagliflozin on chronic kidney disease and the potency of soluble urokinase-type plasminogen activator receptor (suPAR) as a risk marker of the same, we investigated the effect of treatment with dapagliflozin on plasma suPAR in individuals with type 2 diabetes and albuminuria. Secondarily, we examined the association between the level of suPAR and the established early urinary proteomic classifier CKD273.

Methods: Post-hoc analysis of a double-blind, cross-over trial where persons with type 2 diabetes and albuminuria received treatment with dapagliflozin (10 mg/d) or placebo for 12 weeks in random order. The original primary outcome was change in the urinary proteomic classifier CKD273. suPAR level was assessed in plasma samples collected at all 3 visits. Effect of dapagliflozin on suPAR level was determined using unpaired t-test for comparison between baseline and end-of-treatment for the dapagliflozin and the placebo treatment period, and paired t-test for comparison between the two treatment periods. A secondary analysis investigated the association between baseline suPAR and CKD273 using Pearson correlation.

Results: Of the 36 persons who completed study, 11% were female, mean±SD age was 64±8 years, HbA_{1c} 73±15 mmol/mol (8.9±1.4%), eGFR 84±19 ml/min/1.73m^2, and median (IQR) urinary albumin creatinine ratio was 154 mg/g (94-329). Median (IQR) suPAR at baseline was 3.44 ng/ml (2.49;4.35) and CKD273 score was 0.59 (0.18;0.77). suPAR change after 12 weeks dapagliflozin was -0.13 ng/ml (95% CI -0.72;0.36, p=0.50) and placebo -0.19 ng/ml (-0.71;0.33, p=0.46), mean difference 0.06 ng/ml (95% CI -0.15;0.27, p=0.57). Pearson correlation R between baseline suPAR level and CKD273 score was 0.17 (95% CI -0.17;0.48, p=0.32).

Conclusions: This post-hoc analysis could not demonstrate an effect of 12 weeks of treatment with dapagliflozin on plasma suPAR level in individuals with type 2 diabetes and albuminuria. In addition, plasma suPAR was not correlated to the urinary proteomic CKD273 classifier.

PO0785

Predictive Model of Non-Diabetic Nephropathy in Patients Affected by Diabetes

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Background: Between 50-60% of diabetics with renal involvement have non-diabetic nephropathy (NDN). Renal biopsy is crucial for renal diagnosis that includes diabetic nephropathy (DN), NND, or mixed form. The objective of the current study is to provide a tool in the daily clinical practice through a predictive model of NND that is clue for the indication of renal biopsy.

Methods: Observational, retrospective and multicenter study of the pathological results of kidney biopsies in patients with diabetes from 2002 to 2014. A logistic regression analysis and the probability of presenting NND was calculated using a punctuation score.

Results: The cohort of 832 patients includes 621 men (74.6%), median age 61.7±12.8 years, creatinine 2.8±2.2mg/dl and proteinuria 2.7 (1.2-5.4)gr/24h. Time of evolution of diabetes was 10.8±8.6 years. 26.6%(n=221) of patients presented diabetic retinopathy, 18.8% (n=156) peripheral vasculopathy and 17.7% (n=147) ischemic heart disease. 288 patients (34.6%) presented microhematuria. 39.5% (n=329) presented DN, 49.6% (n=413) NDN and 10.8% (n=90) mixed forms. In the multivariate analysis, age (OR:1.03;1.01-1.04; p=0.0002), absence of microhematuria (OR:0.6,;0.4-0.86;p=0.005), absence of diabetic retinopathy (OR:3.97;2.7-5.82;p<0.0001) and absence of peripheral vasculopathy (OR:1.61, 1.03-2.52, p=0.038) were identified as ndependent risk factors for NDN. A ROC curve with an area under the curve of 0.724 was obtained. A predictive model obtaining a score (see figure) for each variable and finally a NDN prediction score was performed. In our new score, the number increases as increased the probability of NDN.

Conclusions: In our study, around 66% of biopsied patients with diabetes presented NDN. Microhematuria, absence of diabetic retinopathy, absence of peripheral vascular disease, and older age were identified as independent risk factors for NDN. We obtained a Score that increases as increased the probability of NDN. This could be in a next future a useful tool for the clinical indication of renal biopsy in patients with diabetes and kidney disease.

PO0786

Metabolic Acidosis and the Risk of Progression to Diabetes in Patients with Prediabetes and CKD

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Background: Diabetes and metabolic acidosis are known risk factors for progression of CKD. Treatment of metabolic acidosis has been shown to reduce insulin resistance among patients with CKD and diabetes, but whether metabolic acidosis predicts progression from prediabetes to diabetes among patients with CKD is unknown.

Methods: Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried for patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate of 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) with ≥1 year prior data and ≥2 years of post-index data or death within 2 years. Patients with prediabetes (HbA1c 5.7 to <6.5%, fasting plasma glucose 100 to <126 mg/dL, or 75 g oral glucose challenge 140–199 mg/dL) were followed for up to 11.5 years for incident diabetes identified through lab values, diagnosis, or prescriptions. Cox proportional hazards models were used to evaluate metabolic acidosis as a predictor of incident diabetes, adjusting for age, sex, race, low-income status, geo-coded education level, and baseline BMI, eGFR, metabolic syndrome and polycystic ovary syndrome. Death was also evaluated as a competing risk.

Results: 7156/136,067 patients had evidence of prediabetes during the pre-index year. 47% (136/292) of patients with baseline metabolic acidosis and 46% (3143/6864) with normal serum bicarbonate developed diabetes during the outcome period (P=0.8).

Patients with metabolic acidosis developed diabetes sooner on average compared with normal serum bicarbonate (544 vs 643 days); however, baseline metabolic acidosis was not a significant predictor of time to incident diabetes in adjusted analyses (HR 1.20, 95% CI:0.96-1.49). Metabolic syndrome (HR 1.26, 95% CI:1.08 1.46), Black race (HR 1.28 [1.11-1.47]), male sex (HR 1.11[1.01-1.21]), and higher BMI (HR 1.03 [1.02-1.03]) were associated with a higher risk of progression to diabetes. Higher baseline eGFR was associated with lower risk of progression to diabetes (HR 0.993 [0.988 0.997]).

Conclusions: In this longitudinal analysis of non-dialysis CKD stages 3-5 patients with prediabetes, metabolic acidosis was not associated with progression to diabetes.

Funding: Commercial Support - Tricida, Inc.

PO0787

The Gut Microbiome-Derived Phenyl Sulfate Is a Novel Predictive Marker and Cause of Albuminuria in Diabetic Kidney Disease

Koichi Kikuchi, Takaaki Abe. *Tohoku Daigaku, Sendai, Japan.*

Background: Diabetic kidney disease (DKD) is one of the major causes of end-stage renal diseases (ESRD), and it is important to prevent from onset or progression of DKD. However, it is difficult to identify type 2 diabetes patients who are at risk of developing progressive DKD based only on measurements of glomerular filtration rate and albuminuria. Therefore, specific biomarkers are needed for a breakthrough in the good management of DKD.

Methods: Among 777 patinets in a multi-center clinical study in diabetic nephropathy cohort (U-CARE), 362 patients with full data were selected. The plasma PS, PCS, IS and TMAO level were measured by LCMS/MS. The correlation between these level and various factors were calculated using the Spearman Rank-Order Correlation. Multiple regression analysis and a logistic regression analysis were used to identify the factors associated with PS, IS, PCS, TMAO, suPAR, urine acid or the development of 2-year ACR deterioration, respectively.

Results: As we previously reported (Kikuchi et al. Nat. Commun. 2019, ASN 2019), serum PS level significantly related with the basal albuminuria level in U-CARE study. In addition, logistic regression analysis showed among known ACR predictive factors, PS was the only factor which significantly related 2-year progression of albuminuria especially in patients with microalbuminuria. These data suggested that PS may have a potential as important predictive marker of DKD. Next, we examined the relationship between albuminuria or renal function and IS, PCS, TMAO which were well-known as gut derived uremic solutes as well as PS. In addition, we examined the relationship between albuminuria or renal function and suPAR, uric acid. As a result, IS, PCS, suPAR were inversely correlated with eGFR. PS, IS, suPAR and uric acid were correlated with albuminuria. Among them, PS and uric acid were the factor which significantly correlated with the 2-year albumin-creatinine ratio (ACR) deterioration. Furthermore, we clarified that serum PS concentration level was high even in same patients who are preserved renal function (eGFR>60 ml/min/1.73cm2), and high PS concentration patients were significantly increased 2-year ACR deterioration rate.

Conclusions: PS is predictive marker of albuminuria in the patients with microalbuminuria in DKD patients.

PO0788

Urinary Biomarkers for Prediction of Estimated GFR Decline in Patients with Type 2 Diabetes and Preserved Kidney Function

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Background: We have previously performed a urinary proteomic analysis of patients with diabetic kidney disease (DKD) and identified the differentially excreted proteins in the patients with DKD (Diabetes Res Clin Pract. 2019; 147:37-46). In this study, we evaluated the association of the differentially excreted proteins with an annual decline in estimated glomerular filtration (eGFR) in patients with type 2 diabetes (T2D) and preserved kidney function.

Methods: In a prospective, observational cohort study, 392 Japanese patients with T2D and baseline eGFR ≥ 60 ml/min/1.73m^2 were followed over one year (mean period 5.5 years; IQR 3.9 – 7.3). Linear regression was used to estimate participants' annual decline rate in eGFR over time. We defined subjects with an annual eGFR decline ≥ 5% per year as rapid decliner and the eGFR decline < 5% as slow decliner. Of the 392 participants, 218 patients were randomly selected and baseline levels of 75 urinary proteins were measured by multiple reaction monitoring (MRM) analysis.

Results: The study population had a median age of 59.0 years (IQR, 56.3 – 58.5) and 78.0% were male. The median duration of diabetes was 10.0 years (IQR, 9.8 – 12.0). During the follow-up period, 44 patients had a rapid decline in eGFR. Median eGFR decline was -6.51% (IQR, -8.54 – -6.47) and -1.29% (IQR, -1.43 – -0.65) per year in rapid decliner and slow decliner, respectively. Compared with slow decliner, rapid decliner had higher HbA1c level and lower levels of HDL-cholesterol (HDL-c), Hb, and Hct at baseline, however, their differences were not significant. In the MRM analysis, we found that 11 urinary proteins were differentially excreted in rapid decliner compared to the urinary proteins of slow decliner ($P < 0.05$). Multivariable logistic regression models revealed that 4 urinary proteins and Hb were independent predictors of annual decline in eGFR adjusted by age, HbA1c, HDL-c, eGFR, and urinary albumin-to-creatinine ratio ($P < 0.005$). When combining the 4 urinary protein levels, an area under the ROC curve for the detection of rapid decliner was 0.781 (95% CI 0.709 – 0.852).

Conclusions: Our findings highlight the important effect of 4 urinary proteins as independent predictors of a rapid decline in eGFR in patients with T2D and preserved kidney function.

Funding: Government Support - Non-U.S.

PO0789

Comorbidity Burden Among Patients with CKD and Type 2 Diabetes in a US Commercially Insured/Medicare Advantage Population

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Background: While it is well-established that T2D is the leading cause of CKD, contemporary data describing the burden of CKD among patients with both T2D and CKD is scarce. We described 3 mutually exclusive patient cohorts: T2D only, CKD with T2D, CKD without T2D in the real-world setting.

Methods: This cross-sectional study utilized 3 calendar years (2017-2019) of administrative claims data from the HealthCore Integrated Research Database. Adults diagnosed with CKD with and without T2D (CKD in T2D and CKD, respectively) and T2D without CKD (T2D) in 2018 were identified. Index date was defined as the first claim with a diagnosis for either CKD or T2D in 2018. Eligible patients were required to have continuous health plan enrollment ≥1 year pre- and post-index. Clinical characteristics, comorbidity burden (as measured by the Quan- Charlson Comorbidity Index (QCI)) and hospitalizations were analyzed descriptively.

Results: Among 203,576 T2D, 22,689 CKD and 38,587 CKD in T2D patients, mean age was 59 (SD: 12), 66 (SD: 16) and 67 (SD: 13) years; 47%, 51%, and 47% were female, respectively. Both pre- and post-index, the CKD in T2D group had the highest proportion of comorbid conditions followed by the CKD and T2D group and overall comorbidity burden was elevated in a similar manner (QCI ≥3 in 6%, 19% and 31%, respectively). Hypertension (79-94%), dyslipidemia (68-87%) and obesity (28-44%) were the most prevalent comorbidities. Atherosclerotic cardiovascular disease (e.g. – myocardial infarction: 6.6%, 4.2%, 2.5%; ischemic stroke/TIA: 7.9%, 6.5%, 2.9%, respectively) and heart failure (19.1%, 13.4%, 4.5%, respectively) were most prevalent in the CKD in T2D group, followed by the CKD and T2D groups. During the year post-index, the proportion of all-cause hospitalization was 11% (T2D), 22% (CKD) and 28% (CKD in T2D).

Conclusions: CKD in T2D was associated with substantial overall and cardiovascular comorbidity burden in this contemporary real-world cohort, followed by CKD and then by T2D patients. Treatment strategies for CKD in T2D should consider the patient's individual comorbidity burden to reduce risk of cardiovascular and overall morbidity and mortality.

Funding: Commercial Support - Bayer US

PO0790

The Usefulness of Calcium/Magnesium Ratio in the Risk Stratification of Early Onset of Renal Replacement Therapy

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Background: Recently, a growing number of studies have reported a close relationship between high serum calcium (Ca) and low serum magnesium (Mg) with vascular calcification. Endothelial dysfunction and vascular inflammation seem plausible risk factors for enhanced progression of kidney disease. The aim of this study is to evaluate the role of calcium/magnesium ratio as risk factor in CKD progression.

Methods: Observational, prospective study involving 693 patients (female=371) with stage 4/5 CKD. Patients were divided into two groups, according to the development of ESRD: G1 (n=541), who did not start renal replacement therapy (RRT) and G2 (n=152), who had started RRT. Several laboratory parameters were measured. Baseline characteristics were recorded and compared. Multivariate Cox regression analysis was used to identify independent factors associated with RRT initiation. A modified Poisson regression with robust error variance was used to estimate the cumulative relative risk for RRT initiation.

Results: The mean age was 70.09±12.51 years and eGFR was 19.91±8.11 mL/min. G2 had significantly lower serum levels of Hb (11.75vs10.95 g/dl,p= 0.000), Ca (9.34vs8.95 mg/dl,p=0.000), Mg (1.92vs1.40 mg/dl,p= 0.0001), albumin (4.00vs3.88 g/dl, p= 0.03) and cholesterol (183.17vs172.39 mg/dl,p=0.01), and higher serum levels of phosphorus (3.88vs4.69 mg/dl,p=0.0001), Ca/Mg ratio (5.73vs7.56,p= 0.0001) and PTH (209.71vs338.84 pg/ml,p= 0.0001). In univariate Cox regression analysis, age, Hb, eGFR, Ca, Mg, phosphorus, Ca/Mg ratio and PTH correlated with onset of RRT, which were further tested using a multivariate COX regression. The results showed a relationship between high levels of phosphorus (HRa=1.638,p=0.001) and Ca/Mg ratio (HRa=1.292;p=0.002), and low levels of Mg (HRa=0.761,p=0.005) and eGFR (HRa=0.934;p=0.0001) were independent risk factors to start RRT. Poisson regression showed that high Ca/Mg ratios (aPR=1.986; 95% CI 1.026-3.051;p=0.002), high phosphorus levels (aPR=1.607;95% CI 1.324-1.950;p<0.0001) and low levels eGFR (aPR=0.927; 95% CI 0.891-0.964;p<0.0001) were associated with a cumulative risk for initiation of RRT.

Conclusions: Our results suggest that the calcium/magnesium ratio is an independent predictive factor for the initiation of RRT. Further studies are required to validate the use of this novel marker as predictor of CKD progression.

PO0791

Disparities in Quality of Care for Dialysis Patients

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Background: An understanding of disparities in quality of care for dialysis patients may inform priorities for quality improvement and approaches for achieving greater health equity. It is also not known whether disparities have been improving or worsening or whether they vary geographically.

Methods: We used Medicare claims and CROWNWeb data to evaluate disparities based on race, ethnicity, dual eligibility, and rural-urban location. Using criteria developed by AHRQ, we identified disparities in 2019 based on a statistically significant regression-adjusted difference in a quality indicator and at least a 10% relative difference between groups. We estimated generalized linear models with clustering for patients and adjustments for age, sex, cause of ESRD, duration of ESRD, and comorbid conditions at ESRD incidence. We examined national trends in disparities from 2015-20 and variation in disparities by ESRD Network in 2019.

Results: There is evidence of disparities in U.S. dialysis patients for a range of quality indicators in 2019 (Table), some of which relate to measures in the ESRD Quality Incentive Program. Disparities involving racial minorities and dual eligible beneficiaries accounted for 13 of 16 measured disparities nationally. These disparities largely persisted over time and were found in most ESRD Networks.

Conclusions: There are ongoing racial, socioeconomic, and rural-urban disparities among dialysis patients in a range of quality indicators. There may be valuable opportunities for quality initiatives in ESRD to improve health equity.

Funding: Other U.S. Government Support

Quality Indicator	Comparison	Disparity Group	Reference Group	Difference (disparity group vs. reference group)	Adjusted difference (all p<0.001)	Relative difference, as % of reference group
AV Fistula (% of patients)	Black vs white	57.6%	67.0%	-9.4	-8.6	-12.8%
Long-term Catheter Use (% of patients)	Dual vs not dual	11.6%	10.0%	1.6	1.3	13.0%
All-Cause Hospital Admissions (per 100 patient-months)	Dual vs not dual	16.1	12.9	3.2	2.1	16.0%
30-day Hospital Readmissions (% of index discharges)	Dual vs not dual	30.6%	25.5%	5.2	3.4	13.4%
Dialysis Access-related Infection Hospital Admissions (per 100 patient-months)	Dual vs not dual	0.8	0.6	0.2	0.1	17.5%
Outpatient Emergency Department (OP ED) Visits (per 100 patient-months)	Dual vs not dual	18.6	12.0	6.6	4.4	36.9%
OP ED Visits (per 100 patient-months)	Black vs white	17.0	14.9	2.1	1.5	10.0%
OP ED Visits (per 100 patient-months)	Rural vs urban	20.9	14.7	6.2	5.4	36.6%
Hemoglobin <10 g/dL (% of patients)	Black vs white	26.5%	23.6%	2.9	3.2	13.5%
Part D Opioid Long Term Use (% of patients)	Dual vs not dual	11.1%	5.9%	5.2	1.8	31.1%
Part D Opioid Long Term Use (% of patients)	Rural vs urban	11.6%	8.7%	2.8	1.8	20.8%
Mortality (per 100 patient-months)	Rural vs urban	1.7	1.4	0.3	0.2	12.0%
Hospice Use at Death (% of patients)	Asian vs white	19.0%	31.6%	-12.6	-13.9	-43.9%
Hospice Use at Death (% of patients)	Amer. Indian/Alaska Native vs white	19.6%	31.6%	-12.0	-7.1	-22.3%
Hospice Use at Death (% of patients)	Black vs white	20.2%	31.6%	-11.4	-8.3	-26.3%
Hospice Use at Death (% of patients)	Pacific Isl. vs white	17.0%	31.6%	-14.6	-11.4	-35.9%

PO0792

Risk Factors and Outcomes of Gout in Dialysis Patients: A Cohort Study of the United States Renal Data System (USRDS)

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Background: Limited research exists regarding gout among dialysis-dependent end-stage renal disease patients. This study aimed to evaluate the epidemiology, risk factors, and outcomes of dialysis patients with gout.

Methods: Using 2017 USRDS data, this study identified dialysis patients ≥18 years of age with Medicare as the primary payer. Baseline characteristics and comorbid conditions for dialysis-dependent patients with gout were assessed at dialysis initiation as well as 3-months preceding their gout diagnosis and compared with non-gout dialysis patients. All-cause hospitalization and mortality risk were also estimated and compared between gout and non-gout patients.

Results: Of 275,651 dialysis patients in 2017, 41,312 (15%) had ≥1 gout claims following initiation of chronic outpatient dialysis. More than 1/3 of gout diagnoses were made by internal and family medicine physicians. Compared to non-gout patients, gout patients were more likely to be older (mean 64.5 vs 56.8 y), male (62% vs 54%), of Asian race (6.2% vs 3.7%), and obese (31.4 vs 30.2 kg/m^2). Gout patients were also found to be more likely to undergo hemodialysis via central venous catheter (15% vs 13%). Gout patients had a higher comorbidity prevalence of diabetes (67% vs 62%), hypertension (93% vs 74%), and cardiovascular conditions (heart failure [49% vs. 30%], ischemic heart disease [49% vs 30%], peripheral vascular disease [32% vs 22%], stroke [12% vs 8%], acute myocardial infarction [7% vs 3%] and angina [4% vs 2%]). Adjusted regression analysis showed that older age (OR=4.23 for ≥65 vs <65 y, 95% CI 4.03-4.43), previous transplant (OR=2.37, 95% CI 2.24-2.50), and comorbid hypertension (OR=2.71, 95% CI 2.59-2.83) are the 3 most significant factors associated with gout diagnosis. In multivariate analysis, risk of hospitalization and mortality was higher by 11% (95% CI 8-13%) and 9% (95% CI 5-12%), respectively in the year after diagnosis.

Conclusions: The prevalence of gout was 15% in the US Medicare dialysis-dependent population. Gout patients had a higher comorbidity burden especially for cardiovascular conditions and higher risk of hospitalization and mortality. Future studies are needed to elucidate whether improved recognition and management of gout may reduce the risk for worse cardiovascular outcomes.

Funding: Commercial Support - Horizon Therapeutics

PO0793

Real-World Clinical Performance Evaluation of the FX CorAL Dialyzer: A Retrospective Cohort Study

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Background: In-vitro dialyzer clearances as outlined in the Instructions for Use may not necessarily reflect clinical reality. Clinically, the in-vivo dialyzer performance is more relevant. Thus, we evaluated the clinical performance of two dialyzers (FX CorDiax, FX CorAL) with slightly different in-vitro clearances.

Methods: 18 Hungarian and 33 Portuguese NephroCare Dialysis centers were randomly allocated to an implementation scheme. European Clinical Database data from 1,924 adult patients who switched from the FX CorDiax to the FX CorAL dialyzer between July 2020 and January 2021 were analyzed. To evaluate the clinical performance, we compared intra-individual changes of various parameters between 3 months before and 3 months after the dialyzer switch using paired t-test or Wilcoxon signed-rank test.

Results: The patients median age was 70 years, 64.2% were male, 38.4% had diabetes and 63.3% hypertension. The median dialysis vintage was 55.1 months. 88.6% of treatments were performed with online hemodiafiltration (HDF); 75.3% of patients had a fistula. After the dialyzer switch, the online clearance monitor Kt/V increased by 0.05 (2.7%). Among HDF patients, the effective infusion and convective volume increased by about 0.5 l and the effective treatment time increased by 4.2 min (1.8%). All mean changes were statistical significant (Table 1).

Conclusions: In this analysis of real-world FX CorAL dialyzer utilization, we observed statistically significant changes in performance parameters. In contrast to in-vitro results, our data suggest that the clinical performance of the FX CorAL and FX CorDiax dialyzer is comparable.

Funding: Commercial Support - Fresenius Medical Care

Table 1: Overall mean change after switch versus before switch

Parameter	Mean before (SD)	Mean diff [95%-CI]	Paired t-test / Wilcoxon
Effective treatment time [min]	235.06 (18.73)	4.21 [3.80; 4.63]	<.0001
Mean blood flow [ml/min]	399.43 (48.49)	-0.58 [-1.45; 0.30]	<.0001
Dialysate flow [ml/min]	420.33 (56.18)	-2.41 [-3.37; -1.45]	<.0001
Effective infusion (HDF) [l]	23.18 (4.56)	0.48 [0.37; 0.59]	<.0001
Convective volume (HDF) [l]	25.33 (4.53)	0.54 [0.44; 0.65]	<.0001
Single-Pool Variable-Volume Kt/V	1.94 (0.33)	0.09 [0.07; 0.11]	<.0001
Urea reduction ratio [%]	79.93 (5.24)	1.29 [0.96; 1.63]	<.0001
Equilibrated Kt/V	1.66 (0.29)	0.09 [0.07; 0.11]	<.0001
Online Clearance Monitoring Kt/V	1.80 (0.39)	0.05 [0.04; 0.06]	<.0001

PO0794

Racial Disparities in Staff CPR Performance Within US Dialysis Clinics: The Role of Clinic Resources and Patient Factors

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Background: Cardiac arrest occurs frequently in outpatient dialysis clinics, and immediate CPR provision improves patient outcomes. However, Black patients in dialysis clinics receive CPR from clinic staff less often compared to White patients. We examined the contribution of dialysis facility resources and patient factors to the observed racial disparity in CPR.

Methods: Retrospective cohort study linking the National Cardiac Arrest Registry to Enhance Survival (CARES) and Medicare Annual Dialysis Facility Report registries. We identified cardiac arrests occurring within US outpatient dialysis clinics via geolocation matching. Differences in facility size, quality, staffing and patient related factors were summarized and compared according to patient race. Multilevel multivariable logistic regression models including these factors were constructed to examine the influence of these factors on the observed disparity in CPR rates between Black and White patients.

Results: From 2013-2017, we identified 1,554 patients experiencing cardiac arrest in dialysis clinics. Compared to White patients, Black cardiac arrest patients dialyzed in larger facilities (26 vs 21 dialysis stations, p<0.001), facilities with less RNs per station (0.29 vs 0.33, p<0.001), and facilities with lower quality scores (# citations 6.8 vs 6.3, p=0.04). Facilities treating Black patients cared for a higher proportion of patients with a history of cardiac arrest (41 vs 35%, p<0.001), HIV/Hepatitis B (5.1% vs 2.9%, p<0.001) and Medicaid enrolled patients (15% vs 11%, p<0.001). After accounting for these differences and other covariates, there was no change in the racial disparity for CPR in Black vs. White patients (OR=0.45 (95% CI 0.27-0.75). The disparity was greater among older Black patients compared to younger patients (interaction p=0.04). Other patient related and facility quality-related factors did not moderate the racial disparity in receipt of CPR.

Conclusions: The racial disparity in CPR delivery within dialysis clinics cannot be explained by differences in facility resources and quality. Reducing this disparity will require a multi-faceted approach including developing dialysis clinic-specific protocols for CPR and addressing potential implicit bias.

Funding: NIDDK Support

PO0795

Weekly Risks of Death and Hospitalization Among Incident Patients Undergoing Dialysis

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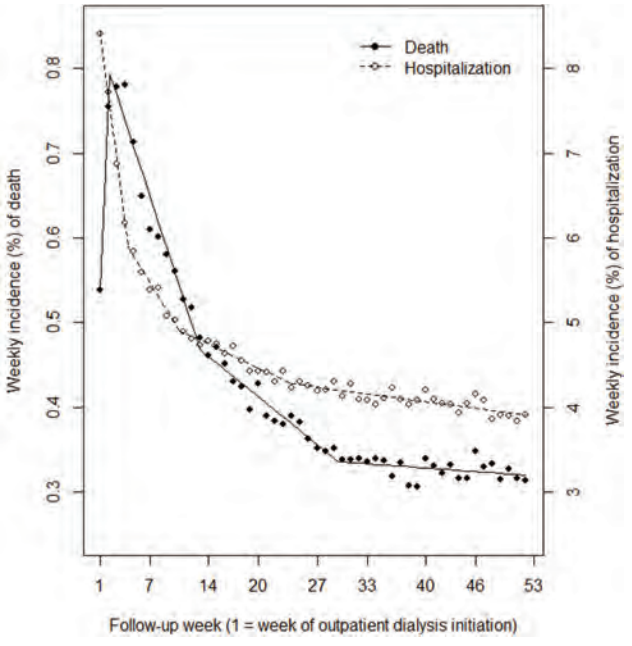
Background: During the first year of hemodialysis, risks of mortality and morbidity are elevated. However, it remains unclear when patients transition from relatively higher "incident" risk to relatively lower "prevalent" risk. We estimated trajectories of weekly risks of death and hospitalization among patients who recently initiated hemodialysis.

Methods: We analyzed data from the United States Renal Data System. The cohort included all patients who initiated outpatient hemodialysis in 2014-2017; for analysis of hospitalization, we limited the cohort to patients with Medicare Parts A and B coverage. We estimated the weekly incidence of each of death and hospitalization during the first 52 weeks of hemodialysis. We used joinpoint regression with a maximum of five knots to estimate best linear interpolations of incidence trajectories.

Results: The cohort included 395,233 incident patients. Risk of death peaked in dialysis week 4. As displayed with joinpoint regression, there were four phases of risk: high and sharply increasing risk from week 1 to 3; high but steadily decreasing risk from week 3 to 13; moderate and gradually decreasing risk from week 13 to 30; and consistent risk from week 30 to 52. Risk of hospitalization was highest in dialysis week 1. There were four phases of risk: high but sharply decreasing risk from week 1 to 5; moderate and steadily decreasing risk from week 5 to 11; moderate and gradually decreasing risk from week 11 to 24; and consistent risk from week 24 to 52.

Conclusions: Weekly risks of death and hospitalization are highest during the first 13 to 14 weeks after initiation of outpatient hemodialysis, and gradually decline thereafter. However, risk trajectory details—including the timing of the transition from "incident" to "prevalent" status—vary among outcomes.

Funding: Commercial Support - AstraZeneca



PO0796

Shortened or Skipped Hemodialysis Sessions Attributed to Uremic Pruritus: A National Kidney Foundation Patient Survey

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Background: Hemodialysis (HD) patients are at risk for uremic pruritus, a common and bothersome condition that may make it difficult for patients to complete the prescribed HD sessions. The purpose of this study is to investigate the extent to which pruritus contributes to patients shortening or skipping HD sessions. Studies have demonstrated that shortening and skipping HD treatments increases mortality risk.

Methods: An online survey of adults (18 years and older), across the U.S. from November 11-27, 2020, was conducted using two links posted on the National Kidney Foundation Facebook page. A $5 electronic Amazon gift card incentive was offered to the first 300 respondents with a valid email address.

Results: There were 692 participants among 2604 initial respondents, after excluding 1,252 for partial survey completion, 516 for not having kidney disease and 144 for kidney disease without HD treatment. Demographics and clinical characteristics include mean age 38.5 years ±11.8, 46.8% under 35 years, 45.5% females, 15% Black or African American, 9% Hispanic, 9% American Indian, 3% Asian, 74.7% employed or attending school, 45.3% with 1-5 years HD vintage, 81% treated with center HD and 19% treated with home HD. This population is younger and enriched for home HD and employment compared to 2018 results from the USRDS 2020 Annual Data Report, with only 11% HD age < 45 years, 2% treated with home HD and low employment prevalence. Pruritus was common with 64.0% (428/669) self-reporting itch that is at least somewhat intense on a Likert scale, including 25.7% (172/669) of patients reporting itch as very or extremely intense. Shortening or skipping an HD session because of pruritus was reported at least some of the time by 55.6% (334/601) and 50.4% (303/601) of participants, respectively. Patients reporting the itch as very or extremely intense were more likely to skip or miss HD treatments. Among the members of the HD care team, nephrologists 43.2% (299/692) were the most likely professional to be identified by patients to talk with about itchy skin.

Conclusions: This survey cohort of HD patients showed pruritus leading to skipped or shortened HD sessions occurred in about half of the patients. The results support uremic pruritus as a significant cause of skipped or shortened HD sessions for the dialysis care team to consider.

Funding: Commercial Support - Cara Therapeutics

PO0797

Association of Length of Interdialytic Interval and Patient-Reported Symptoms

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Background: Symptom burden of patients on in-center hemodialysis (HD) is high. Hospitalization and mortality is higher after the long interdialytic interval due to accumulation of fluid and electrolytes. It is unclear whether symptom burden is affected by the length of interdialytic interval.

Methods: We surveyed patients ≥18 years old, on HD for ≥30 days, and on HD three times a week at the Mount Sinai Kidney Center. Patients completed a survey about presence and severity (5 point scale) of 21 symptoms at the end of their HD treatments for 12 sessions. Symptom severity was calculated by multiplying the symptom with the severity and could range from 0 to 84, it was then summed per survey and the mean value per patient was calculated. We used negative binomial regression to determine the association of interval with symptom count.

Results: During the study period, 97 HD patients completed all surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The majority of patients reported symptoms, which ranged from a low of 8% for chest pain to 61% for fatigue **(Figure 1A).** More patients reported having ≥1 symptom after the long interdialytic interval than after the short interdialytic interval 67% vs 59%, P=0.01. Mean symptom severity was higher after the long interdialytic interval (5.8±0.5 vs. 4.7±0.5, P<0.001) **(Figure 1B)**. Symptoms that tended to be more common after the interdialytic interval were fatigue, itching, dry mouth, bone pain, and restless legs **(Figure 1C)**. After adjustment for age, gender, and race, the incidence rate of symptoms was 20% higher after the long interval (IRR 1.2, 95% CI 1.09-1.33).

Conclusions: Symptoms are common in patients on maintenance HD. Symptom burden is slightly higher after the long interdialytic interval than the short interdialytic interval.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

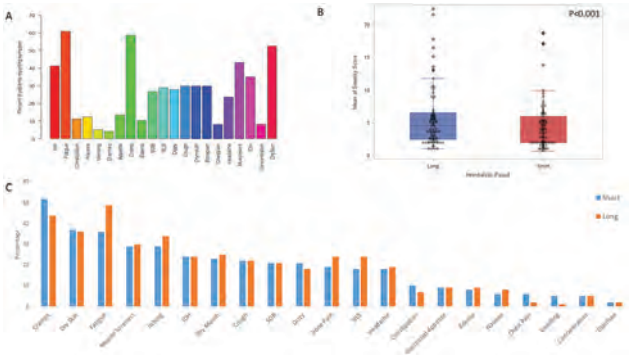

Figure 1: A) Percentage of patients reporting symptom at any point, B) mean severity score by interdialytic period, and C) percentage of patients reporting symptoms by interdialytic interval.

PO0798

Modifiable Risk Factors Associated with Death over the Long Interval for In-Center Hemodialysis Patients

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Background: Routine thrice weekly in-center hemodialysis (HD) is associated with increased risk of death around the long interval without dialysis. We evaluated this risk and explored modifiable risk factors associated with increased risk of death.

Methods: Prevalent Medicare beneficiaries (21,331) receiving maintenance thrice weekly in-center HD in facilities operated by a large not-for-profit dialysis provider from 1/1 2009 -12/31 2016 were included. We calculated daily death rates for an observation week (consisting of days HD-2, HD-1, HD1, HD+1, HD2, HD+2, and HD3) occurring after a week of usual outpatient care, defined by at least 1 outpatient treatment, with no inpatient hospital days, excused absences, or SNF days. HD1 represents the Monday or Tuesday following the long interval. A logistic regression model with patient random effects estimated the effect of patient characteristics, including age and treatment vintage, and treatment parameters including inter-dialytic weight gain (IDWG) >4.6% of estimated dry weight (kg), pre-HD systolic blood pressure (SBP) <120 mm Hg, and intradialytic hypotension, on the probability of dying over the long interval (HD-2, HD-1 and HD1) as compared to either dying on any other day in the week or survival.

Results: Among 2,019 deaths included in analyses, the highest death rates were observed on HD1 and HD3. Factors associated with increased odds of death over the long interval included older age, IDWG >4.6% of estimated dry weight, pre HD SBP <120 mm Hg prior to last treatment in the observation week, and skipped treatment in the prior week (table).

Conclusions: High inter-dialytic weight gain, low pre-HD SBP, and skipped treatments during the preceding week are potentially modifiable factors associated with increased risk of death over the long interval. These factors can help identify patients who will benefit from HD prescription modification.

Variable	Comparison	Odds ratio for dying over long interval vs any other day or surviving (95% CI)
Inter-dialytic weight gain (kg)	≥4.6% vs <4.6%	1.767 (1.456, 2.145)
Age at start	One year change	1.032 (1.025, 1.039)
Vintage	One year change	1.055 (1.011, 1.100)
SBP absolute difference of 30 (mm Hg) pre to post treatment	Yes vs No	0.886 (0.739, 1.061)
Pre-HD SBP <120 (mm Hg)	<120 vs ≥20	2.898 (2.468, 3.404)
Prior week treatment sessions (n)	<3 vs 3	3.079 (2.533, 3.742)

PO0799

Real-World Use of Phosphate Binder Agents Among Dialysis-Dependent Patients with CKD in Medicare Fee-for-Service

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Background: Phosphate binders (PBs) are prescribed to control hyperphosphatemia among patients with chronic kidney disease. The need for phosphate intervention peaks among those with dialysis-dependent (DD) end-stage renal disease (ESRD). We used Centers for Medicare & Medicaid Services 100% Research Identifiable Files (RIF) data, representing 100% of Medicare fee-for-service beneficiaries, to characterize contemporary PB utilization among established and incident patients with DD ESRD across dialysis modalities.

Methods: We identified incident and prevalent patients with DD ESRD in the 2018-2019 RIF data, separating hemodialysis, continuous ambulatory peritoneal dialysis (CAPD), or continuous cycling peritoneal dialysis (CCPD) patients based on frequency of revenue codes. We assessed monthly PB use for calcium acetate, ferric citrate, lanthanum carbonate, sevelamer (hydrochloride and carbonate) and sucroferric oxyhydroxide. PB use was defined as a filled prescription covering 15+ days in a calendar month.

Results: We identified 233,564 patients with DD ESRD, of which 10% were incident. These patients reported 2,439,804 outpatient dialysis months in 2019. Among all patients, 28.4% did not report PB use in 2019 (26.4% among prevalent patients and 46.6% among incident patients). Among patients with any PB use, the average number of outpatient dialysis months was 10.9, of which 6.4 (60%) reported PB use. Average months with PB use were 3.8 for CAPD, 5.3 for CCPD, and 6.4 for hemodialysis.

Conclusions: We found gaps in PB use among patients receiving outpatient dialysis who were also prescribed a binder in 2019. Binder use was reported in 60% of all outpatient dialysis months for patients in our study, suggesting that PBs may have been underutilized or required only intermittently. Further studies are needed to determine the reasons for gaps in PB use and to identify opportunities for control of phosphate levels among patients with DD ESRD.

Funding: Commercial Support - Akebia Therapeutics, Inc.

PO0800

Characterization of Gout in US Patients Treated with Hemodialysis (HD) and Peritoneal Dialysis (PD)

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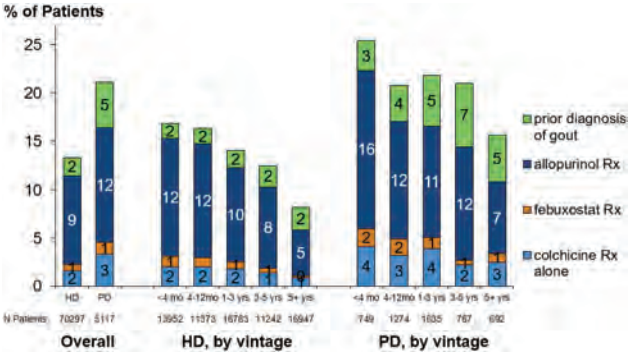
Background: Gout occurs frequently in patients with renal disease and can lead to a significant burden on quality of life and functional status. In the US hemodialysis (HD) and peritoneal dialysis (PD) population, there has been little reported on gout prevalence, patient characteristics, and associations with outcomes.

Methods: We used data from US cohorts of 70,297 HD (DOPPS, 2012-2020) patients and 5,117 PD (PDOPPS, 2014-2020) patients. We took a stepwise approach to define gout based on active prescription of (1) colchicine, (2) febuxostat, or (3) allopurinol; or (4) prior diagnosis of gout. Propensity score matching was used to compare outcomes – including erythropoietin resistance index (ERI = ESA dose/(hemoglobin*weight)), mortality and hospitalization, and baseline patient-reported outcomes (PROs) – among patients with vs. without a history of gout.

Results: Gout prevalence was 13% in HD and 21% in PD, and was highest among incident dialysis patients. Contributions of colchicine Rx (2-3%) and febuxostat Rx (1%) were lower than allopurinol Rx (9-12%), and additional contribution of gout diagnosis was minimal [Figure 1]. Both HD and PD patients with gout (vs. no gout) were older, more likely male, with higher BMI, and higher prevalence of cardiovascular comorbidities. After propensity score matching, mean ERI was 4% higher for gout vs. non-gout patients, while there was minimal evidence of association with clinical outcomes or PROs.

Conclusions: Gout was common in US HD and PD patients, with a large proportion of these patients treated with drugs indicated for hyperuricemia (allopurinol and febuxostat) and gout flares (colchicine). True prevalence was likely higher than observed when considering under-ascertainment of gout diagnosis history. This report provides a snapshot of gout in the US dialysis population and offers opportunities to expand on research to improve awareness and care for patients with gout and ESRD.

Funding: NIDDK Support, Other NIH Support - Agency for Healthcare Research and Quality (AHRQ), Commercial Support - This analysis was supported by Horizon. Other support includes: Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical CO., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torii Pharmaceutical Co.,Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd



PO0801

Fatigue Prevalence and Associations with Non-Diuretic Anti-Hypertensive Medications in the Maintenance Hemodialysis Population

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Background: It is well known that dialysis patients suffer from fatigue post dialysis. It is possible that fatigue is exacerbated by antihypertensive medications. We hypothesized that post-dialysis fatigue (PDF) duration was positively correlated with the number of antihypertensive medications.

Methods: We conducted cross sectional survey and 6 month retrospective medical record chart review at three privately owned dialysis clinics in Illinois. The survey consists of 50 questions related to fluid and blood pressure management, the validated Post-Dialysis Fatigue and Time to Recover from Dialysis Survey (PDF TIRD), and the validated National Institute of Health Patient Reported Outcomes Measurement System fatigue short form. A random mixed effect model was created through a reverse stepwise process in order to assess associations. Chi-squared analysis was performed with categorical symptom data.

Results: One hundred and two patients consented to the study, 96 had complete medical records with all research variables and survey values captured. The average number of dialysis sessions captured per patient was 50.0 +/- 19. The average time on maintenance hemodialysis was 5.06 +/- 4.93 years with a range of 0.2 to 28 years. Seventy six percent (73/96) of dialysis patients suffered from post-dialysis fatigue. Most patients 53/96 reported that their fatigue was the worst after dialysis. On average patients required 462.67 +/- 655.18 minutes (7.7 +/- 10.92 hours) to recover after dialysis. In our random mixed effect model, the time required to recover post-dialysis was positively associated with the number of non-diuretic antihypertensive medications: For every antihypertensive medication, patients experienced an additional 210 minutes (3.5 hrs) of fatigue post dialysis fatigue.

Conclusions: Post-dialysis fatigue is a pervasive problem in the dialysis population that has significant consequences on patients' quality of life. While fatigue has several important contributing factors, the number of non-diuretic blood pressure medications appear to exacerbate patients' fatigue. Further investigation on the survival and quality of life benefits, including fatigue, of patients maintained on antihypertensive medications versus volume control strategies is needed.

PO0802

Dialysis Adequacy and Risk of Dementia in Elderly Hemodialysis Patients

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Background: Dementia is prevalent among elderly patients undergoing hemodialysis. However, the association between dialysis adequacy and the risk of dementia is uncertain.

Methods: A total of 10,567 patients aged >65 years undergoing maintenance hemodialysis who participated in a national hemodialysis quality assessment program were analyzed. The patients were classified into quartile groups based on single-pool Kt/V levels. The associations between single-pool Kt/V and the development of dementia, Alzheimer's disease (AD), and vascular dementia (VD) were examined.

Results: The mean age of the patients was 72.9 years, and 43.4% were female. The mean baseline single-pool Kt/V level was 1.6 ± 0.3. During a median follow-up of 45.6 (45.6–69.9) months, there were 27.6, 23.9, and 2.8 events/1000 person-years of overall dementia, AD, and VD, respectively. The incidences of overall dementia, AD, and VD were lowest in the highest single-pool Kt/V quartile group. Compared with the lowest single-pool Kt/V quartile, the risks of incident overall dementia and AD were significantly lower in the highest quartile (sub-distribution hazard ratio [sHR]: 0.69, 95% confidence interval [CI]: 0.58–0.82 for overall dementia; sHR: 0.69, 95% CI: 0.57–0.84 for AD). Inverse relationships were found between the risks of developing overall dementia and AD, and single-pool Kt/V. However, no significant relationship was observed between single-pool Kt/V levels and VD development.

Conclusions: Increased dialysis clearance was associated with a lower risk of developing dementia in elderly hemodialysis patients.

PO0803

Risk of 30-Day Hospital Readmission in Patients with ESKD with and Without Autosomal Dominant Polycystic Kidney Disease

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Background: Among end stage kidney disease (ESKD) patients with autosomal dominant polycystic kidney disease (ADPKD), relatively little is known about the epidemiology and risk factors for 30-day readmissions in the US. Therefore, we evaluated the 30-day unplanned readmission rates and predictors, and inpatient care costs among ESKD with and without ADPKD patients using a nationally representative, all-payer database.

Methods: We utilized the Nationwide Readmission Database from 2016-2018 to identify patients admitted for ESKD with and without ADPKD using ICD-10 codes. We used a propensity scoring method assigned to each hospitalization computed by multivariate logistic regression model to establish matched cohorts to reduce bias due to confounding covariates (age, gender, patients' insurance type, quartile classification of median household income extrapolated from zip code, Elixhauser comorbidity index (ECI), hospital location and teaching status) between the 2 groups. We used survey logistic regression to evaluate the association of ADPKD with 30-day hospital readmission.

Results: From 2016-2018, after propensity matching, there were 11,578 index admissions for ESKD patients with ADPKD and 11,422 index admissions for ESKD patients without ADPKD. Those who had ADPKD during index admissions had fewer 30 days readmissions(12.8% vs 15.3%, p<.0001). The cost of hospitalizations and readmissions in ESKD patients with ADPKD were higher than non-ADPKD patients (Figure 1A). Patients who were readmitted were more likely to have kidney transplant, non-routine discharges, and have non-elective index admissions. Longer length of stay, Medicaid insurance, discharge to short term hospital, specialized care, home health care and against medical advice were associated with increased odds of readmission, and higher ECI score and ADPKD was associated with decreased odds of readmission(aOR 0.85, 95% CI 0.8 – 0.9) (Figure 1B).

Conclusions: ESRD patients with ADPKD were less likely to have 30-day readmission than patients without ADPKD.

Figure 1A: Mean cost of index hospitalizations and readmissions in no ADPKD vs ADPKD, Figure 1B: Predictors of ESKD readmissions

PO0804

Pruritus in Hemodialysis (HD) Patients: Course of Symptoms After 12 Months

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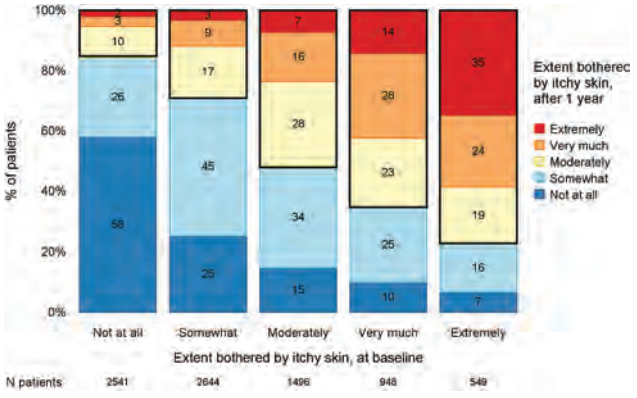
Background: The burden of chronic kidney disease-associated pruritus (CKD-aP) on HD patients has been well-established, including its association with adverse clinical events and patient-reported outcomes (PROs). However, prior studies have focused on a single baseline CKD-aP assessment, and have thus not investigated the course of CKD-aP severity over time.

Methods: We included 8178 HD patients across 21 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) who had 2 CKD-aP assessments 12 months (±6 months) apart. CKD-aP intensity was assessed by a single question on the KDQOL-36 asking about the extent patients were bothered by pruritus over the past 4 weeks (5 categories; Figure 1). We stratified responses at month 12 by baseline responses.

Results: The proportion of patients at least moderately bothered by pruritus was 37% at baseline, 37% 12 months later, and 51% at either assessment (including 28% at least very much bothered). Among patients 'not at all' or 'somewhat' bothered by pruritus at baseline, 22% became at least moderately bothered 1 year later. Among patients at least moderately bothered by pruritus at baseline, 60% remained at least moderately bothered 1 year later. Overall, 43% of patients provided the same response 1 year later, compared to 28% whose pruritus improved and 28% whose pruritus worsened.

Conclusions: Our findings suggest that at least half of chronic HD patients were affected by CKD-aP over the course of 1 year. CKD-aP symptoms remained unresolved 12 months later for the majority of HD patients bothered by itchy skin at baseline, reflecting an unmet medical need. Future research should investigate potential causes of CKD-aP symptoms more systematically as well as treatments used and their effectiveness. This will also highlight how changes in CKD-aP intensity may impact other key PROs.

Funding: NIDDK Support, Other NIH Support - Agency for Healthcare Research and Quality (AHRQ), Commercial Support - This analysis was supported by Vifor. Other support includes: Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical CO., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torii Pharmaceutical Co.,Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd



PO0805

Safety and Efficacy of Difelikefalin in Black or African American Patients on Hemodialysis with CKD-Associated Pruritus: Pooled Analysis of KALM-1 and KALM-2

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Background: Difelikefalin (DFK) is an investigational, peripherally restricted, selective kappa-opioid receptor agonist that significantly reduced itch intensity in hemodialysis (HD) pts with CKD–associated pruritus (CKD-aP) in the Phase 3 KALM-1 and KALM-2 trials. People of Black or African American (AA) race were well represented in these studies. This pooled analysis reports efficacy and safety of DFK in Black or AA pts.

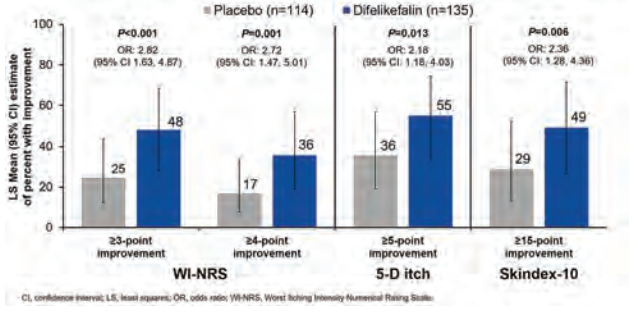
Methods: HD pts with moderate-to-severe CKD-aP were randomized to intravenous DFK 0.5 mcg/kg or placebo (PBO) 3 times/wk for 12 wks. The primary endpoint was the proportion of pts achieving a clinically meaningful ≥3-point improvement from baseline (BL) in the weekly mean of 24-hr daily Worst Itching Intensity Numerical Rating Scale (WI-NRS) scores at wk 12. Secondary endpoints included proportion of pts achieving ≥4-point improvement in WI-NRS score and change in itch-related QoL score (5-D Itch and Skindex-10) from BL to wk 12. Adverse events (AE) through wk 12 were collected.

Results: Of 851 pts randomized in KALM-1 and KALM-2, 249 (29%) pts self-identified as Black or AA (DFK: 135; PBO: 114). Mean BL WI-NRS score was 7.2 and 7.3 in the DFK and PBO groups. A greater proportion of pts who received DFK vs PBO achieved clinically meaningful improvements in itch intensity and itch-related QoL (**Figure**). Most common treatment-emergent AEs (≥5%) with DFK occurring at ≥1% higher incidence vs PBO were diarrhea (10.4% vs 6.2%), dizziness (10.4% vs 2.7%), vomiting (7.4% vs 4.4%), headache (5.2% vs 0.9%), and hyperkalemia (5.2% vs 2.7%). Serious AE incidence was similar between groups.

Conclusions: DFK significantly reduced pruritus intensity and improved itch-related QoL in Black or AA HD pts with moderate-to-severe CKD-aP. DFK was well tolerated with an acceptable safety profile. The safety and efficacy of DFK in Black or AA pts was similar to the overall population.

Funding: Commercial Support - Vifor Pharma

Figure: Black or African American patients achieving clinically meaningful improvements in itch intensity (WI-NRS score) and QoL (5-D Itch and Skindex-10 score) at Week 12



CI, confidence interval; LS, least squares; OR, odds ratio; WI-NRS, Worst Itching Intensity Numerical Rating Scale.

PO0806

Prevalence of Latent Tuberculosis Infection and Its Risk Factors in Japanese Hemodialysis Patients

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Background: The majority of active tuberculosis (TB) cases develop from latent tuberculosis infection (LTBI). Since the risk of TB in hemodialysis (HD) patients is particularly high, interferon-gamma release assay (IGRA) forLTBI screening in HD patients is considered important. However, the prevalence and characteristics of LTBI in Japanese HD patients remain obscure.

Methods: We performed an observational cross-sectional study of LTBI using IGRA QFT-3G tests in 118 HD outpatients enrolled at 3 hospitals of varying location and function.

Results: Of the 118 patients, 96 were QFT negative, 7 were QFT indeterminate, 14 were QFT positive, and 1 was QFT judgment impossible. No patient had active TB. Confirmed (QFT positive) and possible (QFT positive+indeterminate) LTBI patients totaled 14 (11.9%) and 21 (17.8%), respectively. The LTBI possible group was significantly older and had a significantly higher rate of nephrosclerosis versus the QFT negative group. The indeterminate group had a significantly longer HD period. The QFT results were not remarkably affected by other clinical data, including hospital characteristics. The possible LTBI rate increased age dependently, with higher values from 60 years of age.

Conclusions: The prevalence of LTBI is high in Japanese HD patients, especially from the age of 60 years. Older age was a significant risk factor for LTBI, with prediction difficult using other clinical data. Extended HD may mask IGRA results. Therefore, aggressive screening for LTBI is advised in all HD patients regardless of hospital region or type, especially in patients over 60 years of age or newly commencing HD.

PO0807

Associations of Pre-Dialysis Care with Trajectories of Adverse Clinical Outcomes Among Patients Initiating Dialysis

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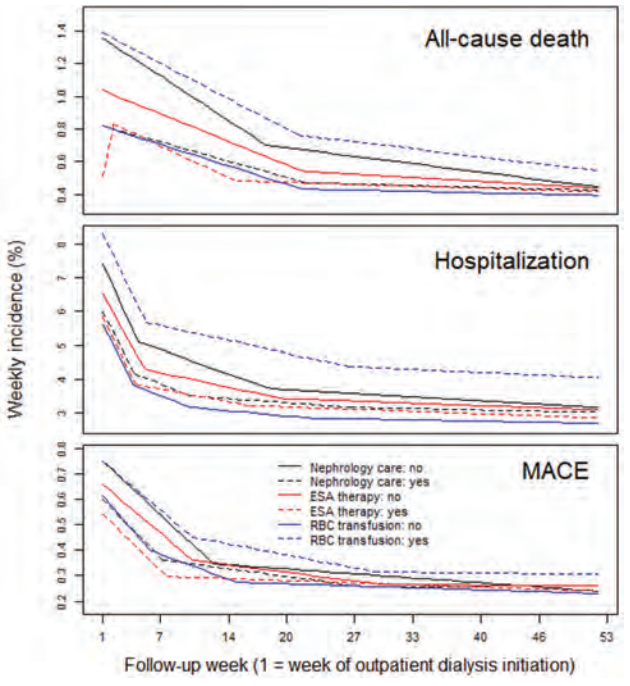
Background: Health care during advanced chronic kidney disease likely influences outcomes during the first year of end stage kidney disease (ESKD). We assessed associations of nephrology care, erythropoiesis-stimulating agent (ESA) therapy, and red blood cell (RBC) transfusion before hemodialysis initiation with trajectories of adverse clinical outcomes during the first year after initiation.

Methods: We analyzed United States Renal Data System data. The cohort included patients who initiated outpatient dialysis in 2014-2017 and carried Medicare coverage during the year preceding dialysis initiation. We stratified the cohort by care in that one-year interval: nephrology care (per ESRD Medical Evidence Report), ESA therapy (per Medicare claims), and RBC transfusion (per Medicare claims). In each stratum, we estimated weekly incidence of all-cause death, hospitalization, and three-point major adverse cardiac events (MACE) during the first 52 weeks of dialysis. We used joinpoint regression to estimate incidence trajectories.

Results: The cohort included 132,879 patients. Before dialysis initiation, 65% received nephrology care, 14% used an ESA, and 32% received an RBC transfusion. As shown, nephrology care and ESA therapy were associated with lower risks of adverse clinical outcomes during the first year of dialysis, whereas RBC transfusion was associated with higher risks. However, trajectories of weekly incidence during the first year were similar in all subgroups.

Conclusions: Pre-ESKD nephrology care and pre-ESKD ESA therapy were associated with lower risks of adverse clinical outcomes during the first year of dialysis, whereas RBC transfusion was associated with higher risks. Regardless of pre-ESKD care, risks were higher during the early part of the first year.

Funding: Commercial Support - AstraZeneca



PO0808

Temporary Changes in Hemodialysis Parameters in Patients Affected by COVID-19 Infection: A Visual Guide

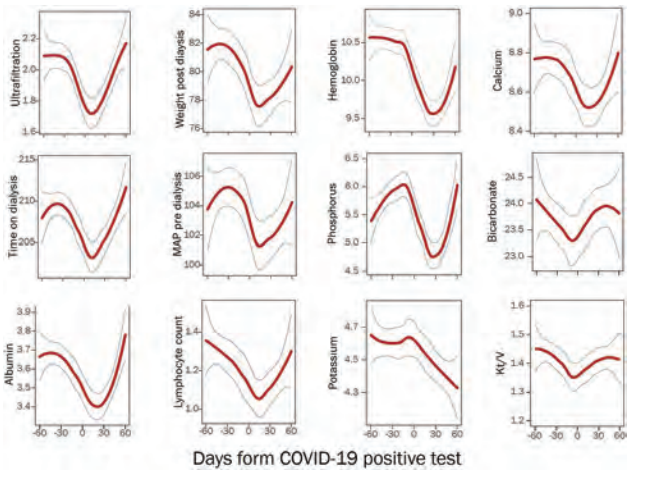
Jose E. Navarrete,[1] Harold A. Franch,[1] Janice P. Lea,[1] Jason Cobb,[1] Frederic F. Rahbari-Oskoui,[1] Ibironke W. Apata.[1,2] Emory Renal COVID-19 Project *[1]Emory University, Atlanta, GA; [2]Centers for Disease Control and Prevention, Atlanta, GA.*

Background: ESKD patients on dialysis have been significantly affected by the COVID pandemic. By now, a substantial number of patients have survived the disease. We display graphically the temporary changes in dialysis parameters of patients that have survived COVID-19 infection.

Methods: All patients receiving hemodialysis at Emory dialysis centers diagnosed with COVID-19 infection between 3/1/20 to 1/31/21 who survived for at least 3 months were identified. The date of COVID-19 diagnosis was used to time-reference dialysis parameters including duration of hemodialysis, weight, ultrafiltration, mean arterial pressure pre-dialysis, hemoglobin, albumin, calcium, phosphorus, potassium, serum bicarbonate, absolute lymphocyte count and Kt/V. The temporary behavior of these parameters is presented graphically. Data manipulation, analysis and graphical display was performed using R-software and tidyverse package.

Results: 96 patients were identified. 82% were African-American with a median age of 64y/o. 52% were male and 60% were diabetics, The median time on dialysis was 2.5 years. All studied parameters showed a significant deviation from baseline measurements obtained in the 60 days prior to the diagnosis of COVID-19. The parameter with the least amount of change was Kt/V. In the subsequent 2 months after diagnosis, all of the parameters studied returned to baseline except for Potassium, that remained below pre-morbid levels 2 months after the COVID-19 diagnosis. These changes are presented in Figure 1.

Conclusions: COVID-19 infection has a significant impact on hemodialysis parameters as presented in figure 1. The temporary variation of the most common parameters associated with COVID-19 infection presented in this study can be used as reference for patients, dieticians, and nephrologists caring for ESKD affected by COVID-19.



PO0809

Reducing Haemodialysis Frequency in a Satellite Unit During the COVID-19 Pandemic

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Background: People dependent on unit HD are vulnerable to COVID-19. We describe the safety and outcomes of reducing HD frequency to minimise patient exposure to the virus.

Methods: HD was reduced from thrice to twice-weekly in selected patients for 9 weeks from March 2020. Urine output, heart failure, fluid-overload, hyperkalaemia, medication and patient preference were considered. Patients were asked to restrict dietary potassium, salt and fluid. Selected patients reducing HD frequency received 10g once-weekly sodium zirconium cyclosilicate (SZC). Group 1: Continue thrice-weekly HD Group 2: Twice-weekly HD +SZC Group 3: Twice-weekly HD -SZC. Pre-HD serum potassium (sK^+) and bicarbonate ($sHCO_3^-$), systolic blood pressure (SBP) and weights were monitored. COVID-19 transmission, hospitalisation and death were recorded.

Results: Of 77 patients (mean age 70 years, 74% male), 17 continued thrice-weekly HD. 60 patients reduced to twice-weekly HD, of which 43 received SZC. There were 494 fewer HD treatments over 9 weeks. There was no significant difference in mean monthly sK^+ in any group between March (pre-intervention), April and May; but 6 patients returned to thrice-weekly HD early due to hyperkalaemia or fluid-overload. SZC was increased to 10g twice-weekly in 15 patients. There was a reduction in mean monthly $sHCO_3^-$ during twice-weekly HD. No changes were made to oral or HD bicarbonate prescriptions. There was no significant difference in pre-HD weight or SBP from baseline in patients dialysing twice-weekly. Only 2 of the 14 admissions over 9-weeks were related to hyperkalaemia or fluid-overload. 5 patients tested positive for COVID-19. 2 of the 3 deaths during this period were due to COVID-19. Both were elderly males with CVD and chronic respiratory disease. 1 patient died of a MI after returning home from HD. No deaths were attributed to a reduction in HD frequency. There was no evidence of COVID-19 transmission on the HD unit. No patients were transferred to the regional hub for HD due to COVID-19.

Conclusions: Reducing HD frequency in carefully selected patients is safe, and with strict infection control and timely COVID-19 testing, can reduce COVID-19 transmission and patient transfer to HD hubs. Dietetic review and SZC can reduce hyperkalaemia. Improved documentation of urinary output and cardiac function would optimise this approach.

PO0810

Paraoxonase 1 Gene Variants Concerning Spontaneous HCV Clearance in Hemodialysis Patients

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Background: We aim to explore associations between three *PON1* SNVs (rs705379, rs854560, and rs662) and spontaneous clearance of HCV infection in uremic patients treated with maintenance HD. Epistatic interactions between tested *PON1* SNVs and the *IFNL4* variant rs368234815 were also investigated.

Methods: The study included 83 HD patients who spontaneously resolved HCV infection (all had known *IFNL4* rs368234815 variant) and 104 subjects with persistently positive blood tests for HCV RNA (102 were successfully genotyped for *IFNL4* rs368234815 variant). We genotyped *PON1* by HRM method (rs662) or predesigned TaqMan SNV Genotyping Assay (rs854560, rs705379). We used a regression model including genetic and clinical data, which significantly differed patients with spontaneous HCV clearance and subjects with persistent HCV infection and could be

used as explanatory variables for HCV outcome. Epistatic interactions between *tested PON1* SNVs and *IFNL4* rs368234815 were analyzed by the multifactor dimensionality reduction method.

Results: *PON1* rs662 GG (OR 9.94, 95% CI 1.20 – 82.7, P = 0.022) and rs854560 TT (OR 4.31, 95% CI 1.62 – 11.5, P = 0.003) genotypes were associated with a higher probability for HCV resolution than the genotypes composed of at least one more frequent allele. The most common haplotype, rs662A_rs854560A, was inversely associated with spontaneous HCV clearance. Compared to this haplotype, the rs662G_rs854560T indicated a 5.09-fold (95% CI 0.99 – 26.2, P = 0.032) higher chance for HCV resolution. The closest to significance was the epistatic gene-gene interaction between *PON1* rs662, *PON1* rs854560, and *IFNL4* rs368234815 (P = 0.094). Regression model, including the *PON1* rs662 GG genotype, the *PON1* rs705379 TT genotype, the *IFNL4* rs368234815 TT/TT genotype, age at RRT onset, RRT duration, and chronic glomerulonephritis as possible explanatory variables for spontaneous HCV clearance, showed that significant predictors of spontaneous HCV elimination were the *IFNL4* rs368234815 TT/TT genotype (HR 2.841, 95% CI 1.434 - 5.625, P = 0.003) and RRT duration (HR 0.946, 95% CI 0.897 – 0.998, P = 0.042). The *PON1* rs662 GG genotype provided P-value of 0.053.

Conclusions: The *PON1* rs662 and rs854560 variant allele homozygotes are associated with a higher frequency of spontaneous HCV clearance in HD patients in univariate analyses.

PO0811

Cost-Effectiveness of Hepatitis C Virus Testing Strategies in US Hemodialysis Centers

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Background: The Centers for Disease Control and Prevention and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend screening all patients for hepatitis C virus (HCV) infection prior to starting outpatient hemodialysis (HD), every 6 months thereafter, and every 1-3 months if a center outbreak is detected. Yet, the cost-effectiveness of such screening frequency is not clear. We therefore sought to compare the clinical and cost-effectiveness of HCV testing strategies in US hemodialysis centers.

Methods: We parameterized the Hepatitis C Cost-Effectiveness (HEP-CE) model to reflect the US HD population, using United States Renal Data System and literature data. We simulated HCV infection, progression, treatment, and outbreaks within dialysis centers at the literature-reported frequency (approximately 1%). We competed 5 strategies to compare clinical outcomes and cost-effectiveness of screening, ranging from no testing at all, to every 6-month HCV testing, each with every 3-month screening during a simulated outbreak in 1% of centers. We estimated life expectancy, quality-adjusted life years (QALYs), total HCV infections identified and cured, liver-related deaths, costs (US$ 2019) and incremental cost-effectiveness ratios (ICERs). We simulated cohorts of 100 million individuals over a 20-year time horizon and assumed a health sector perspective.

Results: With no HCV testing or treatment, average life expectancy was 5.22 years, with 2.5 million HCV infections, 678,350 cirrhotic individuals, and 182,646 deaths from liver disease (Table 1). Screening only at HD initiation increased HCV cure rates by 77% and decreased liver deaths by 79%, with an ICER of $71,533 per QALY saved compared to no screening. Increasing screening to every 2 years decreased liver-related deaths by an additional 51% with an ICER of $119,853 over screening at HD entry only. Screening annually or every 6 months was not cost-effective using a willingness to pay threshold of $150,000, even with halving baseline mortality rates or perfect linkage to care.

Conclusions: Testing for HCV in HD provides good economic value, but current CDC and KDIGO recommended intervals are not cost-effective.

Funding: NIDDK Support, Other NIH Support - NIDA, NIAID, Private Foundation Support

Table 1: Model outcomes and incremental cost-effectiveness ratios, simulated cohort of 100,000,000 individuals on hemodialysis

Strategy	HCV infections, Lifetime[a] (N)	HCV Infections Identified, Lifetime (%)	SVR Achieved (% of total infections)	Liver-related deaths (N)	Remaining Life Expectancy (Years)	Undiscounted Cost ($)	Discounted Cost ($)	Discounted QALYs	Incremental Cost-Effectiveness Ratio (ICER)
No Screening	2,513,110	0.0%	0.0%	182,646	5.2235	$500,893	$435,163	3.6508	Reference
Screen once at dialysis initiation	2,516,450	91.9%	76.9%	38,308	5.2307	$501,685	$435,826	3.6600	$71,533
Screen every 2 years	2,525,933	97.1%	87.4%	18,622	5.2313	$501,814	$435,932	3.6609	$119,853
Screen every year	2,527,643	98.1%	90.1%	14,769	5.2316	$501,924	$436,023	3.6613	$224,778
Screen every 6 months[b]	2,529,823	98.8%	92.3%	12,046	5.2318	$502,130	$436,199	3.6616	$665,164

Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response (cure); QALYs, quality-adjusted life years; ICER, incremental cost- effectiveness ratio

[a]HCV infection numbers include re-infections after cure and are not dependent upon the number of prevalent infections in the population, only upon whether an outbreak is simulated in a center or whether a hypothetical individual is simulated to have ongoing injection drug use.
[b]Reflects current Centers for Disease Control and Prevention and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines

PO0812

Disease Activity and Adverse Events in Patients with ANCA-Associated Vasculitides Undergoing Long-Term Dialysis: The DIAVAS Study

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Background: Kidney impairment of ANCA-associated vasculitides can lead to kidney failure. Patients with kidney failure may suffer from vasculitis relapses, but are also at high risk of infections and cardiovascular events, which questions the maintenance of immunosuppressive therapy.

Methods: Patients with ANCA-associated vasculitides initiating long-term dialysis between 2008-2012 in France, registered in the national REIN registry, and paired with the National Health System database, were included. We analyzed the proportion of patients in remission off-immunosuppression over time, and overall and event-free survival on dialysis (censoring for kidney transplantation). We compared the incidence of vasculitis relapses, serious infections, cardiovascular events and cancers before and after dialysis initiation.

Results: 229 patients were included: 142 with granulomatous polyangiitis (GPA) and 87 with microscopic polyangiitis (MPA); 82 patients received a kidney transplant. Mean follow-up after dialysis initiation was 4.6 ± 2.7 years. The proportion of patients in remission off-immunosuppression increased from 23% at dialysis initiation to 62% after 5 years. Overall survival rates on dialysis were 86%, 66% and 54% at 1, 3 and 5 years, respectively. Main causes of death were infections (35%) and cardiovascular events (26%), not vasculitis flares (6%). The incidence of vasculitis flares decreased from 111 to 7 episodes/100 person-year before and after dialysis initiation (p<0.05). Overall, during follow-up, 53% of patients experienced a serious infection, 52% a cardiovascular event, while 17% experienced a vasculitis relapse.

Conclusions: The proportion of patients with ANCA-associated vasculitis in remission off-immunosuppression increases with time spent on dialysis. In this cohort, patients were far less likely to relapse from their vasculitis than to display serious infectious or cardiovascular events. Therefore, the benefit/risk balance of maintenance immunosuppressive therapies in patients on long-term dialysis should be carefully evaluated.

PO0813

Analysis of Costs, Quality of Life, and Nutritional Status Between Patients with Two Different Models of Hemodialysis in Mexico: Chronic vs. Intermittent Hemodialysis

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Background: In Mexico, access to conventional chronic hemodialysis (cHD) programs (two or three hemodialysis sessions a week) is only possible in a few patients. In contrast, patients without social security usually are undergo intermittent hemodialysis (IHD) sessions, this is weekly, biweekly or even monthly sessions when the signs and symptoms of dialysis urgency are present. We aim was to compare the costs, quality of life and nutritional status among two different model hemodialysis: cHD versus IHD.

Methods: Pilot cost study. Costs generated by HD sessions and indirect costs reported by the patient are evaluated to obtain out-of-pocket expenses (medicines, transportation, food, medical supplies). Nutritional status was evaluated through the malnutrition and inflammation score (MIS) and quality of life through the SF-36 questionnaire.

Results: Twenty patients were analyzed 55% male, with a mean age of 40.5 ± 14.9 years, the main cause of CKD was unknown (60%), and the main comorbidity was HTA (95%). Eleven in cHD and nine in IHD. In Fig 1, shown biochemical characteristics, MIS, grip strength, and costs are presented by study group. The quality of life analysis showed worse scores in symptoms; effects of kidney disease, morbidity of kidney disease; physical component; and mental component (p ≦ 0.05).

Conclusions: Although not statistically significant differences were identified in out-of-pocket spending between models, patients with IHD presented worse score MIS and quality of life. A health policy is necessary that allows universal access to renal replacement therapies in Mexico.

Fig 1. Group Characteristics

	Total n=20	HDc n=11	HDi n=9	P
Biochemistry parameters				
TIBC(Total iron fixation capacity) – ug/dl	236.35±84.8	276.64±82.9	187.11±59.3	0.014
Basal hemoglobin– g/dl	9±2.1	10.3±1.85	7.31±1.09	<0.05
Leukocytes - x10e3/uL	7.1±4.4	5.5±1.53	9.46±5.88	0.07
Platelets - x10e3/uL	234.9±134.0	167.18±69.9	329.89±134	0.05
Albumin - g/dl	3.65±1.0	4.27±0.52	2.89±0.94	0.02
MIS (puntos) X±ds	6.2±3.6	4.27±1.5	9.5±4.6	0.025
Grip Strength (kg) X±ds	20.5±8.8	25.8±5.0	14.50±6.78	0.002
Costs MXN (USD)				
Cost medicines	749±821(37.5±31)	592±479(29.6±23.9)	941±744(47.11±37.2)	0.22
Cost per HD sesión	778±325(38.95±16.27)	798±0(39.9)	754±500(37.7±25)	0.802
Transportation cost	521±388(26.08±19.46)	634±434(31.74±21.73)	382±291(19.13±14.5)	0.13
Food Cost	374±357(18.72±17.87)	385±428(19.28±21.33)	360±276(18.02±13)	0.87
Cost of medical supplies	218±447(10.91±22.38)	276±592(13.82±29.6)	146±158(7.31±7.51)	0.53
Total indirect costs	1113±679(55.72±34)	1297±751(64.94±37.6)	888±535(44.4±26.7)	0.18

PO0814

Potential Cost Savings Associated with the Reduction of Hospital Admissions by Using Online High-Volume Hemodiafiltration (Hv-HDF) vs. High-Flux hemodialysis (Hf-HD)

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Background: On-line HDF for maintenance dialysis patients is available in Europe and Canada but is essentially absent in the US. The National Institute for Health and Care Excellence (NICE) conducted a systematic review and built economic models to compare hemodiafiltration (HDF) with Hf-HD. They found HDF to be cost-effective due to benefits such as increased survival and reduced medication requirements. In addition, NICE found HDF using high convection volumes ~20+ L (HvHDF) had greater mortality benefits compared to Hf-HD. Economic models built upon payment systems outside of

the US may be difficult to apply within the US due to differing payment structures. This analysis estimates the potential cost-savings associated with reducing hospital admissions with online HvHDF (vs Hf-HD) based on published studies and USRDS cost data.

Methods: We updated the NICE systematic literature review on HDF studies, especially for articles on hospitalization by searching EMBASE (Ovid), PubMed and NHS EED from 2010 to present. We used an input-output Microsoft Excel® database to calculate the potential cost-saving of online HvHDF compared to Hf-HD from reducing hospitalization and estimating the savings associated with those averted hospitalization and missed in-center HD. The average cost of hospitalization was derived from USRDS and adjusted to 2021 ($17,181), and the average hospital stay was 6.42 days and assuming thrice weekly would result in 2.75 missed HD treatments. It is assumed that reimbursement rate for in-center HD is $253.13 per treatment and costs of treating with HvHDF and Hf-HD are equivalent.

Results: Out of 107 studies found, 4 reported hospitalization rates for HDF and Hf-HD, and 1 compared HvHDF with Hf-HD. This study found 10.8 fewer hospital admissions with HDF per 100 patient-years (Maduell, et al, High efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol, 2013: 487-97). We identified potential saving of $1,856 per patient per year (PPPY) due to averted hospitalizations and $75 PPPY due to avoiding missed HD treatment for a total of $1,931 PPPY.

Conclusions: The potential annual cost-savings of using HvHDF over Hf-HD in maintenance in-center HD was estimated as $1,931 PPPY or $193,071 per 100 patients.

Funding: Commercial Support - Frresenius Medical Care Renal Therapies Group, Waltham, MA

PO0815

Predicting Decline in Residual Renal Urea Clearance via Random Forest Regression

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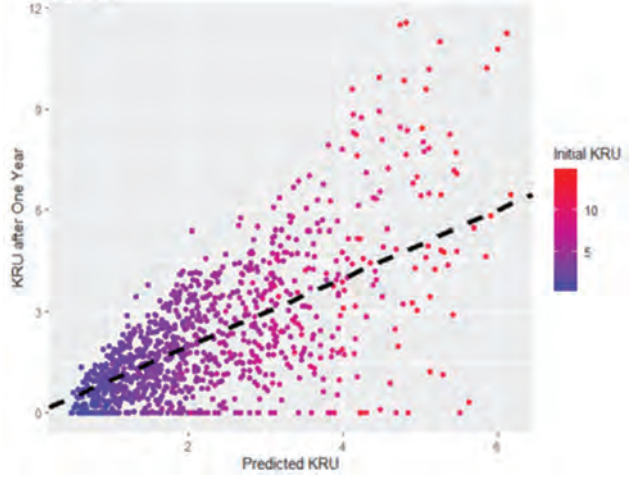
Background: For incident hemodialysis patients, the decline of residual kidney function (KRU) over the first year of dialysis therapy is associated with adverse outcomes such as higher death risk. While several studies have identified biomarkers associated with higher risk of steeper KRU decline, we sought to employ more novel prediction utilizing a random forest regressor to identify important predictors of KRU after one year on hemodialysis.

Methods: We retrospectively reviewed a cohort of 5,141 patients who initiated in-center hemodialysis from 2007 to 2011 and had available KRU data at both baseline and during the 90 days after the one-year mark. 80% of the cohort was selected for the training dataset, with the remaining 20% used to test the model. Cross validation was utilized to optimize the number of trees and the mtry parameter. For feature selection, we used the 20 most important features from a random forest using all available predictors.

Results: In our cohort, mean age was 61 ± 14 years, with 66% men, 25% Black, 70% diabetes, and mean baseline albumin was 3.62 ± 0.42 g/dL. Median baseline KRU was 4.24 (6.39 – 2.69). Median KRU after one year was 1.74 (3.14-0.76). The random forest model yielded an overall mean squared error of 2.13 with noticeably stronger performance on the lower end of final KRU values. Using the median response as a classification threshold, the model achieved an AUC of 0.74. A variable importance analysis revealed that the model's five most important predictors consist of baseline KRU, albumin, weight post treatment session, blood urea nitrogen level, and body mass index.

Conclusions: We showed that a random forest regressor can predict KRU values for hemodialysis patients after one year of treatment with moderately high accuracy. Utilizing our predictive models could aid patients and clinicians in determining the best course of treatment, which should be validated in future studies.

Figure 1



PO0816

Predicting Time to Dialysis and Unplanned Dialysis Start Using Machine Learning Models

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Background: Despite advances in nephrology care, a majority of patients are not well prepared for starting dialysis. This puts patients at a heightened risk of adverse outcomes such as increased hospitalization, higher health care costs and poorer quality of life. Most studies report prevalence of unplanned dialysis start between 40% and 60%. We have implemented a solution that allows the care team to combine their clinical judgement with the outputs of state-of-the-art machine learning models. These models learn patterns in historical data which lead to outcomes of interest.

Methods: We have developed and deployed a set of supervised machine learning models using gradient boosted decision trees that estimate the likelihood a patient with chronic kidney disease (CKD) requiring dialysis and having an unplanned start in the coming 18 months. Unplanned Dialysis Start (UDS) Model sits downstream of Time to Dialysis or Temporal Risk (TR) Model and scores the CKD patients who are predicted to need dialysis. We trained these models in the medical and pharmacy claims and lab data of 751,242 CKD patients spanning multiple years. Input features included demographics, medical history, social determinants of health, and medication adherence. We are using the model output for selection of beneficiaries in a kidney care management program. In addition, the care team is using the risk scores at the point of care.

Results: TR Model has AUC of 93% and F1-score of 0.31 whereas UDS Model has AUC of 71% and F1-score of 0.30. The models are relying on clinically relevant features in making their predictions. Top predictors include serum creatinine, serum albumin, serum phosphate, hemoglobin, CKD Stage, age, comorbidities, nephrologist visits, social determinants of health, and uremic symptoms. We are able to discover patients who are not receiving nephrology care but are at risk for an unplanned start.

Conclusions: Machine learning models developed in large claims and lab datasets can predict time to dialysis and risk of unplanned dialysis starts. These models can be integrated into care management programs to target high risk patients with interventions calibrated to the individual patient's risk. An evaluation study is the next logical step.

Funding: Commercial Support - CVS Health

PO0817

Kidney Function Recovery in Patients Undergoing Maintenance Hemodialysis After AKI Related to Immunological Disorders

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Background: Acute kidney injury(AKI) associated with immunological disorders is an important cause of kidney disease leading to dialysis initiation. In most cases, immunosuppression(IS) is maintained after starting dialysis, hoping for dialysis discontinuation. We analyzed our population with AKI due to immune-mediated disease, who were still dialysis-dependent after hospital discharge and were followed at our outpatient hemodialysis(HD) unit.

Methods: We retrieved the data from our HD unit files. Patients that started maintenance HD due to AKI related to immunologic disorders from 2014 to 2021 were included. We collected data on gender, age, AKI etiology, type and dose of IS, time until kidney function recovery, serum creatinine(sC) at admission and discharge, and the result of kidney biopsy if available. Primary outcome was kidney function recovery (with dialysis independence).

Results: 16 patients were included. The most common diagnosis was ANCA vasculitis(n=4), followed by ANCA-negative crescentic glomerulonephritis (GN)(n=3), IgA nephropathy(n=2), scleroderma renal crisis(n=2), acute interstitial nephritis(n=2), immune complex GN(n=1), granulomatous interstitial nephritis(n=1) and hemolytic uremic syndrome(n=1). Five patients(31,2%) recovered and are still dialysis-free. Concerning primary outcome, there were no differences in gender or age (58,6±15,1years) between the two groups, but sC at admission was greater in recovered patients (mean 10,7±2,3mg/dL vs 8,2±2,0mg/dL, p=0.047). No differences were found between the two groups when the following variables were analyzed: presence of previous chronic kidney disease (CKD), hypertension, diabetes, acute tubular necrosis or interstitial fibrosis/tubular atrophy in kidney biopsy. In patients who received cyclophosphamide(n=8), the outcome was observed only in one patient after eight cycles of IS(vs3,8±1,3 cycles,p=0.034). The time until recovery was 344±446days(range 66-1121days) and sC after discontinuation of HD was 4,0±0,9mg/dL.

Conclusions: Although rare, patients with immunologic kidney disease can recover kidney function more than 90 days after the start of maintenance HD. As nephrologists we should be aware of this situation. The small number of patients limits our analysis. Nevertheless, we concluded that higher pC at admission is not a risk factor for the outcome and that recovery can occur years after starting HD.

PO0818

Clinical Research Offers Potential Benefit to Patients and No Obvious Harm to Clinical Value

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Background: Randomized clinical trials (RCT) are underperformed in nephrology. This may be due to the uncertain impacts on quality measures. We assessed quality outcomes between research-conducting (RF) and research-naïve (NF) dialysis facilities, as well as respective patient outcomes.

Methods: We used data from adult HD patients treated at national provider in the United States from 2017-2018. RF were 1:1 propensity score matched (PSM) to NF on patients/year, patient/facility exposure, % Medicare, % accountable care, region and quality outcomes were compared cross-sectionally. Research participants (RP) from facility analysis were 1:1 PSM to research naïve participants (RNP) at baseline (research participation start or index date) on age, sex, race, Ethnicity, vintage, access, albumin, hemoglobin (hgb), congestive heart failure, ischemic heart disease, diabetes, missed treatments, and hospital day rates. Quality outcomes were compared longitudinally at 6 and 12 months.

Results: We found no differences in quality outcomes between RF and NF facilities. We observed RP had lower hospital day rates at 6 months after research participation start as compared to NRP, as well as higher % with albumin >=4g/dL at 6 and 12 months, higher % with iPTH 150-600 pg/mL within 12 months, and lower anemia target achievement (**Figure 1**).

Conclusions: We observed no significant differences in quality measures between facilities that conducted clinical trials vs those that did not. Participation in trials was associated with lower hospital day rates and better achievement of nutritional targets, but lower achievement of hemoglobin and transferrin saturation targets. Anemia results might be attributable to conservative hgb repletion in trials of new investigational drugs. Trial conduct appeared to do no harm to quality achievement and provide potential benefits to participants, which may be associated with additional evaluations/monitoring provided.

Funding: Commercial Support - Fresenius Medical Care North America

Figure 1		Facility Level Analysis		PATIENT LEVEL ANALYSIS			
Variables		Mean, [LCLM to UCLM], n=165		0-5 months, mean, [LCL to UCL],n=901		0-11 months, mean, [LCL to UCL], n=901	
		Research Facility	Non-Research Facility	Research Patients	Non-Research Patients	Research Patients	Non-Research Patients
OUTCOMES	Hospital days ppy	10.4 (9.9 to 11.0)	10.1 (9.7 to 10.5)	4.2 [3.7 to 4.8] ↓	5.8 (4.9 to 7.0)	4.6 (4.1 to 5.2)	5.7 (4.8 to 6.7)
	Readmission rate	28.7 (27.7 to 29.6)	28.4 (27.5 to 29.3)	21.0 (19.4 to 22.5)	22.1 (20.6 to 23.6)	22.5 (21.3 to 23.8)	23.6 (22.4 to 24.9)
	% patients with unexcused missed treatment per month	19.2 (18.1 to 20.4)	20 (18.8 to 21.2)	1.8 (1.6 to 1.9)	1.7 (1.6 to 1.9)	1.8 (1.6 to 1.9)	1.9 (1.7 to 2.1)
	% patients with catheter exposure >90 days	13.7 (12.8 to 14.7)	14.1 (13.3 to 15.0)	30.8 (28.2 to 33.5)	31.4 (29.2 to 32.6)	34.4 (31.7 to 35.2)	33.3 (31.5 to 33.0)
MBD/NUTRITION	% patients with albumin 24.0 g/dL	33 (32.0 to 34.0)	32.3 (31.3 to 33.2)	38.4 [37.8 to 39.0] ↑	35.6 (33.1 to 36.5)	39.2 [38.5 to 39.9] ↑	35.7 (35.0 to 36.3)
	% patients with Ca 110.0 mg/dL, PO4 3.0-5.5 mg/dL, & iPTH 150-600 pg/mL	49.1 (48.0 to 50.2)	48.4 (47.4 to 49.4)	46.2 (44.6 to 47.8)	47.5 (45.7 to 49.2)	47.2 (45.7 to 48.6)	46.5 (45.4 to 47.5)
	% patients with Ca ≤10.0 mg/dL	98.3 (98.1 to 98.4)	98.3 (98.2 to 98.5)	98.5 (98.3 to 98.8)	98.7 (98.4 to 99.0)	98.5 (98.3 to 98.6)	98.8 (98.4 to 98.8)
	% patients with PO4 3.0-5.5 mg/dL	60.7 (59.80 to 61.5)	59.8 (58.9 to 60.7)	57.5 (56.2 to 58.8)	58.5 (56.2 to 60.8)	59.1 (57.0 to 59.2)	57.6 (56.4 to 58.9)
	% patients with iPTH 150-600 pg/mL	66.7 (65.5 to 67.9)	67.4 (66.3 to 68.6)	67.1 (66.3 to 67.8)	66.8 (66.0 to 67.5)	68.0 [67.0 to 69.0] ↑	65.7 (64.7 to 66.6)
ANEMIA	% patients with Hgb <10.0 g/dL	17.4 (16.6 to 18.1)	16.0 (15.4 to 16.6)	20.5 (18.5 to 22.6)	15.4 (12.0 to 18.9)	21.9 [20.6 to 23.3] ↑	13.8 (12.0 to 15.6)
	% patients with Hgb 10.0-11.0 g/dL	78.6 (77.8 to 79.3)	79.7 (79.1 to 80.4)	50.5 (45.0 to 56.0)	50.3 (49.1 to 51.5)	49.5 (47.0 to 52.0)	50.4 (49.6 to 51.2)
	% patients with Hgb 11.0-12.0 g/dL	3.9 (3.6 to 4.2)	4.1 (3.8 to 4.4)	21.9 (19.4 to 24.4)	28.1 (25.1 to 31.1)	21.7 [20.6 to 22.8] ↓	28.3 (27.1 to 29.6)
	% patients with Hgb >12.0 g/dL	0.2 (0.2 to 0.2)	0.2 (0.1 to 0.2)	7.1 (5.8 to 8.4)	6.1 (5.2 to 7.1)	6.8 (6.1 to 7.6)	7.4 (6.5 to 8.6)
	% patients with TSAT <30%	43.9 (42.4 to 45.4)	41.1 (39.8 to 42.4)	42.3 [41.5 to 43.1] ↑	37.6 (34.3 to 40.9)	43.6 [42.6 to 44.7] ↑	36.4 (34.9 to 38.0)
	% patients with TSAT 30-50%	49.8 (48.6 to 51.0)	51.8 (50.8 to 52.8)	51.0 (50.6 to 51.1)	54.0 (51.5 to 56.4)	50.6 [49.5 to 51.7] ↓	55.5 (54.0 to 57.1)
	% patients with TSAT >50%	6.3 (5.9 to 6.8)	7.1 (6.6 to 7.6)	5.8 [5.2 to 6.4] ↓	8.4 (7.4 to 9.4)	5.8 [5.2 to 6.3] ↓	8.1 (7.4 to 8.8)

PO0819

Novel Insight About Pregnancy in Women on Chronic Dialysis: Systematic Review and Meta-Analysis Correlating Dialysis Regimen and Pregnancy Outcome

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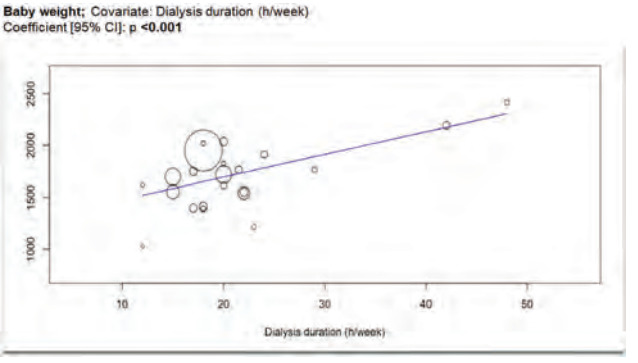
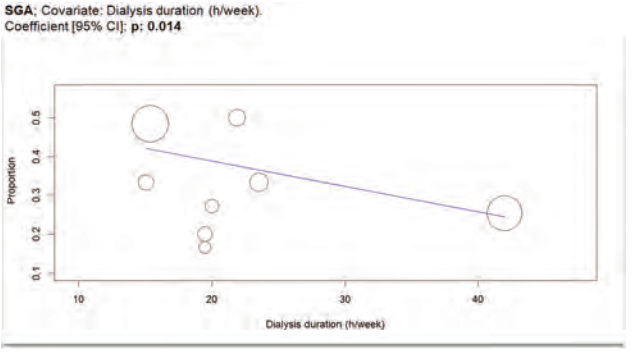
Background: Pregnancy in women on dialysis is an uncommon event, with a high rates of preterm delivery and neonatal death. Guidelines for management of dialysis in pregnancy are still lacking. Our aim is to identify dialysis regimens associated with best maternal-fetal outcomes

Methods: Rapid systematic review. MEDLINE, EMBASE and COCHRANE library were searched (1950–2019: free terms on pregnancy and dialysis). Meta-analysis and metaregression were performed in case series dealing with the larger subset of haemodialysis (HD) patients (>5 patients on chronic HD)

Results: The descriptive of 5204 pregnancies in 4746 HD patients, out of 52 case series and registry data highlighted the importance of intensifying HD in pregnancy (5-6 sessions, >20 hours/week) to achieve a reduction in mortality and an increase in neonatal weight. The meta-analysis showed an increased risk of preterm delivery in women on chronic HD, decreasesing with the increase in hours of HD and number of HD sessions. In addition, the meta regression demonstrated that increasing weekly hours of HD was associated to a lower risk of extreme preterm birth (<28 gestational weeks: p=0.016) and SGA (p=0.014) and with an increase in weight at birth (p<0.001). The same trend was observed for number of HD sessions. The high heterogeneity of data doesn't allow disentangling the effect of the center of care

Conclusions: Extendend hours HD regimens in pregnancy improve maternal fetal outcomes. This improvement is linked both to HD rhythm and duration. The results obtained during pregnancy lead to reconsidering the concept of adequate HD at least in the young population





PO0820

Thrombocytopenia Predicts Mortality in Chinese Hemodialysis Patients: An Analysis of the China DOPPS

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Background: Mortality rate was high in Hemodialysis (HD) patients. Our previous study suggested platelet counts might be a potential risk factor. However, few studies have examined the association of platelet count with mortality in HD patients. The aim is to examine if there is an association of thrombocytopenia (TP) with mortality and cardiovascular (CV) death in Chinese HD patients.

Methods: China DOPPS5 data was used. Fifty-eight of 1427 patients were excluded for missing platelet records. Demographic data, comorbidities, lab data, and death records were extracted. Participants were divided into 2 groups according to their platelet counts as TP group (platelet<100*10^9), and Non-TP group (platelet >=100*10^9). The Non-TP could not be further divided into normal or above normal groups as limited by the sample size. Associations between platelet counts and all-cause and CV mortality were analyzed using Cox regression models. Stepwise multivariate logistic regression was used to identify related impact factors.

Results: Of 1369 patients, 201(14.7%) died and 102 (7.5%) died from CV disease. 11.2% (154) had TP at baseline. The mortality rates were 26.0% vs. 13.3% (p <0.01) in patients with and without TP. TP was associated with higher all-cause mortality after adjusted for covariates (HR:1.75, 95% CI: 1.12- 2.74), but was not associated with CV death after fully adjusted (HR: 1.75, 95% CI: 0. 89, 3.45, Figure 1). Multivariate logistic regression showed that Urine output <200 ml/day, cerebrovascular disease, hepatitis (B or C), and white blood cells were independent impact factors (P < 0.05).

Conclusions: Baseline TP is associated with higher risk of all-cause mortality in HD patients. Platelet counts may be used as early available outcome predictors among HD patients, though additional study is needed.

Funding: Government Support - Non-U.S.

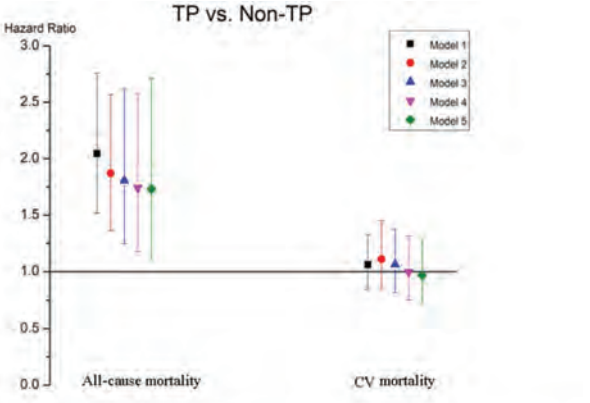


Figure 1. Associations between the platelet counts and all-cause mortality and CV mortality in different COX regression models (TP group: platelet<100*10^9; Nonp-TP group: platelet>100*10^9)

PO0821

Steady Exercise Improves Hand Grip and Leg Muscle Strength in Hemodialysis Patients

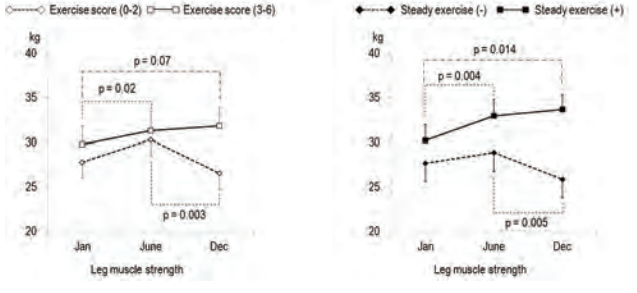
Ran-hui Cha. *National Medical Center, Seoul, Seoul, Republic of Korea*.

Background: Sarcopenia due to chronic inflammation and biochemical disturbances in chronic kidney disease is severer and more prevalent in patients on hemodialysis (HD). We longitudinally evaluated the hand grip (HGS) and leg muscle strength (LMS) in patients receiving HD and tried to find factors associated with muscle strength.

Methods: We screened (January 2020 (n=127)) and followed up (June 2020 (n=110) and December 2020 (n=104)) HGS (opposite the fistula side) and LMS (both sides) at single center by using digital hand and leg dynamometer (T.K.K.5401 and 5710e/5715, Takei scientific instruments Co. Ltd., Niigata, Japan).

Results: HGS and LMS showed good correlation ($r = 0.658$, $p < 0.001$). HGS (24.2 vs. 15.5 kg) and LMS (32.8 vs. 22.5 kg) were better in men ($p < 0.001$ and $p < 0.001$, respectively). Muscle strength was greater in men irrespective of age except for LMS in younger patients (< 60 years). Older patients (≥ 60 years) showed decreased LMS than others in women ($p = 0.01$). Patients who performed steady home- or hospital-based exercise showed marginally higher HGS (23.1 vs. 19.8 kg, $p = 0.07$) and significantly higher LMS (33.7 vs. 25.9 kg, $p = 0.004$). Steady exercise showed improvement of LMS throughout the study period (from January to June, $p = 0.004$, from January to December, $p = 0.014$). Multiple linear regression analysis proved male sex and steady exercise were factors associated with better HGS and LMS. Steady exercise showed greater impact on LMS in male patients with longer HD vintage (≥ 44 months) and on HGS in younger male patients with shorter HD vintage (< 44 months).

Conclusions: Sex, age, and steady exercise were important determinants of muscle strength in HD patients. And serum creatinine and dry weight, which reflects muscle mass, were also important in determining muscle strength. We need to encourage patients to do regular home- or group-exercise from the beginning of dialysis and introduce new feasible form of exercise for HD patients.



PO0822

The Association Between Prevalence of Peritoneal Dialysis vs. Hemodialysis and Patients' Home Distance to Dialysis-Providing Facilities

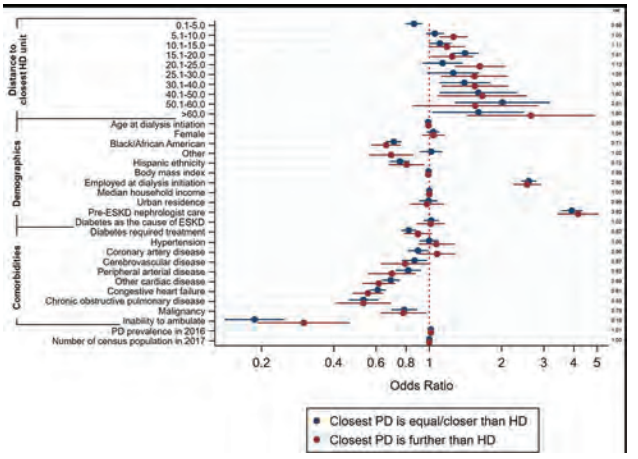
Pattharawin Pattharanitima, Osama El Shamy, Kinsuk Chauhan, Aparna Saha, Huei Hsun Wen, Shuchita Sharma, Jaime Uribarri, Lili Chan. *Icahn School of Medicine at Mount Sinai, New York, NY*.

Background: Accessibility to dialysis facilities should play a role when deciding on a patient's long-term dialysis modality. Studies investigating the effect of distance to nearest dialysis-providing unit on modality choice, however, have yielded conflicting results. We investigated the association between patients' dialysis modality and the distances (driving and straight) to the closest HD and PD-providing units.

Methods: All ESKD patients (USRDS) who initiated in-center HD and PD in 2017, were 18-90 years old, and on dialysis for ≥30 days were included. Patients who resided in non-conterminous US or lived >90 miles from the nearest HD-providing unit were excluded.

Results: Among 102,247 included patients, median driving distance to the closest HD unit was greater for PD patients (3.9 vs 2.9 miles; $p < 0.001$). Compared to HD patients, PD patients had longer driving distances to their nearest PD unit (4.4 vs 3.4 miles; $p < 0.001$). PD utilization increased with increasing distance from patients' homes to the nearest HD unit (OR 1.11, 95% CI 1.08-1.14 per 10-mile increase). This association did not change whether the PD unit was farther/closer than the nearest HD unit (**Figure 1**). This association was not seen when analysis was performed using straight line distance.

Conclusions: PD utilization increases with increasing driving distances from the nearest dialysis providing units (HD or PD). Using driving distance, but not straight line distance affects data analysis and outcomes. Increasing the number of PD units may have a limited impact on increasing PD utilization.



Adjusted OR for PD utilization categorized by the driving distance (miles) from patient's residence to the closest HD-providing unit and distance to closest PD-providing unit (equal/closer or farther than the distance to HD-providing unit)

PO0823

Evaluation of Frailty Assessment Tools and Their Measurement Properties in CKD

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Background: Frailty is three to seven times more common in people with chronic kidney disease (CKD) than in those with normal kidney function. Although frailty and its impact in CKD is well-recognized, the measurement properties of the tools used to assess this syndrome are not known. The aim of this systematic review was to evaluate frailty assessment tools and their measurement properties in CKD.

Methods: The study was conducted using the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) guidelines and Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P 2015). We searched ten electronic databases (eg. OVID MEDLINE, OVID EMBASE, OVID Health and Psychosocial Instruments, Cochrane Central Register of Controlled Trials (CENTRAL)) and screened studies as per the following inclusion criteria: peer-reviewed original research, adults with CKD (non-dialysis, dialysis or kidney transplant (KT)), examines at least one established multidimensional tool used for the assessment of frailty, and presents information to evaluate the measurements properties of the tool. Methodological quality assessment and data synthesis will be performed as per COSMIN guidelines. This review was registered with PROSPERO (CRD42021234558).

Results: We retrieved 647 unique citations with 58 eligible studies (N=16,026) of which 60% were prospective cohort studies. The majority (59%) included patients on dialysis, 19% were KT, and the remaining non-dialysis CKD. The dialysis populations utilized hemodialysis (HD) (38%) and peritoneal dialysis (PD) (34%) modalities. Fried's phenotype was the most commonly tool used to assess frailty (57%). Predictive validity was the most frequently reported measurement property (86%) followed by responsiveness (12%). Thirty-one (53%) of the included studies using the Fried's Phenotype evaluated predictive validity.

Conclusions: In this review, a majority of the studies focused on the dialysis and non-dialysis populations. Fried's Phenotype, the most commonly administered tool, primarily evaluated predictive validity. Future research is required to identify the tool(s) that will be predictive of adverse health outcomes in the KT population and additional studies evaluating these tool's responsiveness to change are needed.

PO0824

Change in Physical Activity and Function in Patients with Baseline Advanced Non-Dialysis CKD

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Background: Progressive declines in physical activity and function are common in individuals with worsening chronic kidney disease (CKD). However, little is known about whether the transition to dialysis is associated with accelerated decline. We aimed to assess temporal rates of change in physical activity level and physical function in people with advanced CKD to determine whether the transition to dialysis was associated with accelerated decline.

Methods: Individuals with advanced CKD stages G4-G5 from the Canadian Frailty Observation and Interventions Trial (CanFIT) were included. Outcomes included change in physical activity level measured using the Physical Activity Scale for the Elderly (PASE) and physical function measured using the chair stand test, 4-meter gait speed, and grip strength. Unadjusted and adjusted generalized linear regression models were conducted to determine whether progression to dialysis was associated with greater decline in physical activity or physical function.

Results: Of 386 individuals, 162 individuals progressed to dialysis during the study period, whereas 224 did not. Both groups experienced statistically significant declines in self-reported physical activity, increased chair stand test times, and decreased gait speed. Compared to individuals with advanced nondialysis CKD, progression to dialysis was associated with greater increase in chair stand test time in unadjusted (beta estimate 6.05 seconds, 95% CI 2.36 – 9.74, p=0.001) and adjusted (beta estimate 5.23 seconds, 95% CI 0.75 – 9.71, p=0.02) models.

Conclusions: Although individuals with advanced CKD experience declines in physical activity and function over time, progression to dialysis is associated with accelerated decline in physical function as measured by the chair stand test. Future studies on interventions to delay or prevent declines associated with CKD progression and dialysis initiation are needed.

PO0825

Validation of the Surprise Question in an Ethnically Diverse Population to Identify Seriously Ill Dialysis Patients

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Background: Use of the surprise question (SQ)—Would I be surprised if this patient died in the next six months?—to estimate prognosis for dialysis patients has been largely studied in dialysis centers in central Massachusetts and West Virginia. Researchers have called for its value to be confirmed in more ethnically diverse dialysis settings. We tested the effectiveness of the SQ in three urban areas to identify seriously ill dialysis patients (SI) who could potentially benefit from being prioritized for goals of care discussions.

Methods: We recruited 10 dialysis centers (6 in NYC, 3 in Denver, CO, and 1 in Dallas, TX) with 1,507 patients. Dialysis staff screened patients monthly for 14 months (May 2019-June 2020) with the SQ to identify those who were SI and recorded outcomes including the number screened and number SI. In this rolling population of patients, we calculated the mortality risk per month of follow-up for SI and not SI and determined the relative risk of death for SI compared to not SI. In addition, after 14 months, the dialysis centers reported the vital status for an initial cohort of 266 SI identified in May 2019.

Results: Over the 14 months, dialysis centers screened a monthly average of 1,342/1,507 (89.1%) and identified 274 (18.2%) as SI. A total of 269 patients died, 134 (49.8%) SI and 135 (50.2%) not SI. The annualized mortality risk was 41.9% for SI and 9.4% for not SI (risk ratio 4.47, 95% CI, 3.49-5.72). For the 266 SI patients identified in May 2019, race included White 153 (57.5%), Black 68 (25.6%), Asian 20 (7.5%), and Other 25 (9.4%); 81 (30.5%) were identified as Hispanic. Vital status was known after 14 months for 231/266 (86.8%) SI: 96/231 (41.6%) had died, 86 (37.2%) were alive and SI, and 49 (21.2%) were alive and no longer considered SI. The annualized mortality rate for these 231 SI patients was 35.6%.

Conclusions: In this ethnically diverse, geographically dispersed dialysis population, we found that use of the SQ was pragmatically feasible and effective in identifying SI who were at considerably increased risk of one-year mortality. Future research is needed to determine if proactive identification of SI in this manner leads to improved palliative care with more goal-concordant care for this at-risk population.

Funding: Private Foundation Support

PO0826

Perspectives on Motivational Strategies to Improve Hemodialysis Treatment Adherence in African Americans: A Qualitative Study

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Background: Compared to White patients, African American (AA) patients have a four-fold higher prevalence of kidney failure and higher hemodialysis non-adherence. Adherence behaviors are influenced by psychosocial factors, including personal meaning of a behavior and self-confidence to enact it. We assessed perspectives of patients and professionals on using motivational interviewing (MI), an evidence-based intervention to improve these psychosocial factors, hemodialysis adherence, and outcomes in AAs.

Methods: Self-identified AA hemodialysis patients (n=21), dialysis clinicians (MDs, NPs, RNs, LCSWs and RDs) and health equity researchers (n=30) watched a brief video describing MI and then completed a semi-structured interview. Planned questions targeted unique barriers to hemodialysis adherence faced by AAs, and the perceived utility of MI to address these obstacles. Verbatim transcripts and an iterative inductive/deductive approach were used to develop a hierarchical coding system. Two researchers independently identified and coded themes informed by social cognitive theory and the social ecological framework.

Results: See table below:

Conclusions: AA patients receiving hemodialysis, dialysis clinicians, and researchers view MI as a means to build trust, clarify patient priorities, and promote the patient-provider therapeutic alliance. Cultural tailoring of MI to address unique barriers of AAs with kidney failure will improve adherence and health outcomes in these vulnerable patients.

Funding: NIDDK Support

Key Themes And Illustrative Quotes

Barriers	
Mistrust	"'There's...a lot of mistrust among AAs.'" (MD)
Amotivation	"'...a lot of my patients are not motivated...'" (RN)
Inconsistent messages	[From] "you might not ... do dialysis that long" [to] "you're on dialysis the rest of your life" (patient)
Poor understanding	"'A man called me the 'N' word...I was sad...my MD said..sorry, I don't understand.." (patient)
Facilitators	
Engagement	"...don't talk in a condescending manner to an AA, talk to him at his level" (patient)
Empowerment	"help them understand, ...to see they're in charge" (RN)
Relationship	"anybody that has a relationship with a patient, can have a [talk] about not getting off [dialysis]" (LCSW)
Cultural awareness	"it would be good if [providers] become more culturally aware of AAs" (patient) "Not all African Americans are the same...get a sense of important nuances of your [AA] patients" (researcher)

PO0827

Feasibility and Acceptability of Electronic Patient-Reported Outcome Measures (e-PROMs) Collection and Feedback in Hemodialysis Patients

Andrea K. Viecelli,[1,2] Emily Duncanson,[5] Paul N. Bennett,[3] Matilda N. D'Antoine,[5] Kathryn Dansie,[5] Allison Tong,[4] Suetonia Palmer,[7] Shilpa Jesudason,[8] Stephen P. McDonald,[5] Rachael L. Morton.[6] SWIFT Investigator Team *[1]Princess Alexandra Hospital, Woolloongabba, QLD, Australia; [2]The University of Queensland Faculty of Medicine, Herston, QLD, Australia; [3]University of South Australia Division of Health Sciences, Adelaide, SA, Australia; [4]The University of Sydney, Sydney, NSW, Australia; [5]Australia and New Zealand Dialysis and Transplant Registry, Adelaide, SA, Australia; [6]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [7]University of Otago, Christchurch, New Zealand; [8]Royal Adelaide Hospital, Adelaide, SA, Australia.*

Background: The "Symptom monitoring With Feedback Trial" (SWIFT) will assess whether 3-monthly symptom monitoring using the IPOS-Renal questionnaire with feedback to patients and clinicians with evidence-based symptom management recommendations, can improve health-related quality of life for adults on hemodialysis (HD). It is unclear whether regular collection of these data using tablet computers, and provision of symptom scores is acceptable and feasible.

Methods: The SWIFT pilot study collected e-PROMs across 4 Australian HD units for 6 months. We conducted semi-structured interviews and focus groups with 38 participants (13 nephrologists, 16 dialysis nurses, 12 patients on HD) about the uptake and implementation of e-PROMs. Transcripts were analyzed thematically.

Results: We identified four themes**:** enabling efficient, systematic and multidisciplinary patient-centered care (facilitating communication and holistic care, reliable assessment of change in PROMs, increased flexibility in data capture, and ease and convenience); limited data and options for symptom management (depersonalization of care, perceived inability to intervene, time lag for feedback, and uncertain validity and reliability of survey data); requiring familiarity with technology and processes (embedding e-PROMs collection into routine care, assistance to enhance uptake, clarity about e-PROMs purpose and use, comfort and willingness to use technology, and individualizing data collection);

and competing interests and barriers to PROMs data collection (physical limitations encumbering survey completion, low educational attainment and language limitations; fitting in with existing routines, and survey fatigue).

Conclusions: Clinicians and patients support the use of e-PROMs with feedback in HD. Clinician engagement and patient support, reliability of technology, timely symptom feedback, and interventions undertaken to address symptom burden are likely to improve acceptability and impact of symptom monitoring.

Funding: Private Foundation Support

PO0828

Symptom Clusters in a Diverse Prospective Hemodialysis Cohort

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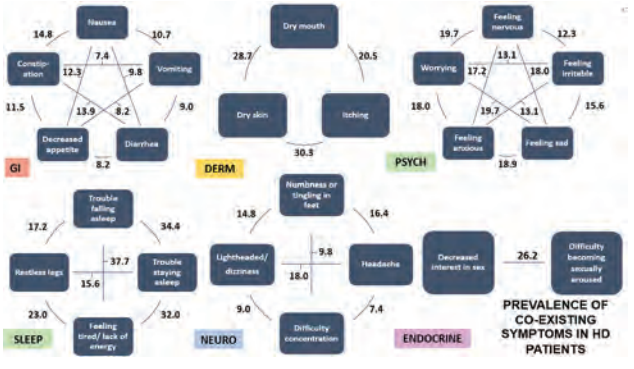
Background: Hemodialysis (HD) patients experience a high symptom burden similar to that of patients with malignancy, which may adversely impact their quality of life and well-being. Given that emerging data in other fields (oncology) show that symptoms often occur in clusters, we examined the presence of symptom clusters in a diverse prospective HD cohort.

Methods: In 122 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Chronic Kidney Disease* study recruited across 16 outpatient dialysis clinics, the presence of CKD-associated symptoms was ascertained by the Dialysis Symptom Index (DSI), a 30-item validated survey that assesses symptom severity (score range 0-120, higher scores indicating greater severity), over 7/2020-8/2020. Using the DSI surveys, we examined the presence of symptom clusters (≥2 symptoms related to each other and occurring together) across domains categorized by organ system.

Results: The mean±SD age of the cohort was 60±13 yrs, among whom 51% were female, 22% were Black, and 62% were Hispanic. Across the 30-item DSI survey, the most common individual symptoms included feeling tired/lack of energy (71%), dry skin (61%), itching (42%), muscle cramps (42%), and numbness/tingling in feet (41%). Upon examining co-existing symptoms, there was a high prevalence of symptom clusters, with the most common pairings including: 1) having trouble falling asleep + feeling tired/lack of energy or trouble staying asleep, 2) having trouble staying asleep + feeling tired/lack of energy, 3) dry skin + itching, 4) dry skin + dry mouth, and 5) decreased interest in sex + difficulty becoming aroused.

Conclusions: We observed a high prevalence of symptom clusters in a well-defined, diverse prospective HD cohort. Further studies are needed to determine the physiologic underpinnings of concurrent symptoms in order to identify targeted therapies that can ameliorate the high symptom burden of HD patients.

Funding: NIDDK Support



PO0829

Implementing a Patient-Centric Educational Handout to Provide the Knowledge of Kidney Disease and Dialysis, Promote Self-Care, and Improve Quality of Life in Patients Starting Hemodialysis

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Background: In the United States about 700,000 people need hemodialysis with most of them starting in the hospital. While patients on hemodialysis account for only 1% of Medicare beneficiaries, they account for 7% of total Medicare spending. While the cost of care is high amongst dialysis patient, the morbidity and mortality remain elevated with majority of deaths in the first 90 days of the start of dialysis. Studies has shown, lack of education in these patients about their treatments, dietary modification, fluid intake and vascular access. Early educational intervention of dialysis patient results in reduce re-hospitalizations and 90 days mortality in this vulnerable population

Methods: Extensive Pubmed search was performed to identify a validated clinical tool which will assess the pre-existing knowledge and post-interventional knowledge. Chronic Hemodialysis Knowledge Survey (CHeKS) was identified as a pre-test and post-test questionnaire to assess the efficacy of the project. CHeKS was distributed to 10 new-start hemodialysis patients admitted at Westchester Medical Center. An evidence based educational handoff was prepared and provided both verbally and in written on 10 new-start hemodialysis patients. Educational material were given to read independently as well. As post-test was performed couple of days later or at the time of discharge using the same CHeKS questionnaire. The mean and median pre-test and post-test scores were analyzed and efficacy of educational intervention was analyzed.

Results: The initial pre-test educational questionnaire on 10 patients showed a median score of 38.4% (5 out of 13 correct) and a mean score of 43.79%. The post-test score showed a median score of 92.3% (12 out of 13 correct) or a mean score of 90.9%. These results showed a 51.8% increase in educational score after the intervention was performed. Highest increase in patient's knowledge were related to renal diet and fluid restrictions.

Conclusions: This study showed that the institution of structured educational activity can result in higher knowledge in dialysis patients, leads to better adherence to dialysis prescription and dietary recommendations. This along with limiting excessive fluid intake can result in reduce re-hospitalization and better self-care.

PO0830

Implementation and Effectiveness of a Supportive Care Learning Collaborative for Hemodialysis

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Background: The objective of this study was to determine whether a learning collaborative for hemodialysis providers improved delivery of supportive care best practices.

Methods: Ten U.S. hemodialysis centers participated in a hybrid implementation-effectiveness pre-post study targeting seriously ill patients between April 2019 and September 2020. The collaborative educational bundle consisted of learning sessions, communication training and implementation support. The primary outcome was change in proportion of seriously ill patients with complete advance care planning (ACP) documentation. Healthcare utilization was a secondary outcome and implementation was assessed qualitatively.

Results: One center dropped out during the COVID-19 pandemic. Among the remaining nine centers, 22.9% (320/1395) of patients were identified as seriously ill in the pre-intervention period and 18.0% (226/1254) were identified in the post-intervention period. From the pre-intervention to post-intervention period, the proportion of patients with complete ACP documentation increased, and hospitalizations and emergency department visits decreased (Table). There was no difference in mortality, palliative dialysis, hospice referral or dialysis discontinuation. Screening for serious illness was widely and sustainably adopted. Goals of care discussions were adopted with variable integration and sustainment.

Conclusions: Supportive care best practices were feasible to implement in hemodialysis centers and largely sustained during the COVID-19 pandemic. We observed increased documentation of ACP and lower healthcare utilization after the intervention which could reflect a combination of collaborative and pandemic effects.

Funding: Private Foundation Support

Table. Advance care planning and health care utilization among seriously ill hemodialysis patients

ACP	Pre-implementation N=258	Post-implementation N=196	p-value
Complete ACP documentation, N (%)	94 (36.0)	77 (39.0)	<.001
Any ACP documentation, N (%)	156 (60.5)	151 (77.0)	<.001
Healthcare Utilization	Pre-implementation N=320	Post-implementation N=22	p-value
Died, N (%)	21 (6.6)	14 (6.2)	0.86
Emergency department visit, N (%)	92 (28.8)	43 (19)	0.005
Hospitalization, N (%)	153 (47.8)	73 (32.3)	<.001
Palliative dialysis, N (%)	4 (1.3)	5 (2.2)	0.29
Referred to hospice, N (%)	7 (2.2)	3 (1.3)	0.44
Discontinued dialysis, N (%)	6 (1.9)	1 (0.4)	0.10

PO0831

Anxiety, Comorbid Depression, and Dialysis Symptom Burden

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Background: Anxiety is an understudied construct in patients with kidney failure. Its relationship to dialysis and patient reported outcomes, including symptom burden, is not well known. 'Anxiety' describes a category of diagnoses and it is unknown if its components of general worry, somatic anxiety, and anxiety sensitivity have differential relationships with outcomes. It is also not known if depressive affect moderates these relationships.

Methods: In this single center survey study, 100 participants completed an assessment of depressive affect (Patient Health Questionnaire-9, PHQ-9), worry (Generalized Anxiety Disorder-7, GAD-7), somatic anxiety (Beck Anxiety Inventory, BAI), anxiety sensitivity

(Anxiety Sensitivity Index, ASI), and dialysis symptom burden (Dialysis Symptom index – DSI). Medical charts were extracted for demographic information, number of missed dialysis sessions in the past 30 days (not rescheduled or due to hospitalization), and average interdialytic weight gain over the past 3 dialysis treatments.

Results: The characteristics of the sample are found in the table below. People with elevated somatic anxiety (BAI >15) had significantly higher rates of depression, worry, anxiety sensitivity, and dialysis symptom burden (p<.001, all cases). In a predictive model of symptom burden, age, race, and gender were not associated with symptom burden, and only somatic anxiety remained significant once adjusting for depression. In the final model, depression accounted for 40% of the variance and somatic anxiety accounted for an additional 37%.

Conclusions: It appears that the impact on symptom burden of depression and worry/anxiety sensitivity overlap significantly, but somatic anxiety, commonly found in panic disorder, may be a unique contributor to excess symptom burden.

Variable	Total Sample	Elevated somatic anxiety (>15 BAI) N=22	Non-Elevated somatic anxiety (>15 BAI) N=77
Age	60.3 (16.0)	57.5 (15.2)	61.1 (16.2)
Gender (% female)	61%	59%	62%
Race/Ethnicity	51% White 36% Black 13% Asian 26% Hispanic	48%White 36%Black 16%Asian 45% Hispanic	60% White 36%Black 2% Asian 20% Hispanic
Average IDWG (3 last visits)	2.06 (1.2)	2.3 (1.8)	2.0 (.9)
Missed dialysis (% who missed at least 1 session in 30 days)	16.5%	18%	15%
Dialysis Symptom Index (symptom number)	10.0 (6.5)	16.6 (5.4)	8.1 (5.4)
Depression (PHQ-9)	5.1 (5.2)	11.3 (4.6)	3.4 (4.0)
Worry (GAD-7)	3.9 (4.8)	9.7 (5.2)	2.2 (3.1)
Somatic Anxiety (BAI)	9.8 (9.0)		
Anxiety Sensitivity (ASI)	11.3 (12.1)	22.3 (15.4)	8.2 (8.9)

Values are expressed as mean (standard deviation) unless otherwise stated

PO0832

Palliative and Conservative Care Consultation in Hemodialysis: A Survey

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Background: Prior to initiating dialysis for patients with End Stage Renal Disease (ESRD), options other than dialysis such as conservative or palliative care are under-utilized. There may be a subset of patients who may not be ideal candidates for dialysis. Conservative kidney management can address the symptoms of kidney failure and can articulate goals of care with or without dialysis. Given the costs of healthcare, high morbidity and mortality in the ESRD population, we believe greater attention to conservative care prior to dialysis would result in patients having more comprehensive information prior to initiating dialysis.

Methods: Patients were surveyed at a large for-profit dialysis center in the suburban Philadelphia area in late December 2020. They were administered a 5 question survey about recalled experiences regarding referral patterns prior to dialysis. Potential responses were "yes," "no," or "do not recall."

Results: 37 patients were surveyed. Mean age was 63 years +/- 14, 70% were male, 95% were black. 24% of subjects reported discussing hospice and palliative care prior to dialysis initiation. 25% of patients >65 years old and 22% of patients <65 years old had such discussions. Chi square analysis was not statistically significant.

Conclusions: Only a small percentage of patients with ESRD on hemodialysis recall discussions about alternatives such as hospice, palliative, or conservative care prior to initiating dialysis. There is likely some recall bias. The current paradigm for initiating dialysis fails to routinely include conservative options potentially exposing subjects to increasing morbidity. We believe conservative care should be part of the informed consent process prior to starting dialysis.

PO0833

Health-Related Quality of Life During Dialysis Modality Transitions: A Mixed-Methods Study

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Background: Dialysis transitions may have an impact on health related quality of life (HRQOL), a patient defined priority for research and clinical care. We measured HRQOL and explored perceptions of adults who were initiating dialysis for the first time or transitioning to a new dialysis modality in a large urban centre in Canada.

Methods: In this prospective convergent parallel mixed-methods study we recruited eligible patients who were transitioning to dialysis from pre-care (n=9, incident) or undertaking a dialysis modality change (n=10, prevalent) between July and September 2017. Patients completed the five domains of the Kidney Disease Quality of Life-36 (KDQOL-36) survey on their first day of dialysis treatment or first day of home dialysis training and underwent a semi-structured interview and follow up KDQOL-36 survey at 3 months.

Results: 19 patients completed KDQOL-36 at baseline and at 3 months; 15 also participated in an interview. Statistically significant increases in all measured domains of the KDQOL-36 were observed from baseline to three months: "Symptoms" [mean difference (MD)=14.9, p<0.01]; "Effects" (MD=14.3, p<0.01); "Burden" (MD=7.3, p=0.04); "PCS" (MD=7.5, p<0.01); "MCS" (MD=7.2, p=0.04). These patterns of change were similar for both incident and prevalent patients and across the different types of transitions. The qualitative interviews identified the following themes: 1) adapting to new circumstances (tackling change, accepting change), 2) adjusting together 3) trade offs, and 4) challenges of chronicity (the impact of dialysis, living with a complex disease, planning with uncertainty.

Conclusions: The transition to a new or different type of dialysis is associated with improvements in HRQOL. In addition, qualitative data provided an in depth understanding of the transition experience, and revealed significant emotional and psychosocial processes that need to be considered during both incident and prevalent dialysis transitions.

PO0834

Prevalence and Demographic Correlates of Pain, Depression, Fatigue, and Readiness to Seek Treatment for These Symptoms in Hemodialysis Patients

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Background: Patients with End Stage Renal Disease on hemodialysis (HD) experience a high burden of pain, fatigue and depressive symptoms. This study aims to better understand demographic differences in symptom burden and readiness to seek treatment among HD patients being recruited for an ongoing multi-center randomized controlled trial (TACcare).

Methods: Patients on in-center HD were screened for clinical levels of pain (Likert scale ≥4), fatigue (Likert scale ≥5), and depression (Patient Health Questionnaire-9 score ≥10) within the last 2 weeks. Patients with at least one clinical symptom were then screened to assess readiness for seeking treatment for symptoms, and eligible to enroll if they were at least in the contemplation stage of Readiness for Behavior Change. Demographic differences in symptom screening and readiness to change (yes/no) were assessed using t-tests (age) and Chi-Square or Fishers Exact tests (race, ethnicity, gender). Symptom burden by readiness to change status was assessed using Chi-Square tests.

Results: Of the 390 patients who met eligibility criteria (mean age 59 years, 45% females, 15% Black, and 32% American Indian/Alaska Native, 29% Hispanic), 303 (78%) displayed at least one clinically significant symptom - pain, fatigue, or depression. Of those experiencing symptoms, 39% reported experiencing 1 clinically significant symptom, 35% reported 2, and 26% reported 3. There were no statistically significant differences by age, race, ethnicity, or gender in those reporting symptoms versus those who were not, or those ready to seek treatment (80%) versus those not ready to seek treatment (20%). Of those who were experiencing symptoms, the percentage of patients willing to receive treatment increased as the number of symptoms increased (71%, 86% and 90% willing to receive treatment with 1, 2 or 3 symptoms respectively, p<.01).

Conclusions: The majority of HD patients report experiencing at least one clinically significant symptom and experiencing more of these symptoms increased readiness to seek treatment. Demographic difference in symptom burden and readiness for treatment were not evident in this sample and should continue to be the focus of additional research.

Funding: NIDDK Support

PO0835

Latinx Patients' Perspectives on Their Kidney Disease Education and Recommendations for Improvement: A Qualitative Study

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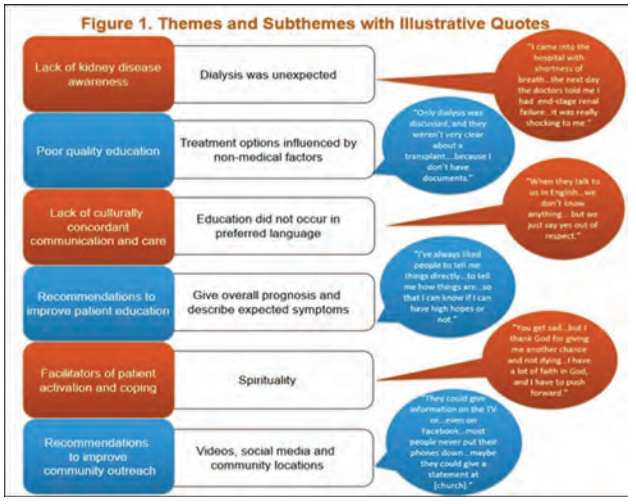
Background: In most states, Latinx immigrants with kidney failure receive dialysis in acute care settings on an emergency-only basis. What and how much kidney disease education they receive, and how to improve kidney disease education and outreach among Latinx populations is unknown. The objective of this study was to understand the kidney disease educational gaps of Latinx individuals who need but lack access to scheduled outpatient dialysis.

Methods: We conducted a qualitative, semi-structured interview study in a Texas hospital system from March 2020 to January 2021 with 15 individuals who received emergency-only dialysis when they were first diagnosed with kidney failure. We collected demographic information, and performed thematic analysis using the constant comparative method on interviews after they were audio-recorded, translated and transcribed verbatim.

Results: All 15 persons interviewed (60% male; mean age 51 years) identified as Hispanic (73% Mexican), and none reported knowing about their kidney disease more than 6 months before starting dialysis. The themes were: 1) lack of kidney disease awareness; 2) education provided was incomplete and poor quality; 3) lack of culturally concordant communication and care; 4) elements Latinx patients receiving emergency-only dialysis want in their education; 5) facilitators of patient activation and coping; and 6) Latinx patient recommendations to improve community outreach.

Conclusions: Latinx adults receiving emergency-only dialysis are usually unaware of their kidney disease until shortly before or after they start dialysis, and the education they receive is poor quality, and often not culturally tailored. Participants made feasible recommendations on how to improve education and outreach among Latinx communities.



PO0836

Improving Education and Satisfaction of Hemodialysis Patients Through Anonymous Feedback

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Background: Patients on outpatient hemodialysis (OHD) are a particularly vulnerable population who may not feel comfortable sharing their experience given the complex and frequent nature of their care. This could lead to conceivable gaps in knowledge pertaining to improving their satisfaction and education. To account for this potential limiting factor and to build on previous surveys performed on OHD patients we conducted a study in nine of our university affiliated OHD units.

Methods: The study had 3 major objectives: 1) apprehend the level of satisfaction of patients with varying aspects of OHD related care, 2) evaluate level of understanding and education of patients regarding issues that pertain to their health and wellbeing, 3) identify potential avenues for improvement based on patients' input. The survey was in English, paper based, with individual answer choices graded using a 1-5 rating scale [1:very poor, 2:poor, 3:neutral, 4:good, 5:excellent]. To ensure anonymity, the completed surveys were folded and dropped into a box.

Results: Among 516 screened patients 228 did not participate. Additional 35 patients were excluded for ≥ 1 reasons: legally blind, unable to read/write/speak English, advanced dementia, too frail. 253 eligible patients completed the survey. While the overall results were reassuring with 18 out of 24 questions yielding an average of ≥ 4.2 per question, we found specific areas for improving care and education. These included providing additional resources and information regarding palliative care, mental health, cardiovascular diseases, transplant process, addressing discomfort during OHD, improving privacy, and improving the time that the nephrologist spends with patients.

Conclusions: The US centers for Medicare and Medicaid services ESRD prospective payment system and quality incentive program requires that dialysis centers meet predefined criteria for quality of patient care to ensure future funding. We took advantage of an anonymous survey to further reflect on the potential needs of this patient population to enhance their quality of life and education. Despite specific limitations, our survey demonstrated patients undergoing OHD were overall satisfied and had a good understanding about their overall health. However, we identified several aspects to improve upon as requested by our respondents.

PO0837

Provider Recognition of Patient-Reported Symptoms in Patients on Maintenance Hemodialysis

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Background: Patients with ESKD on maintenance HD (HD) experience more symptoms than the general population. In order to enable better symptomatic management, it is critical that providers recognize and document these symptoms; however, recognition by nurses and physicians is unclear.

Methods: We surveyed patients that were receiving in-center HD for ≥30 days, and attended HD three times a week at the Mount Sinai Kidney Center. Patients were surveyed on if they experienced 21 symptoms over the past 24 hours at the end of their treatments for 12 sessions. The treating nurses were surveyed at the end of each iHD treatment to identify if the patient had any of the 21 symptoms. We considered a positive response on any of the 12 surveys as a positive during the study period. Physicians were asked during week three of the study period if the patient had experienced any of the 21 symptoms during the past 4 weeks.

Results: Of the 166 eligible patients, 101 consented to the study, and 97 completed all 12 surveys. The mean age was 56±14 years, 52% were female, and 52% were Black. The most common symptoms reported by the patients were fatigue (61%), cramping (59%), and dry skin (53%) **(Figure 1).** Nurses under-recognized 17/21 symptoms, mean relative difference of 54±33%. Physicians under recognized 16/21 symptoms, by a mean difference of 23±56%. Symptoms with the largest degree of under-recognition by nurses were dry skin (difference of 51 percentage points) and fatigue (difference of 42 percentage points). Physicians struggled most with recognition of cramping (difference of 39 percentage points) and fatigue (difference of 34 percentage points).

Conclusions: Patient symptoms were generally under-recognized by both dialysis nurses and physicians. While several symptoms such as shortness of breath, nausea, and vomiting were well recognized by nurses and physicians, nurses under-recognized dry skin and fatigue and physicians under-recognized cramping and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

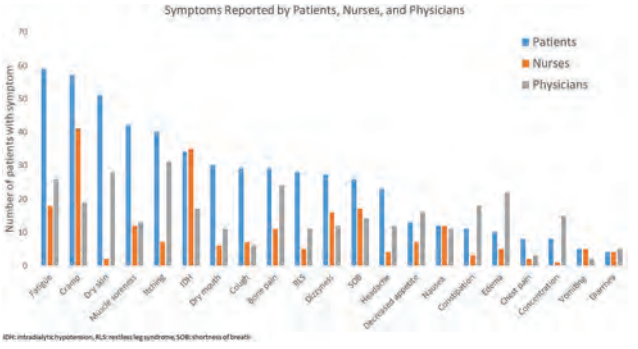

Figure 1: Number of symptoms reported by patients, nurses, and physicians.

PO0838

Improving Food Insecurity in Patients with ESKD on Hemodialysis: Partnership with Local Food Bank

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Background: Nutrition plays an important role in the management of ESKD on HD. Barriers to appropriate nutrition include medical, behavioral and socio-economic factors. Socio-economic factors may include poor purchase power and problems with transportation. Poverty rate at the area of University of Virginia (UVA) is 12.9%, which 1.3 times the state average.

Methods: UVA partnered with the local food bank to meet the basic nutritional needs of our patients by delivering renal appropriate diet to patients at the dialysis unit, with an aim of reducing individual food insecurity.

Results: The current UVA food bank collaboration program distributes more than 50 bags each month and roughly 80% of the entire dialysis program has received at least one bag since the inception of the program. Presently 34 patients consistently received bags each month (bi-monthly or greater distribution of bags). There was no significant changes in weight, serum albumin, calcium, phosphorus or potassium between baseline and 6 months of consistently receiving food bags. 28/34 (82.4%) patients responded to a survey. Patients were 64.3% African American with 57.1% females with average age of 61.3 years. Average household of these patients were 2.2, receiving 2.3 bags/week with an average of 3.3 meals /week. While 50% of patients reported satisfaction with the program, 14.3% were very satisfied, 32.1% neutral and 3.6% were unsatisfied. 57.1% viewed the food as healthy, with 21.4% perceived food to be very healthy, 17.8% were neutral and 3.6% viewed the food to be unhealthy. The majority of the patients reported improved nutrition with these food items (82.1%). While only 10.7% of the patients reported they had to skip a meal because of being short on food, 85.7% reported that these bags helped them eat more meals on a regular basis.

Conclusions: Partnership with local food banks helps decrease food insecurity and improved satisfaction in patients on hemodialysis. Nutritional parameters did not improve, which may be due to consumption of supplemental food outside of the program. Expanding such programs to other dialysis units and provision of more fresh fruits, vegetables, and meats could help decrease dependence on external sources of higher processed foods that contain high levels of potassium and phosphorus and may improve patients' outcomes.

PO0839

Medication Burden and Prescribing Patterns Among ESKD Patients on Hemodialysis in the United States, 2013-2017

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Background: The medication burden of patients with ESKD on HD is amongst the highest of any of the chronic diseases. This study describes the medication burden and prescribing patterns in a contemporary cohort of patients with ESKD on HD in the U.S.

Methods: We used the United States Renal Data System database from January 1, 2013 and December 31, 2017 to quantify the medication burden of patients on HD aged ≥18 years. We included patients who had continuous Medicare parts A, B, and D coverage

for at least 3 months prior to January 1 of the respective year and excluded patients with a history of peritoneal dialysis or kidney transplant at any time prior to the year of interest. Patients could contribute data to multiple yearly cohorts. We calculated the average number of prescription medications per patient during each respective year, number of medications within classes, including potentially harmful medications, and trends in the number of medications and classes over the study period.

Results: We included 163,228 to 176,133 patients from 2013 to 2017. In 2013, the mean age was 63.5 years and increased to 65.1 years by 2017. The percentage in the age 18-64 years category decreased (51.3% in 2013 compared with 45.9% in 2017) and the percentage in the older age categories all increased. In 2013, 51.8% were male and 48.2% were female, compared with 53.6% male and 46.4% female in 2017. The overall burden of medications decreased slightly, from a mean of 7.4 (SD 3.8) in 2013 to 6.8 (SD 3.6) medications in 2017. Prescribing of potentially harmful medications decreased over time (74.0% with at least one harmful medication class in 2013 to 68.5% in 2017). In particular, the prescribing of non-benzodiazepine hypnotics, benzodiazepines, and opioids decreased from 2013 to 2017 (12.2% to 6.3%, 23.4% to 19.3%, and 60.0% to 53.4%, respectively). This trend was consistent across subgroups of age, sex, race, and low-income subsidy status.

Conclusions: Patients with ESKD on HD continued to have a high overall medication burden, with a slight reduction over time accompanied by a decrease in prescribing of several classes of harmful medications. Continued emphasis on assessment of appropriateness of high medication burden in patients with ESKD is needed to avoid exposure to potentially harmful or futile medications in this vulnerable patient population.

PO0840

The Impact of Late Initiation of Chronic Dialysis on Mortality: A National Retrospective Cohort Study

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Background: Current Canadian guidelines recommend deferring dialysis initiation in asymptomatic patients until the glomerular filtration rate (GFR) reaches 6 mL/min/1.73m^2, (an "intent-to-defer" strategy). However, little is known about how dialysis initiation and post dialysis outcomes are impacted when patients start at or below this threshold.

Methods: We sought to characterize the impact of starting dialysis at or below 6 mL/min/1.73m^2 in a national retrospective cohort study of incident dialysis patients from 2004-2019. Dialysis data (excluding Manitoba and Quebec) was acquired from the Canadian Organ Replacement Register (CORR) and linked to hospitalization data using the well-established discharge abstract database (DAD). The cohort was restricted to only those who initiated dialysis as an outpatient and with previous nephrology follow-up of three months or more. Time to death was compared for those starting at or below 6 ml/min/1.73m^2 (using the CKD-EPI formula) to those initiating between an eGFR of 6-15 ml/min/1.73m^2 and analyzed using an adjusted cox proportional hazard model.

Results: A total of 63327 unique patients started dialysis from 2004-2019, of whom 39696 patients started dialysis as an outpatient after at least three months of nephrology follow-up. The mean age was 63+/-14, 68% were white, and 61% were male. 24% of the population started dialysis at an eGFR by CKD-EPI at or below 6 mL/min. Patients starting at 6 mL/min/1.73m^2 or below were more likely to start dialysis with a CVC (59% vs 50%, p<0.001). During the study period 18979 patients died (48%). Starting dialysis at or below 6 mL/min/1.73m^2 was associated with a longer time to death (HR 0.87; 95% CI 0.84,0.90) after adjusting for sex, race, age, dialysis access, diabetic kidney disease, and other comorbidities.

Conclusions: In this cohort of incident dialysis patients, those with an eGFR at or below 6 mL/min/1.73m^2 had a lower risk for mortality compared with those starting with a higher eGFR. These findings support deferral of dialysis initiation beyond the threshold of 6 mL/min/1.73m^2 in the absence of traditional indications.

PO0841

Hurricane Harvey Increased Need for Emergency Care in Patients with ESKD

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Background: During natural disasters, end-stage kidney disease (ESKD) patients may represent a particularly vulnerable population due to interruption in care. We hypothesize that mortality and medical complications significantly increased in ESKD patients as a result of the disruptions in care related to Hurricane Harvey (HH).

Methods: Ten outcome variables for patients receiving outpatient, inpatient and home dialysis in FEMA designate hurricane disaster areas during the months of Aug 2017 – Dec 2017 representing exposure to the effects of Hurricane Harvey, were compared with the same time periods in 2016 and 2018. In this retrospective cohort study, ESKD patients were stratified by dialysis modality. Inclusion criteria were patients identified with ESKD by Medicare, had received at least one dialysis treatment within the observed timeframe, and were continuously enrolled for the four months before and/or four months after HH landfall or enrollment was dropped due to death. Main outcomes of the study included mortality, inpatient admissions, emergency department (ED) visits, and diagnosis of complications.

Results: Using deidentified Medicare Claims data we identified 7,362 patients in the outpatient, 862 in the inpatient, and 810 in the home setting and compared outcomes in approximately stable populations in the years 2016 and 2018. Odds of ED visit was 31% greater (OR= 1.31, CI= [1.19, 1.44]) in 2017, compared to 2016 and 25% greater (OR= 1.25, CI= [1.14, 1.38]) compared to 2018. Odds of hyperkalemia was 37% greater (OR= 1.37, CI= [1.22, 1.55]) in 2017 than 2016. Nonwhite patients and men experienced lower odds of the outcomes of interest compared to white patients and women. Odds of gastrointestinal infection was 2.34 times more likely (OR= 2.33, CI= [1.32, 4.12]) in 2017 versus 2018. Black patients experienced increased odds of cerebrovascular accident (CVA) compared to white patients.

Conclusions: Using Medicare claims data we found significant differences in Emergency Department (ED) visits and incidence of hyperkalemia in HH exposed patients compared to patients receiving outpatient dialysis in 2016 and 2018. Catastrophic events represent dangers for ESKD populations with increased risk of complications and burden on the healthcare system. Better preparation for natural disasters may improve health outcomes associated with limited access to dialysis.

Funding: Private Foundation Support, Clinical Revenue Support

PO0842

Tuscany Network Program for Evaluation of Functional Status in Hemodialysis: The Rehabilitation in Hemodialysis Area Centro Tuscany (REACT) Study

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Background: Frailty is associated with adverse outcomes among hemodialysis patients. Hemodialysis sessions may represent an opportunity to reassess functional status, to plan and monitor long-term physical exercise, leading to considerable improvement of quality of life and physical performance. The objective of our study is to assess the prevalence and predictors of frailty among a cohort of prevalent dialysis patients in our area (REACT Study).

Methods: A regional program was designed to evaluate functional status in all patients performing hemodialysis in the 11 Dialysis Units of USL Toscana Centro. All patients are screened through the following tests: Short Form Health Survey (SF12); Elderly Falls Screening Test; Short Physical Performance Battery (SPPB); Handgrip test. Patients were assigned to three groups on the basis of the SPPB score: poor (SPPB <6), moderate (SPPB 7-9) and good performers (SPPB >9).

Results: Of the 920 hemodialysis patients assessed for eligibility, 446 were enrolled and divided in 3 groups on the basis of SPPB score. Characteristics of the participants and functional status evaluation are shown in Table 1. SPPB score shows a significant correlation with handgrip of right arm (r=.248, p<0.001), with handgrip of left arm (r=.211, p<0.001), with Elderly Falls Screening Test (r=.448, p<0.001), with SF12 physical component (r=.432, p<0.001), with SF12 mental component (r=.146, p<0.001). Principal predictors of SPPB score are Elderly Falls Screening Test (adjusted R^2=.235), and age (cumulative adjusted R^2=.361).

Conclusions: In our hemodialysis population, SPPB allowed identification of 3 frailty phenotypes. The information needed to determine patients' degree of frailty can be gathered relatively easily, making frailty assessment a routine activity in hemodialysis patients' evaluation.

Table 1

Variable	Poor performers (n=119)	Moderate performers (n=119)	Good performers (n=208)	p value
Female sex – no. (%)	57 (47.8)	44 (36.9)	76 (36.5)	
Age - yr	75.1±9.8	72.4±10	60.2±14.7	
Dialytic age – mo	74.7±9.89	72.4±9.99	60.0±14.7	
SPPB score	3.5±2.24	8.2±0.79	11.2±0.87	
Handgrip test - kg (right arm/left arm)	20.9±10.9/19.1±11.4	24.8±14.1/23.2±13.7	30.5±15.1/26.8±14.6	<0.001
Elderly Falls Screening Test - score	2.5±1.4	1.2±1.6	0.7±1.0	<0.001
SF12 physical score	32.8±9.8	38.9±9.9	44.0±9.5	<0.001
SF12 mental score	46.0±12.3	46.9±12.0	49.2±11.2	0.45

PO0843

Functional Prognosis Following Cerebral Hemorrhage in Patients on Hemodialysis

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Background: It has been reported that patients on hemodialysis have a higher morbidity and mortality for hypertensive cerebral hemorrhage. However, little is known about the functional outcomes in the surviving patients.

Methods: We retrospectively analyzed 62 consecutive patients on hemodialysis who developed hypertensive cerebral hemorrhage between 2016 and 2020. Patient background data, data on the clinical presentation of cerebral hemorrhage, and details of the lifesaving brain surgery (craniotomy for removal of hematoma and ventricular drainage) were reviewed. The outcomes examined were in-hospital mortality and Glasgow Coma Scale (GCS), modified Rankin Scale (mRS), and Functional Independence Measure (FIM) scores at discharge.

Results: The median age of the patients was 66.5 years (interquartile range [IQR] 61.8–72.5). The median GCS score at admission was 13 (IQR, 6–14). Ventricular perforation was observed in 46.8% of patients. The median estimated hematoma volume

was 26.9 mL (IQR, 7.7–69.6). The in-hospital mortality rate was 29.0%. Palliative care policy was selected by 16.1% of patients at admission, and 27.4% of patients underwent a lifesaving brain surgery. Compared with survivors, the non-survivors had a lower level of consciousness at admission (GCS score, median [IQR]: 4.5 [3–8] vs. 14 [11–14], respectively, $p<0.001$), higher rate of ventricular perforation (88.9% vs. 29.5%, $p<0.001$), and larger estimated hematoma volume (55.5 [29.6–124.5] vs. 16.3 [5.5–43.6] mL, respectively, $p=0.003$). After excluding patients with palliative care policy at admission, the ventricular perforation rate and estimated hematoma volume were higher in patients who underwent surgery than those who did not undergo surgery. Patients who underwent brain surgery had a lower level of consciousness, mRS score (median [IQR], 4.0 [3.0–4.0] vs. 5.0 [5.0–6.0], respectively $p<0.001$), and FIM score (18 [18–53.8] vs. 59 [20–84.5], respectively, $p=0.009$) at discharge than patients who did not undergo surgery.

Conclusions: In our single-center experience, a lower level of consciousness at admission, larger estimated hematoma volume, and ventricular perforation were associated with high mortality in patients on hemodialysis with cerebral hemorrhage. Survivors who underwent the lifesaving brain surgery had very poor functional outcomes at discharge.

PO0844

Hyperammonemia in an ESRD Patient

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Introduction: Carnitine is an important co-factor in long-chain fatty acid metabolism, and is involved in transport of long chain fatty acids into the mitochondria. Carnitine deficiency can present with hyperammonemia. We present a patient with ESRD with hyperammonemia and encephalopathy.

Case Description: This is a 48-year-old man with End Stage Renal disease due to neprocalcinosis secondary to treatment complications due to X- Linked Hypohposphatemic rickets, presented to emergency room with nausea vomiting and severe confusion. He had no known liver disease or seizure disorder and was not on valproate or any other psychotropic medications. His liver enzymes were normal AST, ALT, albumin levels but he had persistently elevated alkaline phosphatase of 313 unit / L (40-130). PCO2 levels were normal. L. His ammonia level of 578 micro mol/L. There was no intracranial abnormalities on imaging. Free carnitine (FC) levels came back as 26 nmol/ml (25-54), Acyl Carnitine (AC) 13 nmol/ml (5-30) AC/FC ratio of 0.5. Even though he had low normal FC levels, his AC/FC ratio was elevated and it has been proposed that car/acyl car ratio greater than 0.4 represents carnitine deficiency. Patient initiated on IV L carnitine 20 mg/Kg three times weekly without repeat episode of hyperammonia. It was also noted that patient no longer experienced intradialytic hypotension.

Discussion: Carnitine deficiency causes accumulation of non-oxidized fatty acyl-coenzyme A in the mitochondria, which inhibits degradation of ammonia. This typically responds to supplementation. An inverse correlation between plasma carnitine levels and ammonia has been observed in patients treated with valproic acid, and L Carnitine has been used as treatment reduce the ammonia levels in valproate induced hyperammonemia. Carnitine deficiency can present with hyperammonia, and clinicians should have high index of suspicion for this entity in malnourished dialysis patients without significant liver disease. Treatment is directed at replacement with intravenous Carnitine. Oral preparation containing mixture of D and L- carnitine is available but D- Carnitine is toxic. L- carnitine has limited oral absorption and has a limited bioavailability of 15%. The unabsorbed carnitine is degraded by intestinal bacteria to metabolites that are potentially toxic and have been shown to cause cognitive impairment. These limits use of oral supplementation of Carnitine.

PO0845

Neurocognitive Function with Conventional Hemodialysis vs. Post-Dilution Hemofiltration as Initial Treatment: A Randomized Controlled Trial (The DA-VINCI Study)

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Background: The ideal modality choice and dialysis prescription during the first renal replacement therapy (RRT) session remains controversial. We conducted a pilot study to determine the safety risk for hemodialysis versus hemofiltration and its relationship with neurocognitive assessment on incident RRT patients.

Methods: Twenty-four incident RRT patients were included. Patients were randomized the conventional HD group or the post-dilution HF group. MMSE and MOCA tests were applied in all patients before and after RRT and brain MRI was performed in 7 patients from each group before and after the intervention.

Results: Baseline characteristics were similar between groups. Compared to conventional HD, post-dilution HF had longer treatment time and blood volume. There were no significant changes in blood pressure after RRT in both groups. The MMSE test showed no significant differences between groups or within groups. The MOCA test showed an increase in the total score for the post dilution HF group with no significant changes between groups. The magnetic resonance image (MRI) evaluation showed no differences between or within groups.

Conclusions: Post-dilution hemofiltration is a safe alternative for the first hemodialysis session in incidence RRT; it allows longer treatment time if ultrafiltration is required has a similar neurological risk than conventional HD.

Hemodialysis and hemodynamic variables.

	Conventional HD (n = 12)	Conventional HD (n = 12)	Post dilution HF (n = 12)	Post dilution HF (n = 12)
	Before	After	Before	After
Body weight (Kg)	71.6 ± 18.6	67.2 ± 28.3	71.0 ± 17.4	67.7 ± 14.5
SBP (mmHg)	163 ± 29	158 ± 28	161 ± 30	161 ± 21
DBP (mmHg)	88 ± 14	86 ± 13	90 ± 21	87 ± 19
BUN (mg/dL)	137.3 ± 61.7	91.1 ± 39.3 *	124.5 ± 34.8	86.4 ± 25.5 *
MMSE test				
Total score Cognitive impairment	23 ± 3 10 (83%)	26 ± 2 3 (25%)	25 ± 3 2 (17%)	26 ± 2 1 (8%)
MOCA test				
Total score Cognitive impairment	23 ± 3 10 (83%)	25 ± 5 4 (33%) *	22 ± 4 10 (83%)	25 ± 3 * 6 (50%) *
MRI findings Silent infarction Other abnormalities No abnormalities	5 (42%) 0 (0%) 2 (17%)	5 (42%) 0 (0%) 2 (17%)	7 (58%) 1 (8%) 0 (0%)	7 (58%) 1 (8%) 0 (0%)

Data are shown as mean ± standard deviation, median (percentile 25, percentile 75) or absolute frequency (percentage).

* = p ≤ 0.05 compared to before dialysis (within same group)

PO0846

Intradialytic Yoga-Based Breathing and Relaxation to Improve Anxiety, Depression, and Quality of Life: A Pilot Feasibility Study

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Background: In-center hemodialysis patients have high rates of depression and anxiety. Pharmacologic interventions to ameliorate psychological burdens have proven to be limited in efficacy. Alternative therapies are increasingly used for those with chronic disease. A small number of studies have looked at the impact of meditation and yoga to improve symptoms of anxiety and depression and to promote a better quality of life. The aim of this study was to test the feasibility of implementing a chairside intradialytic yoga-based breathing and relaxation technique. A secondary goal was assessing the efficacy of such an intervention.

Methods: Eligible subjects were patients with a below average score on the Mental Component Summary (MCS) of a previously completed Kidney Disease Quality of Life (KDQOL™-36) survey. Following consent, each subject was provided with an MP3 player, pre-loaded with a 12-minute recording of a specific yogic breathing and relaxation exercise, the Three-Part Breath. The intervention consisted of listening to the recording at each dialysis treatment over a 12-treatment period. Subjects completed a KDQOL™-36 survey both at the start and the end of the study. A Likert scale to measure anxiety was completed at each dialysis treatment both pre- and post-intervention.

Results: 11 subjects were enrolled over a 10-month period in 2020; 10 completed the study. As measured by the Likert scale, anxiety was significantly reduced after listening to the recording. Notably, there was a larger reduction in anxiety on a per treatment basis in the period after the start of the Covid-19 pandemic compared to the pre-pandemic period. Over the study period, there was a significant improvement in the scores of the Effects of Kidney Disease on Quality of Life component of the KDQOL™-36, and a trend toward significant improvement in the Mental Component Summary scores.

Conclusions: A chairside intradialytic breathing and relaxation program can be integrated into a dialysis treatment session. The study demonstrates an improvement in scores related to anxiety, depression, and measures of quality of life. Larger and randomized trials using this intervention are needed to better understand its benefits and adverse effects, as well as the obstacles to large scale implementation.

PO0847

Quality of Life and Symptom Burden Before and After Start of Dialysis in Older Patients

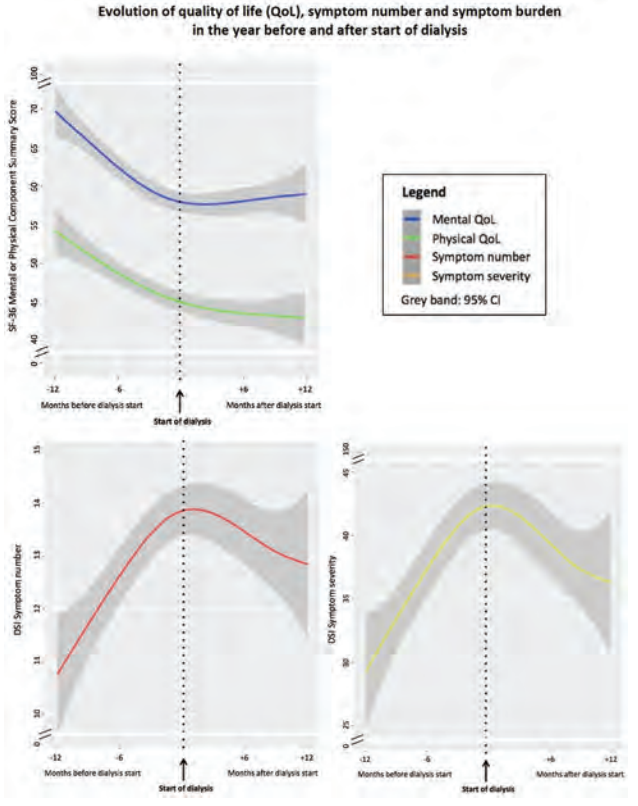
Esther N. de Rooij,[1] Yvette Meuleman,[1] Johan W. De Fijter,[1] Kitty J. Jager,[2] Nicholas C. Chesnaye,[2] Christoph Wanner,[4] Friedo W. Dekker,[1] Ellen K. Hoogeveen.[1,3] the EQUAL Study investigators *[1]Leids Universitair Medisch Centrum, Leiden, Netherlands; [2]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [3]Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, Netherlands; [4]Universitatsklinikum Wurzburg, Wurzburg, Germany.*

Background: The number of ESKD patients ≥65y starting chronic dialysis increases. Many of these patients have low quality of life (QoL) and high symptom burden. Little is known about the effect of dialysis initiation on QoL and symptoms. Therefore, we studied QoL and symptoms before and after start of dialysis in older patients.

Methods: The European Quality (EQUAL) study is an ongoing prospective multi-center cohort study in late stage 4/5 CKD patients ≥65 years. For this analysis, we included all patients who started dialysis. QoL was assessed every 3-6 months using the SF-36, resulting in a physical (PCS) and mental (MCS) component score, with higher scores meaning better QoL. Symptom number and severity were assessed every 3-6 months using the dialysis symptom index (DSI), with higher scores meaning higher burden. With linear mixed models we explored the evolution of mental and physical QoL, symptom number and severity in the year before and after dialysis start.

Results: We included 571 older patients at dialysis start. Mean (SD) age was 77 (6) years, 74% were men, 45% had diabetes or cardiovascular disease and mean eGFR was 8.2 (3.7) ml/min/1.73m^2. In the year before dialysis MCS decreased by -15.7 (95% CI: -19.5 to -11.8), PCS by -12.0 (-15.7 to -8.2), symptom number increased by +3.5 (+2.5 to +4.6) and severity by +14.8 (+10.9 to +18.8). In the year after, MCS increased by +1.9 (-2.7 to +6.4), PCS decreased by -2.1 (-6.9 to +2.7), symptom number by -0.9 (-2.1 to -0.3) and severity by -6.0 (-10.4 to -1.7).

Conclusions: Mental and physical QoL, symptom number and severity, worsened considerably in the year before dialysis, but stabilized after dialysis initiation. These results could inform older ESKD patients who consider starting dialysis.



PO0848

Objective Evaluation of Quality-of-Life Assessment as Predictors of Overall Health in Hemodialysis Patients in KSA

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Background: Dialysis effect on a patient's quality of life (QoL) is associated with death in regular hemodialysis (HD) patients and is a marker of wellbeing. In addition to clincal outcome measures QoL is influenced by socioeconomic status and education. Our aim was to explore the QoL in HD patients in population of prevalent HD patients in KSA.

Methods: The study consisted of 1032 patients undergoing HD in 17 centers. Data were collected by the completion of a specially designed questionnaire The Kidney Disease Quality of Life-Short Form (KDQOL-SF™) Arabic version 1.3 for assessing QoL.

Results: The study included 1032 patients (527 [51%] males and 505 [49%] females) with mean age 54.1 (±16.6) years and undergoing HD for 57.9 (±65.3) months. Multiple logistic regression analysis was done to identify parameters that independently associated with QoL. Lowest score was for the "burden of kidney disease" 33.1 (±23.4). Both "Physical Health Composite" (PHC) and "Mental health composite" (MHC) scores were poor as well, 36.5 (±8.7) and 42.0 (±8.7) respectively. "Patient satisfaction" and "Dialysis staff encouragement" scores were relatively higher 71.5 (±22.7) and 84.4 (±18.8) respectively. Age, duration of HD, cardiac comorbidity and abnormal phosphorus level were significant negative predictors for "overall health" scores while education and home medications' count were significant negative predictors for that domain. Abnormal phosphorus level and longer durations on HD treatment were significant negative predictors for "overall health", "MHC", "Burden of kidney disease" and perceived "Dialysis staff encouragement" scores. Age, female gender and hypoalbuminemia were significant negative predictors of "PHC" sores. Controlling serum phosphorus level and albumin might predict better QoL.

Conclusions: Misconceptions about QoL still represent a substantial barrier among HD patients. Most are educated about fundamental clinical outcomes after initiation of dialysis. In our study, Patients on hemodialysis have a poor QoL score. Different sociodemographic and clinical characteristics affect scores. Initiatives to promote and improve onboarding dialysis education and knowledge about QoL are needed to improve the low QoL in Saudi Arabia. Such patients may benefit from efforts on the part of the health care provider to support patient QoL as part of the monthly care plan.

PO0849

Fatal and Non-Fatal Gastrointestinal Events with Sodium Polystyrene Sulfonate Use in Hemodialysis: DOPPS

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Background: There are increasing concerns regarding the gastrointestinal (GI) safety of sodium polystyrene sulfonate (SPS), a medication commonly used in the management of hyperkalemia. The objective is to compare the risk for fatal, non-fatal and their composite GI events following initiation of SPS in patients on hemodialysis compared to non-use

Methods: An international registry of adults (≥18) on chronic intermittent hemodialysis (Dialysis Outcomes and Practice Patterns Study, DOPPS, Phases 2-6 from 2002 to 2018, 17 countries, n=229,295) who were prescribed SPS (n=24,668, 10.76%) were compared with non-users of SPS. Individual patient and facility-level analysis of fatal and non-fatal GI events were examined using weighted models.

Results: Country-level variation in SPS use ranged from 0.74% (UK) to 47.42% (France). 934 fatal, and 837 non-fatal events occurred [3-year cumulative incidence for fatal GI events: SPS 9.0% vs. no SPS 7.6%; non-fatal: SPS 0.4% vs. non-use 0.5%]. The weighted risk of fatal and composite GI events was elevated with SPS use compared to non-use (fatal HR 1.18 95%CI 1.05-1.32, non-fatal HR 0.73 95%CI 0.64-0.84, composite HR 1.02 95%CI 0.82-1.26). Younger age (<=65), men, country (France, Belgium, Japan), dialysis vintage (>4 years), shorter HD treatment time (<3.5 hours) and a higher K gradient (serum potassium – dialysate potassium) were associated with a higher risk of a fatal GI event with SPS. The findings were consistent when limited to individuals with known vascular access (n=135, 628) and in an analysis examining the fraction of SPS use by facility.

Conclusions: SPS use in patients on hemodialysis is associated with a higher risk of fatal GI events.

Funding: Private Foundation Support

PO0850

Improved One-Year Survival and Decreased Hospitalization Rate in Incident Hemodialysis Patients with Incremental as Compared to Standard Hemodialysis Regimen: A Single-Centre Experience

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Background: Preservation of residual kidney function (RKF) in maintenance hemodialysis (HD) patients is associated with better survival and quality of life. RKF may be better preserved with an incremental HD regimen in patients starting HD. Since 2013, incremental HD (frequency < 3x/week) has been used in our center.

Methods: Incremental HD is implemented in incident HD patients who have a daily residual diuresis > 600 ml, a urea clearance ≥ 2 ml/mn and an interdialytic weight gain < 2.5 kgs. Patients are clinically assessed every week and a 24 hr-urine sample is collected every other month in order to measure RKF.

Results: From January 2013 to March 2020, 295 patients started chronic dialysis in our center, of whom 221 were on hemodialysis. Among them, 63 patients started maintenance HD with an incremental regimen. These patients did not differ significantly from those with a thrice-weekly HD regimen in terms of age, gender and comorbidity score. Residual diuresis, eGFR and urea clearance at incremental HD initiation were respectively 1842 ± 749 ml/day, 6.7± 3.1 ml/mn and 4.0 ± 1.8 ml/mn. Among those 63 patients, four could retrieve a sufficient RKF to become dialysis-independent after a mean 6-month duration of incremental HD and 2 were transplanted while on incremental dialysis. Among the remaining 57 patients, mean duration of incremental HD until transition to a thrice-weekly HD regimen or death was 12 ± 12 months (median, IQR: 10, 6-20). Within the first dialysis year, survival and hospital-free days (median, IQR) were higher in patients starting with incremental HD than in patients with a thrice-weekly HD regimen (91 vs 77%; p=0.02 and 344 (318-360) vs 338 (295-354) days; p=0.03).

Conclusions: These preliminary results show that incremental HD can be implemented in incident HD patients as long as regular clinical and RKF assessments are found adequate. However, randomised clinical trials assessing long-term survival and quality of life in incremental HD are necessary prior to its large-scale implementation.

PO0851

Association Between Systolic Blood Pressure Changes and Residual Kidney Function Decline Among Hemodialysis Patients After 1 Year

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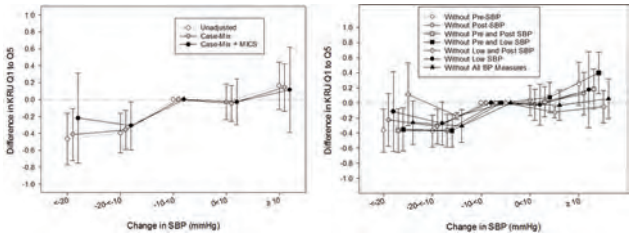
Background: For patients undergoing hemodialysis, large changes in systolic blood pressure (SBP) from before to after the dialysis has been associated with worse survival. Declines in residual kidney function has also been associated with worse survival. However, the association between SBP changes and residual kidney function decline has not yet been examined.

Methods: We constructed a retrospective cohort of 6659 hemodialysis patients who started dialysis between 2007-2011 with data on average baseline changes in SBP and renal urea clearance (KRU) at the 1st and 5th patient quarter (91 day interval from dialysis start). KRU difference was measured as KRU difference between 5th minus 1st patient quarter. The association between baseline average changes in SBP and KRU difference was examined using linear regression analyses. Covariates included age, sex, race, BMI, dialysis modality type, and comorbidities.

Results: Linear regression analysis indicated a linear relationship between change in SBP and KRU decline even after adjusting for covariates. Trends across all models showed hemodialysis patients with increased systolic blood pressure showed increased residual kidney function compared to the reference (-10 to -0 mmHg). After adjusting for covariates, hemodialysis patients with SBP levels that increased by 10mmHg or more had the greatest increase of KRU (0.12, 95% CI (-0.39, -0.62)), while patients with a decrease of SBP by 10-20mmHg had the greatest decline (-0.31, 95% CI (-0.60, 0.02)). Models adjusting for SBP measures showed similar trends, while the model without low-SBP and post-SBP showed an increased in KRU when SBP decreased by 10-20mmHg (0.23, 95% CI (0.01, 0.05).

Conclusions: Increase in SBP was associated with a greater KRU decline in hemodialysis patients. Futher studies should examine the underlying causes of this association and determine if modifications to dialysis treatments can improve preserving KRU and patient survival.



PO0852

Respiratory Fluoroquinolones and the Risk of Sudden Cardiac Death Among Patients Receiving Hemodialysis

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Background: Respiratory fluoroquinolones are one of the most common classes of medications with QT prolonging potential prescribed to patients receiving hemodialysis. Some studies in the general population have linked their use to sudden cardiac death (SCD). However, evidence linking respiratory fluoroquinolones to adverse cardiac outcomes in dialysis patients, a population with an exceptionally high baseline risk of SCD, is limited to case reports of torsades de pointes.

Methods: Data were obtained from a cohort of Medicare-enrolled hemodialysis patients in the U.S. Renal Data System registry (2007–2016). Using a new-user design, we conducted a retrospective cohort study to assess the comparative 5-day risk of SCD between hemodialysis patients initiating a respiratory fluoroquinolone (levofloxacin or moxifloxacin) vs. an amoxicillin-based antibiotic (amoxicillin or amoxicillin/clavulanic acid). We used an intention-to-treat analytic approach and propensity score weighted survival models, adjusting for numerous demographic and clinical covariates, to estimate weighted hazard ratios (HRs) and their 95% confidence intervals (CIs). Non-SCD was treated as a competing event.

Results: The study cohort included 264,968 unique hemodialysis patients and 626,322 study antibiotic treatment episodes: 251,726 (40.2%) respiratory fluoroquinolone treatment episodes and 374,596 (59.8%) amoxicillin-based antibiotic treatment episodes. Respiratory fluoroquinolone vs. amoxicillin-based antibiotic treatment was associated with a higher 5-day risk of SCD, weighted HR (95% CI) = 1.95 (1.57, 2.41). The association was more pronounced among individuals concurrently taking other QT prolonging medications, weighted HR (95% CI) = 2.50 (1.61, 3.88). Sensitivity analyses 1) using longer follow-up durations and 2) evaluating a composite outcome of SCD or new-onset ventricular arrhythmia yielded similar results.

Conclusions: Respiratory fluoroquinolone (vs. amoxicillin-based antibiotic) treatment was associated with an increased risk of SCD. Future research is needed to determine optimal strategies for cardiac monitoring when these medications are prescribed to patients receiving hemodialysis.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO0853

Variability of Plasma Refill Rate and Risk of Intradialytic Hypotension During Maintenance Hemodialysis

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Background: Continuous hematocrit data can be combined with time-updated ultrafiltration data to non-invasively estimate a semi-instantaneous plasma refill rate (PRR) throughout hemodialysis. The PRR is a dynamic metric that varies throughout hemodialysis, even during periods of constant rates of ultrafiltration, and is influenced by oncotic and hydrostatic forces. We aimed to determine whether variability in PRR is associated with intradialytic hypotension (IDH).

Methods: We used data from continuous hematocrit monitoring performed at 17 dialysis units from January 2017-October 2019 to calculate intradialytic plasma refill rates standardized to weight and height. PRR variability was defined as the coefficient of variance in PRR (PRR_{cov}) every 15 minutes and categorized into three groups: low (PRR_{cov} < 1.0), moderate (PRR_{cov} 1.0-2.0) and high (PRR_{cov} > 2.0). IDH was defined in three ways: (1) nadir systolic blood pressure (SBP) < 90 mmHg, (2) SBP < 90 mmHg or associated symptoms, and (3) either drop in SBP of 20 mmHg or mean arterial blood pressure of 10 mmHg with associated symptoms. Cox proportional hazard regression was used to assess the impact of starting PRR variability on time to first IDH. Marginal structural modeling was used to assess the impact of time-updated plasma refill rate variability on the risk of IDH.

Results: Among 2350 patients and 184,453 hemodialysis sessions, mean session time was 220 ± 26 min and ultrafiltration rate was 9.0 ± 3.3 ml/kg/hr. Median PRR_{cov} was 1.20 (IQR 0.68, 2.18) across all sessions. Compared to hemodialysis sessions with low PRR_{cov}, sessions with high PRR_{cov} in the first 15 minutes of treatment were associated with a 1.14 hazard of intradialytic hypotension (95% CI 1.05, 1.24). Accounting for repeated measures and changes in systolic blood pressure and ultrafiltration, sessions with high PRR_{cov} throughout the duration of hemodialysis were associated with an increased risk of IDH based across definitions: definition 1 (OR 1.29, 95% CI 1.16, 1.43), definition 2 (OR 1.85, 95% CI 1.77, 1.94), and definition 3 (OR 1.87, 95% CI 1.78, 1.98).

Conclusions: PRR variability was associated with higher risk of IDH, independent of time-varying confounding from SBP and UFR. PRR variability could be a promising bedside metric for hemodynamic instability during hemodialysis.

Funding: NIDDK Support

PO0854

Systemic Parameters of the Renin-Angiotensin-Aldosterone System Remain Unaffected by Changes in Fibroblast Growth Factor 23 Levels in Hemodialysis Patients

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Background: Fibroblast growth factor 23 (FGF23) is elevated in patients with chronic kidney disease and promotes the development of left ventricular hypertrophy (LVH). Decreasing the levels of FGF23 with the calcimimetic drug etelcalcetide can abate that effect in hemodialysis patients. It is unknown if the prohypertrophic effect of FGF23 is modified by the renin-angiotensin-aldosterone system (RAAS). The aim of the analysis was to determine whether changes in FGF23 levels are associated with differences in RAAS-parameters in hemodialysis patients, possibly explaining its influence on LVH.

Methods: Serum samples were obtained at baseline and one year from participants in the randomized EtECAR-HD trial. In this study 62 hemodialysis patients were treated with either calcimimetic or vitamin D treatment, which have opposite effects on FGF23. We analyzed PRA-S as the angiotensin-based marker for renin activity, angiotensin II (AngII), angiotensin-converting enzyme-2 (ACE2) and aldosterone using a high throughput mass spectrometry assay.

Results: The median levels of FGF23 were 2386 pg/ml (1st to 3rd quartile 819–5166) and 1386 pg/ml (288–4068) at baseline and end of study, respectively. The association of changes between baseline and end of study in FGF23 with the levels of the RAAS-components (i.e. PRA-S, AngII, ACE2, aldosterone) estimated by linear regression models was weak, with effect sizes for log2-fold-change in FGF23 close to zero. The amount of explained variation by FGF23 fold-change was generally small (drop-in-R^2 values all below 0.03). The median overall levels of PRA-S were 130 pg/ml (1st to 3rd quartile 46-269), of AngII 70 pg/ml (28-157), of aldosterone 130 pg/ml (54-278) and of ACE2 1.4 ng/ml (1.1-1.8), as compared with healthy controls (PRA-S 196 pg/ml [98-238], AngII 137 pg/ml [76-201], aldosterone 335 pg/ml [139-454], ACE2 1.38 ng/ml [1.17-1.65]).

Conclusions: In the present study we were able to show that systemic RAAS activity was grossly unaffected by the treatment induced changes in FGF23 levels in this cohort. Overall, the levels of PRA-S, AngII and aldosterone were well below the ranges measured in healthy controls suggesting that the RAAS is not systemically activated in hemodialysis patients.

Funding: Commercial Support - Investigator-initiated research grant from Amgen

PO0855

Prediction of Left Ventricular Function Using Electrocardiogram Data in Patients on Hemodialysis

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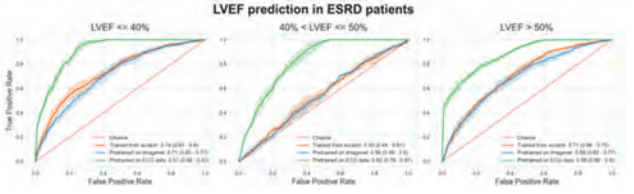
Background: Left ventricular (LV) systolic dysfunction is common in patients on maintenance hemodialysis (HD). Early identification of patients with depressed left ventricular ejection fraction (LVEF) can facilitate disease modifying treatment. Electrocardiograms (ECGs) are routinely performed in patients on HD, however they have not been used for estimating LVEF in this population.

Methods: We analyzed data from five Mount Sinai facilities. Patients on HD with a transthoracic echocardiogram within 7 days of an ECG were identified using diagnostic and procedure codes. ECG data were preprocessed to remove recording artifacts, plotted to an image, and along with patient demographics were analyzed using a model comprised of a Multi-Layer Perceptron and a Convolutional Neural Network. We developed three models; 1) trained from scratch in only HD patients, 2) pre-trained on natural images (Imagenet), and 3) pre-trained on all LVEF:ECG pairs (n=696,890) excluding those for ESRD patients. Models 2 and 3 leverage transfer learning, which reuses knowledge gained from a task to perform a similar task. All models were trained/tested on LVEF:ECG pairs for ESRD patients within a Group Stratified K Fold (K=5) Cross Validation design, and performance was compared per Area Under Receiver Operating Characteristic curve (AUROC) for each category of LVEF, ≤40%, 41 to ≤50%, and >50%.

Results: We extracted 18,626 LVEF:ECG pairs for 2,168 ESRD patients. For detection of LVEF ≤ 40%, models trained from scratch and pre-trained on Imagenet had AUROCs of 0.74 (95% CI: 0.67-0.80) and 0.71 (95% CI: 0.65-0.77) respectively. These were outperformed by the model pre-trained on ECG data [AUROC of 0.91 (95% CI: 0.88-0.93)]. Similar results were seen at detection of LVEF 41 to ≤50% with the AUROC being 0.55 (95% CI: 0.49-0.6) for both the model trained from scratch and the Imagenet model, while the model pre-trained on ECG data achieved an AUROC of 0.82 (95% CI: 0.78-0.87).

Conclusions: A model pre-trained on non-HD LVEF:ECG pairs using transfer learning consistently outperformed models trained from scratch or pre-trained on Imagenet. This model can facilitate identification of LV systolic dysfunction in patients on HD.



ROC curves

PO0856

Clinical Outcomes of Bioimpedance Analysis-Guided Hemodialysis: A Meta-Analysis of Randomized Controlled Trials

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Background: Determination of fluid status in hemodialysis patients could be a great challenge for providers. Body composition monitoring using bioimedance analysis (BIA) is an emerging tool in guiding fluid removal in hemodialysis population. However, although there are some randomized controlled trials (RCT), the reported outcomes remain heterogenous and inconclusive across studies.

Methods: Ovid MEDLINE, EMBASE and the Cochrane Library were searched for eligible articles through May 2021. Inclusion criteria were: 1) RCT comparing BIA against clinical assessment, 2) sample size > 50, 3) adults > 18 years on hemodialysis (HD), 4) clinical outcomes were reported. No publication bias detected by Egger's regression intercept analysis.

Results: A total of seven RCTs (n = 1029 total; 519 BIA, 510 control), dated from 2010 to 2019, with a mean follow-up duration of 15.0±10.6 months were identified. There was no difference in mortality between BIA and clinical group (odds ratio [OR] 0.797; 95% CI 0.431, 1.472; I2 13.2%). BIA group had significantly lower weight change during follow-up duration compared to clinical group (standard means difference [SMD] -0.270; 95% CI -0.532, -0.008; I2 9.6%). Clinical group had significantly higher systolic blood pressure compared to BIA group (SMD 0.157; 95% CI 0.034, 0.280; I2 2.3%) with a mean difference of 3.052 mmHg (95% CI 0.851, 5.253; I2 0%). Clinical group had significantly higher pulse wave velocity compared to BIA group (SMD 0.795; 95% CI 0.545, 1.045; I2 0%). Clinical group had significantly higher pre-HD body weight (SMD 0.280; 95% CI 0.130, 0.430; I2 48.1%) with a mean difference of 0.370 kg (95% CI 0.178, 0.563; I2 47.8%) compared to BIA group. There was no difference in post-HD body weight between the two groups (SMD 0.156; 95% CI -0.055, -0.366; I2 0%).

Conclusions: There was no mortality benefit to BIA-guided HD compared with clinical-guided HD. However, BIA-guided HD improved systolic blood pressure and weight gain compared to clinical-guided HD. Pulse wave velocity, which represents arterial stiffness, was also lower in BIA group. Although our findings suggest some non-mortality benefits to BIA-guided HD, however, the clinical impact of BIA-guided HD on cardiovascular events, intradialytic complications, and patients' quality of life remain to be elucidated in future RCTs.

PO0857

Point-of-Care Ultrasound Measurements to Predict Intradialytic Hypotension: A Cross-Sectional Pilot Study

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Background: Intradialytic hypotension (IDH) results from excessive ultrafiltration in patients on chronic hemodialysis (HD) and has been linked to increased mortality. Prescribing the right amount of ultrafiltration can be challenging, partly due to the poor sensitivity of physical examination for detection of volume overload in HD patients. POCUS is emerging as a valuable tool in the assessment of volume status. The goal of this study is to determine whether pre-dialysis POCUS measurements are associated with development of IDH.

Methods: Patients >18 years old on HD for at least 6 months and ordered for 2 or more liters of ultrafiltration were included. Two blinded POCUS-trained physicians obtained the following measurements within the first 30 minutes of HD: left ventricular septal and lateral E/e', portal vein (PV) pulsatility and IVC size. The primary outcome was development of IDH events or post HD orthostasis. IDH was defined as a decrease in systolic blood pressure by ≥ 20 mmHg plus symptoms of IDH. Fischer's and Mann Whitney tests were used to examine the association between IDH events and various demographic, clinical, and POCUS related parameters.

Results: 54 measurements on 27 patients were obtained. Average time required by each examiner to obtain all images was 6 minutes (95% confidence interval [CI] 4.2,7.8). Average age was 57 (95% CI 52, 62), 85% were black and 44% were females. Average BMI was 32 (95% CI 28, 36), Charlson comorbidity index (CCI) score 7 (95 % CI 6,8), number of anti-hypertensive medications 2.1 (95% CI 1.5, 2.8) and average dialysis vintage 3.9 years (95% CI 2.1, 5.7). 8 out of 27 patients developed the primary outcome. There was no association between age, sex, ethnicity, BMI, dialysis vintage, Charlson comorbidity index, interdialytic weight gain, IVC size, PV pulsatility, septal E/e' and the primary outcome. There was a significant association between lateral E/e' and IDH events or post HD orthostasis (p=0.05).

Conclusions: In this pilot study, an elevated lateral E/E' was associated with lower rates of IDH events or post HD orthostasis. The role of POCUS in guiding fluid removal during HD warrants further exploration

PO0858

A Clinical Approach of Intradialytic Creatine Supplementation in Dialysis-Dependent CKD Patients: A Rationale and Study Design

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Background: There is great need for identification of new, potentially modifiable risk factors for the poor HRQoL and excess risk of mortality in dialysis-dependent chronic kidney disease patients. Creatine is an essential contributor to cellular energy homeostasis, yet on a daily basis 1.6-1.7% of the total creatine pool is non-enzymatically degraded to creatinine and subsequently lost via urinary excretion, thus necessitating a continuous supply of new creatine to remain in steady-state. Due to an insufficient ability to synthesize creatine, unopposed losses to the dialysis fluid, and insufficient intake, hemodialysis patients are prone to creatine deficiency, and may benefit from creatine supplementation. To avoid problems with compliance, fluid balance and, furthermore, to prevent intradialytic losses of creatine to the dialysate, we aim to investigate the potential of intradialytic creatine supplementation in improving outcomes.

Methods: Here, we describe the rationale and design for a block-randomized, double-blind, placebo-controlled pilot study. A total of 16 hemodialysis patients will be included, divided into four groups receiving intradialytic creatine supplementation (0.5mM, 1.0mM, 1.5mM, 2.0mM), or a placebo for six weeks. The aim of the pilot study is to explore the creatine uptake in the circulation and tissues following different creatine supplementation dosages.

Results: The main parameters for the pilot study are the plasma creatine concentration and intra-erythrocytic creatine concentration of both pre- and post-hemodialysis samples. Secondary study parameters are handgrip strength as a measure of muscle strength, combined interdialytic urinary and intradialytic dialysate excretion of creatinine as a measure of muscle mass, and body composition measured with bioelectrical impedance analysis (BIA).

Conclusions: Intradialytic creatine supplementation may help to maintain creatine homeostasis among dialysis-dependent chronic kidney disease patients, and consequently improve important causes for impaired HRQoL, including protein energy wasting (PEW), fatigue, muscle weakness, depression, and cognitive impairment. The results from the pilot-study will serve as a basis for a larger double-blind, placebo-controlled supplementation trial.

PO0859

Relationship Between Fluid Overload and Hemoglobin Concentration in Hemodialysis Patients: A Longitudinal Analysis

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Background: Quantification of fluid status by bioimpedance spectroscopy (BIS) has become routine outside United States (US). We performed the first assessment of fluid status in US hemodialysis (HD) clinics using a BIS device. We studied the longitudinal association between fluid overload (FO) and hemoglobin (Hgb) concentration adjusting for inflammation and erythropoiesis-stimulating agents (ESA).

Methods: Measurement of FO [Body Composition Monitor (BCM); Fresenius Medical Care] was conducted cross-sectionally in chronic HD patients in 4 HD clinics in New York. We built linear mixed effects models with Hgb as the dependent variable and calculated FO longitudinally to include as a fixed effect. We tested the robustness of the association to account for the influence of inflammation by including the neutrophil-lymphocyte ratio (NLR) as an additional fixed effect. As a subset analysis 2 separate models were built in subjects with or without ESAs. To corroborate the dilutional effect of FO we exchanged Hgb for albumin as a fixed effect.

Results: We studied 169 patients (Figure1). FO was inversely associated with Hgb [Estimate -0.16 (-0.20 to -0.12) g/dl per 1L of FO], a significant fixed effect that remained unchanged in magnitude even after inclusion of NLR [Estimate 0.04 (-0.05 to 0.06) g/dl per 1 unit of NLR]. The effect was larger in patients without ESA prescription [Estimate -0.22 (-0.32 to -0.12) g/dl per 1L of FO]. FO was a significant determinant of albumin [Estimate -0.02 (-0.03 to -0.01) g/dl per 1L of FO] with NLR being a significant fixed effect [Estimate -0.03 (-0.04 to -0.01) g/dl per 1 unit of NLR].

Conclusions: Hgb is inversely affected by FO, a significant effect independent of inflammation (NLR). The impact of FO on Hgb concentration is larger in those with no ESA treatment emphasizing that fluid status has to be considered in anemia management. The effect of FO on albumin supports hemodilution as the principal cause for the changes seen on Hgb.

Funding: Commercial Support - Fresenius Medical Care

	All Patients	Tertile FO 1 [-6.5 to 1.3] [L]	Tertile FO 2 [1.3 to 2.9] [L]	Tertile FO 3 [2.9 to 13.4] [L]	P-values
Number of Patients	169	57	56	56	
Gender					
Male [count (%)]	101 (60%)	29 (50.88%)	31 (60.71%)	33 (67.86%)	
Age [mean +/-sd]	61.62 +/- 14.36	55.14 +/- 13.52	63.91 +/- 13.63	63.20 +/- 13.74	
Race					
Black [count (%)]	49 (32.68%)	16 (31.37%)	24 (50%)	25 (44.64%)	
White [count (%)]	91 (60.99%)	34 (28.07%)	20 (35.71%)	25 (44.64%)	
unknown [count (%)]	12 (7.50%)	4 (7.02%)	5 (8.93%)	3 (5.36%)	
Other [count (%)]	5 (2.96%)	2 (1.75%)	2 (3.57%)	2 (3.57%)	
Asian [count (%)]	3 (1.18%)	0 (0%)	1 (1.79%)	1 (1.79%)	
Height [m] [mean +/- sd]	170.1 +/- 10.53	169.98 +/- 11.68	168.66 +/- 9.26	171.98 +/- 10.38	
NLR [mean +/- sd]	3.49 +/- 1.95	3.92 +/- 2.52	3.09 +/- 2.21	3.54 +/- 1.72	
Hbv [mean +/- sd]	76.90 +/- 20.66	80.72 +/- 21.26	71.61 +/- 20.33	72.59 +/- 20.58	
TSAT [mean +/- sd]	32.59 +/- 17.69	34.92 +/- 18.99	31.48 +/- 17.66	31.84 +/- 15.95	
Albumin [mean +/- sd]	3.88 +/- 0.31	3.82 +/- 0.29	3.89 +/- 0.28	3.87 +/- 0.37	
Ferritin [mean +/- sd]	978.5 +/- 483.35	974.30 +/- 488.26	988.38 +/- 484.65	972.93 +/- 387.58	
OH [mean +/- sd]	2.29 +/- 2.42	-0.03 +/- 1.38	2.08 +/- 0.45	4.71 +/- 1.99	
Hemoglobin [g/dl] [mean +/- sd]	10.93 +/- 1.31	11.17 +/- 1.24	10.87 +/- 1.48	10.74 +/- 1.09	Anova: 0.0015
Hemoglobin between 10 and 12 g/dL [count (%)]	103 (60.95%)	37 (64.91%)	28 (50%)	38 (67.86%)	
Pooled, Bonferroni-Adjustment for hemoglobin	Reference Tertile	T2 vs. T3: 0.9996	T1 vs. T3: 0.0021	T1 vs. T2: 0.1086	
Medication [count (%)]	132 (78.21%)				Chi-squared: 0.0263
Vitamin D [mg] [median (25th % to 75th %)]	50 (50 to 75)				
Vitamin A/B+ (Epoetin) [units] [median (25th % to 75th %)]	5800 (3000 to 7400)				

Demographics.

PO0860

Interpreting Home Blood Pressure Measurements in Haemodialysis: A Post Hoc Analysis of a Randomized Cross-Over Study

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Background: Home BP correlates better with ambulatory BP, target organ damage and mortality in dialysis patients. We aimed to determine the agreement of in-centre BP with home BP.

Methods: A post-hoc analysis of a pilot-scale, randomised two-period cross over study comparing self-monitoring of BP over 4 weeks with usual care in 41 haemodialysis patients. www.clinicaltrials.gov. NCT0340349. Dialysis clinic BP and home BP (using A&D model UA-651BLE device) were averaged over 2 weeks. Agreement was determined using kappa statistics and Bland Altman plots. BP variability was analysed using average real variability (ARV). Mixed effects models for repeated measures with a moving average window of 2 weeks were used to examine associations with BP and ARV.

Results: 33 out of 41 participants had sufficient home BP measurements for inclusion (mean age 52 +/- 13 years, 65% male). Post-dialysis SBP had moderate agreement with home SBP measurements (K = 0.6) compared with pre-dialysis SBP measurements (K = 0.4). The mean bias between home SBP and post SBP measurements was -4.15 mmHg (95% CI 23.5 to -31.8 mmHg) (Figure 1). Home SBP ARV (16 +/- 6) was as high as pre SBP ARV (14 +/-5) and post SBP ARV (13 +/-5). In univariate analysis only calcium channel blockers were consistently associated with pre-dialysis (P= 0.02), post-dialysis and home SBP (both P<0.001).

Conclusions: Post-dialysis SBP demonstrates moderate agreement with home BP when two week BP averages are used. Home BP measurements are as variable as clinic BP measurements and isolated measurements may lack interpretability. Averaging the home BP over two weeks may improve the utility of home BP monitoring.

Funding: Commercial Support - patientMpower

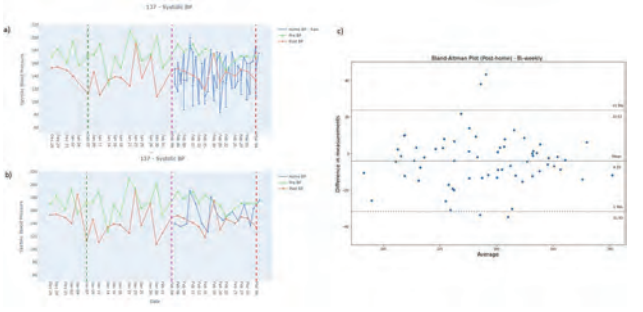

Figure 1: An illustrative BP profile for one study participant a) All home BP raw data compared to in-centre data b) Averaged home BP data on non-dialysis days c) Bland Altman plot of all patients comparing home and post-dialysis BP using 2 week averaged values.

PO0861

Increased Tricuspid Regurgitation Jet Velocity as a Predictor of Acute Decompensated Heart Failure in ESRD Patients on Maintenance Hemodialysis

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Background: Many patients with end-stage renal disease (ESRD) on hemodialysis (HD) experience left ventricular hypertrophy and reduced vascular compliance and are likely to develop heart failure (HF). We aimed to determine the hemodynamic factors associated with acute decompensated events among ESRD patients undergoing HD.

Methods: We retrospectively investigated ESRD patients on HD through a medical record review. We excluded patients with significant ischemic heart disease (IHD), percutaneous coronary intervention or coronary artery bypass graft, significant valvular heart disease (VHD), or malignancy. We divided patients into those experience who experienced any admission due to acute decompensated HF (ADHF) and those who did not.

Results: Of the 188 ESRD patients on HD, 87 were excluded, and 101 were enrolled (mean age: 63.7 years, 52.1% male). The ADHF group demonstrated significantly higher tricuspid regurgitation (TR) jet velocity (2.9 ± 0.6 vs. 2.5 ± 0.4 m/s, respectively; p=0.004) than the non-ADHF group. Multivariate logistic regression analysis demonstrated that TR jet velocity (odds ratio: 8.356, 95% confidence interval: 1.806–38.658; p=0.007) was an independent predictor of ADHF after adjusting for age and sex, while LVEF and E/E' were not. Per receiver operating characteristic curve analysis, TR jet velocity > 2.8 m/s was associated with ADHF with 47.7% sensitivity and 76.4% specificity (area under the curve: 0.656).

Conclusions: Our data showed that increased TR jet velocity was an independent predictor of ADHF events in ESRD patients on HD, but LVEF and E/E' were not.

Table 1. Baseline characteristics

Variable	Pt without admission for ADHF (n=71)	Pt with admission for ADHF (n=30)	p-value
Age, mean (year)	64.1±13.7	65.5±12.5	0.629
Male, n (%)	37 (52.1)	16 (53.3)	0.911
HTN, n (%)	45 (63.4)	22 (73.3)	0.367
DM, n (%)	35 (49.3)	14 (46.7)	0.831
Dyslipidemia, n (%)	28 (39.4)	17 (56.7)	0.129
Stroke, n (%)	7 (9.9)	5 (16.7)	0.333
Thyroid disease, n (%)	2 (2.8)	2 (6.7)	0.580
Atrial fibrillation, n (%)	4 (5.6)	5 (16.7)	0.121
Body weight, pre HD, kg	57.5±16.8	49.2±28.2	0.139
Body weight, post HD, kg	54.2±17.4	46.9±26.9	0.178
IDWG, kg	-2.3±1.0	-2.8±1.2	0.080

All values are presented as mean± SD. HTN: Hypertension, DM: Diabetes Mellitus, HD: Hemodialysis, IDWG interdialytic weight gain

Baseline characteristics

PO0862

Benefit of More Frequent Dialysis on Dialysis Recovery Time in Nursing Home Patients with ESRD

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Background: Dialysis patients admitted to a skilled nursing facility (SNF) are characterized by advanced age, frailty, and multiple comorbidities. Based on prior studies which demonstrated shortened dialysis recovery time (DRT) with more frequent dialysis (MFD) in populations aged ~50s living at home (FREEDOM Study 2010, FHN trial 2006), it was postulated that dialysis patients in a SNF would benefit from MFD.

Methods: Patients studied were admitted to SNFs in OH, TX, FL, NY, and PA from November-December 2019 (pre-COVID) and could reliably answer questions about DRT. 80% were undergoing subacute rehabilitation and 20% were permanent residents of the SNF. Patients received NxStage on-site staff assisted MFD 5x (80%) or 4x (20%) per week. StdKt/V was ≥ 2.1. At every dialysis, patients were asked by their RN caregiver "How long did it take you to recover from your last HD session?" Responses were deemed unreliable if a patient had cognitive impairment. Reliable responses were used for outcome analysis. In the present study, DRT data was collected by a caregiver nurse, differing from the methodology of the FREEDOM/FHN studies which collected DRT data via KDQOL form or phone interview. The implications of these differences in data collection methods are currently unknown.

Results: 485 unique patients were included in the study. Demographics included 53% males, mean age 67.5 +/- 13 years, African American 19%, Caucasian 25%, Hispanic 5%, Asian 0.4%, unknown or other 51%. Mean DRT was 1.5 +/- 2.6 hours. Mean DRT was calculated using the midpoint recovery time for intervals, or 18 hours when DRT was the next morning or beyond. In 69%, DRT was < 2 hours.

Conclusions: In the FREEDOM and FHN conventional HD 3x per week study arms, DRT averaged 6-8 hours. MFD reduced DRT to ~1.0 hour in those relatively young patients living at home. In our study, HD patients residing in a SNF and receiving MFD experienced DRT of 1.5 hours. Age, frailty and comorbid conditions therefore do not prevent DRT benefits of MFD. DRT benefits could stem from more effective, gentler fluid management by MFD. Further studies are needed to fully explore the impact of shortened DRT on rehabilitation scores, hospitalizations and deaths in elderly patients residing in SNFs.

Funding: Commercial Support - Dialyze Direct

PO0863

The Combination of Arterial Stiffness and Peripheral Vascular Disease Aggravates Survival Among Hemodialysis Patient Using Competing Risk Analysis

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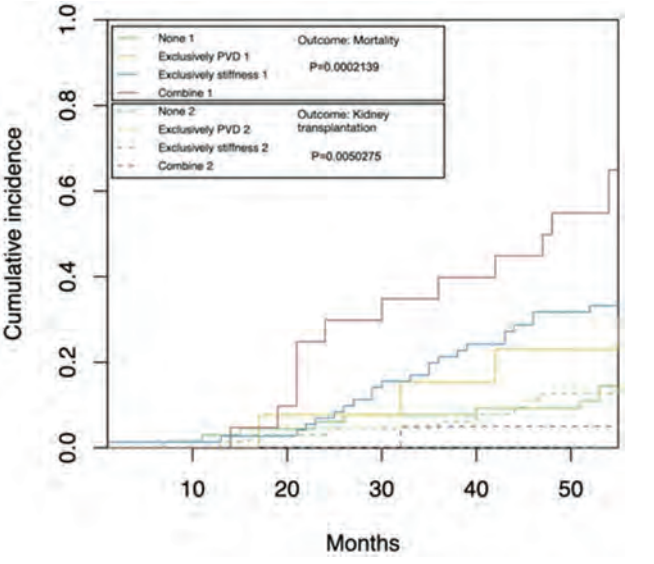
Background: The survival in end state renal disease (ESRD) patient is unacceptable high. The Skin autofluorescence (SAF) for advance glycation end products (AGEs), peripheral vascular disease (PVD) (ankle-brachial index, ABI ≤0.9) and arterial stiffness (cardio ankle vascular index, CAVI>9) were reports as predictors of mortality. However, kidney transplantation (KT) competes the mortality outcome. We aim to explore these markers for precisely prediction of mortality using competing risk method.

Methods: Retrospective chart review in chronic hemodialysis patients was done in 3 hemodialysis centers in North Bangkok during November 2015 and March 2016. Arterial stiffness, SAF, IMAR and PVD were collected as a clinical predictor. Cumulative incidence of mortality was used as was a primary outcome. Logistic regression with competing risk model was used to analyze the factor affecting mortality.

Results: A Total of 176 patients were eligible and classified into 4 groups according to PVD and stiffness status. During follow up 44.5±14.8 months, the overall mortality rate was 27% which is 13.2, 28.6, 31.5 and 61.9% in no PVD and stiffness, exclusively PVD, exclusively stiffness, and combine group respectively. The PVD (HR 2.93, CI 1.2 to 7.14, P=0.018) and stiffness (HR 2.57, CI 1.16 to 5.73, P=0.021) were independent predictors of mortality. In competing risk method, the combination of PVD and stiffness associate with highest mortality (P=0.0002139), while the patients who no PVD and stiffness had the highest rate for KT (P=0.0050275).

Conclusions: The PVD and stiffness were an independent risk of mortality among hemodialysis patients. The combination of PVD and stiffness may stratify risk of mortality in hemodialysis patient using competing risk method.



Cumulative incidence of death and KT according to PVD and stiffness status in competing risk method

PO0864

Body Fat Mass Plays an Important Role in Over- or Underestimation of Bioimpedance Spectroscopy-Based Dry Weight for Patients with Hemodialysis

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Background: Accurate dry weight (DW) estimation is important for hemodialysis patients. Although bioimpedance spectroscopy (BIS) is commonly used to measure DW, the BIS-based DW frequently differs from the clinical DW.

Methods: We analyzed the characteristics of patients whose BIS-based DWs were over- and underestimated. In this retrospective cohort study, we evaluated 1,555 patients undergoing maintenance hemodialysis in Chungnam National University Hospital. The gap (DW_{CP-BIS}) was calculated by comparing the BIS and clinical DWs.

Results: We analyzed the clinical characteristics of patients with positive (n = 835) and negative (n = 720) gaps. Compared with other patients, the DW_{CP-BIS}-positive group was taller, had higher extracellular water (ECW) level and extracellular/intracellular water index (E/I); and had lower weight, body mass index (BMI), lean tissue index (LTI), fat tissue index (FTI), fat mass (FAT), and adipose tissue mass (ATM), as well as lower levels of hemoglobin, total protein, albumin, and phosphorous. The DW_{CP-BIS}-negative group exhibited higher levels of hemoglobin, total protein, albumin, and phosphorous, as well as elevated BMI, FTI, FAT, and ATM; however, it had lower height, ECW, and E/I. Linear regression analysis revealed that FAT significantly predicted DW_{CP} accuracy.

Conclusions: The clinical DW of patients with malnutrition and a low fat mass tended to be underestimated, while the clinical DW of patients with comparatively large fat reserves tended to be overestimated. These characteristics of dialysis patients will aid in the correction of BIS-associated DW errors

PO0865

Consistency of the Dry Weight of Hemodialysis Patients Predicted Using Bioelectrical Impedance Analysis Between Standing and Lying-Down Positions

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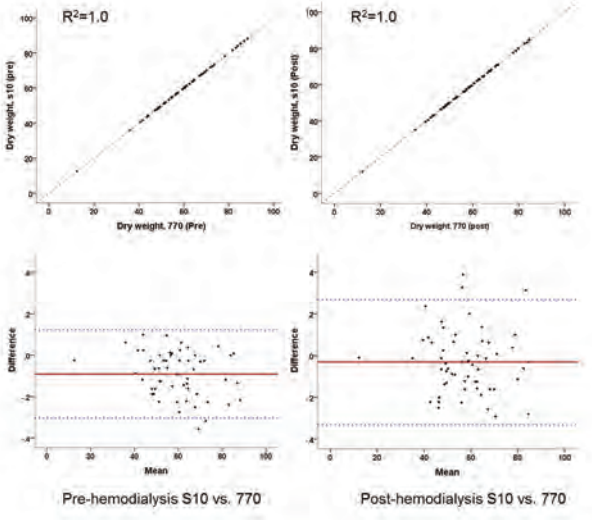
Background: Although the InBody S10 is widely used for hemodialysis patients in the lying position, clinicians must make the measurements in person. In contrast, patients can use the InBody 770 to obtain measurements by themselves in the standing position according to instructions provided by the machine, which may be more convenient. Therefore, this study compared the measurements of hemodialysis patients' dry weight obtained lying down using the S10 to those obtained in the standing position using the 770.

Methods: Measurements from 56 patients before and after hemodialysis were obtained. Dry weight was calculated using the ratio of extracellular water to total body water, taking into consideration diabetes status and albumin levels, and comparing the results according to body position (lying vs. standing).

Results: The patients' median age was 64 years old, and 51% were men. Their mean dry weight before hemodialysis was 60.0±12.5 kg using the S10 device and 60.1±12.5 kg using the 770 device (paired t-test; t=-6.472, *P*<0.001). The correlation between these

measurements was high (R^2=1.0000). Patients' mean dry weight after hemodialysis was 58.4±12.2 kg using the S10 device and 58.5±12.0 kg using the 770 device (paired t-test; t=-1.560, *P*=0.124). The correlation between these measurements was also very close (R^2=1.0000). The Bland-Altman test yielded similar results.

Conclusions: This study showed that patients' predicted dry weights in the lying position using the InBody S10 device and in the standing position using the InBody 770 device were consistent in both pre- and post-hemodialysis states. It can be concluded that the dry weight of a patient in the standing position can be measured with more convenience and autonomy using the InBody 770 device.



PO0866

Use of Crit-Line to Reduce Intradialytic Hypotension in Hospitalized Patients Receiving Dialysis

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Background: Intradialytic hypotension (IDH) is a frequent complication of hemodialysis (HD) in hospitalized patients with acute kidney injury (AKI) and end stage kidney disease (ESKD). Crit-Line is a device that monitors absolute hematocrit and oxygen saturation during dialysis and reads out the percent blood volume change. Whether the use of Crit-Line during HD in hospitalized patients results in less IDH is unknown.

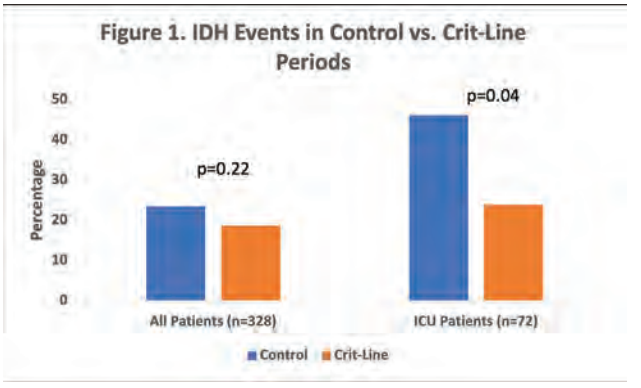
Methods: We performed a time series study in all hospitalized adult AKI/ESKD patients undergoing acute HD at the University of Colorado. During the control period baseline data was collected. During the intervention period, Crit-Line was used on all hospitalized patients undergoing HD including those receiving portable HD treatments in the ICU. During both time periods, nurses recorded number of hypotensive events, patient symptoms and modifications that were made to the dialysis prescription. The primary outcome was number of IDH events defined by the NKF KDOQI Guidelines.

Results: 328 patients were included, 161 from the control period and 167 from the intervention period. Patient characteristics were similar in both time periods and are shown in Table 1. IDH occurred in 23.5% of treatments during the control period and 18.7% during the intervention period, but the difference was not significant, p=0.22 (Figure 1). When examining portable dialysis treatments in the ICU, there was a significant reduction in IDH with Crit-Line compared to control (Odds Ratio 0.71 95% CI 0.51-0.99, p=0.04).

Conclusions: Use of Crit-Line in hospitalized patients undergoing dialysis in the ICU resulted in less IDH.

Funding: Commercial Support - Fresenius Renal Therapies

	Control Period (n=161)	Crit-Line Period (n=167)
Age (years)	56.9 ± 15.0	56.2 ± 15.0
Female N(%)	68 (40.7)	66 (41.3)
Race White N(%)	82 (50.9)	86 (51.5)
ESKD N(%)	114 (70.8)	120 (71.9)
Diabetes N(%)	84 (52.2)	81 (48.5)
ICU N(%)	33 (20.5)	39 (23.4)
Number of dialysis treatments N(%)	357 (52.7)	321 (47.4)



PO0867

Dry Weight Adjustments for Hemodialysis Patients Using Machine Learning

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Background: Knowledge of the proper dry weight plays a critical role in the efficiency of dialysis and the survival of hemodialysis patients. Recently, bioimpedance spectroscopy(BIS) has been widely used for set dry weight in hemodialysis patients. However, BIS is often misrepresented in clinical healthy weight. In this study, we tried to predict the clinically proper dry weight (DW_{CP}) using machine learning for patient's clinical information including BIS. We then analyze the factors that influence the prediction of the clinical dry weight.

Methods: As a retrospective, single center study, data of 1672 hemodialysis patients were reviewed. DW_{CP} data were collected when the dry weight was measured using the BIS (DW_{BIS}). The gap between the two (Gap_{DW}) was calculated and then grouped and analyzed based on gaps of 1 kg and 2 kg.

Results: Based on the gap between DW_{BIS} and DW_{CP}, 972, 303, and 384 patients were placed in groups with gaps of <1 kg, ≧1kg and <2 kg, and ≧2 kg, respectively. For less than 1 kg and 2 kg of GapDW, It can be seen that the average accuracies for the two groups are 83% and 72%, respectively, in usign XGBoost machine learning. As Gap_{DW} increases, it is more difficult to predict the target property. As Gap_{DW} increase, the mean values of hemoglobin, total protein, serum albumin, creatinine, phosphorus, potassium, and the fat tissue index tended to decrease. However, the height, total body water, extracellular water (ECW), and ECW to intracellular water ratio tended to increase.

Conclusions: Machine learning made it slightly easier to predict DW_{CP} based on DW_{BIS} under limited conditions and gave better insights into predicting DW_{CP}. Malnutrition-related factors and ECW were important in reflecting the differences between DW_{BIS} and DW_{CP}.

PO0868

Interdialytic Weight Gain in Long Intervals and Mortality Among Maintenance Hemodialysis Patients

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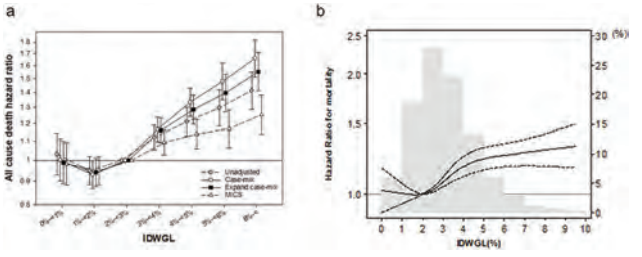
Background: Interdialytic weight gain (IDWG) is an important factor for sudden death on the first dialysis day right after long interdialytic intervals (i.e. 2-day breaks between dialysis treatments) in hemodialysis patients. We defined IDWG in long intervals (IDWGL) as the IDWG during 2-day breaks. In this study we examined the association between IDWGL and medium-term mortality.

Methods: This retrospective cohort study included patients who initiated hemodialysis in a large dialysis organization in the United States from 2007 to 2011. We examined the association between seven categories of IDWGL and all-cause mortality using Cox regression model. Seven categories of IDWGL were as follows: 0-<1%, 1-<2%, 2-<3%, 3-<4%, 4-<5%, 5-<6%, and ≥6%. We also examined continuous associations between IDWGL and mortality using restricted cubic spline analysis.

Results: We examined mortality in 35225 patients. The mean age (and standard deviation) was 62±15 years, and 8112 died during the median follow-up period of 1.4 years. Higher categories of IDWGL were associated with increased risk of mortality. The hazard ratios (95% confidence intervals) of all-cause mortality for 3-<4%, 4-<5%, 5-<6%, and ≥6% were 1.09 (1.03-1.16), 1.14 (1.06-1.23), 1.17 (1.06-1.29), and 1.25 (1.14-1.38) (Reference: 2-<3%) (Figure a). The restricted cubic spline analysis showed that risk of mortality increased when IDWGL exceeded 2% (Figure b).

Conclusions: IDWGL exceeded 2% was associated with higher risk of mortality. Our results suggest IDWGL can be a risk parameter for medium-term mortality.



PO0869

Coronary Artery Calcification Is a Risk Factor for Intradialytic Hypotension in Hemodialysis Patients

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Background: Vascular calcification and intradialytic hypotension (IDH) share common risk factors in hemodialysis (HD) patients, but there are few reports about the association. We investigated the association between IDH and coronary artery calcification (CAC) and their effects on mortality in HD patients.

Methods: Subjects were consecutive maintenance HD patients. IDH was defined as nadir systolic blood pressure <100 mmHg, or the requirement for bolus infusion of saline and vasopressor (etilefrine hydrochloride) during at least two of 10 HD sessions. Laboratory data and Agatston coronary artery calcium score (CACS) were obtained at baseline. Logistic regression analyses for CACS and Cox analyses for mortality were conducted.

Results: In all subjects (n=173), age and dialysis vintage were 66±12 years and 102±89 months, respectively. IDH occurred in 37 patients (21.4%), and CACS was higher in the IDH group than in the non-IDH group [1,845 (243–3,774) vs. 884 (161–2,465)]. IDH was significantly (P<0.05) associated with CACS [odds ratio (OR): 1.01], diabetes (OR: 2.90), mean predialysis systolic blood pressure (OR: 0.93), mean ultrafiltration (OR: 1.92), Kt/Vurea (OR: 11.27) and erythropoietin responsive index (ERI) (OR: 0.91), but not with serum albumin or use of calcium channel blockers. For 3-year all-cause mortality, the cut-off value of CACS, determined by receiver operating characteristics curve analysis, was 1,829 with sensitivity of 69% and specificity of 77%. Of the 173 patients, 45 all-cause deaths and 19 cardiovascular (CV) deaths occurred for 3 years. Patients with both IDH and CACS ≥1,829 had the highest 3-year cumulative CV death rate (33.3%, P<0.01) compared with 19.7%, 11.5%, and 4.5% in those with CACS ≥1,829 only, IDH only, and neither, respectively. In Cox models including age, sex, diabetes, albumin, phosphate, CRP, ERI and FGF23, hazard ratios (HRs) for 3-year all-cause mortality of IDH, CACS ≥1,829, or IDH with CACS ≥1,829 were similar, but HR for 3-year CV mortality was the highest in IDH with CACS ≥1,829 (9.68, P<0.001) compared with 7.29 (P<0.01) and 6.77 (P<0.01), in those with CACS ≥1,829 only, and IDH only.

Conclusions: CACS is an independent risk factor for IDH, and CACS provide additional risk-discrimination over IDH for CV mortality in HD patients.

Funding: Private Foundation Support

PO0870

Cardiac Arrests During Hemodialysis Among Maintenance Hemodialysis Patients in a Large Dialysis Network in India

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Background: Cardiac arrest (CA) during a HD session carries a high mortality and is reported associations inclue age, comorbiity, dialysis characteristics. Since much is unknown in India, we aimed to study Incidence of CA, prediposing factors and outcome of CPR following intra HD cardiac arrests

Methods: Consecutive CA in a large dialysis network from July 2019 to March 2021 were reviewed for age, gender, HD frequency, adequacy, vascular access, HD facility location, size, nephrologist coverage, h/o DM and IHD, HD session timing, delivered HD frequency & hospitalization in recent past & ultrafitltration rate. Survivors vs non-survivors of CPR were compared with t-test, Chi-square test or Fisher's exact statistic and risk ratio (RR) for significance of associated factors were analyzed using STATA, v 14. 2. Two-sided tests with a P-value < 0.05 was considered significant

Results: 122 CA occured among 2,981,759 sessions; rate of 1/24441. 71 survived CPR and 51 died. μ age: 55.5 ± 1.2 yrs, M;F =77%:23%. Tier 1/2/3 cities: 11.4%,37.7% 50,8%, daily Nephrologist visits: 67.2%, Facilites monthly sessions: < 250 : 10.6%, 250-749: 42.6%, >750 :46.7%. μ Hb: 8.7 ± .2 g% Temp access: 43.4%, HD freq 1/2/3 per wk: 36.9/28.7/34.4%, DM: 48.4% IHD: 26.2%. Morn afternoon, eve session(%): 39.3/15.6/39.3%, hospitalized < 2mon: 40%, < 2HD/week in recent past: 27%, μ UFR: 10.4 ± .5 ml/kg/hr. RR for signifcant factors are shown in Table 1.

Conclusions: Incidence of CA in India mirrors developed countries experience; larger facilities & smaller cities form a high proportion of events. Age > 80 ↑ risk of death. Female, ↓ Hb & adequacy, UFR >10ml/kg/hour, low HD freq in 2 months prior to CA show tendency to higher risk for non survival. Limitation includes lack of analysis of CPR and post CPR hospitalization course

Relative risk of major factors associated with non-survival following CPR for CA

Factors	Relative risk (95% CI)
Age <39 ref ≥80	1.4 (1.1-2)
Gender (male: ref) Female	1.8 (.8 - 3.7)
Hb (10-12 g ref) <8	1.1 (0.7-1.5)
Recent HD freq (2X ref) 1x 3x	1.3 (0.7-1.5) 1.7 (0.7 - 4.1)
Adequacy (≥ 1.2 ref) Abnormal	1.1 (0.5-2.2)
UF rate (< 7ml/kg/hr ref) 10-14 >14	1.2 (0.7 - 2.3) 1.5 (0.7-2.9)

PO0871

Clinical Significance of Plasma Matrix Metalloproteinase-2 and Matrix Metalloproteinase-9 Levels to Assess the Cardiovascular Risk in Hemodialysis Patients

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Background: Matrix metalloproteinases (MMPs) are endopeptidases that control extracellular matrix synthesis and degradation. Two MMP subtypes, MMP-2 and MMP-9, are known to play important roles in the development and progression of cardiovascular (CV) disease, but its clinical relevance as predictors of cardiovascular events is unclear in hemodialysis patients.

Methods: We prospectively enrolled 435 patients undergoing maintenance hemodialysis from K-cohort between June 2016 and April 2019. Plasma MMP-2, MMP-9 levels, and several biomarkers were measured at the time of study data entry. Primary endpoint was defined as a composite of cardiovascular events.

Results: Plasma MMP-2 level were increased in patients with incident CV events than those without CV events, whereas plasma MMP-9 levels were not different between groups. MMP-2 levels were positively correlated with circulating cardiac markers including brain natriuretic peptides (BNP), N-terminal proBNP, and heart-type fatty acid binding protein. The cumulative event rate of the composite of CV events was significantly greater in patients with higher MMP-2 tertile 3 than in those with other MMP-2 tertile 1 ($p = 0.015$). MMP-2 tertile 3 was associated with a 2.77-fold higher risk of the composite of CV events (95% CI, 1.40–5.45) and 4.67-fold higher risk of cardiac events (95% CI, 2.06–10.56) after multivariable adjustments. However, plasma MMP-9 levels were not positively correlated with circulating cardiac markers, and not associated with risk of incident CV events.

Conclusions: Higher plasma MMP-2 levels, but not MMP-9 levels, had the positive relationship with circulating levels of cardiac pathology markers, and were associated with increased risks of incident CV events and cardiac events among hemodialysis patients.

PO0872

Utility of CHA2DS2-VASc Score to Predict Mid-Term Clinical Outcomes in Hemodialysis Patients

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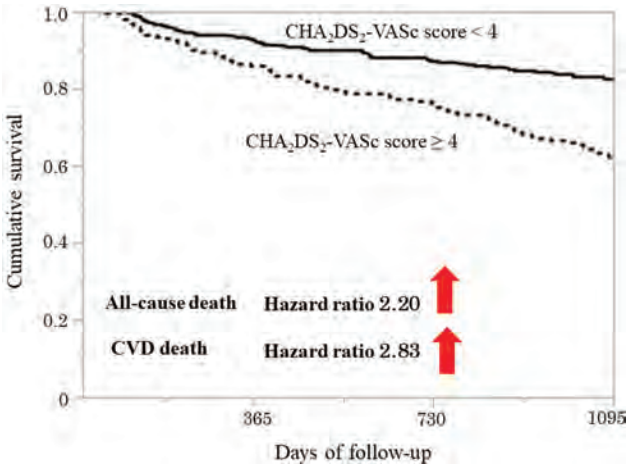
Background: The CHA_2DS_2-VASc score has been widely used as a predictive score for stroke in patients with atrial fibrillation (AF). Recently, it was reported that the CHA_2DS_2-VASc score is useful for predicting cardiovascular disease (CVD) or all-cause mortality in patients with or without AF. However, few reports have examined the association between this score and mortality in hemodialysis patients.

Methods: We analyzed 525 consecutive patients who started hemodialysis at our facilities from March 2006 to October 2017. CHA_2DS_2-VASc score was calculated at time of initiation of hemodialysis. Multivariate Cox proportional hazards analysis was used to assess independent risk factors for 3-year all-cause mortality.

Results: During the 3-year follow-up period, 153 (29.1%) patients died (cardiovascular death, n=88). According to multivariate analysis, serum albumin [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.43–0.89, P=0.01], creatinine (HR 0.81, 95% CI 0.71–0.99, P=0.03), and CHA_2DS_2-VASc score (HR 1.33, 95% CI 1.21–1.46, P<0.001) were associated with 3-year all-cause mortality. Patients with CHA_2DS_2-VASc score ≥4 had higher risk of all-cause and CVD mortality than those with CHA_2DS_2-VASc score <4 (all-cause mortality: HR 2.20, 95% CI 1.42–3.71, P<0.001; CVD mortality: HR 2.83, 95% CI 1.37–5.44, P<0.001).

Conclusions: The CHA_2DS_2-VASc score is a useful predictor of 3-year all-cause and CVD mortality in incident hemodialysis patients.



PO0873

Fibrosis-4 Index May Predict Mortality and Non-Fatal Cardiovascular Events in ESKD Patients Starting Dialysis

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Background: CKD and ESKD are known risk factors of heart failure(HF). And liver dysfunction as congestive hepatopathy due to HF is also common. Recent studies report that Fibrosis-4(FIB4) index(age×AST(IU/L)/platelet count(10^3/uL)×square root of ALT(IU/L)), which was known to be useful tool for evaluating liver stiffness, can be prognostic factor of HF. Therefore, this study investigated whether FIB4 index may predict mortality and cardiovascular events(CVE) in patients with ESKD starting dialysis.

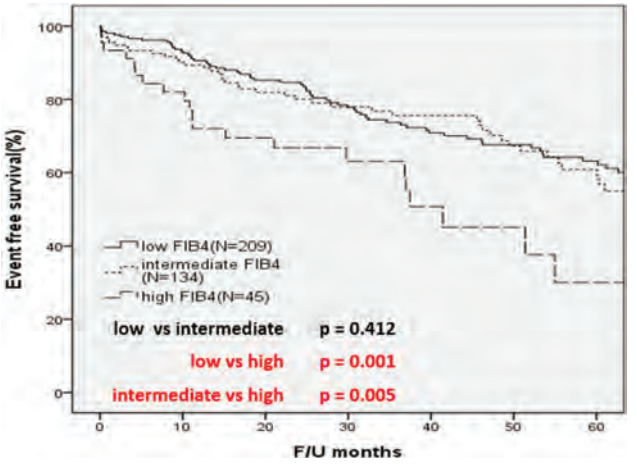
Methods: This was a retrospective cohort study including 388 patients who started dialysis at a single center. FIB4 index at dialysis initiation was calculated. Patients were stratified into three groups according to FIB4 index(<1.45:low, 1.45~3.25:intermediate, >3.25: high). The association between FIB4 index and event free survival rates for all-cause mortality and non-fatal CVE was analyzed. In addition, the association between FIB4 index and echocardiographic findings was analyzed.

Results: During a median follow-up duration of 40.0(0.03-142.3) months, 84 deaths(21.6%) and 83 non-fatal CVE(21.4%) occured. Event free survival rates were lower in high-FIB4 group, compared with those in low-FIB4 group(p=0.001) and intermediate-FIB4 group(p=0.005), respectively. In Cox proportional hazard model, the high FIB4 index was independently associated with event free survival rates (HR, 2.21; 95% CI, 1.17-4.18; p=0.015). When comparing echo findings, only left atrial diameter(LAD) showed difference among groups(p=0.033). However, there was no significant correlation between LAD and FIB4 index.

Conclusions: In conclusion, FIB4 index is associated with event free survival rates for all cause mortality and non-fatal CVE in ESKD patients starting dialysis.

Cox proportional hazard model of event free survival in ESKD patients who started maintenance

	Unadjusted model		Adjusted model	
	HR(95% CI)	P-value	HR(95% CI)	P-value
FIB4 trial		0.003		0.027
Low vs interdediate	1.166(0.81-1.68)	0.411	1.053(0.64-1.73)	0.838
Low vs high	2.351(1.43-3.86)	0.001	2.21(1.17-4.18)	0.015



PO0874

NT-ProBNP for Heart Function and Volume Status in Hemodialysis Patients

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Background: N-terminal pro brain natriuretic peptide (NT-proBNP) is a biomarker that predicts heart failure and evaluates volume status in Hemodialysis (HD) patients. However, it is difficult to determine the cutoff value of NT-proBNP in HD patients. In this study, we analyzed whether NT-proBNP helps with predicting heart function and volume status in HD patients.

Methods: Retrospective study was conducted on 96 end-stage renal disease patients with HD. All patients underwent echocardiography and Bioelectrical Impedance Analysis (BIA) after a post HD session. Overhydration (OH) was measured by BIA. Laboratory data were obtained on preHD during the mid-week HD sessions. Serum NT-proBNP was measured after HD.

Results: There was an inverse correlation between NT-proBNP and ejection fraction (EF) (β= -0.34, P=0.001). Overhydration (OH) (β=0.33, p=0.001) and presence of diastolic dysfunction (β=0.226, P=0.027) had positive correlations with NT-proBNP. In the subgroup analysis with diastolic dysfunction grade, NT-proBNP increased as the dysfunction grade increased. (diastolic dysfunction grade 0; 4177(2637-10391), grade 1; 9736 (5471-21110), grade 2,3; 24627(16975-44988)) Elevation of NT-proBNP above 4058 pg/ml was associated with the presence of diastolic dysfunction (p<0.001) and Left ventricular hypertrophy (LVH) (p=0.004). Elevation of NT-proBNP above 11576 pg/ml was associated with the presence of diastolic dysfunction (P<0.001), LVH (p<0.001) as well as EF<55% (P=0.07). The group with lowered dry weight followed up NT-proBNP one month later, compared to the group with no change in dry weight, NT-proBNP showed a tendency to decrease, and the group with no change in dry weight showed a relatively low level of NT-proBNP variability. (-210 (-12899 - 3142) vs 330(-1090 - 3858); interquartile range, p=0.104)

Conclusions: We confirmed that NT-proBNP is associated with volume status as well as heart functions such as diastolic dysfunction, LVH and EF in HD patients.

Heart function according to NT-proBNP level

Variables		NT-proBNP		P value	NT-proBNP		P value
		<4058 (n=24)	≥4058 (n=72)		<11576 (n=48)	≥11576 (n=48)	
EF (%)	<55	1 (4.2)	12 (16.7)	0.174	3 (6.3)	10 (20.8)	0.070
	≥55	23 (95.8)	60 (83.3)		45 (93.7)	38 (79.2)	
Diastolic dysfunction	Yes	7 (29.2)	53 (74.7)	<0.001	20 (41.7)	40 (85.1)	<0.001
	No	17 (70.8)	18 (25.4)		28 (58.3)	7 (14.9)	
LVH	Yes	4 (16.7)	37 (51.4)	0.004	7 (14.6)	34 (70.8)	<0.001
	No	20 (83.3)	35 (48.6)		41 (85.4)	14 (29.2)	

PO0875

Dysregulation of Fatty Acid Binding Protein and Their Relationship with Inflammatory Biomarkers in ESRD

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Background: End stage renal disease (ESRD) patients are at high risk of cardiovascular disorders and hemostatic complications. Fatty acid binding proteins (FABPs) regulate the transport of fatty acids and other lipophilic mediators such as eicosanoids and retinoids by both intracellular and extracellular mechanisms. While upregulation of FABPs have been reported in ESRD, their relationship with inflammatory biomarkers is not fully understood. Liver fatty acid binding protein (L-FABP) also known as FABP-1 is a 14kDa protein expressed in the liver. This protein is also expressed in tubular kidney cells. Kidney damage and other pathologic conditions result in the marked upregulation of this protein.

Methods: Citrated blood samples from 95 ESRD patients undergoing maintenance hemodialysis were collected prior to hemodialysis. For comparison purposes normal human plasma collected from 50 normal healthy male and female individuals were used. Plasma prepared from these patients and normal individuals was analyzed for FABP-1 and such inflammatory biomarkers as IL-6, TNFa and inflammasomes as using commercially available ELISA methods. All results were compiled and correlation analysis between FABP-1 levels and biomarkers of inflammation was carried out using GraphPad prism software.

Results: The ESRD patients showed a marked increase in FABP levels (106 ng/ml ± 18ng/ml SEM) with a broad range (8 – 974 ng/ml) in comparison to normal (5.1 ± 0.2ng/ml SEM) with a range of (3.4 – 9.2 ng/ml). Marked increases in IL-6, TNFa and inflammation were also noted (2 – 4 fold). FABP-1 showed varying degrees of positive correlation with inflammatory biomarkers.

Conclusions: These studies suggest that plasma levels of FABP-1 is markedly increased (up to 10 fold) in ESRD patients undergoing maintenance hemodialysis. Other biomarkers of inflammation are also upregulated and demonstrate varying degrees of correlation suggesting inter-relationship between FABP-1 and inflammatory processes. These results also suggest that impaired renal function and tubular damage contribute to the marked increase of LFABP in ESRD patients. Simultaneous measurement of LFABP with biomarkers of inflammatory responses and kidney damage may be helpful in the risk stratification and prediction of the adverse outcome in ESRD patients.

Funding: Private Foundation Support

PO0876

Transcapillary Refilling Rate Profile in Hemodiafiltration

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Background: Reaching dry weight in end-stage kidney disease (ESKD) patients is subject to high ultrafiltration rates (UFR) during their hemodiafiltration (HDF) sessions. We seek to profile the transcapillary refilling rate (TRR) during HDF, which we infer to be an important protective factor against intradialytic hypotension (IHD).

Methods: We studied 30 patients in HDF scheduled 3 times a week. Absolute blood volume was measured with the dilutional method and plasma volume was calculated based on the patient's hematocrit. Each session was divided in 18 intervals of 10 minutes each, we used a fixed UFR during each one in order to calculate the expected plasma volume. Real plasma volume at the end of each interval was calculated on the basis of the relative blood volume. The difference between the real and the expected plasma volume was the plasma refill volume, which divided by the time of each interval gave us the TRR. The HDF session prescription was determined by the nephrologist in charge of the HDF clinic.

Results: 84 HDF sessions were recorded. Mean age was 44 years (+/- 18.8), 66% were female. TRR:UFR ratio difference between patients with and without IDH was statistically significant (p <0.001, CI 95%), as well as the UFR-TRR delta (p <0.001, CI 95%). This ratio achieved stability after 30 minutes. Eight patients (27%) presented an IDH episode during HDF, during a total of 9 sessions (10.7%); 8 (89%) occurred in the final hour and 1 (11%) occurred in the first 10 minutes and corresponded to a patient who presented fever and bacteremia.

Conclusions: Both the TRR:UFR ratio and UFR-TRR delta were statistically significant for predicting IDH. Understanding each patient's TRR will help us plan interventions in order to try and optimize it and reduce the risk of IDH.

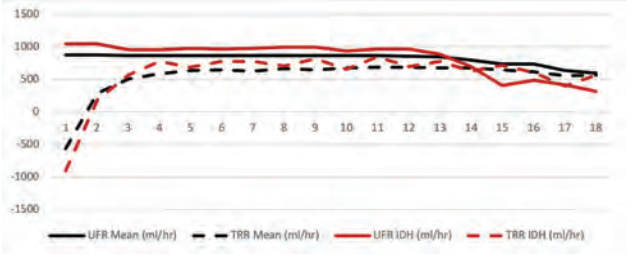

Figure 1. UFR (solid lines) and TRR (dashed lines) profiles.

PO0877

Impact of Hydration Status Measurement by Bioimpedance Analysis (BIA) on Haemodialysis Patients

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Background: Volume status in haemodialysis patients is an important prognostic factor. Overhydration is associated with a higher frequency of mortality while dialysis-induced volume depletion is also an independent mortality risk factor. Clinical indices do not always accurately reflect volume status. Bioimpedance analysis (BIA) is used as a simple, noninvasive method which can measure normovolumic status in haemodialysis patients by measurement of height, weight, and body composition. Fluid overload is calculated by subtracting the normovolumic status from the overhydration status.

Methods: All patients at Queens satellite dialysis unit, Romford, United Kingdom, which has a prevalent population of 106 patients had BIA based assessment of fluid status every 3 months from July 2020 to May 2021 and dry weight adjusted accordingly. Outcomes were noted for blood pressure, overhydration, Interdialytic weight gains, intradialytic hypotension, hospitalisation and mortality.

Results: 121 haemodialysis patients were followed with male to female ratio of 55:66, mean age of 62 (25-87) of whom 46 were diabetics. By end of assessment period, 21 patients had died (13 due to COVID related illness). In July 2020, 31 patients had overhydration of 2 litres or more, which reduced to 20 patients, in May 2021. The number of patients who had underhydration of -1 litre or more remained similar with 12 patients in July 2020 compared to 11 in May 2021 in spite of more aggressive approach to reduction in dry weight. The dialysis population had high turnover due to deaths as well and 2 transplantations and 2 transfers out of the unit. During the time of study 15 patients were admitted to hospital with features of fluid overload.

Conclusions: Bioimpedence analysis (BIA) is a simple, non invasive tool helpful in assessing fluid status in haemodialysis patients. It is easier to convince a patient about their volume status by providing a machine assessed figure rather than clinical parameters. There was significant improvement in overhydration without increasing the number of dehydrated patients. The high mortality in prevalent patients during COVID pandemic highlights the need for continued body composition measurements in a larger population once COVID cases subside to come to a significant conclusion about the impact of BIA in improving patient outcomes including effect on residual renal function.

PO0878

Association of Different Definitions of Intradialytic Hypertension with Long-Term Mortality in Hemodialysis

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Background: Hypertension is common in patients receiving maintenance hemodialysis (HD). A subset of patients experience increases in systolic blood pressure (SBP) from pre- to post-HD (intradialytic hypertension). This phenomenon is known to be associated with adverse short and long-term outcomes, but there is little consensus on an evidence-based definition.

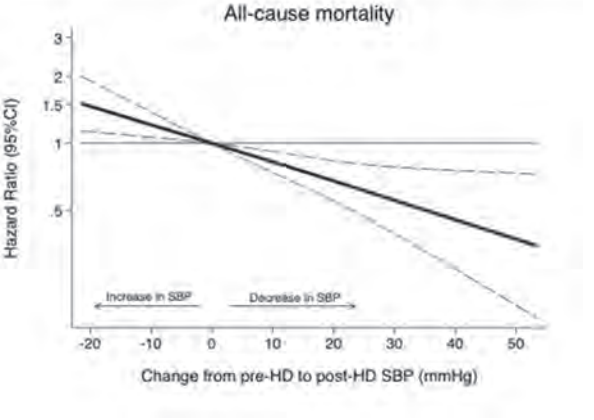
Methods: In a retrospective cohort of 3,198 HD participants, unadjusted and adjusted Cox proportional hazards models were fit to examine the association of various definitions of intradialytic hypertension (≥30% of baseline sessions with an increase in pre- to post-HD SBP of 1) ≥0 mmHg [Hyper0]; 2) ≥10 mmHg [Hyper10], or 3) ≥20 mmHg increase [Hyper20]) with all-cause mortality. Interaction terms were used to assess for effect modification according to pre-specified demographic (age, sex), HD-related (pre-HD SBP, ultrafiltration rate), and comorbid disease variables (diabetes, heart failure, and peripheral vascular disease [PVD]).

Results: At baseline, mean age was 62 ±15 years, 57% were male, and 14% were Black. Average change in BP from pre- to post-HD was 13 ±16 mmHg (median 12 [3 to 22] mmHg). During the baseline period, 47% of individuals met the Hyper0 definition and were at a 29% (HR 1.29; 95%CI 1.03 to 1.62) higher adjusted risk of death, compared with participants with no SBP increase. Hyper10 was present in 21.2% and associated with a 21% higher adjusted risk of death (HR 1.21; 95%CI 0.96 to 1.51). Hyper20 was present in 6.8% and associated with a 5% higher risk of death (HR 1.05; 95%CI 0.76 to 1.46). There was evidence for effect modification by age and PVD (P-interaction=0.02 for both), with a higher risk of death in those aged 45-70 years and those without PVD.

Conclusions: Individuals with any increase in SBP from pre- to post-HD experienced the highest adjusted risk of mortality, compared with other threshold-based definitions with effect modification by age and PVD.

Funding: NIDDK Support

Figure 1. Adjusted association of change in pre- to post-HD systolic BP with mortality.



PO0879

Outcomes of ESKD Patients on Hemodialysis vs. Peritoneal Dialysis Post Open Heart Surgery

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Background: ESKD patients on dialysis suffer from poor outcomes following cardiac surgery compared to the non-dialysis populations. However, the impact of the dialysis modality and the type of cardiac surgery are not well studied.

Methods: We identified 590 patients with ESKD on HD or PD who underwent Coronary Artery Bypass Graft (CABG) and/or valvular cardiac surgery using our Electronic Health Records-based Cardio-Thoracic Surgery (CTS) registry from 2009-2019. Baseline demographics and comorbidities of PD and HD were compared using Chi-square, and t-tests for categorical and continuous variables, respectively. In hospital death, hospital length of stay (LOS), intensive care unit LOS, red blood cell transfusions required, and the incidence of post-operative complications including (pericardial effusions requiring intervention, gastro-intestinal bleed (GIB), and sternal wound infections) were compared using Kruskal-Wallis test, Chi-square and Fisher's exact tests.

Results: Out of 590 patients, 62 (11%) were on PD, and 528 (89%) were on IHD. 277 (47%) underwent Valvular Surgery (VS) only, 158 (26.7%) CABG only, and 155 (26.3%) had combined CABG and VS. Baseline characteristics and comorbidities were similar between the PD and HD groups. In patients undergoing CABG only, PD patients

had more pericardial effusions (12.5% vs 2.3% p = 0.048) and more GIB (12.5% vs 2.2% p = 0.046) (Table 1). There were no differences in in-hospital mortality, hospital length of stay (LOS), ICU LOS, and sternal wound infections between groups across the different surgeries. 16 PD patients were converted to HD post-surgery, intent to treat analysis was applied for these patients.

Conclusions: In patients on maintenance dialysis, patients who underwent CABG, VS, and combined surgery had similar outcomes. PD patients appeared to experience more GIB and pericardial effusions requiring intervention in the CABG group.

	CABG (N=158)		Valve (N=277)		CABG+Valve (N=155)	
Factor	CABG HD (N=134)	CABG PD (N=24)	Valve HD (N=257)	Valve PD (N=20)	CABG+Valve HD (N=137)	CABG+Valve PD (N=18)
Units of RBC Intraoperative	1[0,2]	2[1,3]	2[0,3]	2[0,3]	3[2,4]	2[1,3]
Hospital length of stay (Days)	10[7,13]	9.5[7.5,15.5]	12[8,19]	7.5[6,14.5]	15[10,23]	12[9,20]
ICU length of stay (Hours)	70[46,113]	93[60,125]	96[515,211]	71[50,159]	139[78,345]	120[68,231]
Pericardial effusion requiring intervention	3(2.3)*	3(12.5)*	18(7.1)	0(0.0)	11(8.2)	1(5.6)
In Hospital Death	4(3.0)	0(0.0)	9(3.5)	1(5.0)	12(8.8)	0(0.0)
Sternal Wound Infection In-Hospital	1(0.75)	0(0.0)	2(0.78)	0(0.0)	2(1.5)	0(0.0)
Gastrointestinal Bleed	3(2.2)*	3(12.5)*	21(8.2)	0(0.0)	18(13.1)	3(16.7)

Statistics presented as Median [P25, P75], or N (column %).
p-values: Kruskal-Wallis test, Pearson's chi-square test, or Fisher's Exact test
*Significantly different between PD and HD, p<0.05

Table 1

PO0880

Progression of Coronary Artery Calcification in Unit vs. Nocturnal Haemodialysis Patients

Karen E. Brown,[1] Thomas Bucknall,[1] Giles Greene,[4] Helen Jefferies,[3] Ashraf I. Mikhail,[1] Sarah L. Prior,[2] Jeffrey W. Stephens,[2] Daniel R. Obaid.[1,2]
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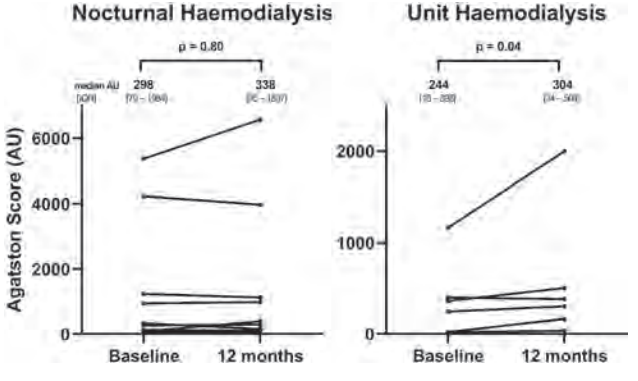
Background: CT coronary artery calcium (CAC) predicts future cardiac events. Inflammation and deranged bone mineralisation may contribute to atherogenesis and arterial calcification. We compared progression of CAC in unit and nocturnal haemodialysis patients.

Methods: Patients commencing unit haemodialysis (UHD=7) and nocturnal haemodialysis (NHD=10) were prospectively enrolled. CAC scores (Agatson) were obtained at 0 and 12 months. Inflammatory (hsCRP, IL-18, hepcidin) and bone mineralisation (PO4-, Ca2+, PTH) biomarkers were obtained at 0, 3 and 12 months.

Results: Groups were well matched for age, gender, aetiology of ESRD and cardiovascular risk factors. Average baseline CAC scores were similar between UHD and NHD but significant progression occurred only in UHD (Figure). The relative increase in CAC score was significantly higher for UHD (71.2%) than NHD (6.7%), p=0.04. Over the study there were no significant changes in markers of bone mineralisation or inflammation for either group except patients undergoing NHD had a significant reduction in IL-18 (117pg/ml ± 59 to 75pg/ml ± 30, p=0.04). Significant CAC progression (increase in CAC >20AU and >15% occurred in 4/7 (57%) of UHD patients compared with 2/10 (20%) undergoing NHD. CAC scores regressed in 1/7 (14%) of UHD patients and 4/10 (40%) of NHD. Hepcidin was the only biomarker associated with CAC progression, it was higher in the progressors: 370pg/mL [321– 398] than regressors: 243pg/ml [138–349], p=0.045 with increase in CAC score correlated to the level hepcidin r=0.51.

Conclusions: Extended hours NHD significantly decreased progression of CAC compared with UHD. Progression appeared to be more dependent on levels of inflammation than deranged bone mineralisation with hepcidin the best predictor of CAC progression, but larger scale studies are required.

Funding: Private Foundation Support



PO0881

Prevalence and Risk Factors for Development of Cardiac Arrhythmias and Electrocardiographic Abnormalities in Hemodialysis Patients: A Single-Center Experience in Mexico.

Andrea San-German Morales,[1] Pedro A. Escamilla Galindo,[2] Armando Castillo García,[1] Paulina Paniagua,[1] Juan M. Ardavin Ituarte,[2] Mario Jimenez Hernandez.[1,2]
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Background: Mexico is among the countries with the highest number of patients on kidney replacement therapy (RRT). Despite this, the incidence and prevalence of CKD in Mexico is unknown, due to the lack of a national registry as a result we do not know risk factors associated to this population. Electrocardiographic abnormalities or arrhythmias are among the most frequent cardiovascular pathologies, being the first cause of death during the first month in RRT. That is why the present study aims to identify the prevalence of arrhythmias in a group of Mexican patients on hemodialysis as well as their associated risk factors.

Methods: A non-experimental, observational, descriptive, and cross-sectional study was carried out in the period from March to July 2020 with Mexican patients older than 18 years in maintained hemodialysis. The electrocardiograms and blood test analysis were taken on the day of hemodialysis therapy.

Results: The mean age of the population was 42.37 years, 57% were male. Arrhythmias were found in 50 patients (41.67%), the prevalence of arrhythmias found was bundle branch block (17.50%), sinus tachycardia (12.50%), sinus bradycardia (7.50%), atrial fibrillation (2.50%), extrasystoles (1.67%). A significant difference in mean ages was found between patients with (47.14) and without arrhythmia (38.97) (P = 0.041). A history of heart disease (OR 7.54 95% CI 1.05-184.7), and the diagnosis of chronic renal failure secondary to diabetic nephropathy (OR 2.5459 95% CI 1.1026-5.8785) were identified as risk factors. The diagnosis of chronic renal failure secondary to arterial hypertension was no related as risk factor (p=0.86). No laboratory study was identified as a risk or protective factor for the development of arrhythmia either the vascular access type.

Conclusions: The studied population presented similar characteristics to the described previously, a high prevalence of electrocardiographic abnormalities was identified, laboratory studies were not related to the presence of arrhythmias. History of heart disease and kidney disease secondary to diabetic nephropathy were associated as a risk factors, while the presence of arterial hypertension was not identified as risk factor.

PO0882

Evaluation of Venous Congestion in Chronic Hemodiafiltration Patients During Ultrafiltration: A Prospective Cohort Study

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Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico.

Background: Fluid overload is deleterious in chronic hemodialysis patients. The combination of multiple POCUS markers can identify significant venous congestion. These markers have not been prospectively studied in this population.

Methods: We measured inferior vena cava (IVC) diameter, portal vein pulsatility fraction (PVPF), jugular vein at rest (YVR) and hepatic vein flow (HVF) at five points: pre-dialysis, three times during dialysis and post-dialysis. All measurements were done three times and averaged. All patients had at least 3% weight gain based on their estimated dry weight. We recorded ultrafiltration volume at each point.

Results: We performed measurements during 30 on-line post dilution hemodiafiltration sessions in 20 patients (13 were female, mean age 38.6 years old). The average total ultrafiltration (UF) volume was 2501.5 cc (1250-4250 cc). There was a significant reduction in PVPF, IVC diameter, YVR, HVF during sessions. See Figure 1. Likewise, UF volume correlated with IVC diameter: R -0.38 p<0.001; PVPF: R -0.31 p<0.001; and HVF: R -0.19 p=0.035.

Conclusions: In chronic hemodialysis patients, even in the absence of a dilated IVC, markers of venous congestion tracked ultrafiltration volume. This study warrants further research with regards to clinical decision to continue fluid removal in chronic hemodialysis patients.

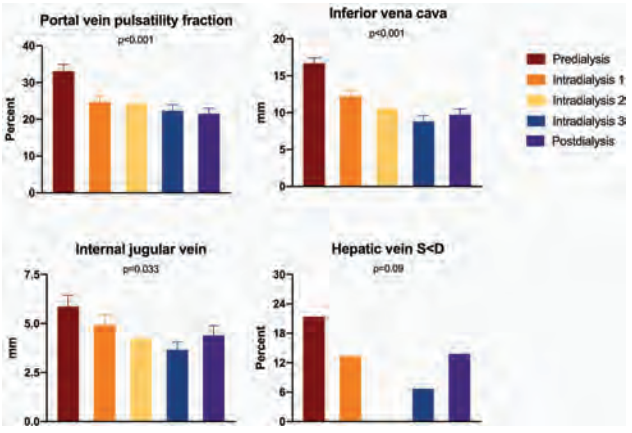

Figure 1. Different POCUS venous congestion markers measured pre-dialysis, intradialysis and post dialysis.

PO0883

Knowledge and Practice of Incremental Dialysis: A Survey of Canadian Nephrologists

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Background: Incremental hemodialysis, a strategy to individualize dialysis prescription at initiation, is being linked to enhanced quality of life and acceptability by patients and decreased health care costs. We aimed to explore knowledge and practice pattern regarding facility-based incremental hemodialysis in Canada.

Methods: A web-based survey of nephrologists, elicited current incremental hemodialysis (HD) prescribing practices, clinical and patient factors used to determine suitability for treatment, and potential barriers to implementation. The survey was circulated over a period of six weeks (September 21, 2020 and October 30, 2020).

Results: The overall response rates 35% (243/691 nephrologists surveyed). Majority (66/111, 59%) of respondents prescribed incremental HD using an individualized approach at the discretion of the nephrologist. Most centers (200/203, 98%) did not report policy or guidance for implementation. Residual urine output was identified as the most important factor for eligibility (112/172, 65%), electrolyte stability (76/172,44%) and existing patient goals of care (69/117, 40%). The majority of nephrologists agreed that dialysis prescriptions are dynamic and should take residual kidney function into consideration; however, 74% of nephrologists did not think there was strong evidence supporting incremental dialysis. Potential barriers identified were patient safety, logistics of scheduling, limited evidence, and acceptance of dose escalation. Despite these barriers, 82% of participants felt that that facility-based incremental dialysis is feasible with their current resources and 78% agreed that with specific exclusion and inclusion criteria, incremental dialysis is a safe option.

Conclusions: Incremental hemodialysis is commonly practiced amongst Canadian nephrologists despite a lack of formal criteria for initiation and treatment escalation. This highlights a need for research to guide policy and practice for incremental hemodialysis in Canada.

PO0884

Thrice vs. Twice Weekly Hemodialysis in a Rural Community Center

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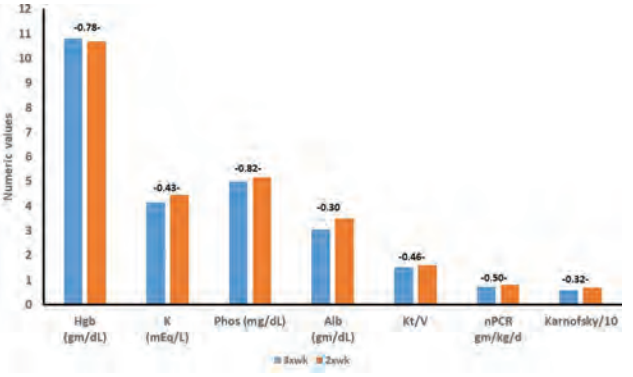
Background: Converting stable ESRD patients from thrice to twice weekly HD sessions.

Methods: ESRD patients on 3xWkly HD sessions for at least 3 months duration were screened for eligibility for conversion to 2xWkly HD schedule in a university-affiliated community dialysis program. Eligibility criteria were: residual renal function > 3ml/min; urine output >500mL/day; intradialytic weight gain <2.5kg; hemoglobin >8gm/dL; manageable phosphorus and potasium levels. Clinical parameters on 3xwkly vs. 2xwkly HD sessions were then performed in the eligible patients. Patients were followed for 6 months post conversion.

Results: 9.8% of total HD pts were eligible. Baseline characteristics: age 65.1±4.5yrs, F 57.1%, HTN 71.4%, DM 14.2%, MM 14.2%. Major indication for HD initiation was symptomatic progression of disease. Less than 50% of patients had a functioning arteriovenous fistula at initiation of HD. In the current cohort, residual renal function > 3mL/min was maintained for > 200 days after initiation of HD. There were no significant changes in electrolytes, hemoglobin, nutrition staus or adequacy of dialysis. PTH levels were not significantly different: 3xwkly, 625.7±546.2pg/mL vs. 2xwkly, 399±344.2pg/mL; p=0.374). Karnofsky Performance Status Scale improved post conversion but did not achieve statistical significance (3xwkly, 57.1 vs. 2xwkly, 70; p=0.316). There were no hospital admissions since conversion to 2xwkly schedule during the study period.

Conclusions: 10% of total HD patients qualified for conversion from 3xWkly to 2xWkly maintenance HD without significant changes to laboratory or clinical performance measures. These observations stimulate discussion regarding increased application of incremental dialysis initiation strategies to preserve residual renal function, increase dialysis-free days and alleviate transportation and care provider-related burden to patients and families, especially in underserved areas.



Comparison of Clinical and laboratory parameters.

PO0885

Impact of the Ratio of Monocyte to High-Density Lipoprotein Cholesterol on Cardiovascular Outcome in Incident Dialysis Patients

Min Gyo Jeong, Hye Eun Yoon, Seok Joon Shin, Yeonhee Lee, Da won Kim. *Catholic University of Korea, Incheon, Republic of Korea.*

Background: Monocyte count to high-density lipoprotein ratio (MHR) is a well known risk factor of cardiovascular (CV) complications as an indicator of inflammation and atherosclerosis. We evaluated the impact of the MHR value on the CV outcomes in end-stage kidney disease (ESKD) patients. The primary outcome was comparison of cardiovascular event-free survival rate between the low MHR group and the high MHR group. The secondary outcome included all-cause mortality, overall CV mortality and possibility of MHR as an independent risk factor for CV complication.

Methods: The medical records of 719 ESKD patients who started maintenance dialysis between January 2006 and July 2017 were reviewed. Patients were divided into low MHR and high MHR groups based on the median MHR value.

Results: Overall CV event was 130 cases, 55 in the low MHR group and 75 in the high MHR group, respectively. The CV event-free survival rate was significantly lower in the high MHR group compared to the low MHR group (47.6% vs. 57.5%, $P = 0.017$). Of the 577 enrolled patients, there was no statistical difference in all-cause mortality between the two groups during a mean follow-up of 3.2 years ($P = 0.371$). Overall CV mortality rate was also comparable between the two groups ($P= 0.615$). In multivariate Cox regression analysis, high MHR was an independent predictor for CV events (HR 1.463, 95% CI, 1.019 – 2.102; $P = 0.039$) even after adjustment for age, smoking, diabetes, body mass index, C-reactive protein, and previous CV disease.

Conclusions: In conclusion, high MHR at the time of dialysis initiation in the incident ESKD patients may be a simple and useful method for predicting development of CV complication.

PO0886

Differences in Clinical Characteristics and Outcomes Between Hemodialysis-Dependent and Non-Hemodialysis-Dependent Patients with Gram-Negative Bacteremia

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Background: Gram-negative bacteremia (GNB) is a common and potentially lethal infection among hemodialysis (HD)-dependent patients. The determinants of clinical outcomes in HD-dependent patients with GNB are incompletely understood. We compared clinical characteristics and outcomes between HD- and non-HD-dependent patients with GNB in a large cohort of hospitalized patients and subsequently examined associations between specific characteristics and all-cause mortality among HD-dependent patients.

Methods: Hospitalized, non-neutropenic adults with GNB were prospectively enrolled from Jan 1, 2002 to July 1, 2015. Clinical characteristics and outcome data were collected. Differences between HD- and non-HD-dependent patients were estimated using means/standard deviations or counts/percentages with statistical significance evaluated with independent sample T-tests or Pearson's chi-squared test. Associations between clinical characteristics and outcomes were estimated using logistic regression.

Results: Among 1,827 unique participants, 180 were HD-dependent (9.9%). Compared to non-HD-dependent patients, HD-dependent patients were younger (58.6 vs 61.0 years, p=0.05) and more likely to be Black (55.6% vs 26.4%, p<0.001), to have diabetes (56.1% vs 32.1%, p<0.001), and to die prior to hospital discharge (28.9% vs

19.9%, p=0.01). Among HD-dependent patients, having a higher total APACHE II score (Odds Ratio [OR] 1.15, Confidence Interval [CI] 1.08-1.23), non-central venous access source of infection (OR 8.00, CI 2.71-23.60) or hospital-acquired infection (OR 4.46, CI 2.19-9.09) were associated with in-house mortality, while Black race (OR 0.31, CI 0.16-0.63) was inversely associated with mortality.

Conclusions: Clinical characteristics and outcomes differed significantly between HD- and non-HD dependent patients with GNB. Mortality among HD-dependent patients may be partially explained by source of infection, site of acquisition, and severity of illness at time of infection. The association between race and patient outcome requires further study.

Funding: NIDDK Support, Other NIH Support - K24-AI093969

PO0887

Predictors of Hyperkalemia Among Chronic Hemodialysis Patients Transported to the Emergency Department

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Background: Chronic hemodialysis (HD) patients often present to the emergency department (ED) with hyperkalemia, which in turn, is associated with morbidity and mortality. In this study we sought to identify pre-hospital predictors of hyperkalemia in patients transported to the ED via ambulance (ambulance-ED).

Methods: We analyzed all ambulance-ED transports in a cohort of chronic hemodialysis patients from 2014-2018 (using a province-wide emergency medical services database). The outcome was severe hyperkalemia using the first blood draw after ambulance-ED transport and defined as ≥6 mmol/L. Characteristics of interest included vital signs prior to transport, days from last dialysis and prehospital electrocardiograms (ECGs) interpreted by paramedics prior to transport. The association between prehospital factors and hyperkalemia was analyzed using adjusted logistic regression.

Results: A total of 270 dialysis patients had 704 ambulance-ED transports followed by an ED potassium blood draw. Severe hyperkalemia occurred after 75 (11%) transports. In an adjusted parsimonious model (Table 1, N=609), age, dialysis vintage, bradycardia and days from last dialysis were associated with severe hyperkalemia. Among those with prehospital ECGs (N=377), presence of a prehospital ECG abnormality (i.e. peaked t-waves and/or first-degree atrioventricular block) was strongly associated with ED hyperkalemia (odds ratio 6.64, 95% confidence interval 2.31-19.12). Overall, 45% of hyperkalemic patients versus 24% of non-hyperkalemic patients required re-transport to another hospital to facilitate dialysis in a monitored setting after initial presentation.

Conclusions: A longer interval from last dialysis and prehospital ECG changes are strongly associated with hyperkalemia after transport to the ED. Having an awareness of these associations may allow healthcare providers to define novel care pathways to ensure timely diagnosis and management of hyperkalemia.

Adjusted predictors of severe hyperkalemia after transport to the emergency department (n=609)*

	Adjusted OR		
	OR	95% CI	P
Age at transport *(each year)*	0.97	0.95-0.99	0.009
Male Sex	1.14	0.61-2.15	0.681
Hemodialysis vintage *(each year)*	1.18	1.08-1.28	<0.001
Days from last HD relative to ED transport			
Same day but prior to ED transport	Reference		
One	5.11	1.08-24.14	0.040
Two	18.49	4.99-68.49	<0.001
Three or more	24.43	5.48-109.04	<0.001
Heart Rate prior to ED transport			
60 - 99 *(beats/min)*	Reference		
<60 (beats/min)	3.15	1.05-9.45	0.040
≥100 (beats/min)	0.83	0.43-1.58	0.562

OR, Odds ratio; CI, confidence intervals; HD, hemodialysis; ED emergency department
*Included variables had a P<0.10 in univariable logistic regression analysis

PO0888

Association of Potassium with Decline in Residual Kidney Function in Incident Hemodialysis Patients

Jessica A. Edward,[1] Cachet Wenziger,[1] Jui-Ting Hsiung,[1] Fridtjof Thomas,[2] Csaba P. Kovesdy,[2,3] Kamyar Kalantar-Zadeh,[1] Elani Streja.[1] *[1]University of California Irvine, Irvine, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]VA Memphis Medical Center, Memphis, TN*.

Background: Hyperkalemia has been associated with higher risks for renal decline in non-dialysis kidney disease patients. However, it is unclear whether this relationship exists in hemodialysis (HD) patients.

Methods: A retrospective cohort study was conducted on 6,655 incident HD patients who received treatments from January 2007 to December 2011 and had renal urea clearance (KRU) data in the first and fifth patient quarter (91 day interval) post dialysis initiation. Renal decline was estimated by both KRU difference in the fifth minus first patient quarter as well as by a mixed-effect linear regression to estimate KRU slope over the first year. Baseline potassium levels were stratified into four groups: (≤4.0, > 4.0 to ≤4.5 (reference), > 4.5 to ≤5.0, >5.0 mEq/L) and linear regression models were used to analyze the relationship between potassium and KRU renal decline across models adjusted for demographics (case-mix), malnutrition-inflammation (MICS), and baseline KRU. Mediation analysis was also conducted to analyze if renal decline is a mediator in the association between potassium and mortality.

Results: The median (IQR) of one year difference in KRU was -1.24 (-2.91, 0.12) while the median KRU slope was -1.64 (-2.53, -0.95). Compared to the reference, potassium > 4.5 mEq/L was associated with the greatest difference in KRU in both the case-mix model (-0.28, 95% CI -0.44, -0.11) and in the case-mix + MICS model (-0.20, 95% CI -0.50, -0.06) [Figure 1A]. Similar results were seen for KRU slope [Figure 1B]. It was also observed that KRU slope mediated the relationship between potassium and mortality by 1.78%.

Conclusions: Hyperkalemia shows associations with renal decline over the first year on HD. Future studies should be conducted to investigate the pathways underlying these associations.

Figure 1A

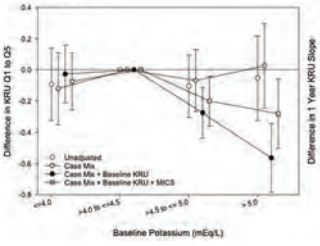
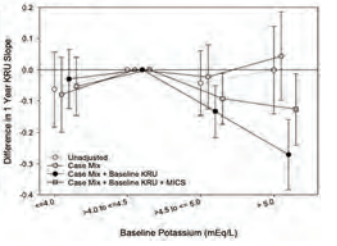


Figure 1B



PO0889

Efficacy of Patiromer and Sodium Polystyrene Sulfonate on Potassium Levels in Chronic Hemodialysis Patients

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Background: While hyperkalemia is frequent in haemodialysis (HD) patients and is associated with increased mortality, evidences regarding treatment options are limited. We compared the effect of sodium polystyrene sulfonate (SPS) and patiromer on potassium control in this population.

Methods: After screening 180 prevalent chronic HD patients, we included 52 patients with pre-HD potassium >5.1 mmol/l without potassium binder in a cross-over trial comparing on non-dialysis days SPS 15 g before each meal to patiromer 16.8 g once a day. Treatment duration was four weeks with a 2-week intermediate wash-out period. Treatment attribution order was randomized. Pre-HD potassium level was measured at each dialysis session and tolerability assessed on a semi-quantitative scale from 0 to 10.

Results: 45 patients terminated the study without missing values on considered variables. Mean age was 66.3 +/- 19.2 with 74 % male and 44% diabetic patients. Mean weekly pre-HD potassium were 4.5 +/- 0.7 mmol/L and 5.0 +/- 0.5 mmol/L under SPS and patiromer respectively. In mixed linear regression, treatment with SPS was associated with a decrease of 0.47 mmol/L in mean weekly pre-HD potassium compared to patiromer ($p<0.001$). Tolerability score was 6.0 +/- 2.4 and 7.0 +/- 1.8 under SPS and patiromer respectively ($p<0.001$).

Conclusions: In chronic HD patients, SPS 15 g before each meal on non-dialysis days resulted in lower pre-HD potassium values as compared to patiromer 16.8 g once a day, although tolerability was poorer. Those findings as well as dose titration need to be tested in larger randomized trials.

Funding: Clinical Revenue Support

PO0890

Associations of Serum and Dialysate Potassium Concentrations with Incident Atrial Fibrillation in Older US Persons Initiating Hemodialysis for Kidney Failure

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Background: Atrial fibrillation (AF) is the most common arrhythmia and affects more than a third of U.S. patients with kidney failure on hemodialysis (HD). Hyperkalemia is a common concern in the HD population and been associated with higher mortality, especially sudden death. However, little is known about the associations of serum potassium ($S\text{-}K^+$) and prescribed dialysate potassium ($D\text{-}K^+$) concentrations with incident AF in persons on HD.

Methods: We used health records data of a large dialysis provider merged with the US Renal Data System (2006-11). We identified persons aged 67+ when initiating HD who had 2+ years of prior Medicare coverage and not been diagnosed with AF by day 120 after start of HD. Subsequent 30 day periods were created during which $S\text{-}K^+$ measurements were averaged; the most recent $D\text{-}K^+$ in the preceding 30 day window was also recorded. Demographic, comorbidity, and health utilization variables were defined as were other laboratory/biometric characteristics. The outcome, newly-diagnosed AF during the subsequent 30 days, was recorded from claims. This process was repeated after frameshifting all measurements by +30 day increments. Cox regression was used to estimate hazard ratios.

Results: We studied 15,190 persons on HD without prior AF diagnosis; average age was 76 yrs, 49% were male; 69% were white, 26% black, and 8% Hispanic. At baseline, 7183 persons had a S-K^+ ≥4.5 and 6988 <4.5 mEq/L. With the exception of race and ethnicity, all other characteristics, including D-K^+, which was 2 mEq/L in 52% and 3 mEq/L in 34%, were balanced between groups. During a mean follow-up of 527 days the overall incidence of AF was 13/100 person-years. Modeling S-K^+ as squared-term variable fit the data best. After multivariable adjustment, AF was associated with lower, but not with higher S-K^+ concentrations unless extreme values >6.5 mEq/L were reached. D-K^+ of 3 mEq/L, *vs.* 2 mEq/L, was associated with 14% (95%CI, 5-24%) lower adjusted rates of AF. No interaction between S-K^+ and D-K^+ was found (P=0.34).

Conclusions: Hypokalemia was strongly and independently associated with incident AF whereas hyperkalemia was not. However, choice of D-K^+ of 2 mEq/L *vs.* 3 mEqu/L did associate with higher AF rates, independent of S-K^+ and other measured characteristics.

Funding: NIDDK Support

PO0891

Serum Potassium Changes in US Veterans Receiving Patiromer with Dialysis-Dependent ESKD and Hyperkalemia

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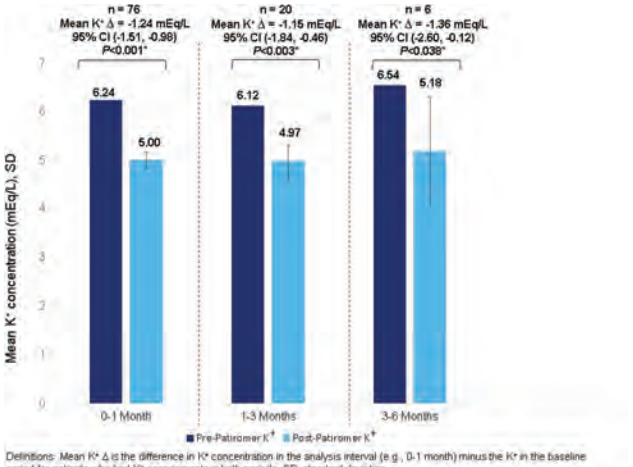
Background: Patiromer is a sodium-free, non-absorbed, potassium (K^+)-binding polymer approved for the treatment of hyperkalemia (HK). This retrospective cohort study aimed to describe serum K^+ changes in Veterans with HK and end-stage kidney disease (ESKD) receiving dialysis who initiated patiromer.

Methods: Serum K^+ concentrations were evaluated pre- and post-patiromer initiation using the National VA Corporate Data Warehouse (1/1/16–8/31/18). Changes in mean serum K^+ concentration were compared at 1, 3, and 6 months following first patiromer dispensing (index date) using the paired t-test (pre K^+ versus post K^+). All patients had a baseline K^+ ≥5.1 mEq/L and ESKD. Patients with continuous exposure to patiromer were analyzed. Follow-up began on the index date and ended at first censoring event (discontinuation or switch of index K^+ binder, death, end of follow-up, or 6 months post-index).

Results: 98 patients with ESKD requiring dialysis and HK initiated patiromer. Patient characteristics at baseline were median age 66 years, African-American race 39%, diabetes 71%, heart failure 40%, and mean K^+ value of 6.1 mEq/L (standard deviation = 0.7). The initial dose of patiromer was 8.4 g in 96% of patients with few observed increases in unit dose during the follow-up period. Following patiromer initiation, statistically significant reductions in serum K^+ concentration were observed at 1 month (–1.24 mEq/L), 3 months (–1.15 mEq/L), and 6 months (–1.36 mEq/L; Figure).

Conclusions: Among dialysis-dependent US Veterans with HK, patiromer was associated with clinically relevant reductions in serum K^+ concentrations at all study time points. These findings warrant additional investigation in a larger dialysis cohort with HK.

Funding: Commercial Support - Vifor Pharma, Inc.



Definitions: Mean K⁺ Δ is the difference in K⁺ concentration in the analysis interval (e.g., 0-1 month) minus the K⁺ in the baseline period for patients who had K⁺ assessments in both periods. SD, standard deviation
*P values and 95% confidence intervals were estimated using the paired t-test (H_0: Δ=0). The paired t-test compared the highest K⁺ value in the 3 months prior to initiating patiromer to the last K⁺ value in each monthly follow-up interval post-patiromer initiation

PO0892

Hyperkalemia: Medical Management vs. Hemodialysis

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Background: Hyperkalemia is a life-threatening electrolyte disorder for which there exists a paucity of data regarding benefit of urgent hemodialysis over medical management. We hypothesized there would be no difference in potassium levels among hyperkalemic patients who received *only* medical management compared to those who received hemodialysis, with out without hemodialysis.

Methods: This is a retrospective study of patients 18+ years old with hyperkalemia (K ≥ 5.5mmol/L). One group (medical management, or MM) had medication(s)—including insulin/dextrose, sodium zirconium cyclosilicate, sodium polystyrene sulfonate, calcium gluconate, albuterol, or furosemide—ordered within 3h of initial elevated potassium. The other group (hemodialysis, or HD), had hemodialysis ordered—with or without medical management—within 3h of elevated potassium. The initial potassium level was considered "time-zero" and subsequent timepoints were followed up to 100h. T1 readings were established between 0–3 hours; T6: 3–8h; T12: 8–16h; T24: 20–28h; T48: 40–56h; T72: 60–100h.

Results: Of 1365 patients screened between 2015 and 2020, we excluded 796 who were <18 years old or potassium level <5.5 mmol/L or without follow-up potassium levels. There were in-total 569 patients with 682 eligible patient visits; 64 (9%) of the 682 visits in HD group and 618 (91%) in MM group. The mean initial potassium was 6.45 ± 0.08 mmol/L in HD, versus 6.21 ± 0.03 mmol/L in MM. There was a progressive reduction in potassium levels over time in both groups. The reduction in potassium was similar in both groups across all timepoints (4.5-5.0 mmol/L in HD and 4.4-5.1 mmol/L in MM). The only timepoint that showed statistical difference was T12 where potassium level in HD was lower than in MM by 0.45 mmol/L (p-value = 0.0153). This may be secondary to the efficiency and permanence of potassium removal with dialysis or due to the relatively small sample size of the HD group; this difference is not clinically relevant.

Conclusions: Among patients presenting with hyperkalemia, we found no difference in potassium levels between those who received only medical management and those who received hemodialysis, with or without medical management. Further studies are necessary to confirm these findings. Nationally standardized treatment algorithms ought to be developed; a randomized trial would be conducive to that end.

PO0893

Metabolic Alkalosis in Hemodialysis Patients

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Background: Hemodialysis (HD) typically employs a high dialysate alkali concentration to counteract interdialytic acid production. Since acid production varies due to the amount and type of protein consumed, some patients may remain alkalotic throughout the interdialytic period and be more alkalotic during HD. This could have adverse effects including arrhythmias, hypotension, hypoventilation, and vascular calcification but dialysate alkali is rarely adjusted. Pre-HD alkalosis is usually ascribed to chronic illness and poor nutrition, but this has not been carefully examined.

Methods: We conducted a retrospective case-control study of all in-center HD patients from 2010 - 2020 at 4 outpatient HD units using citrate-containing dialysate (34.6 meq/L HCO3, 0.4 meq/L acetate, 2.4 meq/L citrate; citrasate, Fresenius). Interdialytic alkalosis was defined as pre-HD serum [HCO3] ≥26 in ≥ 7 months of any 12-month period. Persistent alkalosis was defined as interdialytic alkalosis in every subsequent 12-month period. Patients with serum [HCO3] 19-23 in ≥ 7 months of every 12-month period constituted the control cohort.

Results: Of 1271 patients with at least 12 months of HD, 444 met the alkalosis criteria for at least one 12-month period and 73 had persistent alkalosis. 189 patients met the control criteria for every 12-month period. Patients with persistent alkalosis were older (66 vs 55 years, p<0.001) and weighed less (69 vs 82 kg, p= 0.003), but the prevalence of comorbidities including cardiovascular disease, neoplasia, and diabetes was not increased. HD dose (kT/V) was greater (1.47 vs 1.37, p<0.001), protein catabolic rate was lower (0.85 vs 0.96 g/kg/day, p <0.001), and interdialytic weight gain was less (1.62 vs 2.28 kg, p<0.001). Despite significant weight loss over time (7 ± 13 vs. 0 ± 9 kg, p <0.001), mortality was not increased when adjusted for age, serum albumin was only slightly lower (3.71 vs 3.80 g/dl, p=0.03), and other markers of malnutrition/chronic illness such as serum cholesterol and hemoglobin did not differ from control patients.

Conclusions: Transient interdialytic alkalosis was common in this HD population and persistent alkalosis was not rare (>5%). Alkalosis appeared to result from a greater dialysis dose and lower protein intake but not chronic illness. Further studies are needed to determine whether this alkalosis is detrimental and adjustment of dialysate [HCO3] is indicated.

PO0894

Metabolic Alkalosis in Hemodialysis Patients: Worse Outcomes?

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Background: The ideal serum bicarbonate levels in prevalent hemodialysis (HD) patients is still debatable. Metabolic alkalosis in these patients has been associated with increased morbimortality. The aim of this study was to evaluate the association between serum bicarbonate and nutritional and cardiovascular risk markers, hospitalizations and mortality.

Methods: This was a single-center, retrospective study, of a cohort of 158 in-center HD patients, with a duration of 24 months. Serum bicarbonate levels were evaluated predialysis every 3 months. Body Composition Monitor was used to assess nutritional and hydration status. Electrocardiogram and echocardiogram data were obtained to calculate the QTc interval and the left ventricular mass index, respectively. Vascular calcifications were assessed using the Adragão score (SVCS).

Results: Mean age of the population was 69.8±12.6, 73% were male and 45% had diabetes. Median HD vintage was 59 months (IQR: 65 months). Mean serum bicarbonate was 23,5±1,57 mEq/L. There was as inverse association between serum bicarbonate and body mass index (r=-0.22, p=0.006), lean tissue index (r=-0.35, p<0.001), hemoglobin (r=-0.19, p=0.016), albumin (r=-0.30, p<0.001), phosphorus (r=-0.33, p<0.001) and nPCR

(r=-0.41, p<0.001). Patients with greater SCVS (≥3) had higher mean serum bicarbonate (24.1±1.29 vs. 22.4±1.36 mEq/L, p<0.001). Higher serum bicarbonate was associated with an increased number of infection-related hospitalizations (p=0.009) and mortality (p=0.024), as well as all-cause mortality (p=0.012). Kaplan-Meier analysis revealed a significantly higher all-cause mortality in patients with serum bicarbonate ≥ 24.5 mEq/L at 24 months. The Cox regression analysis showed that serum bicarbonate was a predictor of all-cause mortality (p=0.004) in a model adjusted for age, dialysis vintage and the presence of diabetes.

Conclusions: In this population, higher serum bicarbonate was associated with a worse nutritional status and a higher cardiovascular risk, assessed by Adragão score. There was an association with an increased number of infection-related hospitalizations and mortality, as well as higher all-cause mortality. Serum bicarbonate levels ≥24.5 mEq/L were associated with lower survival at 24 months. Prospective studies are needed to determine the ideal serum bicarbonate levels in HD patients.

PO0895

The Use of Caffeine to Treat Intradialytic Hypotension

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Introduction: Intradialytic hypotension (IDH) affects over 10% of individuals on hemodialysis (HD) and can cause long-term multisystem ischemic damage. One proposed mechanism for IDH is the accumulation of local adenosine causing vasodilation. Agents such as midodrine and caffeine counter these vasodilatory effects. Herein we present a case of IDH where the ingestion of caffeine prior to HD sessions significantly reduced the severity of IDH.

Case Description: A 77-year-old female with CKD-5, longstanding hypertension, and type 2 diabetes mellitus was admitted for initiation of HD. During her 1st HD session, she experienced IDH with a sudden drop in her systolic blood pressure (SBP) from the 193 to 113, accompanied by loss of consciousness and convulsions of the bilateral upper extremities. She regained consciousness without a postictal state and no significant changes on ECG. Echocardiography ruled out pericardial effusion. On subsequent HD sessions, the patient continued to experience IDH with average decreases of over 100mmHg in her SBP. Initial management by lowering blood flow rate, lowering dialysate temperature, and holding the patient's pre-dialysis antihypertensive regimen had only a mild effect in preventing IDH. Given previous studies showing the efficacy of 250 mg caffeine capsules in preventing IDH, we tested the effect of caffeine on this patient's IDH. 30 minutes prior to her next inpatient HD session, we administered 10 oz of coffee (150 mg of caffeine). Her drop in SBP during that session was markedly reduced from 187 to 149.

Discussion: Non-pharmacological measures to prevent IDH have previously been implemented but lack well-powered clinical trial evidence. Using coffee as a vehicle for caffeine administration was an effective preventive measure for IDH in our patient. We hypothesize that this effect is adenosine inhibition mediated. Adenosine is released by cells undergoing localized ischemia during HD, causing vasodilation. Studies show an increase of serum adenosine during IDH. Caffeine is a non-selective adenosine receptor antagonist, and can prevent sudden vasodilation during dialysis. Thus, coffee may be an effective alternative to midodrine for the prevention of IDH. In conclusion, coffee provided a readily available, inexpensive, patient-centered, non-pharmacological measure to reduce IDH while also decreasing the risk of polypharmacy.

PO0896

A Case of Posterior Reversible Encephalopathy Syndrome (PRES) in an ESKD Patient with COVID-19

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological syndrome first reported in 1996 which describes the presence of a wide range of neurological symptoms, and posterior brain white matter edema on imaging studies which may be reversible. The clinical presentation is characterized by headache, altered consciousness, visual disturbances and seizures; hypertension is frequent, although not invariable.

Case Description: A 37-year-old male with past medical history of hypertension and end stage kidney disease on hemodialysis who presented with shortness of breath, occipital headache, and bilateral acute vision loss. On admission, he was afebrile with a blood pressure of 274/147 mmHg, RR of 16, HR 98 bpm and oxygen saturation of 89% on room air. Due to acute vision loss, a stroke alert was initiated. A head CT scan showed subcortical hypodensities in the bilateral occipital lobes consistent with PRES. He was started on Nicardipine drip in the ICU with subsequent decrease in blood pressure to 166/105 mmHg. His vision restored fully without further episodes of vision loss. Patient was found to be positive for COVID-19 and did not receive treatment for it as his shortness of breath and hypoxia resolved. The patient received maintenance hemodialysis, Nicardipine drip was weaned, and he was transitioned to oral blood pressure medications.

Discussion: The relationship between kidney disease and PRES is not fully understood. Reported cases of PRES have been linked with hypertension, autoimmune disease, and immunosuppressive states, common diseases in ESKD. The pathophysiology of PRES appears to be related to cerebral blood flow dysregulation and endothelial cell dysfunction. The proinflammatory response in COVID-19 produces dysfunction and death of endothelial cells which may increase vascular permeability, promoting the cerebral edema seen in PRES. The estimated prevalence of PRES in COVID-19 patients is between 1-4%. Reports of PRES in ESKD are rare. PRES may not be readily recognized given the heterogeneity of presentation. Therefore, high index of suspicion is needed in the ESKD population.

PO0897

Eye Pain During Hemodialysis: Ocular Dialysis Disequilibrium?

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Introduction: Changes in Intraocular pressure (IOP) during hemodialysis (HD) are underrecognized. We report a case of increased IOP during HD, successfully treated with adjustments to dialysis prescription.

Case Description: 39-year-old African American man with End Stage Renal Disease (ESRD) secondary to diabetic nephropathy on HD since 2017, presented with excruciating right eye pain during HD for 2 weeks. He described increasing right eye pain during HD, requiring early termination of dialysis after 3 hours. He has known right eye glaucoma with no vision. He was on atropine sulfate, prednisolone acetate, latanoprost, dorzolamide/timolol, and brimonidine tartrate eye drops. IOP in right eye were 63 and 80 mm of Hg, before and after hemodialysis, respectively. Left eye IOP were < 20 mm of HG and did not change significantly with dialysis. Due to concerns for ocular dialysis disequilibrium; blood flow rate, dialysate flow rate, dialysate temperature, and dialysate sodium were changed to 400 ml/minute from 450 ml/minute, 500 ml/minute from 800 ml/minute, 35.6 C from 37 C, and 145 mEq/L from 140 mEq/L, respectively. Subsequent to changes to dialysis prescription, patient was able to complete dialysis with no worsening of right eye pain and IOP (62 and 64 mm of HG before and after dialysis, respectively).

Discussion: Increase in IOP during HD is thought be due to rapid decline in plasma osmolality relative to aqueous humor, creating an osmotic gradient that causes movement of water into the eye. Patients with normal eye outflow have minimal rise in IOP as aqueous humor is drained simultaneously. However, patients with glaucoma are not able to drain excess water, causing increase in IOP and eye pain. Older age, diabetes mellitus, and African-American race are risk factors for ESRD and Glaucoma. Early recognition of ocular disequilibrium syndrome can allow for safe delivery of dialysis in patients with glaucoma. While acetazolamide is an effective treatment for raised IOP, it's efficacy and safety in ESRD remains unknown. Similarly role of Mannitol in mitigation of ocular dialysis disequilibrium is unclear. Our patient had resolution of ocular dialysis disequilibrium with decrease in blood and dialysate flow rates, increase in dialysate sodium, and decrease in dialysate temperature. Increase in ultrafiltration may also reduce risk of ocular dialysis disequilibrium by raising extracellular oncotic pressure.

PO0898

The Association of Interdialytic Weight Gain in Long Intervals with Residual Renal Function Decline

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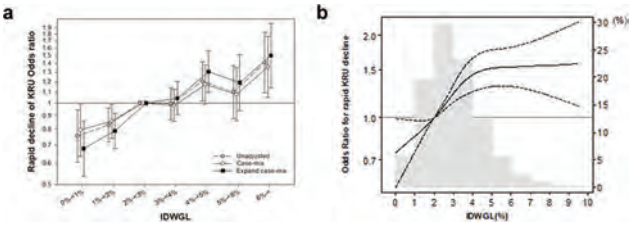
Background: Preservation of residual renal function (RRF) in dialysis patients is important for better prognosis. The effect of interdialytic weight gain (IDWG) on change of RRF has not been investigated well. We examined the association of IDWG in long intervals (i.e. 2-day breaks between dialysis treatments) with rapid decline of RRF.

Methods: This retrospective cohort study included 6425 patients who initiated hemodialysis in a large dialysis organization in the United States from 2007 to 2011. We examined the association between seven categories of IDWG in long intervals (IDWGL) and rapid decline of RRF using logistic regression model. Rapid decline of RRF was defined as the percent decline in renal urea clearance (KRU) greater than the median value of the cohort in the first year after dialysis initiation. Seven categories of IDWGL were as follows: 0-<1%, 1-<2%, 2-<3%, 3-<4%, 4-<5%, 5-<6%, and ≥6%. We also examined continuous associations between IDWGL and rapid decline of RRF using restricted cubic spline analysis.

Results: Higher categories of IDWGL were associated with increased risk of rapid decline of RRF. The odds ratios (95% confidence intervals) of rapid decline of RRF for 3-<4%, 4-<5%, 5-<6%, and ≥6% were 1.04 (0.90-1.20), 1.31 (1.09-1.56), 1.19 (0.94-1.51), and 1.50 (1.14-1.97) (Reference: 2-<3%) (Figure a). The restricted cubic spline analysis showed that risk of rapid decline of RRF increased when IDWGL exceeded 2% (Figure b).

Conclusions: Our results showed higher IDWGL was associated with higher risk of rapid decline of RRF. IDWGL exceeded 2%, especially ≥4%, seems to be thresholds for higher risk of RRF decline.



PO0899

Prevalence of Anti-Erythropoietin Antibodies in Patients with ESRD on Regular Hemodialysis: A Single-Centre Experience

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Background: Recombinant human erythropoietin (rHuEPO) is a glycoprotein that acts as a biological substitute for the endogenous substance used to treat anaemia in individuals with end-stage renal failure. Patients with rHuEPO resistance have been described, requiring higher and higher dosages of the drug to maintain an appropriate haemoglobin level. These antibodies probably cross react with the patient's endogenous EPO and lead to anemia that can be more severe than even before the onset of EPO therapy. The prevalence of anti-erythropoietin antibodies in renal patients who respond poorly to erythropoetin is unknown.

Methods: We screened 262 patients who were on maintenance haemodialysis and excluded patients who were malnourished and had chronic liver disease, hypothyroidism, ongoing active autoimmune disease, active infection, on steroid therapy, with bleeding or hemolysis and elderly. 96 ESRD patients who were on recombinant human erythropoietin > 6 months and hemoglobin < 10 g /dL were included. Serum anti-EPO antibodies were detected by enzyme-linked immunosorbant assay technique. All patients were subjected to full history taking and clinical examination. Complete blood count, reticulocytes count, serum creatinine, blood urea, serum albumin, serum ferritin, and hepatitis markers were performed for all patients.

Results: Results showed that 26 patients (27.08%) had the anti-EPO antibodies in their blood, while 70 patients (72.91%) did not have the circulating antibodies. The mean hemoglobin (Hb) level was significantly lower in the antibody positive group (8.4 g/dl ± 1.52) than in the antibody negative group (9.68 g/dl ± 1.14) (P = 0.000). The dose of EPO administrated in both studied groups were significantly different. Logistic regression analysis also revealed that gender or age were not associated with any significant variation of serum antibody level. High levels of serum antibodies to EPO are a risk factor for EPO resistance.

Conclusions: Many anaemic ESRD patients treated with recombinant human erythropoetin have a low-affinity immune response to the recombinant protein that is readily detected. Antibodies to rHuEPO were shown to be greater in patients who received high EPO weekly dose. More research into anaemia management protocols in HD patients with positive anti-EPO antibodies is needed.

PO0900

Posterior Ischemic Optic Neuropathy After Hemodialysis In a Patient with Uncontrolled Diabetes Mellitus

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Introduction: Posterior ischemic optic neuropathy (PION) results from ischemic damage to the retrobulbar optic nerve and presents as severe acute painless unilateral or bilateral loss of vision. Any procedure that results in sufficient optic nerve hypoperfusion can cause retrobulbar optic nerve damage. Hemodialysis (HD) as a cause of peri-procedural bilateral PION is a rare complication. While there are reports of successful cases of treatment with hyperbaric oxygen treatment and steroids, there is no established treatment protocol and the prognosis for recovery of vision in patients with peri-procedural PION is poor.

Case Description: A 34-year-old male with end-stage renal disease on HD presented with respiratory complaints and hypertensive emergency (BP 224/135 mmHg). His past ocular history was significant for proliferative diabetic retinopathy. Due to volume overload, he underwent emergent HDovernight with ultrafiltration of 3 L. He underwent a subsequent HD treatment with additional ultrafiltration of 3 L the following morning with lowest BP 117/73 mmHg. Shortly after the second HD treatment, he complained of bilateral painless complete loss of vision. He was found to have no light perception in either eye. Pupils were 3 mm and amaurotic. A dilated fundus exam showed perfused-appearing optic nerves. A presumptive diagnosis of bilateral PION was made due to relative hypotension during HD. The patient was treated with erythropoietin (EPO) 10,000 units twice daily and IV methylprednisolone for 3 days according to the protocol suggested by Nikkah et al for non-arteritic anterior ischemic optic neuropathy. Examination 14 hours after the first dose showed marked clinical improvement and he regained his vision. The patient underwent two more HD sessions with careful attention paid to avoiding hypotension. He had no subsequent vision loss. When he was seen in the eye clinic 4 days after discharge, his visual acuity remained stable.

Discussion: EPO has been proposed as a treatment agent for ischemic optic neuropathy. Bilateral loss of light perception is a rare complication related to hypotension on HD. The presumed etiology in this case was PION. Prompt treatment with EPO and intravenous steroids should be considered in similar situations that result in PION related to procedure-based hypotension.

PO0901

Ocular Dysequilibrium with Eye Pain During Hemodialysis

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Introduction: Eye complications may occur ESRD patients with glucoma. Hemodialysis (HD) may lower plasma osmolality at a faster rate than changes in ocular osmolality can adapt. Here we are presenting two cases of ESRD patients who repeatedly developed eye pain only during HD.

Case Description: A 54 y/o Hispanic male with ESRD, right eye blindness & glaucoma who developed right eye pain only during dialysis treatments. The maintenance HD prescription was with duration of 4.5 hr, blood flow rate (BFR) 450mL/min, dialysate flow 800 ml/min, Sodium (Na) 138 meq/L, potassium 2meq/L, Calcium 2.5 mEq/L, CO2 30mEq/L & an average 2L fluid removal per HD. His BP was 130-140mmHg/ 80-90 mmHg. In response to the eye symptoms, the BFR was reduced to 350 ml/min & time was increased to 4.5 hr. This change gave the patient initial relief from intradialytic eye pain. Eventually, Ophthalmologist was able to perform a surgical procedure which would eliminate the intradialytic eye pain. The 2nd case was a 64 y/o AA female with ESRD and glaucoma developed recurrent left eye pain with headaches only during HD. She went to her Ophthalmologist who renewed her glaucoma medications. This relieved her eye symptoms, and normalized her intraocular pressure off of dialysis. By taking her eye medications, she no longer developed eye pain or headaches during HD.

Discussion: Glaucoma is an ocular disorder where there is an increased IOP most commonly >22mmHg, this elevated pressure can cause blinding optic neuropathy. The current hypothesis for the rise of IOP during HD is related to an osmotic disequilibrium between the plasma & IO fluid, where the IO fluid is slightly hypertonic compared to plasma. Several medical therapies have been reported to mitigate the IOP increase during HD, such as the use of daily acetazolamide, mannitol infusion or 20% hyperosmolar glucose solution, or modified dialysis parameters with colloid infusion to raise plasma tonicity and decrease fluid shift during HD. However, these maneuvers have not been proven to relive ocular symptoms. In general, use of higher dialysate Na conc. at hemodialysis are not considered a long term solution to intradialytic ocular hypertension, due to the tendency for increaser fluid intake between HDs. Lower BFR with longer duration of hemodialysis treatments has been beneficial in some cases.

PO0902

Transient, Severe, Unilateral Eye Pain and Vision Loss Associated with Hemodialysis

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Introduction: Acute on chronic angle-closure glaucoma with elevated intraocular pressure is a well-established etiology of severe eye pain and profound vision loss, if not treated emergently. This case is a recurrent and episodic eye pain with transient visual loss during HD.

Case Description: 64 year-old Caucasian female with comorbidities including poorly-controlled insulin dependent type 2 diabetes, uncontrolled hypertension, obesity. She is on intermittent hemodialysis three times weekly the last 5 years. She was previously followed by a retina specialist for proliferative diabetic retinopathy with subsequent neovascular glaucoma. Initial onset approximately 1 year prior, with episodic pain and blurred vision with severe eye pain and complete unilateral vision loss start at initiating dialysis, symptoms resolved with cessation of treatment. Due to worsening pain symptoms, patient compliance becomes an issue, leading to frequent missing Dialyiss and Pulm edema required hospitalization. A glaucoma specialist, diagnosed neovascular glaucoma of the right eye. Maximal topical and oral tolerated medical therapy was started, but her disease was refractory to conservative management. Surgical intervention was pursued, Valved Drainage Device (New World Medical) was placed under topical anesthesia. Post-operatively, the patient was able to undergo dialysis sessions without ocular symptoms and compliance has improved.

Discussion: The effect of hemodialysis (HD) on intraocular pressure (IOP) is variable and the exact mechanisms are still not clear. Previous reports in the literature suggest both increased and decreased intraocular pressure during fluid shifts associated with hemodialysis. Argon Pan-retinal laser photocoagulation is known to reduce angle neovascularization induced by peripheral retinal ischemia in Neovascular glaucoma patients, IOP reduction is typically achieved with topical and systemic medications. Shunting and filtering procedures, including glaucoma valve implants and trabeculectomy surgery, may restore outflow and reduce IOP. After appropriate surgical intervention, the patient reported resolution of symptoms and improved tolerance to dialysis sessions.

PO0903

Caffeine Overdose Requiring Extracorporeal Mechanical Oxygenation (ECMO) and Hemodialysis

Luke Lundeen, Connie J. Wang. *Hennepin Healthcare, Minneapolis, MN.*

Introduction: Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychostimulant in the world. It is considered safe if consumed in moderation but can lead to cardiovascular collapse if the dose exceeds 150-200mg/kg. Extracorporeal removal of caffeine with intermittent hemodialysis (IHD) has been reported to improve outcomes. However, continuous veno-venous hemodiafiltration (CVVHDF), which is a routinely used extracorporeal therapy in patients with severe hypotension, is traditionally less favored for caffeine overdose because of inadequate rate of clearance. We present a case of combination therapy using both IHD and CVVHDF in the treatment of life-threatening caffeine overdose.

Case Description: A 33-year-old female weighing 63kg presented after ingestion of approximately 100g of guarana powder (22g of caffeine). She presented with refractory ventricular tachycardia (140-170 BPM) and severe hypotension (blood pressure 50/40 mmHg) resistant to 4 vasopressors at maximal dose. She required extracorporeal membrane oxygenation (ECMO). Baseline renal function was normal. IHD was initiated with blood flow rate (BFR) 200ml/min and dialysate flow rate (DFR) 500ml/min, which was gradually increased over 4 hours to a BFR of 400ml/min and DFR of 800ml/min; IHD continued for an additional 4 hours at this rate. During this 8-hour IHD treatment, her initial 4 pressor doses were halved, and she was transitioned to CVVHDF; the caffeine level remained unavailable. However, after 12 hours of CVVHDF, the patient did not experience continued hemodynamic improvement, so IHD was reinitiated for 12 hours. Following this second prolonged session of IHD, she was weaned down to moderate doses of just two pressors. She was then transitioned back to CVVHDF for an additional 36 hours, at which time she was able to come off ECMO and all pressors. She had a full neurologic recovery. We later received a serum caffeine level of 425mg/L (drawn soon after arrival at the hospital), which is the second-highest level ever reported; the established lethal concentration is 80mg/L.

Discussion: Despite continuous dialytic therapies being generally favored in patients with hemodynamic instability, a combination of IHD and CVVHDF may be used for hemodynamically unstable patients who ingest extremely high dose of caffeine. However, in such patients, continuous therapies are unlikely to supplant prolonged and repeated IHD treatment sessions.

PO0904

Anaphylaxis Secondary to Citric Acid Allergy in ESKD Patients

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Introduction: Dialysis reactions are common in ESKD patients undergoing hemodialysis (HD). We report first case of anaphylaxis related to citric acid solution used for dialysis disinfection & descaling.

Case Description: 61-year-old male with history of ESKD on HD for 7 years, presented after missing dialysis. Patient underwent urgent HD upon presentation and developed signs of angioedema within first 30 minutes, requiring nasal intubation & treatment with epinephrine, steroids & antihistamine. While intubated and hypotensive, patient had uneventful Slow Low Efficiency Dialysis. Angioedema was presumed secondary to antiemetics, which patient required due to severe nausea shortly after starting HD. Post extubation, patient developed similar reaction with milder symptoms with HD that responded to stopping HD and medical therapy. He had normal complement and mildly elevated tryptase. He was presumed to have a dialyzer reaction therefore, the dialyzer was changed from Revaclear to REXEED & it was tolerated well. He had similar severe reaction a week later while using the REXEED dialyzer. Investigations showed elevated anti-ethylene oxide antibodies (ETO) but clinical significance was questionable given the reaction only developed in inpatient setting. Later we discovered that dialysis machines are disinfected/descaled differently between inpatient & outpatient dialysis, even though both utilize citric acid, which might have led to more exposure to citric acid solution in inpatient setting. For next 2 weeks, patient was dialyzed using different combinations of dialysis machines, dialyzer & dialysis circuits including ones sterilized with ETO, however, all machines were disinfected/descaled using a combination of bleach & heat. After elimination of citric acid, patient had no further anaphylactic reaction.

Discussion: Dialyzer membrane reactions have been commonly described as Type A reactions mediated by dialyzer membrane (IgE mediated) and Type B membrane reactions mediated by complement activation. In our case clinical significance of ETO antibody was not clear, & angioedema was eliminated after removing citric acid from the machine disinfection process. Industrial citric acid mediated angioedema has not been reported before, & it might be an important mediator of allergy in ESRD, & careful review of the dialysis machine preparation should be reviewed in every case of severe allergic reaction.

PO0905

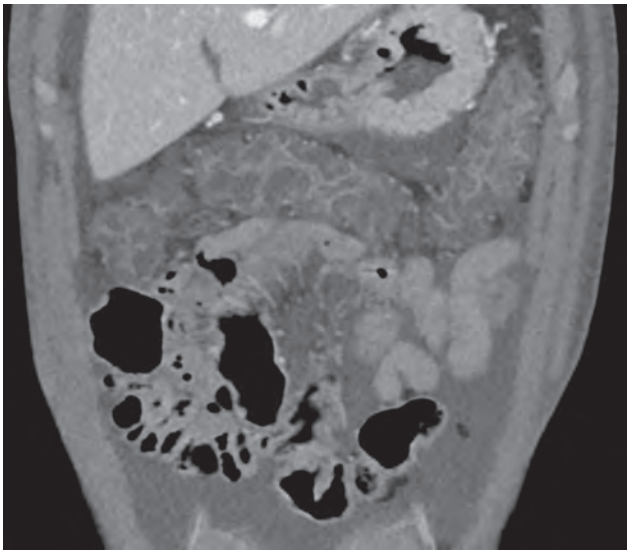
An Unexpected Cause of Colitis

Alon Bnaya, Ofer Benjaminov, Eyal Itzkowitz, Jawad Atrash, Omar Abu Lybdeh, Mohsen Abu Alfeilat, Linda Shavit. *Shaare Zedek Medical Center, Jerusalem, Israel.*

Introduction: Gastrointestinal manifestations are common among patients with advanced kidney disease. However, uremia associated colitis is rarely described in patients with ESKD. We present a unique case of uremic pancolitis in a patient with ESKD of unknown cause.

Case Description: An 18-year-old male with a history of asthma was admitted with nausea, vomiting and diffuse abdominal pain. He had no fever, arthralgias, rash, respiratory symptoms, or diarrhea. Mild peripheral edema and flapping tremors were noted on physical examination. Laboratory blood tests revealed severe kidney injury (creatinine 18.2 mg/dL, BUN 129 mg/dL). Urinalysis was positive for blood and protein. Immunologic and infectious serologies were unremarkable. An abdominal CT scan detected two small atrophic kidneys and diffuse severe bowel wall thickening of the colon with thumb printing noted (Figure 1), mimicking a pseudomembranous colitis pattern. Abdominal ultrasound revealed severe edema along with high vascularization of the colon wall. Uremia associated colitis was suspected due to the patient's extreme uremic state and hemodialysis was initiated. Following three weeks of hemodialysis, an abdominal ultrasound showed a significant improvement in edema and vascularization of the colon wall.

Discussion: Patients with advanced CKD often have a variety of gastrointestinal symptoms. However, severe uremic colitis mimicking pseudomembranous pattern is extremely rare in ESKD. Extensive literature review revealed only single case report of uremic pancolitis in a patient with severe kidney injury related to IgA nephropathy. With the improvement of care of patients with kidney disease, uremic colitis is rarely seen in the routine nephrology practice. However, it should be included in the differential diagnosis and evaluation of patient with ESKD, particularly if other more frequent etiologies of colitis have been excluded.



PO0906

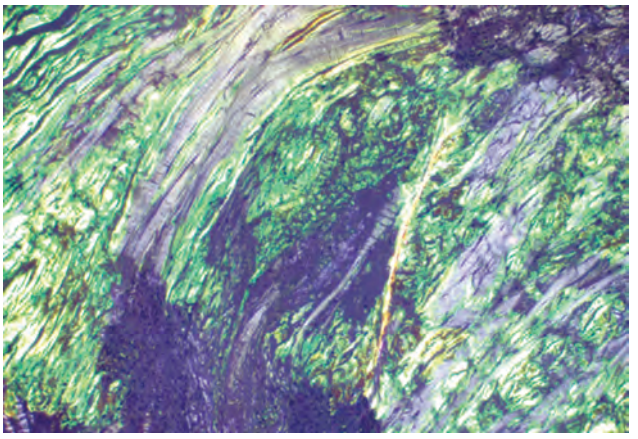
Reverse Shoulder Arthroplasty in Dialysis Amyloidosis

Jessica Schilling,[1] Srinath Kamineni,[2] Dana Richards,[2] Marie-Claude M. Faugere,[2] Florence Lima,[2] B. Peter E. Sawaya,[2] Madhumathi Rao.[2] *[1]University of Kentucky College of Medicine, Lexington, KY; [2]University of Kentucky Medical Center, Lexington, KY.*

Introduction: The use of high-flux over cuprophane dialyzers, has led to Beta-2 microglobulin amyloidosis (B2M) becoming rare in long term hemodialysis (HD) patients. Amyloid fibers embed systemically, skeletal involvement producing bone cysts, tendinopathy and fractures.

Case Description: A 65-yo male on chronic HD for 30 years presented with progressive, right (R) shoulder intractable pain and limited range of movement (ROM). X-ray/MRI identified severe glenohumeral osteoarthritis (OA), tendinopathy and large irreparable rotator cuff tear. Past history included heart failure, pulmonary hypertension, hepatitis C, severe secondary hyperparathyroidism and chronic anemia. Surgical history included bilateral (b/l) total hip arthroplasties, b/l carpal tunnel release, R nephrectomy for renal cell carcinoma in renal cystic disease. Due to the intractable pain, disability and failure of physical therapy and corticosteroid injection therapy he underwent reverse shoulder arthroplasty. Operative findings showed large soft tissue deposits about the subscapularis, glenoid and labrum, attributed to amyloid. Histology of intra-articular soft tissue, labrum and synovium confirmed amyloid (apple-green birefringence by Congo Red Staining) with focal calcium pyrophosphate deposition. Undecalcified histology of humeral head showed moderate secondary hyper-parathyroid bone disease with peri-trabecular amyloid deposits. Following surgery patient noted marked improvement in pain and partial improvement in shoulder ROM.

Discussion: No treatment exists for HD patients with B2M, ineligible for kidney transplant. Physicians are tasked with treating clinical manifestations that severely impact quality of life (QOL). Concern for adverse outcomes and paucity of surgical precedent should not deter appropriate surgical intervention. This patient illustrates the clinical and surgical decision-making targeted to improving (QOL).



PO0907

Prediction of Severe Gastrointestinal Bleeding Events in Hemodialysis: Collaborative Development of Machine Learning Model Within INSPIRE

Suman K. Lama,[1] Sheetal Chaudhuri,[1] Joanna Willetts,[1] John W. Larkin,[1] Anke Winter,[2] Manuela Stauss-Grabo,[2] Len A. Usvyat,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux,[6] David C. Wheeler,[3] Peter Stenvinkel,[4] Jürgen Floege.[5] On behalf of the INSPIRE Core Group *[1]Fresenius Medical Care, Global Medical Office, Waltham, MA; [2]Fresenius Medical Care, Global Medical Office, Bad Homburg, Germany; [3]University College London, London, United Kingdom; [4]Karolinska Institutet, Stockholm, Sweden; [5]RWTH Aachen University Hospital, Aachen, Germany; [6]Fresenius Medical Care AG und Co KGaA, Bad Homburg, Germany*.

Background: **IN**itiative**S** on advancing **P**atients' outcomes In **RE**nal disease (INSPIRE) is an academia and industry collaboration set forth to identify critical investigations/models needed to advance the practice of nephrology. As an inaugural effort, INSPIRE group aims to develop a machine learning (ML) model that can identify a hemodialysis (HD) patient's 30-day risk for hospitalization due to gastrointestinal (GI) bleeding.

Methods: We used data from adult (age ≥18 years) HD patients (Jan 2017-Dec 2020) in the United States to build a XGBoost model considering 2,292 variables for classification of 30-day GI bleed hospitalization risk. Data were randomly split in 50%:20%:30% ratio for model training, validation, and testing. Unseen data by model (testing) was used for assessing performance via area under the curve (AUC) and feature importance of predictors via Shapley (SHAP) values.

Results: Among 58,187 HD patients included in the testing dataset, 1150 had a GI bleed hospitalization. ML model showed AUC=0.67 and top predictors of a GI bleed hospitalization in 30 days were the minimum hemoglobin level in prior 180 days, time since prior GI bleed hospitalization, and higher vitamin D levels (**Figure 1**).

Conclusions: ML model appears to have suitable performance for identifying a patient's 30-day risk for GI bleed hospitalization. Albeit further model iterations/tuning are needed, ML techniques that account for collinearity and missingness hold promise for early detection of potentially avoidable GI bleeding admissions. Model identified an important association between higher vitamin D levels and GI bleeding events, which is consistent with the increasing evidence suggesting antithrombotic and anticoagulant actions of vitamin D derivatives.

Funding: Commercial Support - Fresenius Medical Care

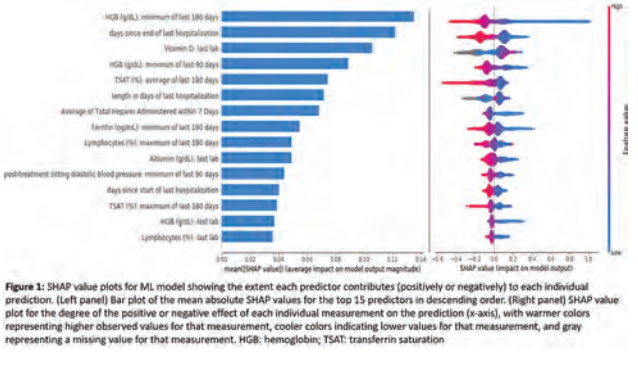


Figure 1: SHAP value plots for ML model showing the extent each predictor contributes (positively or negatively) to each individual prediction. (Left panel) Bar plot of the mean absolute SHAP values for the top 15 predictors in descending order. (Right panel) SHAP value plot for the degree of the positive or negative effect of each individual measurement on the prediction (x-axis), with warmer colors representing higher observed values for that measurement, cooler colors indicating lower values for that measurement, and gray representing a missing value for that measurement. HGB: hemoglobin; TSAT: transferrin saturation

PO0908

Artificial Intelligence-Driven System to Automatically Identify Arterial Oxygen Saturation Saw-Tooth Pattern in Hemodialysis

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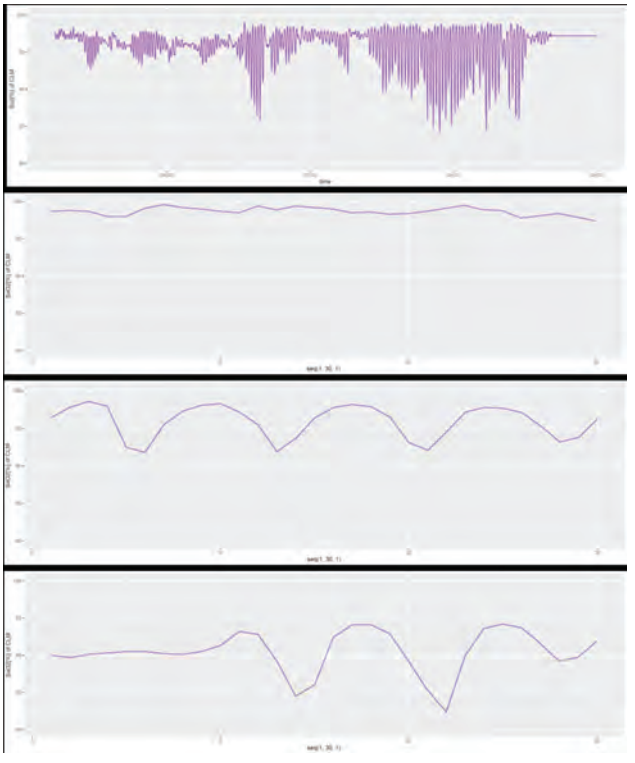
Background: Sleep apnea (SA) is a condition where normal respiration is disrupted by episodes of apnea because of disturbed respiratory control (central SA) or upper airway obstruction (obstructive SA). Arterial oxygen saturation (SaO2) saw-tooth pattern indicate respiratory instability. We aimed to automatically identify patients with repetitive episodes of intermittent SaO2 saw-tooth pattern.

Methods: The analysis was based on SaO2 recordings taken at a frequency of 0.1 by the Crit-Line® device (Fresenius Medical Care, Waltham, MA). Segments of 30 consecutive SaO2 recordings (i.e., 5 minutes of SaO2 time series) were adjudicated and categorized as (a) no saw-tooth pattern; (b) mild saw-tooth pattern; and (c) severe saw-tooth pattern (examples shown in Figure 1). We used one-dimensional convolutional neural networks (1D-CNN) for time series classification. We randomly assigned SaO2 time series segments to training (80%) and validation (20%) sets, respectively.

Results: We analyzed 89 hemodialysis (HD) treatments with 4,075 adjudicated SaO2 time series segments. Their distribution across the 3 categories was 78% (a), 11% (b), and 11% (c), respectively. In the validation data set of 815 SaO2 time series segments, we achieved an accuracy of 93.9%, 95.8% of category (a), 91.2% of category (b) and 82.8% of category (c) pattern were classified correctly by our 1D-CNN.

Conclusions: Our 1D-CNN algorithm accurately classifies saw-tooth pattern in SaO2 time series recorded in HD patients. The SaO2 pattern classification could be performed in real time during an ongoing HD treatment and provide timely alert in the event of respiratory instability.

Funding: Commercial Support - Fresenius Medical Care North America



Panel A: Intradialytic SaO2 saw-tooth pattern. Panel B to D: SaO2 time series with no saw-tooth pattern (B); mild saw-tooth pattern (C); severe saw-tooth pattern (D)

PO0909

Leveraging Dynamic Data to Predict Mortality Risk in Patients Undergoing Chronic Hemodialysis

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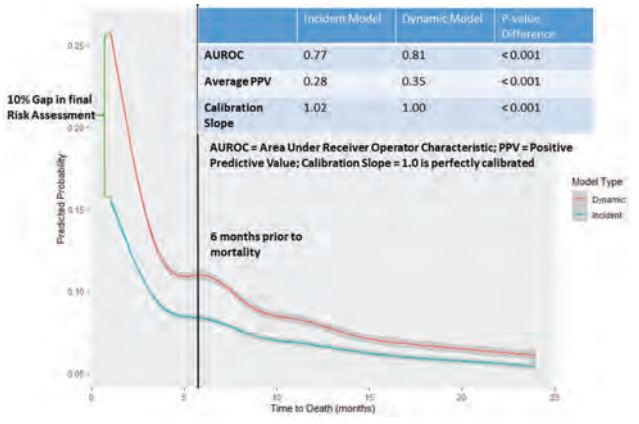
Background: Predictive models of mortality on HD typically use data collected at HD initiation. This is a missed opportunity that does not leverage the regularly collected data at HD treatments and is not reflective of how models would be used in practice. We compare performance of a risk model that uses static baseline data at incidence vs inclusion of time-varying data.

Methods: We used EHR data on pts new to HD between 2003-2016 from a national provider (n=54,148) linked with USRDS. We abstracted 86 predictor variables organized into person-mth and divided into training (n=32,488) and testing sets (n=21,660). The dynamic training set contributed > 800k person months. The static training set contained the first pt-month for those who initiated HD within 90-days (n=24,026). We fit LASSO logistic regression to predict mortality in the next 6-months and assessed both models on a time-varying test dataset. We report overall predictive performance metrics as well as visualization of time varying patient risk in the 24 mths before a pt dies.

Results: Pt median age at initiation was 64 yrs; 43% female, 63% Caucasian; 7% died w/in 6 mths of initiation and 53% w/in 5 yrs. Top predictor variables were similar between the two models: age, serum chloride and serum albumin. The table shows performance metrics for the two models on the test data with the dynamic model performing significantly better. The plot shows the predicted risk for pts in the 24 mths prior to mortality. The dynamic model more quickly responds to pts changing risk, producing a higher predicted probability leading up to mortality.

Conclusions: A risk model built using time-varying data performs better than one using baseline data. Incorporation of dynamic models in dialysis-EHR could be used as to direct appropriate population health interventions to the highest risk pts. Examination of dynamic risk models can elucidate pt-risk trajectories.

Funding: NIDDK Support



Predicted risk from each model as pts approach mortality. Dynamic data produces higher average risk more quickly.

PO0910

Machine Learning Classification of Tweets for Patient Dialysis Experience

Alexander S. Leidner, Hawkins Gay, Bing Ho. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

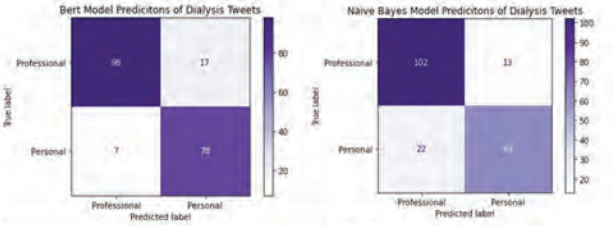
Background: Popular microblog (e.g. Twitter, Facebook) services provide a continuous stream of public health information. This data has been used to monitor viral spread, medication adherence, and false health information. There are thousands of posts on Twitter daily regarding personal dialysis experience, access, and side effects. While these posts include valuable public health information, evaluating these posts to meaningfully assist dialysis patients is difficult as there are even more tweets mentioning dialysis in a professional context. We aimed to modify a state of the art natural language model to classify posts about dialysis as personal or professional.

Methods: We filtered posts containing the word dialysis. Posts were manually labeled as personal or professional by a nephrologist depending on the context dialysis was mentioned. The data was randomized and split for 60% training, 20% validation, and 20% testing. The text was preprocessed to remove extraneous characters and input into a Bidirectional Encoder Representations from Transformers (BERT) model for fine tuning, and a term frequency inverse document frequency vectorized Multinomial Naive Bayes Classifier.

Results: We collected 6011 tweets from May 3, 2021 to May 14, 2021.1000 tweets were randomized and labeled. 57% were categorized as professional. BERT and Naive Bayes models attained 88% and 82% accuracy, respectively, on the testing data. The BERT model classified far less false negatives with a small increase in false positives (**Figure 1**).

Conclusions: BERT's semantically rich word embeddings can enhance social media mining algorithms on dialysis content. We show superiority of a BERT model over a traditional count-based language model. This method can be easily applied as a pre-processing step to remove noisy posts to better study dialysis and other health trends in social media. This novel processing task and pipeline have broad clinical and public health implications for reducing the amount of data and time required for accurate, real-time monitoring of patient level posts.

Figure 1: Model Test Set Classification Metrics



Model	Accuracy	Positive Precision	Positive Recall	Positive F1
BERT	0.88	0.82	0.92	0.87
Naïve Bayes	0.82	0.83	0.74	0.78

All metrics reported on 0 to 1 scale. Positive refers to 'personal experience'. All predictions performed on a held-out test set of data.

PO0911

Automating Dialysis Machine Alarms During Sustained Low-Efficiency Dialysis (SLED)

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Background: Sustained low-efficiency dialysis (SLED) with regional citrate anticoagulation (RCA) is frequently employed at our institution. RCA requires constant monitoring because a dialysis machines alarm that stops the blood pump (BP) or bypasses dialysate leads to an increased rate of citrate infusion into the patient, with consequence of ionized hypocalcemia. To enhance safety and surveillance efficiency, we developed an innovative computer/phone system that identifies SLED machine alarms and notifies clinical care staff directly via aproprietary phone network.

Methods: In 2017, we linked onboard SLED computer Wi-Fi systems to the hospital's internal phone network (ASCOM). An alarm recorded by the SLED machine's computer delivers an email to a dedicated email account that is subsequently transmitted to the ASCOM MailGate System. Mailgate produced and relayed text message alarms to dedicated ASCOM phones of dialysis technicians or nurses. Importantly, no additional training or changes in workflow are required for adoption of this method.

Results: This innovation has increased safety and efficiency. Response times for machine alarms improved and downtimes on dialysis were reduced, increasing dialysis dose of dialysis. To ascertain end-user satisfaction of the automated alarming system, we conducted a survey that demonstrates high-level satisfaction with the system (Table 1.)

Conclusions: Currently, no medical alert companies connect dialysis machine information to a medical alert phone system. ASCOM provides wireless messaging systems for dedicated hospital applications. Notably, ASCOM does not directly connect to dialysis machines. In addition, Email Alerts can be browsed by managers for archival retrieval, quality and safety report generation, and investigation of unanticipated events.

Funding: Clinical Revenue Support

Staff Satisfaction Survey

Survey Question	Response
Frequency of SLED alarm using ASCOM alert system per shift	65% respondents felt they receive between 1-3 per hour, 25% less than 1 per hour, 12.5% 4-6 per hour
Enhances Patient Safety	78% agreed, while 22% strongly agreed
Dialysis Technician Response Time	100% of respondents felt it improved response time
Need for ICU nurse to contact Dialysis Tech	75% strongly agreed that alert system reduced ICU nursing calls, 25% had no opinion

PO0912

Users of a Web-Based Communications Platform for Care Coordination of Hospitalized Dialysis Patients

Laura Plantinga,[1] Courtney E. Hoge,[1] Janice P. Lea,[1] Christopher M. O'Donnell,[1] Ann E. Vandenberg,[1] Kyle P. James,[1] Tahsin Masud,[1] Bernard G. Jaar,[2] Carol A. Gray,[1] Rich Mutell.[3] *[1]Emory University, Atlanta, GA; [2]Johns Hopkins University, Baltimore, MD; [3]Apex Health Innovations, Williamsburg, VA.*

Background: Better care coordination between dialysis clinics and hospitals may improve outcomes among hospitalized dialysis patients. To fill the gap created by separate electronic health record systems across the two settings, we rolled out a web-based communications platform ("DialysisConnect") in four dialysis clinics and one hospital in Atlanta. Here, we examine usage patterns of DialysisConnect.

Methods: DialysisConnect included automatically uploaded clinical information from dialysis clinics, forms for entering critical admission and discharge information, and a direct communications channel. Two nephrologists and two hospitalists served as project champions at the dialysis clinics and hospital, respectively. DialysisConnect was made available to 106 potential users [hospitalists, nephrologists, advanced practice providers (APPs) at the hospital and dialysis clinics, care coordinators (hospital), and nurses/nurse managers (dialysis clinic)] starting 10/29/20. Descriptive statistics were used to describe patterns overall and by user role through 4/15/21.

Results: While physicians comprised most of the potential users, APPs and dialysis nurses were the most active users (Table). Additionally, activity was unevenly distributed among users: *e.g.*, one hospital-based APP recorded most of the admissions (*n*=225, 89%) and discharges (*n*=226, 93%) among patients treated at the dialysis clinics included in the pilot.

Conclusions: We found that physicians were unlikely to use DiaylsisConnect. Our user statistics suggest that APPs and nurses may be the most likely to engage with a care coordination system, which informs future pragmatic research in this area.

Funding: NIDDK Support

User Role	No. (%) of all users	No (%) of all users who were active users*	No. (%) of all users who were top users**	No. (%) of admissions entered	No (%) of discharges entered	Total no. of logins (% of all logins)	Total no. of messages (% of all messages)
Total	106	48 (45.3%)	27 (25.5%)	252	243	1812	939
Hospitalist	49 (46.2%)	8 (16.3%)	1 (2.0%)	0 (0.0%)	2 (0.1%)	18 (1.3%)	7 (0.7%)
Hospital APP	4 (3.8%)	3 (75.0%)	2 (50.0%)	225 (89.3%)	229 (94.2%)	200 (14.6%)	712 (75.8%)
Renal Fellow	4 (3.8%)	4 (100%)	2 (50.0%)	27 (10.7%)	12 (4.7%)	39 (2.8%)	43 (4.6%)
Care Coordinator	3 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nephrologist	12 (11.3%)	7 (58.3%)	2 (16.7%)	—	—	50 (3.6%)	7 (0.7%)
Dialysis APP	2 (1.9%)	2 (100%)	2 (100%)	—	—	221 (16.1%)	156 (16.6%)
Nurse	18 (17.0%)	13 (72.2%)	11 (61.1%)	—	—	842 (61.5%)	14 (1.5%)

Other users (n=3) included vascular access team and dietitian; none were active users. *Active = logged into the system at least once. **Top users = ≥75th percentile (≥6 logins).

PO0913

Family-Friendly, Work-Friendly, Home-Hemodialysis and In-Center Hemodialysis Hybrid: The First of Its Kind

Adam Locke, Macaulay A. Onuigbo. *University of Vermont College of Medicine, Burlington, VT.*

Introduction: Hybrid dialysis is traditionally defined as the combination of peritoneal and hemodialysis (HD) in patients with end-stage renal disease. Its reported use is quite limited outside of Japan. We recently encountered major family-related and employment-related constraints that prevented a 39-yo man with ESRD on home HD from completing the four-times weekly HD treatments with HD inadequacy and worsening of patient's physiology. We successfully switched him to a new hybrid of twice-weekly Home HD + twice weekly In-Center HD. This is the first such report.

Case Description: A 41-yo male with ESRD secondary to SLE and hypertension on home HD, 4 x weekly, for some years experienced family-related constraints including non-availability of day-care for two young children due to COVID-19 pandemic, spousal illness and new work-related challenges with more travel and was missing his HD sessions. The result was inadequate HD delivery and worsening laboratory indices. He now receives 2 in-center HD treatments on Tuesdays and Thursdays, and 2 home HD treatments, one during the weekend and one during the week. This was started in February 2021. Each HD session lasts for 3.5 hours, 2000 units Heparin bolus, and his left brachiocephalic AVF is accessed by the button-hole method. The Home Dialysis Staff coordinates his dialysis care. Standardized Kt/V for May 2021 was 2.6.

Discussion: Hybrid dialysis is traditionally defined as the combination of peritoneal and HD in patients with ESRD. A 2020 Italian report described another type of hybrid dialysis that consisted of once-weekly in-hospital HD and home peritoneal dialysis to limit patient exposure to the hospital environment during the COVID-19 pandemic. We have described the successful application of a new Hybrid HD system that combined Home HD + In-center HD. To our knowledge, our report is the first of its kind and was designed and implemented primarily for the purpose of overcoming increasing family and employment demands on the patient. This new hybrid dialysis option was designed to facilitate a family-friendly work-friendly HD on a long-term continuous basis. The patient, the family with two young children and his employers are happy and very satisfied. Simultaneously, the patient has continued to do well with adequate dialysis and meeting all the required goals of management in the past 3 months.

PO0914

Triple I Study: Hubs of Care Survey

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Background: The Can-SOLVE CKD Triple I Study identified continuity of care; access to a primary care provider (PCP) in the hemodialysis (HD) unit; and access to care for other medical conditions as key challenges to in-centre HD care (www.betterkidneycare.ca). The Hubs of Care project aims to address these challenges by incorporating health care providers (HCPs) from other settings in the HD unit; firstly, we identify current practice, potential interest and need and desire for different HCPs in HD units.

Methods: A cross-sectional self-reported survey administered Feb-May 2021 with HD patients and staff at four academic sites across Canada. Eligible participants included adults fluent in English or French who could complete the survey independently. The survey asked which HCPs are currently in HD units, which additional HCPs would be most useful to add and whether patients are in favor of other HCPs visiting them either virtually or in-person. Additional data were solicited by free text. Preliminary analyses using descriptive, median (IQR) and proportion and summative content analysis, are presented.

Results: Surveys were completed by 393 individuals (252 HD patients and 141 HCPs). Eighty-three percent of patients and 34% of HCPs were ≥50 years old. Forty-five percent of patients had been on HD >3 years. The majority of patients (81.5%) and HCPs (91%) agreed that having other HCPs in HD units would be beneficial; both prefer the addition of diabetic specialists/endocrinologists, mental health specialists and podiatrist/foot care specialists (Table 1). Patients indicated a need for cardiologists. Patients (85%) would like to see a PCP in the HD unit; of those, 87% prefer in-person and 13% prefer virtual. Qualitative analysis reveals privacy concerns due to the open concept of HD Units; however, the concept of bringing HCPs into the HD unit is regarded as beneficial and time-saving.

Conclusions: In this cross-sectional survey both HD patients and staff identified that, despite privacy concerns, bringing HCPs that provide foot, diabetic and mental health care into the HD unit was a priority with potential for benefit.

Funding: Government Support - Non-U.S.

Table 1; Preferences for Type of HCP

	Patients n=155		Healthcare providers n=103	
Type of health care provider	**N**	**%**	**N**	**%**
Cardiologist	29	18.7	6	5.8
Diabetes Specialist	21	13.5	37	35.9
Mental health specialist	20	12.9	33	32
Foot care specialist	18	11.6	30	29.1
Dermatologist	17	10.9	6	5.8
Primary care practitioner	17	10.9	20	19.4
Rehabilitation Specialist	5	3.2	17	16.5

PO0915

Utilization of the Tablo Hemodialysis System's Data Platform: An Analysis of 100,000 Acute Dialysis Treatments

Josh Schumacher, Brittany Lim, Michael A. Aragon. *Outset Medical, Inc., San Jose, CA.*

Background: The Tablo® Hemodialysis System (Tablo) is an all in one, easy-to-learn device featuring integrated water purification, on demand dialysate production and two-way wireless data transmission capable of providing therapy up to 24 hours in a hospital setting. Limited connectivity of traditional hemodialysis systems constrains the ability to drive improvement in quality and efficiency of dialysis care. Tablo's cloud-based data platform expedites care delivery in real time and informs on dialysis program metrics to facilitate quality improvement. The objective was to demonstrate Tablo's automated wireless data capabilities through analysis of 100,000 Tablo acute treatments.

Methods: Tablo data were collected through real-time transmission via a cloud-based, HIPAA compliant platform. Analysis was performed by combining prescribed and achieved data on consecutive treatments. Treatments were divided into groups based on treatment time of less than 6 hours (conventional therapy) or greater than 6 hours (extended therapy).

Results: A total of 100,000 treatments between April 2020 and May 2021 were analyzed. Treatments ranged from 2-24 hours. Treatment time success, defined as achieved within 10% of prescribed time, was 90.7% across the population. The most common reason for early termination was "User ended" (8.6%), with 0.7% due to "Device Directed". Mean total number of alarms per treatment was 2.5 across the population with no difference in alarm frequency (0.7 alarms per hour) between treatment groups. The most frequent clinically significant alarms were high and low venous pressures. Mean time to alarm resolution was 14 seconds with shorter alarm resolution time demonstrated in the IHD group (13 vs 22 secs).

Conclusions: With high utilization across a wide range of treatment times in the acute setting, Tablo successfully achieved treatment goals. The few observed alarms were quickly resolved by clinical users. Tablo's robust data reporting capability enables the identification of treatment trends that can be used to drive quality improvement.

Funding: Commercial Support - Outset Medical, Inc.

Summary of Tablo Treatment Parameters

Treatment Group	Treatment Parameters						Clinically Significant Alarms		
	Treatments Performed	Prescribed time (hours)	Actual Time (hours)	Actual Fluid Removal (L)	Alarms per treatment (mean)	Time to Alarm Resolution (seconds)	High Venous Pressure	Low Venous Pressure	Air Venous Bloodline
IHD (≤6 hrs)	94603	3.4 ± 0.6 (2.0 – 6.0)	3.3 ± 0.7	1.7 ± 1.1	2.3 ± 5.5	12.8 ± 32.1	1.7 ± 5.1	0.6 ± 1.6	0.1 ± 1.0
Extended (6< to ≤24 hrs)	5397	11.8 ± 3.4 (6.1 – 24.0)	9.7 ± 3.9	1.9 ± 1.7	6.7 ± 16.8	22.3 ± 55.9	5.0 ± 14.7	0.9 ± 2.6	0.1 ± 2.2
Overall:	100,000	3.8 ± 2.1 (2.0 – 24.0)	3.6 ± 1.8	1.7 ± 1.2	2.5 ± 6.7	14.2 ± 36.6	1.8 ± 5.9	0.6 ± 1.7	0.1 ± 1.1

PO0916

Impact of Medication Reconciliation by a Dialysis Pharmacist

Summer Dyer, Linda Awdishu, Sally Rafie, Victoria T. Nguyen. *University of California San Diego, La Jolla, CA.*

Background: Medication reconciliation (MR) improves patient outcomes, reduces cost, and is a reporting measure for the CMS End-Stage Renal Disease Quality Incentive Program. Most dialysis facilities do not have a clinical pharmacist to perform MR. The purpose of this study is to evaluate the impact of a pharmacist performing MR and medication management for patients receiving outpatient chronic hemodialysis at an academic institution.

Methods: We conducted a retrospective study from 10/1/18 to 11/2/20 to determine if MR by a pharmacist reduced medication discrepancies (MDs) and medication related problems (MRPs) over time. Secondary outcomes were to describe the type of MDs, type and severity of MRP, impact of a pharmacy delivery service, and number of emergency department (ED) visits and hospitalizations pre- and post-pharmacist integration. Discrepancies were categorized as: unintentional discrepancy, undocumented intentional discrepancy, and MRPs. MRP severity was categorized using the National Coordinating Council for Medication Error Reporting and Prevention index. Descriptive statistics were calculated for each variable and a repeated measures ANOVA test was conducted to determine if MDs or MRPs changed over time.

Results: A total of 135 patients with 479 unique pharmacist encounters were included. The mean (SD) age was 61.7 (14) years, 58% were male, 63% caucasian, mean (SD) time on dialysis 6.7 (6.4) years and most common comorbidities were diabetes and hypertension. The pharmacist conducted 3.5 MR/patient with a mean time spent of 39.7 (16) minutes and 16% required an interpreter. Unintentional discrepancies were noted in 53% encounters, undocumented intentional discrepancies in 71%, MRP in 59% but decreased significantly from the first to the second encounter (1.9 vs 0.9, 1.9 vs 1.2, and 1.1 vs 0.5 per patient, respectively, $p<0.05$). Most common MRP types included non-adherence, prescription renewals, and excessive drug doses. Over half (54%) were enrolled in a pharmacy delivery service and had significantly fewer undocumented intentional discrepancies compared to non-enrollees ($p<0.05$). ED visits and admissions pre- and post-pharmacist integration were not statistically different.

Conclusions: Integrating a pharmacist into a hemodialysis unit enabled effective medication reconciliation and management to significantly reduce medication discrepancies and problems, and improve safety.

PO0917

Interim Analysis of the Extension of Tablo Treatment Duration (XTEND) Study

Yaadveer Chahal, Josh Schumacher, Michael A. Aragon. *Outset Medical, Inc., San Jose, CA.*

Background: The Tablo® Hemodialysis System (Tablo) is an all in one, easy-to-learn device featuring integrated water purification, on demand dialysate production and two-way wireless data transmission and is approved for use in the acute, chronic and home settings. Prior reports have demonstrated Tablo's ability to achieve clinical goals, seamlessly integrate into hospitals and reduce cost across a wide range of treatment times. Extension of the Tablo cartridge to 24 hours (extended therapy; "XT") allows even greater flexibility for prescribers in the acute setting. The objective is to report on the experience with Tablo extended therapy between 12 and 24 hours utilizing an interim review of the XTEND study (NCT04912050).

Methods: Nursing staff were trained during a single training session on Tablo XT. After a run-in period of 5 treatments, Tablo data were collected via real-time transmission to a cloud-based, HIPAA compliant platform and reviewed by site staff. Clinical treatment success was defined as either ending within 10% of prescribed time or site investigator assessment that all patient treatment goals were met.

Results: Fifty (50) Tablo XT treatments had a median prescribed treatment time of 24 hours and a median achieved treatment time of 23.5 hours. Median cartridge use was 1.0 per treatment. Clinical treatment success was 84%. Treatments ended due to clotting/clogging were 4% (2 of 50). Median total ultrafiltration (UF) rate was 1.7 mL/kg/hr. Clinically significant alarms occurred at a median rate of 7 per treatment with a resolution time of 14 seconds. Most frequent alarms experienced were arterial and venous pressure (39% and 58%, respectively), of which none resulted in an end treatment.

Conclusions: Tablo's XT successfully achieves prescribed treatment time and favorable ultrafiltration rates with minimal therapy interruptions from alarms or cartridge changes. This data demonstrates the effectiveness of Tablo's newly expanded versatility in achieving personalization of treatments necessary for unstable patients and enabling successful delivery of extended therapy with minimal clotting. Tablo's 24-hour therapy meets the needs of critically ill patients that require renal replacement therapy for greater than 12 hours.

Funding: Commercial Support - Outset Medical, Inc.

PO0918

Feasibility Study of Wrist-Based Wearable Activity Tracker in Hemodialysis Patients

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Background: Increased physical activity (PA) is associated with reduced risk of cardiovascular disease which is prevalent in hemodialysis (HD) patients. Wearable activity trackers (WAT) allow remote monitoring of PA. We aim to explore the feasibility of using a WAT for 1 year in HD patients.

Methods: HD patients from 4 NYC clinics were enrolled on a rolling basis starting June 2018 and followed for up to 1 year. Ambulatory patients ≥18 years, on maintenance HD, and owning a mobile device were included. Each patient was provided with and taught how to use the Fitbit Charge 2. A stepwise intervention plan was used to assess feasibility (Figure 1). We used Kaplan-Meier analysis to determine mean and median time to withdrawal for non-compliance (TW) and predictors of TW were assessed by univariate Cox Regression.

Results: 119 patients were enrolled into the study. Patients were 54±12 years old, 59% African American, 37% lived alone, and 54% had an education level of college and above. 16% of patients were withdrawn for non-compliance. Mean and standard deviation TW was 175 ± 103 days. Median and interquartile range of TW was 133 and 181 days (98 to 280 days), respectively. The probability of not being withdrawn for non-compliance is shown in Figure 2. Age, gender, race, living status, and education were not associated with non-compliance.

Conclusions: A small portion of patients were continuously non-compliant with wearing/syncing their Fitbit devices in our study. Based on a low risk (<20%) of being withdrawn for non-compliance, we determined that it is feasible to use a wrist-based wearable device in HD patients for up to a year. However, prolonged use of these devices may require additional counseling to patients.

Funding: Commercial Support - Fresenius Medical Care

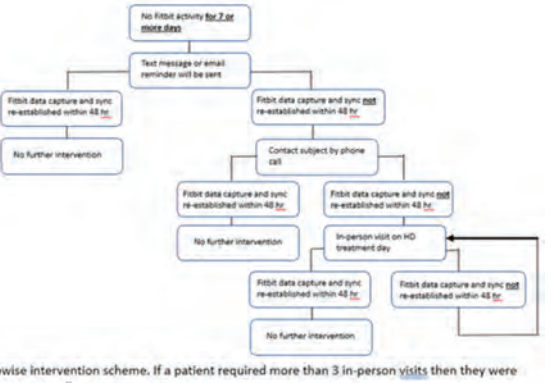


Figure 1. Stepwise intervention scheme. If a patient required more than 3 in-person visits then they were withdrawn for non-compliance.

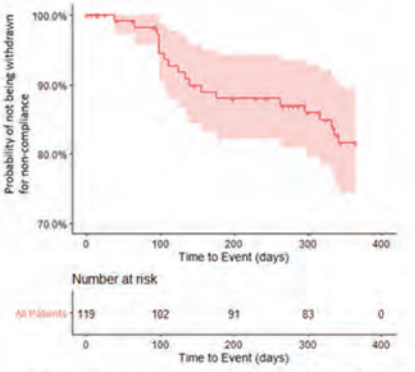


Figure 2. Kaplan-Meier curve demonstrating time to withdraw (non-compliance)

PO0919

Glycemic Status Ascertained by Continuous Glucose Monitoring in a Prospective Hemodialysis Cohort

Yoko Narasaki, Kamyar Kalantar-Zadeh, Amy S. You, Rene Amel Peralta, Andrea C. Daza Aguilar, Alejandra Novoa-Vargas, Tracy Nakata, Danh V. Nguyen, Connie Rhee. *University of California Irvine, Irvine, CA.*

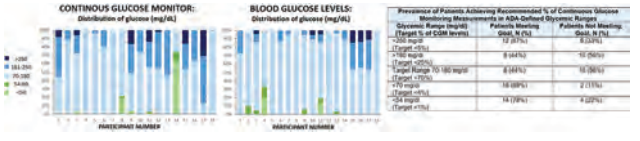
Background: Hemodialysis (HD) patients with diabetes are at heightened risk of hypo- and hyperglycemia due to multiple pathways. While self-monitored blood glucose is the standard approach for glucose assessment in HD patients, it may not adequately capture glycemic status given its infrequent nature. We thus sought to measure glucose levels using continuous glucose monitoring (CGM) as a more frequent (every 5-minutes), convenient, and automated method of glycemic status in a prospective HD cohort with diabetes.

Methods: Among 18 HD patients with diabetes hospitalized during 10/2020-5/2021, we conducted simultaneous protocolized glucose measurements using 1) CGM measured by Dexcom G6 devices vs. 2) blood glucose levels using capillary fingerstick or venous blood glucose, with the latter measured ≥4 times per day (before each meal and at night), plus every 30 minutes during HD (total of 6-8 measures during HD). Using American Diabetes Association (ADA)-defined CGM targets, we examined the prevalence of patients achieving the recommended percentage (%) of CGM levels in the ranges of <54, <70, 70-180, >180, and >250mg/dl (ADA target % of glucose levels <1%, <4%, >70%, <25%, and >5%, respectively).

Results: Whereas 64% of CGM measurements (N=9444) were within target glucose range (time in range [TIR] 70-180mg/dl), 80% of blood glucose levels (N=100) were within TIR. The proportion of patients achieving the recommended % of CGM measurements within ADA-defined glycemic ranges of >250, >180, 70-180 (target range), <70, and <54mg/dl were 67%, 44%, 44%, 89%, and 78, respectively.

Conclusions: In a cohort of hospitalized diabetic HD patients who underwent concomitant CGM and blood glucose measurements using the Dexcom G6 remote access system, blood glucose testing overestimated the % of time patients were in target glycemic range as compared with CGM. CGM showed that less than half of patients achieved the recommended % of CGM measurements within target range. Further studies are needed to determine whether CGM can improve the glycemic management of HD patients compared to conventional approaches.

Funding: Commercial Support - Dexcom, Inc.



PO0920

Validation of Automated Sodium Control in a Novel Dialysis System

Brandon D. Borrillo, Tzu Tung Chen, Osman Khawar, Clayton Poppe. *Diality Inc, Irvine, CA.*

Background: The Diality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To test an automated feedback program designed to regulate the infusion of an alkali needed to maintain proper sodium concentration in a dialysate solution

Methods: A 125L volume of simulated dialysis was circulated at ~400 mL/min and ~37 C through a sorbent cartridge which removed the urea from the solution. The fluid exiting the cartridge had no Ca, Mg or K. These chemicals were reinfused through a pump in a solution containing Ca, K and Mg salts. A conductivity sensor (cond) was used in a feedback control of the alkali infusion pump. The feedback control adjusted the pump flow rate to maintain the conductivity of the infusate at 14.0 mS/cm. The sensor was programmed from a curve model of the alkali over time from previous experiments. Occasional spikes of Na^+ were added to test the feedback control. The experiment ran until a NH_4 reached 10ppm which defined filter breakthrough.

Results: The results are depicted in table 1. TP1, the mean sodium concentration [Na] in the dialysate at pump 1, after mixing in a 125L tank was in the range 139.8 – 141.7 mEq/L. TP2, the mean dialysate [Na] at pump 2 after leaving the sorbent filter was 124.2 (+/-2.4) mEq/L. This correlates with cond1 and was 12.8 (+/- 0.4) mS/cm. TP3, the mean dialysate [Na] after being replenished with the alkali solution immediately prior entering the tank for remixing was 139.5 (+/- 1.9) mEq/L and correlated with cond2 of 14.1 mS/cm).

Conclusions: The results validate the accuracy of the conductivity sensor in correctly regulating the alkali infusate.

Funding: Commercial Support - Diality Inc

	Sodium (mM)				
Time (min)	TP1	TP2	TP3	Cond1	Cond2
0	140				
6		123.4	136.3	13.6	14.1
20		125.9	136.5	13.1	14.0
30		131.7	140.9	13.2	14.0
70	139.8	126.1	137.8	12.8	13.8
90	139.8	123.5	140.5	12.6	13.9
120		121.7	139.9	12.4	13.9
150	140.1	120.6	140.3	12.3	13.8
180		121	140.9	12.3	13.9
210	141.7	124.2	143.7	12.6	14.1
225	141.2	126.0	142.7	12.8	T

PO0921

Difference in Therapeutic Effects Between Roxadustat and Daprodustat, HIF-PH inhibitors, Depending on the Blood Type in Hemodialysis (HD) Patients

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Background: Human blood group antigens are glycoproteins and glycolipids expressed on the surface of red blood cells and a variety of human tissues. This study aimed to determine if there is an association between ABO blood type and the efficacy of HIF-PH inhibitors. Roxadustat and daprodustat are potent inhibitors of HIF-PH and capable of stimulating erythropoiesis in patients on patients with impaired renal function. These two compounds are reported to act mechanistically similar but display differences in their effects on cells, and the differences may affect their efficacy in the treatment of renal anemia in HD patients. In this study we compared the response rate by blood type between roxadustat and daprodustat, respectively.

Methods: Sixty-eight HD patients treated with roxadustat (20-100mg, 3/week) and ninety-five treated with daprodustat (1-12mg, daily) were recruited in our observational study. We defined >1.5g/dL increase in hemoglobin as effective, and <1.5g/dL decrease as ineffective.

Results: As shown in the figure, type A had the highest response rate at 47% in HD patients treated with roxadustat. On the other hand, type O had the highest response rate at 55% in those who were treated with daprodustat.

Conclusions: We found the association in the effectiveness of roxadustat on the treatment for anemia in HD patients in type A, while the effectiveness was higher in type O treated with daprodustat. The results suggest that the therapeutic effect of HIF-PH inhibitors may differ depending on the blood type.

Funding: Private Foundation Support

roxadustat

blood type	effective	stable	ineffective	total	efficacy(%)
A	15	12	5	32	47
B	6	10	4	20	30
O	4	5	2	11	36
AB	3	2	0	5	60

daprodustat

blood type	effective	stable	ineffective	total	efficacy(%)
A	7	14	22	43	16
B	2	14	9	25	8
O	11	6	3	20	55
AB	0	5	2	7	0

PO0922

Nanostructured Capillary Membranes for Size-Selective Hemofiltration

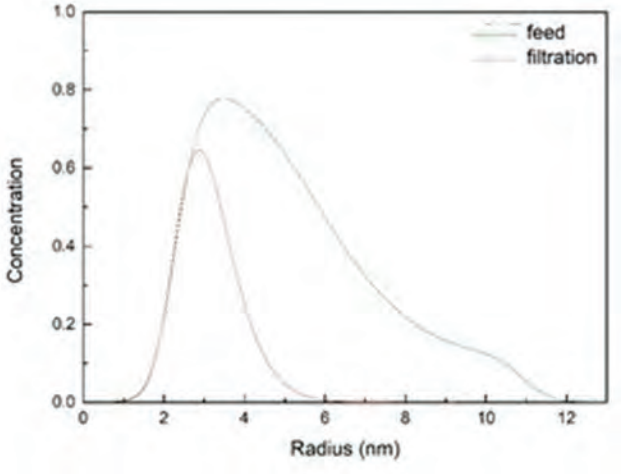
Peifu Cheng,[1] Francesco Fornasiero,[3] Nicholas J. Ferrell,[1] Shuvo Roy,[2] William H. Fissell,[1] Piran Kidambi.[1] *[1]Vanderbilt University, Nashville, TN; [2]University of California San Francisco, San Francisco, CA; [3]Lawrence Livermore National Laboratory, Livermore, CA.*

Background: Size-selective separations offer potentially transformative advances for hemofiltration. In the context of hemodialysis, the tradeoff between selectivity and permeability often results in large package sizes and high driving pressures that limit wearable and implantable options of therapy. Here, we report on composite membranes with vertically aligned precise nanoscale capillaries with improved permeability.

Methods: Arrays of carbon nanotubes (CNTs) were synthesized via chemical vapor deposition and the catalyst composition was carefully selected to achieve a uniform distribution of diameters. The area between the CNTs were filled with a polymer to form a membrane. The CNT membranes were backed with microporous silicon supports and mounted into a filtration cell. Hydraulic permeability was calculated from gravimetric flow rates at stepped transmembrane pressures. Size-selectivity was measured by filtering fluorescently-labeled polydisperse Ficoll in phosphate-buffered saline. Size-specific Ficoll concentrations in feed and filtrate were measured by size-exclusion chromatography.

Results: CNT membranes membrane exhibited a cut-off ~6nm and the measured hydraulic permeability was 102.3 ml h^{-1} m^{-2} $mmhg^{-1}$ compared to published data of 30 ml h^{-1} m^{-2} $mmhg^{-1}$ for conventional high flux dialyzers. CNT membranes retained large molecules while passing small and medium-sized molecules. Sieving coefficient at 2 nm, approximately the size of b2 microglobulin, was unity (Figure).

Conclusions: The CNT membranes provide excellent middle molecule clearance and hydraulic permeability multiples of conventional membranes. Further research is necessary to move to clinically implement this technology.



PO0923

Delivered Dialysate Potassium Is Higher Than What Is Prescribed When High Sodium and Low Bicarbonate Are Prescribed

Saiyed W. Ali, Andrew I. Chin. *University of California Davis Department of Internal Medicine, Sacramento, CA.*

Background: Most hemodialysis machines utilize the 3-stream method of making dialysate. In hospital settings, dialysate prescriptions are customized to the clinical setting. We determined the differences between delivered and prescribed dialysate K+ in unusual prescriptions.

Methods: Dialysate samples drawn 15 minutes into HD were analyzed via indirect ion-specific electrodes for Na^+, K^+, and HCO3-. 5200 HDs with extremes of ordered Na^+ and HCO3- were analyzed. Outcome was measured versus ordered K^+. Analysis used ANOVA using SPSS.

Results: Means of the difference between measured and ordered K+ and Na+ are shown in figure 1. For K+ there was significant difference amongst the groups ($p<0.001$). There were no differences amongst the groups for Na+.

Conclusions: When a very high Na+ is prescribed along with a low HC03- the the dialysate Na+ remains close to prescribed Na+. As the acid concentrate contains both Na+ and K+, a high Na+ and low HC03- prescription will use a relatively more of the acid concentrate and less of the bicarbonate concentrate. Dialysate prescriptions with a high Na+ and low HCO3- increased delivered dialysate K+ by an average of 0.5 mEq/L; we observed some HDs where dialysate K+ was 1 mEq/L higher than prescribed.

Ordered dialysate groups based on Na+ and HCO3-. The difference between measured and ordered potassium levels in the dialysate are shown

Groups based on ordered dialysate Na+ and HCO3-	Measured minus ordered K+	N
1. Na >145 and HCO3 ≤25	0.50 ± 0.38	43
2. Na 135-145 and HCO3 ≤25	0.37 ± 0.52	242
3. Na ≤130 and HCO3 ≤25	0.08 ± 0.60	19
4. Na ≤130 and HCO3 ≥35	-0.10 ± 0.35	11
5. Na 135-145 and HCO3 ≥38	-0.08 ± 0.39	61

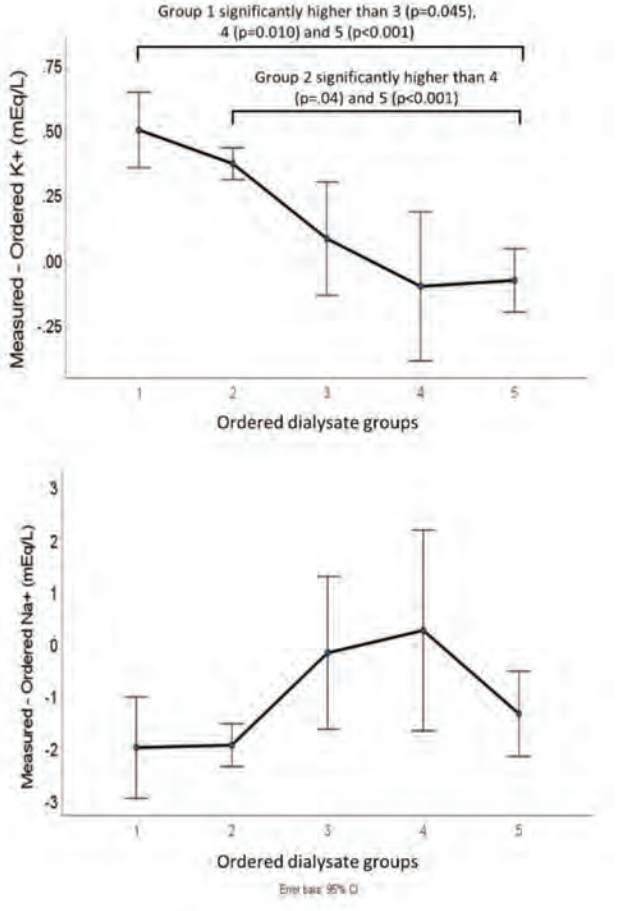


Figure 1: Means of the difference between measured and ordered K+ and Na+

PO0924

Urea Clearance Performance in a Modified Batch Dialysis System

Clayton Poppe, Nicholas Hyun, Sean C. Nash, Melany Yeung, Brandon D. Borrillo, Osman Khawar. *Diality Inc, Irvine, CA.*

Background: Urea clearance is the key measure of dialysis adequacy. The Diality Hemodialysis Machine will provide good clearance performance to ensure an adequate dose of dialysis. Specific Aims: To assess clearance performance during simulated dialysis utilizing a novel modified batch process. In this setup, dialysis was conducted by alternating dialysate delivery from subsequent two-liter reservoirs.

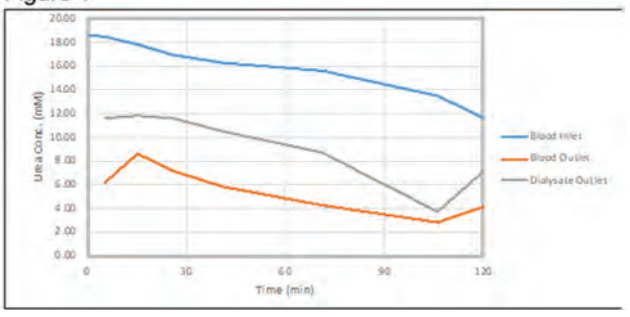
Methods: Simulated dialysis sessions were conducted utilizing blood flowrates of 300 ml/min, dialysate flowrates of 500 ml/min and no ultrafiltration. Dialysis occurs off of a two-liter batch of dialysate. Once two liters of dialysate has been circulated through the dialyzer, the spent dialysate is discarded and dialysis switches to a separate two-liter reservoir of dialysate while the first reservoir is drained and filled with fresh dialysate. A single compartment simulated patient was created by combining 50 L of DI water with a 20mM concentration of urea. Simulated blood samples were collected at the dialyzer inlet and outlet and dialysate samples collected at the dialyzer outlet to determine urea concentrations over the course of the simulated treatment.

Results: The results are provided in Figure 1. The urea concentrations in the blood decreased over the course of treatment as expected given the stated clearance values of the dialyzer used in the simulated treatment.

Conclusions: The initial experiments using a modified batch system show promising urea clearance. Future tests will better characterize performance compared with conventional devices that do not use a modified batch configuration.

Funding: Commercial Support - Diality Inc

Figure 1



PO0925

Increasing the Clearance of Protein-Bound Uremic Solutes by Introducing an Activated Carbon Block into the Dialysate Stream

Seolhyun Lee,[1,2] Tammy L. Sirich,[1,2] Timothy W. Meyer.[1,2] *[1]Stanford University School of Medicine, Stanford, CA; [2]VA Palo Alto Health Care System, Palo Alto, CA.*

Background: The hemodialytic clearance of protein-bound solutes is limited because only the free solute concentration drives diffusion across the membrane. This study tested whether an activated carbon block could reduce accumulation of these solutes in the dialysate and thereby increase their clearance.

Methods: In vitro dialysis of artificial plasma containing urea and the protein-bound solutes p-cresol sulfate (PCS) and indoxyl sulfate (IS) was performed using two dialyzers in series with and without an activated carbon block at the midpoint of the dialysate stream (Figure). Six dialysis experiments were performed each with plasma flow 240 ml/min and dialysate flows of 200 ml/min and 600 ml/min. Nine additional experiments tested the capacity of the carbon block to take up solutes by measuring solute removal from spent dialysate collected at patient treatments. Spent dialysate was passed through the carbon block at 600 ml/min and fractional removal of solutes was assessed after more than 180 liters had passed through the block.

Results: Use of the carbon block increased the clearances of the tightly bound solutes PCS and IS by 70 ± 13 and 64 ± 19 %, respectively, when the dialysate flow was 200 ml/min. Lesser increases occurred when the dialysate flow was 600 ml/min (PCS 38 ± 5%, IS 33 ± 8%). Urea clearance was unchanged by the carbon block. The carbon blocks removed 97 ± 4 % of PCS and 96 ± 2 % of IS but only 2 ± 5 % of urea from spent dialysate flowing at 600 ml/min.

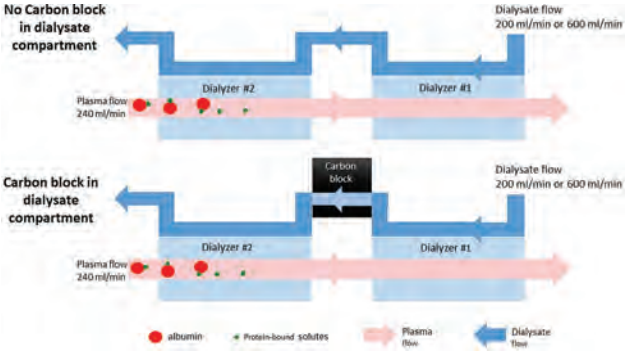
Conclusions: Use of a carbon block can increase the clearance of protein-bound solutes particularly at the low dialysate flows often used for home hemodialysis.

Funding: NIDDK Support, Private Foundation Support

Clearances of solutes with or without activated carbon block

	Qd 200 ml/min			Qd 600 ml/min		
	Clearance without carbon (ml/min)	Clearance with carbon (ml/min)	% increase in clearance with vs. without carbon	Clearance without carbon (ml/min)	Clearance with carbon (ml/min)	% increase in clearance with vs. without carbon
Urea	170 ± 21	185 ± 13	10 ± 9	226 ± 13	232 ± 17	3 ± 7
PCS	15 ± 2	25 ± 2	70 ± 13*	33 ± 4	45 ± 4	38 ± 5*
IS	17 ± 3	27 ± 3	64 ± 19*	36 ± 4	47 ± 5	33 ± 8*

*P <0.01, clearances with vs. without carbon block, Qd = dialysate flow



PO0926

Comparative Effectiveness Between Novel Medium Cut-Off Membrane Hemodialysis and Mixed-Dilution Online Hemodiafiltration on Middle Molecule Uremic Toxins Reduction: A Prospective Cross-Over Study

Jirarat Eiamcharoenying, Pajaree Chariyavilaskul, Kullaya Takkavatakarn, Paweena Susantitaphong, Yingyos Avihingsanon, Somchai Eiam-Ong, Khajohn Tiranathanagul. *King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Background: Mixed-dilution online hemodiafiltration(mixed HDF), one of the best hemodialysis(HD) modes, provides superior removal of middle molecule uremic toxins to standard HD using high flux dialyzer. Due to the limited availabilities and high cost of HDF, we performed standard HD utilizing a novel medium cut-off membrane with a larger pore size and compared the effectiveness in removal of middle molecule uremic toxins with mixed HDF.

Methods: A prospective cross-over randomized controlled trial was conducted in 14 prevalent HDF patients who were randomly allocated into group1 (n=7): mixed-dilution online HDF with high flux dialyzer ELISIO21H and group2 (n=7): standard HD with MCO membrane, Theranova 500. In this 8-week study, the primary outcome was a reduction ratio(RR) of Beta$_2$-microglobulin (B_2M). Other small to middle molecules and protein-bound uremic toxins reduction ratio, dialysate albumin loss, and nutritional parameters were also compared.

Results: In this 8-week study, B_2M RR from both modalities was higher than the survival benefit cut-point of 80%. In comparison, B_2M RR was slightly lower but significant in MCO HD than mixed HDF (82.57±5.34% vs 85.12±3.87%, respectively) with the mean difference of 2.55 (95% confidence interval [CI], -4.07 to -1.03; P=0.001). The spKt/Vurea and URR, a small uremic toxin removal marker, were comparable. κFLC and Indoxyl sulfate RR also were similar in mixed HDF and MCO HD. Whereas RR of the larger middle molecule uremic toxin, Alpha$_1$M and λFLC was lower with mixed HDF compare to MCO HD (30.13±15.90 vs 41.49±11.46 and 40.85±13.92 vs 50.81±13.18, respectively; P <0.001). Dialysate albumin loss was 3.51 g/session with MCO HD and 0.58 g/session with mixed HDF (P=0.025). Regarding, nutritional parameter, serum albumin levels were not different.

Conclusions: Mixed HDF and MCO HD provided the RR values of B_2M and small uremic toxins above the recommended cut-point. Despite mixed HDF provided higher B_2M RR, MCO HD also provided more performance in the clearance of the larger middle molecules, particularly a_1M and λFLC. However, mixed HDF loss lower albumin than MCO HD. Therefore, both techniques can be used as alternative options.

Funding: Government Support - Non-U.S.

PO0927

Clearance of Protein-Bound Uremic Toxins on the Tablo Hemodialysis System

Logan Rivas, Dean Hu, Michael A. Aragon. *Outset Medical, San Jose, CA.*

Background: The Tablo Hemodialysis system (Tablo) is an all in one, easy-to-learn device. While clearance of small and middle molecules has been documented in modern dialysis, the clearance of Protein Bound Uremic Toxins (PBUTs) merits further exploration. Clearance of albumin bound toxins such as indoxyl sulfate (IS) and p-cresol sulfate (PCS) can be limited in dialysis where removal is based on molecular size. Although a clear association has yet to be demonstrated, PBUTs have been considered to be a possible cause of adverse outcomes in patients requiring renal replacement therapy.

Methods: A simulated hemodialysis treatment using Tablo was performed with solution of bovine serum albumin and urea. PCS and IS were added to the solution to maintain a constant concentration. A screening design of experiment was performed utilizing the factors of dialysis flow rate (Qd), blood flow rate (Qb), and ultrafiltration (UF). After each factor was changed and allowed to equilibrate, samples were collected from the venous, arterial and spent dialysate lines. Samples of Urea, PCS and IS were analyzed and compared to predicted values from previously published models.

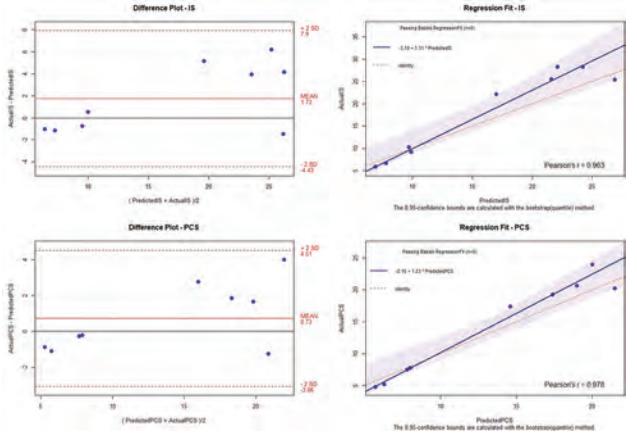
Results: The Tablo system cleared ICS and PCS as predicted or better at all conditions. See table and images for details.

Conclusions: The Tablo system aligned with the PBUT clearance model over the range of system flow settings. Continued investigation into the clinical benefits of PBUT removal is merited to better understand their impact on the overall quality of care for dialysis patients.

Funding: Commercial Support - Outset Medical

Clearance Data

Blood Pump Flow (ml/min)	Dialysis Flow Rate (ml/min)	Ultra-Filtration Rate (ml/min)	Arterial IS Conc. (mg/dL)	Spent Dial. IS Conc. (mg/dL)	Predicted IS Rate (ml/min)	Actual IS Rate (ml/min)	Arterial PCS Conc. (mg/dL)	Spent Dial. PCS Conc. (mg/dL)	Predicted PCS Rate (ml/min)	Actual PCS Rate (ml/min)
350	300	0	1.8	0.15	26.9	25.4	2.49	0.17	21.5	20.3
350	300	0	1.6	0.15	24.2	28.4	2.21	0.18	20	24.0
200	300	0	1.5	0.15	22.1	28.3	2.26	0.16	19	20.7
350	100	0	1.6	0.16	9.7	10.3	2.32	0.18	8	7.8
200	100	0	1.7	0.15	9.9	9.1	2.49	0.19	7.8	7.5
350	300	17.9	1.6	0.14	21.6	25.5	2.32	0.16	17.4	19.2
200	300	17.9	1.8	0.13	17	22.2	2.71	0.16	14.6	17.4
350	100	17.9	2.0	0.13	7.8	6.7	2.96	0.15	6.3	5.2
200	100	17.9	2.4	0.14	6.9	5.9	3.45	0.17	5.7	4.8



PO0928

Dialysis Disequilibrium Syndrome (DDS) in Hemodialysis Patients: Systematic Review

Rupesh Raina,[1,2] Siddhartha S. Singh,[1,2] Ronith Chakraborty.[1,2] *[1]Cleveland Clinic, Akron, OH; [2]Akron Children's Hospital, Akron, OH.*

Background: Dialysis disequilibrium syndrome (DDS) affects patients who have missed multiple dialysis treatments, especially new initiates of hemodialysis (HD), and presents as a rare neurological complication. The conceptual pathogenesis of DDS is likely a result of multiple physiological abnormalities which we explore in this systematic review alongside preventive measures with focus on effective management strategies.

Methods: A literature search was conducted on PubMed/Medline and Embase and included studies if the patient developed DDS irrespective of age and gender. Two independent reviewers conducted the process of article selection with a thrid reviewer present to resolve any conflicts. The data was analyzed and a summary table was extracted with the following variables: study type, population group, age, patient characteristics, blood and dialysate flow rate, and study outcome. A descriptive analysis was performed analyzing the population size and frequency of symptoms and treatments utilizing the R software.

Results: A total of 49 studies (321 samples) were identified and analyzed. There were 72.4% of patients (based on 48 studies) who reported having DDS with most common symptoms of headache (39.4%), nausea (40.4%), vomiting (39.1%), confusion (66.7%) and seizure (78.6%). Within this sample, 12 studies switched from HD to alternative dialysis modalities including continuous venovenous hemofiltration/hemodiafiltration (CVVH/CVVHDF) or peritoneal dialysis (PD) with no further reported DDS symptoms.

Conclusions: We have provided a comprehensive clinical practice points for both the pediatric and adolescent and young adult population; interestingly, DDS was reported more often in the early dialysis era prior to recent advances and improvement of resource allocation. Existing literature shows it is crucial to recognize symptoms of DDS and implement timely prevention to improve outcomes.

PO0929

Protein Loss with Medium Cut-Off and High Flux Dialyzer: A Proteomic Analysis

Xiaoling Wang,[1] Xia Tao,[1] Leticia M. Tapia Silva,[1] Amrish U. Patel,[1] Mohamad I. Hakim,[1] Nadja Grobe,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

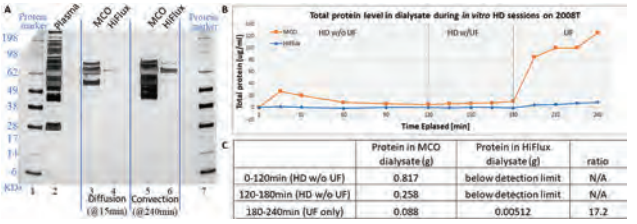
Background: Hemodialysis (HD) patients frequently suffer from low serum albumin levels, making dialytic albumin and protein loss a concern. Medium cut-off (MCO) dialysis membranes reportedly show a greater albumin loss compared to high-flux (HiFlux) membranes. To better understand the spectrum of proteins cleared with MCO membranes, we set up an *ex vivo* dialysis system and perform proteomic analysis of the dialysate.

Methods: Eight liters of human plasma (EDTA added) are split into two 4-liter batches and dialyzed for 4 hrs in single-pass, either with an MCO (Theranova 400) or HiFlux dialyzer (Optiflux F180NR) using a Fresenius 2008T machine. Blood flow was 400 ml/min. Dialysate flow was 600 ml/min for the first 3 hrs and zero for the 4th hr. Ultrafiltration rate was zero for the first 2 hrs and switched to 1 L/hr thereafter. This design allowed us to study three HD modes: diffusion only (2 hrs); diffusion with convection (1 hr); convection only (1 hr). Dialysates were sampled at multiple time points (**Fig 1B**).

Results: Three µg of initial plasma and 23 µl dialysate were loaded on an SDS-page gel and silver stained **(Fig 1A)**. Lanes 3 and 5 were from MCO, lanes 4 and 6 from HiFlux. Lanes 3 and 4 were collected 15 mins into dialysis, lanes 5 and 6 at 240 mins. Results show that dialysates contain less high molecular weight proteins compared to plasma, and MCO dialysates contain much more proteins compared to HiFlux dialysates. The strong band at ~62 kD is most likely albumin. Using mass spectroscopy, we can identify 56 different protein species in MCO dialysate. Dialysate protein levels (measured by Bradford assay) with the 3 dialytic modalities are shown in **Fig 1B,** the total protein losses are listed in **Fig 1C**. The ratio of protein loss between MCO and HiFlux dialyzers is 17-fold in the convection only mode.

Conclusions: Our results show a higher diffuse and convective protein loss with MCO compared to HiFlux membranes. Further characterization and quantitation of proteins cleared *in vivo* during HD are necessary to better understand the clinical impact of our *ex vivo* observations.

Funding: Commercial Support - Renal Research Institute



	Protein in MCO dialysate (g)	Protein in HiFlux dialysate (g)	ratio
0-120min (HD w/o UF)	0.817	below detection limit	N/A
120-180min (HD w/o UF)	0.258	below detection limit	N/A
180-240min (UF only)	0.088	0.00512	17.2

Figure 1: dialysate protein analysis.

PO0930

Intradialytic and Interdialytic Urea Dynamics in Blood and Cerebrospinal Fluid in Hemodialysis Patients

Xia Tao,[1] Lin-Chun Wang,[1] Xin Wang,[1] Ohnmar Thwin,[1] Nadja Grobe,[1] Amrish U. Patel,[1] Stephan Thijssen,[1] Joshua E. Chao,[1] Ludovic Debure,[2] Thomas Wisniewski,[2] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]NYU School of Medicine, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

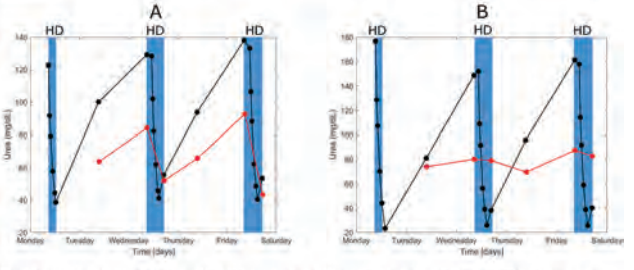
Background: Modern, highly efficient hemodialysis (HD) results in rapid decline of blood urea. Urea gradients across the blood-brain barrier (BBB) can drive water movements. A positive urea gradient, i.e. brain urea to plasma urea, can result in brain swelling and impair brain function. We explored the dialytic changes of urea in blood and cerebrospinal fluid (CSF) to better understand intradialytic osmotic gradients across the BBB and provide insights that support the development of brain-protective HD.

Methods: Two HD patients (39 and 26 years old) with ventriculo-peritoneal (VP) shunts were enrolled into this one-week IRB-approved study with a Monday/Wednesday/Friday dialysis schedule. CSF was collected via VP shunt tap 2 hrs before and 2 hrs after HD (Wednesday and Friday), and Tuesday and Thursday. Plasma samples were collected concurrently with CSF and during HD. In addition, the patients underwent test of executive function (Trail Making Test Part B; TMT B) and global cognitive function (Montreal Cognitive Assessment; MoCA) on Monday.

Results: Urea was removed efficiently from patients' blood by HD. While patient A showed a small post-HD plasma-to-CSF urea gradient, it was highly positive (~ 60 mg/dL) in patient B (Fig. 1). TMT B and MoCA score were normal for patient A but not patient B (TMT B 415 sec; TMT B error count: 2; MoCA score: 11).

Conclusions: Our patients showed very different post-HD plasma-to-CSF gradients. Theoretically, the positive gradient in patient B would favor intradialytic brain swelling. Patient B showed impaired neurological testing results which are not related to patient's pre-existing neurological conditions. We can only speculate if and to what extent trans-BBB water movements driven by dialytic urea dynamics may have impacted the patient's cognitive functions. We believe that patient-specific levels of osmotic stress need to be considered when developing neuro-protective HD technologies.

Figure 1. Urea concentrations in plasma (black line) and CSF (red line) (left panel: patient A; right panel: patient B).



The blue areas indicate duration of HD (1st session) and the period between 2 hrs pre-HD to 2 hrs post-HD (2nd and 3rd session).

PO0931

High-Throughput Analysis of Changes in Protein Biomarkers During Hemodialysis

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Background: The impact of hemodialysis on the concentration of circulating protein biomarkers remains unclear. Biomarkers may decrease in concentration due to filter adsorption, diffusive clearance, or convective clearance, while others may increase in concentration due to production and secretion or intracellular release. Ultrafiltration of water is expected to also increase biomarker concentration. We sought to evaluate the impact of hemodialysis on 1,163 protein biomarkers in a high-throughput fashion.

Methods: A nested cohort of 44 patients (25 male, 19 female) including 29 with intradialytic hypotension and 15 without were selected from the prospective Hemodialysis Outcomes and Symptoms assessment (HOST) cohort. Intradialytic hypotension was stringently defined as a 60 mmHg drop in systolic blood pressure or a nadir systolic blood pressure of less than 70 mmHg during hemodialysis treatment. All hemodialysis treatments were done using the same hemodialysis filter type. 1,163 unique biomarkers were measured in each patient before and after a hemodialysis session using the Olink proximity extension assay (www.olink.com). Paired sample t-tests were used to compare pre- and post-dialysis concentrations with a Bonferroni-corrected significance threshold ($P < 5 \times 10^{-5}$).

Results: 54 biomarkers (5%) significantly increased during hemodialysis treatment, while 243 (24%) significantly decreased. Change in biomarker concentration was significantly associated with biomarker molecular weight ($r = 0.37$, $P = 2.8 \times 10^{-16}$), isoelectric point ($r = -0.26$, $P = 6.4 \times 10^{-14}$), and pre-dialysis concentration ($r = -0.21$, $P = 3.0 \times 10^{-9}$). There was a significant enrichment of cardiovascular biomarkers in the top 20 biomarkers associated with drop in systolic blood pressure ($P = 2.8 \times 10^{-10}$), including Kidney Injury Molecule 1 (KIM1, $P = 0.005$).

Conclusions: Hemodialysis is associated with significant changes in protein biomarker concentrations related to protein properties and clinical events during treatment. These changes are measurable on a high-throughput platform. Further high-throughput biomarker studies could assess dialysis adequacy, test biomarker-symptom associations, and improve risk prognostication.

Funding: Private Foundation Support

PO0932

Feasibility of Allo-Hemodialysis: First Experience from Porcine Studies

Xin Wang,[1] Amrish U. Patel,[1] Anil K. Gothi,[2] Dejan Nikolic,[6] Alexander Heide,[6] Jiaming Dong,[3] Hao Zhang,[3] Vaibhav Maheshwari,[1] Nadja Grobe,[1] K S Nayak,[5] Peter Kotanko.[1,4] *[1]Renal Research Institute, New York, NY; [2]Vivo Bio Tech Ltd, Hyderabad, India; [3]Fresenius Medical Care Shanghai Co Ltd, Shanghai, China; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]Virinchi Hospitals, Hyderabad, India; [6]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany*.

Background: Annually, millions of kidney patients, predominantly in low and low-middle income countries, die prematurely because of unavailability of affordable kidney replacement therapy. We previously demonstrated through mathematical modeling and bench testing the feasibility of alloHD, an alternative low-cost hemodialysis treatment approach where the blood of a kidney failure patient flows counter-current to that of a healthy subject ("buddy") through a dialyzer. Herein we report first results from an alloHD feasibility study in a porcine model. We aimed to specifically address questions around hemolysis and coagulation of the dialysate compartment.

Methods: Ethics protocol was approved by Committee for the Purpose of Control and Supervision of Experiments on Animals, India. Under general anesthesia, healthy female white Yorkshire pigs of 30 to 80 kg with central venous catheter as vascular access were dialyzed 1-3x weekly for 2-4 hours. Ultrafiltration volume goals were set between 0 and 1000 mL. "Patient" and "buddy" pigs were connected to the dialysate and blood compartments, respectively, of a Nipro Cellentia 17H (Fig. 1). Pigs were anticoagulated with 5000 IU heparin per hour. Pre- and post-treatment blood samples were collected for biochemical measurements.

Results: We successfully completed 10 alloHD sessions. No coagulation was observed. Visual inspection of plasma samples indicated no signs of hemolysis. This was further corroborated by measurements of lactate dehydrogenase and haptoglobin, which were available in seven experiments (Fig. 2).

Conclusions: We found no indication of hemolysis and dialysate compartment coagulation in our experiments. Upcoming studies in a porcine renal failure model will address *in vivo* solute clearances by alloHD.

Funding: Commercial Support - Renal Research Institute

Figure 1. AlloHD setup.

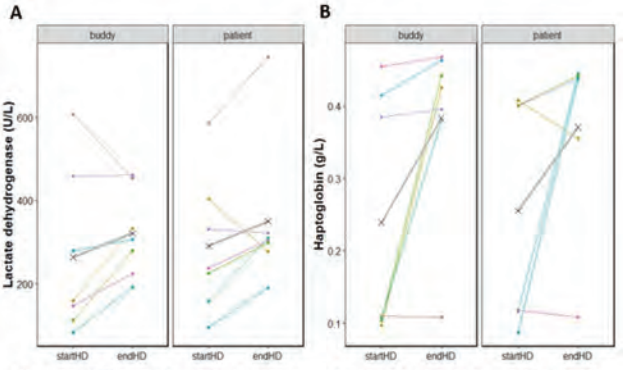

Figure 2. Plasma lactate dehydrogenase (A) and haptoglobin (B) levels in "patient" and "buddy" pigs dialyzed by alloHD (N=7). Individual experiments are color coded; the means are shown in grey.

PO0933

Can Plasma Filters Be Reused for Plasmapheresis in Resource-Poor Settings? Experience from a Tertiary Care Hospital

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Background: Therapeutic plasma exchange (TPE) is used in the management of various life-threatening illnesses. It is widely performed by nephrologists, intensivists, pathologists, or experts of transfusion medicine worldwide. However, the costs of TPE sessions are exceedingly high and it has a huge impact on patients' financial burden. Most of the patients cannot afford such a high-cost treatment. Herein, we investigated the outcomes of reuse of plasma filters in TPE for several occasions

Methods: This was an ambidirectional study that included retrospective analysis of patients receiving TPE from January 1, 2020, to December 31, 2020, whereas the patients receiving TPE from January 1, 2021, to April 30, 2021, were prospectively analysed. The procedure was performed in our hospital's dialysis unit. Formulation of 4% peracetic acid and 24% hydrogen peroxide acid with RO water was used for reprocessing. Fresenius Plasma Flux P2 (0.6 m2) was used in the study. Clinical outcomes, risks, and cost-benefit were evaluated and compared between the plasma filter reuse group (GP-1) and no reuse group (GP-2).

Results: 46 patients were included in the study. 26 patients were in the Plasma filter reuse group. 122 and 119 TPE sessions were performed in GP-1 and GP-2 respectively. A total of 58 plasma filters were used in GP-1. In six patients single plasma filter was used on 3 occasions whereas, it was used for 2 occasions in other patients. The most common indication for TPE in both groups was Guillain barre syndrome. The rates of clinical improvement in disorders for which the TPE were performed were similar in both GP-1 and GP-2 (88 % vs 90%, p=0.4). None of the patients in either group had clotting of plasma filter, any allergic reaction, or increased bleeding risk. No higher chances of sepsis were noticed in GP-1 (P=0.08). No difference in patient survival was noticed between the two groups (97% vs 96 %, p=0.5). The cost of overall treatment was 2.5 times higher in GP-2, (P=0.003).

Conclusions: Reuse of plasma-filter is a safe and effective method for cost minimization in patients requiring TPE. This method can effectively be utilized in resource-poor settings without any increased risk of adverse effects

PO0934

A Forgotten Technique of RRT for Correction of Severe Hyponatremia in CKD: Case Report

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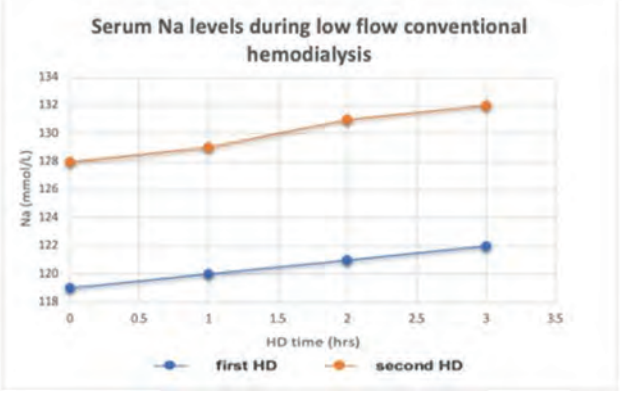
Introduction: Patients with chronic kidney disease (CKD) present electrolytes disorders. This represents a challenge when hyponatremia is below 125mmol/L associated with any criteria for urgent renal replacement therapy (RRT) with conventional hemodialysis because of higher risk of over correction above the security threshold of 10mmol/L/day and osmotic demyelination syndrome.

Case Description: A 49-year-old Guatemalan female with history of 15 days of edema and slurred speech. Only history of T2DM. Was brought to the ER with BP 100/80mmHg and anasarca. Initial laboratories: negative COVID-19Ag, Cr 5.12mg/dl, (previous 2mg/dl) BUN 105mg/dl, glucose 156mg/dl, Na 108mmol/L, K 5.2meq/L, Cl 70meq/L. SOsm 224mOsm/kg, UOsm 875mOsm/kg, UNa 28meq/L. Because of neurologic symptoms, received a 150ml bolus of 3% saline twice with a rise to 112mmol/L. After the bolus, we initiated a 24-hour infusion with 3% hypertonic solution reaching a rise of Na up to 119mmol/L in 48 hours, but because of persistence of neurologic symptoms plus fluid overload >10% of body weight and hyperkalemia, we initiated RRT. In the absence of CRRT or CVVH we planned a *conventional HD* with blood flow of 100ml/min, dialysate flow 600ml/min, dialysate Na 130meq/L (the lowest Na possible) and 3 hours duration. After the first session had neurological and edema improvement. After two sessions with interdialytic period of 48 hours, Na control of 122mmol/L and 132mmol/L respectively with resolution of uremic syndrome. Later was diagnosed with hospital-acquired pneumonia receiving antibiotic treatment for 14 days and was discharged home with ambulatory HD.

Discussion: In undeveloped countries where the access to CRRT or CVVH is unavailable, conventional modalities can be used with low blood flows and modification of the dialysate Na to a minimum (130mmol/L) offering a safe option to Na correction for patients with severe hyponatremia and any other HD criteria.



PO0935

Single-Bolus Tinzaparin Anticoagulation in Extended Hemodialysis Sessions: A Feasibility Study

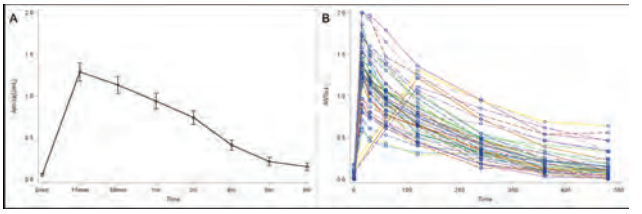
Benoît Harvey,[1] Simon Leclerc,[2] Naoual Elftouh,[2] Michel Vallee,[2] Louis-Philippe Laurin,[2] Annie-Claire Nadeau-Fredette.[2] *[1]Universite de Montreal, Montreal, QC, Canada; [2]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.*

Background: Few studies have assessed the use of low-molecular weight heparins for anticoagulation during extended hemodialysis (HD) sessions. This study aimed to evaluate the safety and efficacy of tinzaparin for anticoagulation of the extracorporeal circuit and dialyzer in extended, 8-hour, sessions.

Methods: This single-center study included all patients who underwent a single in-centre 8-hour session as part of their nocturnal home HD training between 2009 and 2020. Tinzaparin was delivered as a single bolus injection at time 0 with dosing based on the patient's weight and doubling of standard 4-hour session dose. Tinzaparin safety was assessed via anti-Xa measured at 15-, 30-min, 1-, 2-, 4-, 6-, 8-hour. Efficacy was examined via visual observations (score 1-4) of the dialyzer and venous bubble trap at the end of dialysis. Predictors of clotting levels were assessed in exploratory logistic regressions.

Results: Forty-seven patients were included: age 45 ±14 yrs, 28% women, 9% on warfarin, 42% on antiplatelets, BMI 29±7 kg/m^2, hemoglobin 114±15 g/L and platelet 203±61 10^9/L. Mean tinzaparin dose was 107 ± 20 IU/kg. Anti-Xa levels peaked at 15-min with 1.3 ± 04 IU/mL and progressively declined reaching 0.9 ± 0.3 IU/mL at 1-hour, 0.4 ± 0.21 IU/mL a 4-hour, and 0.15 ± 0.15 IU/mL after 8-hour. **Figure1** After the 8-hour session, none of the patients had severe clotting of their dialyzer or venous chamber. Moderate blood clotting was observed in the dialyzer of 6 (20%) patients and in the venous chamber of 22 (61%) patients. Tinzaparin dose was increased for 27 (81%) patients with a mean maintenance dose of 123 ± 28 IU/kg. None of the main baseline characteristics (including tinzaparin dose per kg) were associated with clotting scores.

Conclusions: This study shows that anti-Xa levels stabilize rapidly after administration on tinzaparin for 8-hour HD. Administration of a single bolus tinzaparin at the start of an eight-hour dialysis session appeared safe and effective, although dose adjustment may be required.



PO0936

Green Hemodialysis: Is It Really Possible to Save Water and Plastic Without Affecting the Quality of the Treatment?

Ismael A. Gómez Ruiz, Geovana Martin-Alemañy, Juan M. Ardavin Ituarte, Rossana Olmedo Ocampo. Santa Carmen *Médica Santa Carmen, Ciudad de México, Mexico.*

Background: Hemodialysis (HD) is essential for the preservation of life in many patients but represents a complex issue in ecology producing a large waste load that affects the environment. Sustainable waste management policies are scarce. The aim of the present study was to show the particular water and plastic savings in a mexican HD center that practices the reuse of dialyzers and reject water (RW) without affecting the quality of care provided for patients.

Methods: Prospective cohort study performed between January and May 2021 in a HD center with 90 patients (AK 98 Baxter®). HD center has 15 employees, 5 bathrooms and 12 sinks. Volumes of produced and reused RW were measured by flow meters. A detailed analysis of the residual biochemical content of RW was performed. The weight of plastic waste was compared between patients with reused membranes and patients with non-reused membranes. Finally, to evaluate the quality of the HD treatment in reused dialyzers (1-12 reuses), the difference between 5 monthly measurements of the spKt/V was determined using a repeated measure ANOVA considering a p>0.05 for no difference.

Results: During the study period 4158 HD sessions were provided, 394 m3 of RW were produced, 312 m3 (79%) were reused for all center sanitation purposes. Analysis of the residual biochemical content of RW is shown in Table 1. A total of 1902 HD sessions were performed with reused dialyzers. With each dialyzer reuse (Revaclear Baxter®) 0.88 lbs of plastic waste was spared. This translates into 1.53 tons less waste. No adverse effects were observed. No statistical significance difference was observed in single pool Kt /V between treatments with reused filters.

Conclusions: These results suggest that reuse of RW in the sanitation of the centers and dialyzer reuse resulted in significant savings in water and plastic without affecting the quality of treatment received by patients.

Table 1 | Assay results for RW compared with US Environmental Protection Agency (EPA) and the Association for the Advancement of Medical Instrumentation (AAMI standards)

Analyte	Our HD center-RW	US EPA standar	AAMI standar
Aluminum mg/dl	< 0.049	< 0.05	0.05
Arsenic mg/L	<0.012	< 0.01	0.01
Bacteria limit CFU/ml	<10	0	<100
Cadmium mg/L	<0.005	< 0.005	0.005
Calcium mg/L	< 0.064	0.1	0.1
Chloride mg/L	0.02	< 4	4
Conductivity(µS/cm)	440	< 2500	No std
Copper mg/L	< 0.058	< 1.3	1.3
Dichloramine mg/L	<0.1	< 0.8	<0.1
Fluoride mg/L	1.25	< 4	4
Iron mg/L	< 0.032	< 0.3	0.3
Lead mg/L	0.001	< 0.015	0.015
Magnesium mg/L	0.053	0.1	0.3
Manganese mg/L	< 0.031	< 0.05	0.05
Mercury mg/L	< 0.00089	< 0.002	0.002
Nitrate mg/L	< 10	< 10	10
pH units	7.5	7.5 ± 1.0	No std
Potassium mg/L	**1.49**	0	0.2
Selenium mg/L	**< 0.128**	0	0.09
Silver mg/L	< 0.003	0	<0.005
Sodium mg/L	155.38	< 200	200
Sulfate mg/L	78.84	< 250	250
Total hardness mg/L	0.1	No std	No std
Zinc mg/L	< 0.073	5	5

Abbreviations: No std, no standard set; CFU, colony forming unit.

PO0937

Targeted Alteplase Administration to Improve Hemodialysis Catheter Patency: A Quality Improvement Pilot Study

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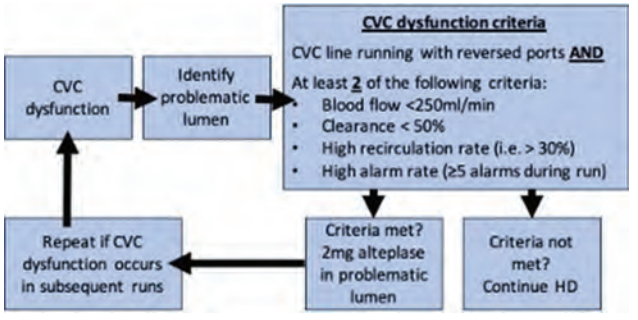
Background: Catheter dysfunction (CD) is a frequent complication during the provision of hemodialysis. Thrombolytic agents (i.e. alteplase) are the mainstay for resolving CD, however, alteplase usage has increased 16% (~$440,000CAD) annually in the Alberta Kidney Care South program without improved patient or dialysis outcomes. We assessed the implementation of a protocolized algorithm to reduce alteplase usage.

Methods: In this pilot quality improvement study, we designed an algorithm where CD was treated with high-dose (2mg) alteplase therapy to the problematic lumen only, after meeting pre-specified criteria (Fig 1). This protocol was implemented in a satellite hemodialysis unit (~110 patients) from Jan 2021 to Mar 2021. The baseline comparison period was Jan 2020 to Dec 2020 when CD was treated with low-dose 1mg/lumen alteplase. Outcome measures included total alteplase usage, changes in Kt/V, recirculation, clearance, line interventions and hospitalization rates. Statistical analysis was completed using Mann-Whitney and Z-score calculations.

Results: Sixty-nine alteplase administrations occurred over the two-month period, versus 438 in the baseline period. Patients in the 2mg group were more likely to achieve an increase in Kt/V of at least 10% in the next dialysis session (34.7% vs 28.9% p=0.04). Otherwise the 2mg alteplase with our protocol was not inferior to baseline with respect to blood volume processed (26.1% vs 20.1% p=0.13) and average clearance (37.7% vs 28.5% p=0.37). A 12% decrease (88 vs 100mg/mo p<0.05) in alteplase use was observed with no differences in frequency of hospitalizations (8% vs 5.9% p=0.39) or line interventions (12.3% vs 7.3% p=0.20).

Conclusions: Our protocol with 2mg alteplase therapy to the problematic lumen was not inferior with respect to patient outcomes compared to baseline practices and resulted in lower alteplase use. An expanded multi-center prospective study is underway to further assess the broader applicability of these findings.



Alteplase administration protocol.

PO0938

The Effect of Predilution Online Hemodiafiltration on Body Composition, Nutritional Status, and Mortality

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Background: We evaluated the effect of predilution online hemodiafiltration (HDF) on body composition, nutritional status and all-cause and cardiovascular (CV) mortality in maintenance dialysis patients.

Methods: All subjects (n=215) had blood flow rate of ≥200 mL/min and underwent HDF with a convective volume of 40 L/session or hemodialysis (HD), 4h/session, 3 times/week. Predialysis clinical data and same day postdialysis body composition parameters based on BCM (Fresenius) were obtained at baseline in 46 patients on HDF and 169 patients on HD, and followed over 5 years. Logistic regression analysis for HDF, Kaplan–Meier analysis and Cox hazard analysis were conducted.

Results: In all subjects, age and dialysis vintage were 72±12 years and 73±6 months, respectively. Body mass index [22.4 (20.6–27.0) vs. 19.8 (16.4–22.7) kg/m^2], lean tissue index (LTI) [13.2 (10.8–15.7) vs. 11.0 (9.3–13.2) kg/m^2], geriatric nutritional risk index [94 (88–97) vs. 88 (81–93)], serum albumin [3.6 (3.3–3.8) vs. 3.3 (2.9–3.5) g/dl], creatinine, phosphate and magnesium were higher, but LDL-cholesterol (LDL-C) was lower in patients on HDF than those on HD (P<0.05). There were no significant differences in fat tissue index (FTI) [8.0 (5.5–11.2) vs. 7.8 (5.7–10.6) kg/ m^2], overhydration (OH) [0.8 (–0.5–2.2) vs. 0.9 (0.3–2.1) L], C-reactive protein (CRP), Kt/Urea or β2-microglobulin (β2m) between the groups. HDF was significantly (P<0.05) associated with serum albumin [odds ratio (OR):2.99], LDL-C (OR:0.98) and LTI (OR:1.22), but not with FTI, OH, CRP, Kt/Urea or β2m. Cumulative 5-year survival rate was significantly higher in patients on HDF than those on HD (67.9 vs. 43.7%, P<0.01). For 5-year all-cause mortality, HDF [hazard ratio (HR):0.31], age (HR:1.03), albumin (HR:0.48) and LTI (HR:0.91) were significant predictors (P<0.05), while FTI and OH were not. For 5-year CV mortality, HDF (HR:0.20), age (HR:1.05), diabetes (HR:2.61) and LTI (HR:0.80) [or either FTI (HR:1.08) or OH (HR:1.22)] were significant predictors, respectively (P<0.05).

Conclusions: Predilution online HDF with substitution volume 40 (20–40) L/session, 3 times/week is associated with better nutrition, increased muscle mass, and improved all-cause and CV mortality, but not with body fat and OH in dialysis patients.

Funding: Private Foundation Support

PO0939

Monitoring of Intradialytic Sleep Apnea in Hemodialysis Patients

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Background: Breathing disorders are frequent in end-stage kidney diseases, with more than 50% of hemodialysis (HD) patients experiencing sleep apnea syndrome (SAS). SAS is associated with lower health-related quality of life and represents a significant cardiovascular risk factor. HD patients with SAS are at greater risk of mortality. The study aimed to monitor intradialytic SAS in HD patients using oxygen saturation (SaO_2) measurements.

Methods: Crit-Line® monitor was used to record SaO_2 at 1 Hz, for 2 HD sessions with a mean duration of 3.5±0.5 h. For each patient, we calculated: oxygen desaturation density (ODD_{10}), which counts 3% drops in SaO_2 from a baseline for at least 10 s long; a10th order permutation entropy to quantitate complexity; and optimal recurrence threshold ($\varepsilon_{optimal}$) to account for dynamic variations and degree of predictability in the SaO_2. These quantities were subjected to machine learning methods to predict intradialytic SAS, as quantified by the ODD_{10} value and the SAS classification by the American Sleep Disorders Association.

Results: We examine intradialytic SAS severity in 16 patients (age of 54±11 years, 63% males, 69% Black) with arteriovenous vascular access. Mean SaO_2 was 94.3±2.1%. Figure 1A shows a typical SaO_2 annotated with the SAS intensity assessed by ODD_{10} (Fig. 1B). The two calculated metrics are plotted in Figs. 1C-D. The results reveal dynamic characteristic patterns of SAS with differential severity scores during HD. Figures 1E-G show the ROC for the classifiers when considering episodes of at least mild, moderate, or severe SAS, respectively. The maximum AUC is 0.93 for severe SAS episodes.

Conclusions: Our analysis suggests that entropy and recurrent-based quantifiers could be used as predictive indicators of intradialytic SAS. However, further studies are needed to assess their relationships to clinical outcomes.

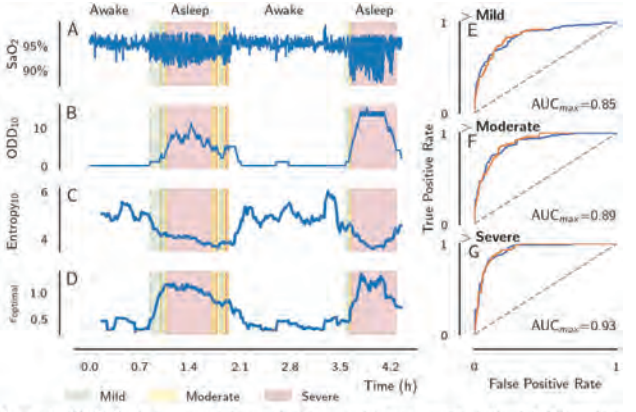

Figure 1: (A) SaO_2 for a representative patient, the shaded areas annotate different SAS intensities classified by (B) the oxygen desaturation density (ODD_{10}). (C) Entropy and (D) optimal recurrence threshold ($\varepsilon_{optimal}$) calculated from the SaO_2 time series (A). SAS intensity measured by ODD_{10} was classified based on ASDS categories as (E) mild, 5 – 15 events/hour of sleep, (F) moderate, 15 – 30 events/hour of sleep, and (G) severe, > 30 events/hour of sleep. Here, AdaBoost and Random Forest binary classifiers were used to predict SAS severity.

PO0940

DENALI, a Phase 3b Multicenter, Open-Label Single-Arm Study of Roxadustat: Operational Learnings Within US Dialysis Organizations

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor that promotes erythropoiesis and improves iron availability in patients with anemia of chronic kidney disease (CKD). This trial aims to provide practical data on roxadustat use in dialysis patients with anemia via a semi-pragmatic evaluation of introduction into providers' practices (Fresenius Medical Care).

Methods: This open-label, single-arm study assesses the efficacy and safety of roxadustat in correcting/maintaining hemoglobin (Hb) in patients with CKD-related anemia receiving in-center/home dialysis at nine US sites (NCT04410198). Initial roxadustat dose is weight-based (erythropoiesis-stimulating agent [ESA]-naïve patients) or guided by an ESA dose-conversion algorithm (ESA patients), in this trial targeting Hb=11±1 g/dL. Roxadustat dose is titrated every 4 weeks based on Hb level or rate of change, with 24-week treatment duration and up to 1-year extension. Efficacy is assessed by change from baseline in Hb and proportion of patients achieving mean Hb ≥10 g/dL averaged over weeks 16-24. Exploratory endpoints include time to first red blood cell transfusion, proportion of patients achieving mean Hb ≥10 g/dL in first 8 weeks, intravenous iron use, and dosing adherence. Safety endpoints include treatment-emergent adverse events (AE), with COVID-19 positivity an AE of special interest.

Results: This ongoing trial was successfully initiated and enrolled (n=203) during the COVID-19 pandemic, with modifications for home dialysis. Baseline characteristics appear representative of the US dialysis population (Table).

Conclusions: This trial adds to phase 3 studies of roxadustat by evaluating its use in treating anemia of CKD in home/in-center dialysis patients during the COVID-19 pandemic, while providing a view into operationalization and ease of real-world use. Full study results will be presented.

Funding: Commercial Support - FibroGen and AstraZeneca

Characteristic*	Roxadustat (n=203)	Characteristic*	Roxadustat (n=203)
Race, n (%): Black	84 (41)	Baseline ESA: Mircera[a], n (%)	196 (97)
White	105 (52)	Duration of ESA use, wk	116 (109)
Hemoglobin, g/dL	10.4 (0.8)	Dialysis duration, wk	204 (232)
<10.0, n (%)	57 (28)	Hemo- vs. peritoneal dialysis, n (%)	173 (85) vs. 30 (15)
Ferritin, µg/L	1278 (692)	History of CVD/stroke/VTE, n (%)	195 (96)
Baseline ESA use, n (%): ESA naïve	5 (2.5)	Diabetes mellitus, n (%)	123 (61)
Stable ESA	198 (97.5)	Hypertension, n (%)	191 (94)

*Data are mean (SD) unless otherwise stated.
CVD, cardiovascular disease; VTE, venous thromboembolism; Mircera[a] (methoxy polyethylene glycol-epoetin beta)

Table: Key Baseline Characteristics in DENALI Patient Population.

PO0941

Modeling Low Muscle Mass Screening in Dialysis Patients

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Background: Sarcopenia, regarded as low muscle mass, affects the prognosis of dialysis patients, and is a serious problem. Though bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA) are used in conventional sarcopenia screening, BIA and DXA may not accurately predict muscle mass because dialysis patients are easily affected by water content. On the other hand, computed tomography (CT) can measure muscle mass with accuracy even in dialysis patients. However, it is not easy to use CT at bedside screening. We aimed to create a prediction model of low muscle mass that can be used at bedside using the psoas muscle mass index (PMI) from CT measurement as the gold standard.

Methods: This is a multi-center, prospective cohort study. Between June 29, 2019 and December 31, 2020, outpatients who had been screened by dialysis and CT imaging for more than 6 months at each facility were included. They were divided into a development group and a verification group based on geographical factors. The PMI was manually measured from abdominal CT to diagnose low muscle mass. From the development group, a logistic regression model was created using 42 items of clinical information as predictor variables, and variables were selected by the stepwise method. External validity was examined using the verification group, and area under the curve (AUC), sensitivity, and specificity were calculated.

Results: Of the 619 subjects, 220 (35.6%) were diagnosed with low muscle mass. The subjects were divided into a development group of 441 and a verification group of 178 patients. A predictive model of low muscle mass was created with 6 variables (mean grip strength, height, dry weight, dialysis water removal, pre-dialysis albumin, and comorbidity of liver disease). The adjusted AUC of the development group was 0.78, sensitivity 82.7%, and specificity 63.3%. The adjusted AUC of the verification group was 0.71, sensitivity 64.3%, and specificity 72.2%.

Conclusions: It is expected that muscle mass screening of dialysis patients will be possible easily, and it is expected to support prevention and intervention decisions for sarcopenia. This study did not directly compare with BIA or DXA and did not show our model is superior to BIA or DXA. Therefore, further researches are needed to support its use.

PO0942

Validation of Urea Removal in Novel Sorbent Dialysis System

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Background: The Diality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To assess urea mass removal during a simulated dialysis utilizing a novel sorbent filter.

Methods: Nine simulated dialysis sessions were conducted utilizing between 50L and 125L volumes of dialysate circulated at approx. 400 mL / min & 37 C through a sorbent cartridge with a standard dialysate. (Table 1) It is expected that with each pass through the filter the dialysate urea mass will decline. The experiment is continued until breakthrough occurs or the infusate outlet reaches 10 ppm of NH_4. A solution containing K, Ca and Mg salts were constantly infused to replenish electrolytes lost in each pass. Another solution was infused at a variable rate as determined by conductivity to maintain Na Balance.

Results: The results are provided in table 1. The average URR was 63.8 % ranging from 53.3 to 87.0 %. The average starting BUN was 48.2 mg/dL and the average ending BUN was 16.8 mg/dL.

Conclusions: The initial experiments using a sorbent filter demonstrate a URR of near 65 is feasible. Future design changes will be scaled to handle larger amounts of urea and provide acceptable clearances.

Funding: Commercial Support - Diality Inc

Table 1:

Start BUN (mg/dl)	End BUN (mg/dL)	URR	Circulation Volume (L)	Breakthrough (mins)
42.0	19.6	53.3	125	225
42.0	20.2	52.0	125	242
42.0	16.2	61.3	125	265
42.0	16.8	60.0	125	262
56.0	7.3	87.0	50	249
42.0	18.8	55.3	50	232
56.0	23.2	58.5	75	229
70.0	17.6	74.8	75	242
42.0	11.8	72.0	75	229

PO0943

Effect of Hemodialysis on Amyloid-β in Cerebrospinal Fluid and Plasma

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Background: Hemodialysis (HD) can reduce amyloid-beta (Aβ) species in whole-body circulation by 30 to 50%. Due to the dynamic exchange of Aβ between the brain and the blood, we hypothesized that HD might lower Aβ levels in the cerebrospinal fluid (CSF).

Methods: In a dialysis network with over 160,000 patients, we identified three maintenance HD patients (age 36±9 years) with ventriculo-peritoneal (VP) shunts who were subsequently recruited for this IRB-approved research study. Study subjects were dialyzed on Monday, Wednesday, and Friday. Plasma samples were collected at 6 timepoints during the 3 HD sessions. One subject was withdrawn over safety concern related to the VP shunt tap procedure. Two subjects further underwent VP shunt taps for CSF sample collection before and after the Wednesday and Friday HD sessions, and once on interdialytic days (Tuesday, Thursday). $A\beta_{1-42}$ and $A\beta_{1-40}$ were quantified by Neuro 3-Plex SIMOA assays (Quanterix, MA, USA).

Results: HD effectively reduced plasma $A\beta_{1-40}$ by 41% and $A\beta_{1-42}$ by 34% (**Fig 1a and 1b,** $p < 0.01$). In CSF, levels of Aβ increased after Wednesday HD sessions in subject 1 ($A\beta_{1-40}$: 4.2-fold, $A\beta_{1-42}$: 5.5-fold) and subject 2 ($A\beta_{1-40}$ and $A\beta_{1-42}$: 1.06-fold), while Aβ decreased after Friday HD sessions in both subject 1 ($A\beta_{1-40}$: 0.1-fold, $A\beta_{1-42}$: 0.1-fold) and 2 ($A\beta_{1-40}$: 0.7-fold, $A\beta_{1-42}$: 0.7-fold) shown in **Figure 1c**–**f**.

Conclusions: This is the first report of Aβ dynamics in the CSF and plasma of HD patients. While plasma levels were in similar ranges, we found high inter-individual variations of CSF levels. Different plasma-to-CSF ratios after HD may reflect individual brain Aβ pools that are accessed by HD. We corroborate previous reports demonstrating the removal of Aβ from the blood compartment by HD.

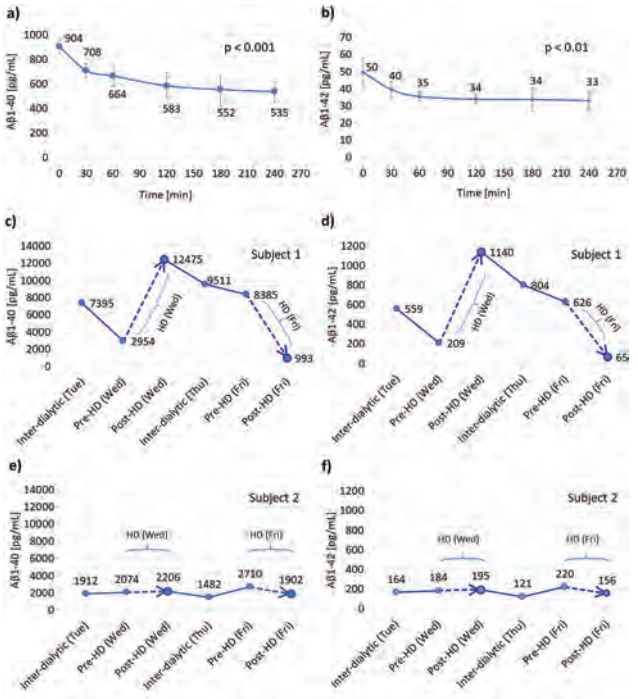

Figure 1. Values are means ± standard deviations in pg/mL. Plasma levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ from three (n=3) study subjects and a total of seven treatments are shown in **a)** and **b)**. Analysis was done by linear mixed effect model, considering random effects over time throughout the hemodialysis treatments. Individual levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ in cerebrospinal fluid (CSF) from the two study subjects who underwent ventriculo-peritoneal shunt tap are shown in **c)** CSF levels of $A\beta_{1-40}$ in subject 1, **d)** CSF levels of $A\beta_{1-42}$ in subject 1, **e)** CSF levels of $A\beta_{1-40}$ in subject 2, and **f)** CSF levels of $A\beta_{1-42}$ in subject 2.

PO0944

Circulating Microbiome and Cardiovascular Death in Patients with ESRD

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Background: Patients with end-stage renal disease (ESRD) suffer from disproportionately high cardiovascular (CV) mortality. Accumulating evidence suggests a role for the circulating microbiome (CM) in the pathogenesis of CV disease; however, little is known about its association with premature CV mortality in ESRD.

Methods: In a pilot case-control study of 17 hemodialysis (HD) patients who died of a CV event and 17 matched HD controls who remained alive during a median follow-up period of 2.0 years, we compared the levels and composition of CM, including Bacteria, Archaea, and Fungi in serum samples by quantitative PCR and 16S or Internal Transcribed Spacer (ITS) ribosomal RNA (rRNA) sequencing, respectively. Association of the CM with CV death were examined using multivariable conditional logistic regression.

Results: 16S and ITS rRNA was detectable in all (except 3 for ITS) examined patients' serum samples. Despite no significant difference in 16S rRNA levels and α diversity between cases and controls, taxonomic analysis demonstrated differential community membership between groups, with significantly greater Actinobacteria and less Proteobacteria observed in cases than controls at the phylum level. At the genus level, *Staphylococcus* was numerically higher in cases than in controls, albeit not reaching statistical significance. Proportions of Actinobacteria and Proteobacteria phyla were marginally associated with risk of cardiovascular death (adjusted ORs [95% CI], 1.12 [0.98-1.29] and 0.88 [0.76-1.02] for 1% increase, respectively; **Table**). Although circulating fungal community α diversity was significantly elevated in cases than controls, no significant association was observed with CV death.

Conclusions: Alterations of the CM may be associated with a higher risk of premature CV mortality in ESRD patients.

Funding: NIDDK Support

Association of circulating microbiome with cardiovascular death in hemodialysis patients

Characteristics	Adjusted Odds Ratio	95% CI
16S rRNA (per log10 ng/uL)	0.38	0.002 to 85.7
Shannon Index (per unit)	0.92	0.17 to 4.92
Actinobacteria (per percent)	1.12	0.98 to 1.29
Proteobacteria (per percent)	0.88	0.76 to 1.02

Model was adjusted for age, sex, race, dialysis vintage, and vascular access type.

PO0945

Dysregulation of Fibrinolytic Process Contributes to the Thrombotic and Bleeding Complications in ESRD Patients

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Background: End stage renal disease (ESRD) is a complex syndrome involving both cellular and humoral mechanisms. Both thrombotic and bleeding complications are observed which may result in cardiovascular and cerebrovascular adverse outcomes. Fibrinolytic system placed an important role in the regulation of hemostatic process. A comprehenhesive profiling of the components of fibrinolytic process may provide additional understanding of the bleeding and thrombotic complications in ESRD.

Methods: Citrated whole blood samples were collected from a cohort of ESRD patients (n=95). Normal citrated plasmas were obtained from healthy male and female individuals. These samples were analyzed for prothrombin time (PT), activated partial thromboplastin time (aPTT), prothrombinase-induced clotting time (PiCT) and thrombin time (TT) using clot based technique. Fibrinolytic parameters such as urokinase type plasminogen acticator (uPA), plasminogen activator inhibitor-1 antigen (PAI-1A), and D-Dimer were measured by using ELISA method. Funtional PAI-1 was measured by using an amydolytic method. All results were compiled as group means ± SEM and respective ratios were calculated.

Results: All of the clotting results showed varying levels of elevated values in comparison to normal plasma. uPA levels showed wide variations and were increased (1.6 fold). D-Dimer was markedly increased in the ESRD patients (11.53 fold). Both functional (1.2 fold) and antigenic (3.07 fold) levels of PAI-1 were increased. Interestingly, the PAI-1 antigen levels was much higher in contrast to the functional levels suggesting a progressive consumption of this mediator.

Conclusions: These results suggest that the overall hemostatic system in ESRD patients is dysregulated due to the imbalance of the inhibitors such as PAI-1. The persistent activation of fibrinolysis is due to the increase production of uPA which facilitates endogenous fibrinolysis resulting in the elevation of D-Dimer. The generation of fibrinolytic enzymes results in increased fibrin/fibrinogen degradation products which may contribute to the observed intrinsic and extrinsic coagulation defects as measured by the elevation of PT and aPTT. Monitoring of fibrinolytic parameters along with clotting test may be helpful in the risk stratification and prediction of adverse outcomes in ESRD patients

PO0946

Successful Treatment of Systemic Calcinosis in a Teenager on Hemodialysis

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Introduction: Systemic calcinosis is rare in pediatric ESKD patients compared to adults. The subcutaneous tissues are most frequently involved. We present teenager in whom calcinosis was detected incidentally on chest radiograph, and review its successful treatment.

Case Description: A 15 yo anuric female who had received hemodialysis(HD) for 18 months after renal transplant failure, was treated for progressive respiratory distress in the ICU. Significant history included osteoporosis, hypertensive cardiomyopathy, and renal failure since age 1. Chest-XR revealed bilateral pulmonary infiltrates and calcified lesions. Thoracic CT scan demonstrated calcified tracheal and bronchial cartilage rings. Flexible bronchoscopy revealed diffuse white/gray nodules throughout the wall of tracheobronchial tree. All cultures were negative. When notified of the finding of calcifications on CT scan, patient's mother also asked about the firm nodules in the space between patient's fingers. Dialytic phosphate (P) clearance, and non-calcium(Ca), non-aluminum(Al) based binder use were maximized, using sevelamer and lanthanum carbonate. Sodium thiosulfate and etalcalcetide were given iv post each dialysis. Dialysate Ca varied between 2.5-3 meq/L, to avoid hypocalcemic stimulation of PTH and high CaXP. Lanthanum was discontinued after 3 months, once P levels declined. Other therapies were continued for 10 months; with monthly dose adjustment. PTH level decreased and P levels normalized. Etelcalcitide was reduced to maintain normal Ca level. After 10 months, iv pamidronate was initiated to prevent further demineralization. This led to transient marked elevation in PTH. Combined therapies led to resolution of calcinosis. However, tracheobronchial calcifications have not been reassessed, since neither chest imaging nor bronchoscopy have been clinically indicated.

Discussion: Calcinosis is an uncommon, yet treatable condition in pediatric dialysis patients. Combined use of old and new therapies was successful. Adverse side effects of therapies affect dosing. Etelcalcitide often causes hypocalcemia. Thiosulfate use is associated with nausea. Lanthanum is an effective metal Ca binder, but prolonged use may lead to accumulation and systemic deposition. The emergence of new P binders: ferric citrate, sucroferric oxyhydroxide, and bixalomer will offer exciting new treatment options.

PO0947

Severe Thrombocytopenia due to Electron-Beam Sterilized Polysulfone Dialyzer Membrane Reaction

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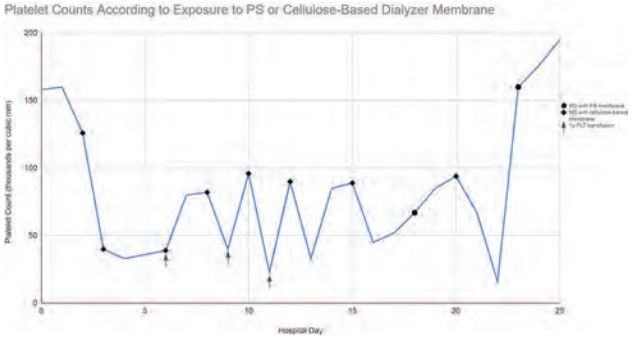
Introduction: We describe a case of severe thrombocytopenia due to reaction with an electron-beam sterilized polysulfone (PS) membrane. This phenomenon has been previously described but is rarely reported. E-beam sterilized PS membranes are classically more biocompatible than cellulose-based membranes but adverse reactions may occur as demonstrated in our case.

Case Description: A 74 y.o. woman with CKD Stage 4 and secondary hyperparathyroidism presented for evaluation of generalized weakness, anorexia, and weight loss. Her past medical history included gout, short bowel syndrome following prior bowel resection and osteoporosis. Home medications were allopurinol, calcitriol, gabapentin, fluoxetine, and mirtazapine. She was started on hemodialysis (HD) for suspected progression to ESRD. She developed progressive thrombocytopenia (Figure 1) that was worse following HD with improvement on non-HD days. Evaluation of usual culprits of thrombocytopenia was unrevealing. Reaction to the polysulfone filter was suspected and she was switched to a cellulose-based filter with resolution of her thrombocytopenia. She was dialyzed with a PS membrane on HD20 as proof of concept with recurrent thrombocytopenia following HD. She was dialyzed with cellulose-based filter thereafter with no further thrombocytopenia.

Discussion: We describe a case of PS-membrane induced thrombocytopenia. It is hypothesized that e-beam radiation may affect membrane integrity or structure, or produce intermediary products which may cause platelet activation, aggregation, and adsorption, and therefore thrombocytopenia. This entity should be considered in the differential diagnosis of patients undergoing HD who develop thrombocytopenia. Early recognition may reduce incidence of bleeding and need for blood products in these patients.



PLT counts during admission. HD days with PS membrane are denoted with a diamond label and HD days with cellulose-based membrane are denoted with a circle label. Single unit PLT transfusions are denoted with arrows.

PO0948

What Actually Happens at Home? A Data Linkage Study Between ANZDATA Registry and Sharesource

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Background: In late 2018, the Claria automated peritoneal dialysis (APD) system was introduced into Australia and New Zealand. This device provides APD in a nocturnal setting, and automatically transmits data on the treatment session delivered utilising an inbuilt SIM card to a central database (Sharesource). We linked this with clinical and demographic information from the ANZDATA Registry to allow examination of actual events and delivered treatments and alerts.

Methods: Records from Claria APD treatments delivered in 2019 were linked with corresponding ANZDATA records using probabilistic linkage. The data structure (of repeated sessions per individual) was addressed using hierarchical (random effects) models for analyses.

Results: A total of 1641 people had 314,461 APD treatment sessions recorded over 2019. There were a median 189 treatments recorded per individual. Median age of participants was 62.0 years; median time from first kidney replacement therapy was 379 days. 33% of APD sessions had 4 drain cycles, 39% had 5 cycles and 16% 6 cycles. Mean drain time was 20.9 (SD 7.9) minutes; shorter with greater cycle number. Recorded treatment events included one cycle bypass in 8% of sessions, two bypassed sessions in 8 % and thee or more in 4% of sessions. At least one manual drain in 3.8% of sessions and 0.5% of sessions were user-terminated. One patient alert was recorded during therapy during 27% of sessions, and more than one in a further 10% of sessions. Of all recorded alerts the most common were "low drain volume", "Check patient line" and "low UF", all approximately 25% of alerts. The frequency of alerts did not vary across the day of week, but did vary with age, gender and diabetes (lower among older people, females). The frequency of treatments reported on a Saturday was only 92% of that on a Tuesday. The frequency of bypass (or alerts) was not related to day of week

Conclusions: The variation in frequency of treatment by the day of week suggests "social" causes --- i.e. a "night off" is more frequent on the weekend. Either some form of treatment event or alert is present in a substantial minority of APD sessions. The relationship of these events with technique survival is important, but not yet known. In time this linked data will allow examination of events recorded during treatment with patient outcomes.

Funding: Commercial Support - Baxter Healthcare

PO0949

Evaluation and Measurement Properties of a Patient-Reported Experience Measure for Home Dialysis

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Background: There are no validated patient-reported experience measures (PREMs) for use among patients undergoing home dialysis in the United States. We sought to test the home dialysis care experience (Home-DCE) survey, a newly developed 26-item PREM, in a sample of patients from 30 dialysis facilities operated by a single dialysis organization in the United States.

Methods: Using mail and phone survey modalities, we approached 1372 patients treated with peritoneal dialysis (PD) or home hemodialysis (HD) for participation. Using results from completed Home-DCE surveys, we hypothesized multi-item scales and used factor analysis to assess model fit. We assessed scale internal consistency reliability, and assessed floor and ceiling effects for scales and individual items. We evaluated test-retest reliability using intra-class correlation coefficients (ICCs) in a subset of patients who completed the Home-DCE twice. Finally, we evaluated patient demographic and home dialysis facility characteristics (nurse-to-patient ratio, hospitalization rate, star rating, and census) associated with Home-DCE scores.

Results: Overall, 495 eligible patients completed at least one survey (response rate 36%), including 399 treated with PD and 88 treated with home HD; 7 did not indicate their modality. Of these, 49 completed the Home-DCE in Spanish and 61 completed a second survey within 30 days. Analyses supported one 12-item composite scale with high internal consistency reliability: Quality of Home Dialysis Care and Operations (Cronbach alpha = 0.85). This scale was strongly correlated with overall staff rating (r = 0.73) and overall center rating (r = 0.70). ICCs in the test-retest population were 0.73 for the Quality scale, 0.88 for the overall staff rating, and 0.9 for the overall center rating. Patient demographic and dialysis facility characteristics were not consistently associated with Quality scale scores or overall staff or center ratings.

Conclusions: The Home-DCE includes one statistically robust multi-item scale and two global rating scores, and is an informative tool to evaluate patient-reported experience of care for home dialysis. Additional studies are needed to further evaluate the Home-DCE among different dialysis care providers, and to assess the feasibility of electronic administration.

Funding: Private Foundation Support

PO0950

Feasibility of a Staff-Assisted Peritoneal Dialysis Program in the United States: Results of a Pilot Study

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Background: Staff-assistance can support patients to utilize peritoneal dialysis (PD) and is available in many countries but not in the US. We report on the initial experience from a feasibility study for staff-assisted PD in the US.

Methods: An assisted PD program was initiated at one home dialysis center in Aug 2020, and expanded to a total of 6 centers by Feb 2021. Home assistance by non-registered nurse staff was offered to patients with barriers to self-care with the aim to support patients and families to become independent from staff assistance.

Results: Participating centers referred 33 patients (range: 0 – 16 referrals/center). 16 referrals were cancelled [admission from HD to the home program cancelled (3 referrals), transfer from PD to HD prior to starting staff assistance (5), resolution of the issue requiring assistance(7), and death (1)], 3 referrals are pending, and 14 patients received staff assistance at home. Of those who received assistance, median age was 72 (range 43-87) years, and 8 were new to PD. Indications included: physical weakness (10 patients), cognition (8), and psychosocial issues (7). One prevalent PD patient required assistance following a PD peritonitis episode. Anxiety and lack of confidence were common among referred patients. Staff member attending the patient's home assisted with removal and replacement of PD bags (5 patients), machine setup (9), dressing of exit site (7), checking the blood pressure (2), and other requests (8) such as documentation. Assisting staff worked with patients to build problem-solving skills, gain self-confidence, and arrange a safer home environment. Median length of time on the service was 17 (IQR: 6 – 23, range: 2 – 49) days, and median number of visits was 15 (range: 4 – 38, IQR: 5 – 26) visits/patient. Median visit duration was 64 (IQR: 55 – 90) minutes. Seven of the patients who finished are more than 90 days after starting assistance. Six of them remain on PD and one patient transferred to HD.

Conclusions: Staff-assistance can support patient transition to, and maintenance on, PD. Such programs are operationally feasible with non-RN staff in the US and should be supported by Medicare and regulatory agencies.

PO0951

Increasing the Prevalent Peritoneal Dialysis Patient Population Can Be Challenging

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Background: Peritoneal dialysis (PD) can provide better quality of life for patients requiring renal replacement therapy compared to in centre dialysis. It can be challenging to increase prevalent patient population on PD after a certain number is reached. We did a retrospective analysis to assess the turnover of patients on PD over a 8 year period and to understand the reasons for a stagnant prevalent PD population in the renal unit in Royal Derby Hospital.

Methods: Electronic database (Vital data, ICM) were used to document the number of patients starting and stopping PD each year from 2013 to 2020. The reasons for stopping PD and duration of technique survival were noted. If technique failure resulted in conversion to haemodialysis (HD) for more than 3 months, the cause of the failure was also noted. Patients who converted to HD for less than 3 months were excluded from the study.

Results: The number of patients starting (n=324) and dropping off PD (n=322) was similar for each year between 2013 to 2020 .Modality switch to haemodialysis accounted for 40-60% of patients stopping PD, followed by death (15-30%) and patients receiving renal transplantation (10-35%). Modality switch to haemodialysis was primarily due to infection (60- 80%), poor clearances and ultrafiltration failures (10-30%), social reasons (10-15%). Among patients who switched to HD due to an infection, peritonitis accounted for 75-85% of the cases followed by exit site and tunnel infections (15-25%). Introduction of Kidney quality improvement project in 2018 reduced numbers switching from PD to HD, with no affect on prevalent patient population due to decrease in incident patient population.

Conclusions: Increasing the prevalent population on PD can be challenging even with a high incident PD population. Having mechanisms which prevent infections, early identification and treatment of infections may help improve prevalent PD population.

PO0952

Disparities in Kidney Care: Where Care Needs to Be Equal

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Background: Disparities in kidney care are widespread and gaining more attention. This research focuses on care differences that existed between home hemodialysis (HHD) and in-center hemodialysis (ICHD) patient from 2017 to 2020.

Methods: Using a HIPAA-compliant, online chart review tool, nephrologists submitted de-identified clinical and non-clinical demographic information beginning at the time of patient referral and concluding with details from the most recent visit. These data, from 2017 through 2020, were then merged with the physician demographic profile and attitudinal responses. The full data set of 4,062 patient charts submitted from 1,021 nephrologists was analyzed in SPSS.

Results: Given the new efforts to promote home modalities, nephrologists are following status quo and continue to initiate new dialysis patients on in-center hemodialysis. Nephrologists' current patient loads consist of, on average, 5 HHD patients and 96 ICHD patients. On average, they initiate one new patient on HHD compared to 17 new ICHD patients per year. When comparing HHD and ICHD patient charts there are substantial differences between the two patient types. HHD patients tend to be Caucasian and from higher education and socioeconomic levels: 52% are Caucasian and 25% are African American, 37% have some college (14% have an advanced degree), and 67% are middle or upper class. Conversely, ICHD patients tend to be more diverse (40% are Caucasian, 40% are African American), less educated (24% have some college and 5% have an advanced degree) and from lower socioeconomic classes (44% are lower or lower-middle class). Further, 40% of patients on home modalities are employed part- or full-time, versus 18% of patients on ICHD. Insurance coverage – both at dialysis initiation and current – influence modality choice as well. Notably, 70% of patients on home modalities were followed prior to dialysis, whereas only 48% of patients on ICHD were followed pre-dialysis, and patients on home modalities are substantially more likely to be on the transplant list versus ICHD patients (62% versus 37%).

Conclusions: Disparities in care exist between patients receiving home hemodialysis versus in-center home hemodialysis. As kidney care continues to evolve, physicians will need to account for these differences in their treatment paradigms to ensure they provide comparable care across patients.

PO0953

Characteristics and Treatment Patterns of Dialysis Providers Randomly Assigned to the Medicare ESRD Treatment Choices Model

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Background: In January 2021, Medicare's End-stage Renal Disease Treatment Choices (ETC) model randomly assigned 30% of US dialysis facilities to receive financial bonuses and penalties on the basis of home dialysis use, waitlisting, and living-donor transplantation among their patients, compared with benchmarks from non-ETC-assigned facilities. We assessed whether sampling variance may influence ETC performance assessments by comparing pre-ETC treatment use among ETC-assigned and non-assigned facilities.

Methods: We compared rates of transplantation (living and deceased donor transplant, waitlisting) and home dialysis use (peritoneal dialysis, home hemodialysis) at 12 months among patients with incident kidney failure during July 2014-June 2018 in future ETC and non-ETC dialysis facilities (n=7527 facilities, n=192755 patients). In logistic regression models with region random effects and Bonferroni-adjusted robust standard errors, we assessed the adjusted relationships between ETC-assignment and facility characteristics (ownership, home dialysis offerings, staffing), patient case-mix (demographic, clinical, and insurance characteristics; mortality), and area-level socioeconomic status (e.g., median household income).

Results: Prior to ETC implementation, patients in ETC-assigned facilities had 22% (0.71 pp) higher rates of living-donor transplant receipt (p=0.005), 24% (0.89 pp) higher rates of deceased-donor transplant receipt (p<0.001), and 9% (3.3 pp) lower mortality rates (p<0.001) at one year versus in non-assigned facilities. Rates of home dialysis use were similar. Relative to non-assigned dialysis facilities, ETC-assigned facilities were 21% (2.0 pp) more likely to be owned by a small for-profit chain and 16% (5.8 pp) more likely to be owned by the second largest dialysis organization (p<0.001). Adjusting for other factors, dialysis facilities were more likely to be ETC-assigned if their patients were younger and if they had a lower percentage of patients who were Hispanic (both p<0.001).

Conclusions: Due to sampling variance, ETC-assigned facilities may be disproportionately likely to receive bonuses (vs penalties) under the model, even if they do not increase home dialysis treatment and transplant receipt among their patients.

Funding: NIDDK Support

PO0954

Novel Transitional Care Unit Design Achieves >50% Home Dialysis Choice in Incident ESRD Patients

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Background: In 1983 Eschbach reported that a 6 station Home Dialysis (HD) Oriented Unit at Northwest Kidney Center had a 62% success rate in incident ESRD pts choosing HD.The RVCARE study of intensive in center HD education during routine thrice weekly dialysis had 38% of pts chose HD. Satellite Dialysis found that with their Transitional Care Unit (TCU) 30 % of pts chose HD.

Methods: We designed a 6 station dedicated TCU staffed with the added benefit of its main teaching nurse having 4 years each of being a home hemodiaysis (HHD) & peritoneal dialysis (PD) nurse coordinator. The unit contains 3 NxStage & 2 Liberty Select Peritoneal cyclers. Pts are dialyzed 4 times weekly on the Nxtage or eventually the cycler. Added support is given by dialysis nurses trained in HHD & PD as are the social worker and dietitian educators. Intensive education with a defined curricula in all forms of HD are given including shared decision making with families. A medical director highly skilled in HD therapies also re-enforces the education delivered by the entire team every week. All 67 of our pts starting dialysis since July 2020 received standard dialysis education with several phone or virtual education sessions from our outpatient CKD coordinator, description of the TCU, plus a home visit by one of our HD coordinators.

Results: Since July, 2020 67 pts have started ESRD therapy, with 35 choosing not to enter the TCU and 32 choosing the TCU. Only 7 of 35 pts educated the standard way chose HD, 4 PD & 3 HHD but 17 TCU pts out of 32 chose HD, 10 HHD & 7 PD, 53%, p=.004 compared to standard education. There were no signiicant differences in duration of nephrology followup, age, sex or causes of ESRD between the 2 groups.

Conclusions: We conclude: The success of our TCU is due to it design using: 1) Pre-ESRD educaton about the benefits of starting dialysis in a TCU & 2) Most importantly having a skilled and experienced home HD and PD nurse coordinator to be the main educactor and pt champion for both HHD adn PD. 3) Utilizing a HD skilled medical director & social worker using shared decision making adds confirmational education on the benefits of HD.

Funding: Clinical Revenue Support

PO0955

Home Hemodialysis with the Tablo System: The First 1000 Real-World Treatments

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Background: The Tablo® Hemodialysis System is an all in one, easy-to-learn device capable of achieving clearance goals in as little as three treatments per week. It features integrated water purification, on demand dialysate production and two-way wireless data transmission. Tablo obtained FDA clearance for home hemodialysis (HHD) in March 2020. Approval was based on a prospective, crossover trial (in-center and at home dialysis) where Tablo successfully met all safety and effectiveness endpoints, reported high rates of treatment adherence and patient retention, with greatly reduced training time (NCT02460263). The objective is to report on the first 1,000 treatments performed on Tablo by patients at home in the real-world.

Methods: Incident and prevalent patients currently performing in-center dialysis, PD, or HHD were initiated on Tablo at participating Home Dialysis programs. Patients underwent training by facility nurses on the Tablo device prior to beginning treatments at home. Data on the first 1000 treatments was obtained wirelessly via Tablo's data platform along with corresponding patient training data.

Results: The first 1000 treatments occurred in 20 patients, with a mean follow-up duration of 3.4 months. Patient training on Tablo was completed over an average of 7.4 training days. Patient retention was 100% with no patients opting out of HHD with Tablo. Mean prescribed treatment time was 3.2 hours with a mean frequency of 3.7 treatments

per week. Mean total UF per treatment was 1.9 L. Mean UF rate per treatment was 7.3 mL/kg/hr. Treatment adherence was 93%, with 95% of treatments completing within 10% of prescribed time. The mean number of clinically significant alarms per treatment was 1.0 (± 3.0), with an average time to resolution of 10.7 (± 18.5) seconds.

Conclusions: Results from the Tablo IDE demonstrating reduced training time, increased treatment adherence, high treatment success rate and a low occurrence of treatment alarms are reproducible in the real world at a frequency of 3-4 treatments/week. This data supports that Tablo is capable of successfully achieving clinical goals while reducing the overall patient burden often associated with HHD.

Funding: Commercial Support - Outset Medical, Inc.

Tablo Home Hemodialysis Data

Patient Training (Mean ± SD (n, median, min-max))		Treatment Data (Mean ± SD (n, median, min-max))					Treatment Success / Adherence (% (n))		
Training Time (hrs)	Training Sessions (days)	Prescribed Weekly Dialysis (hrs/week)	Patient Weight (kg)	Actual UF Volume (L / treatment)	Actual Treatment Time (hours)	Actual UF Rate per treatment (mL/kg/hr)	Treatment Success	UF Success	Treatment Adherence
27.4 ± 11.1 (n=12, 4.0, 12.5 - 43.5)	7.4 ± 1.5 (n=12, 8.0, 4 - 10)	3.7 ± 0.6 (n=20, 4.0, 3.0 - 5.0)	89.8 ± 25.4 (n=1000, 87.3, 41.3 - 153.5)	1.93 ± 0.98 (n=1000, 2.0, 0 - 5.2)	3.2 ± 0.8 (n=1000, 3.0, 0.4 - 8.0)	7.3 ± 4.1 (n=1000, 7.0, 0 - 24.5)	95.4% (954/1000)	92.2% (922/1000)	93.2% (1000/1073)

PO0956

Recent Trends in Utilization of Home Dialysis Modalities, Overall and by Duration of ESKD

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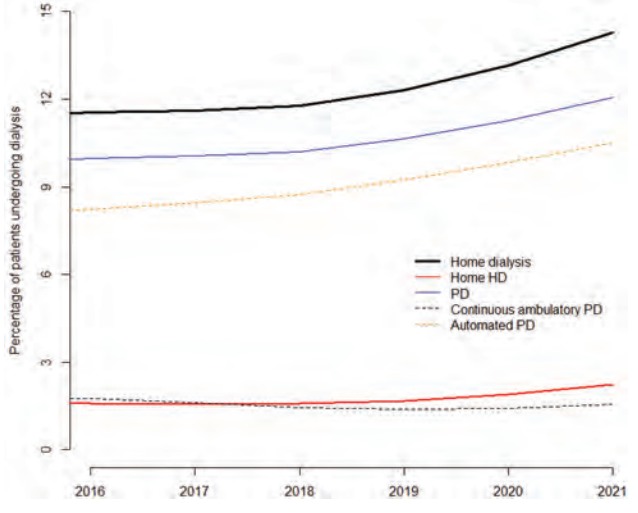
Background: The Executive Order on Advancing American Kidney Health and the End Stage Renal Disease Treatment Choices payment model have focused attention on increasing utilization of home dialysis. We assessed trends in home dialysis utilization between 2016 and 2021, including variability in trends among strata defined by duration of end stage kidney disease (ESKD).

Methods: We analyzed dialysis facility admission and discharge data extracted from the End Stage Renal Disease Quality Reporting System in May 2021. During the first epidemiologic week of each year from 2016 to 2021, we identified patients undergoing maintenance dialysis at the beginning of the week. For each patient, we identified the current dialytic modality. We estimated trends in utilization of each modality, overall and by duration of ESKD at the beginning of the week (<2, 2-4, 5-9, and ≥10 years).

Results: Between 2016 and 2021, home dialysis utilization increased from 11.5% to 14.3%, with the majority of growth occurring since the beginning of 2019 (figure). Concurrently, HHD utilization increased from 1.57% to 2.23%, whereas PD utilization increased from 10.0% to 12.0%. Among patients with ESKD duration <2 years, home dialysis utilization increased from 14.8% in 2016 to 20.0% in 2021, with >90% of utilization in this stratum due to PD. Among patients with ESKD duration of 2-4 years, home dialysis utilization increased from 11.7% in 2016 to 13.7% in 2021. Among patients with ESKD duration ≥10 years, home dialysis utilization hovered around 9%, although HHD utilization reached a high of 3.65% in 2021, representing nearly 40% of home dialysis utilization in this stratum.

Conclusions: Growth of home dialysis utilization has accelerated since 2019, with greater absolute growth of PD and greater relative growth of HHD. Longer duration of ESKD is associated with lower utilization of PD, but higher utilization of HHD.

Funding: NIDDK Support



PO0957

The Impact of Seasonality on Crash Starts and Home Dialysis Use

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Background: The US has made a concerted effort to increase home dialysis use. Dialysis "crash starts," when patients emergently initiate dialysis in the hospital, are a barrier to home dialysis because they often preclude successful planning. We studied whether the season of the year was associated with crash starts and with home dialysis use among incident patients with end-stage kidney disease (ESKD).

Methods: From the United States Renal Data System, we identified all adults with at least 30 days of continuous Medicare Parts A and B coverage initiating dialysis from 2007-2017. We identified home dialysis use and whether patients were hospitalized within 14 days prior to the first outpatient dialysis treatment (i.e., "crash start"). Using multivariable logistic regression, we studied the association between season, likelihood of crash start, and starting dialysis at home. We used a Cox model to study whether crash starts were associated with **ever** using home dialysis in the first year. We adjusted for demographics, comorbidities, facility and geographic characteristics, and year of dialysis start.

Results: After adjusting for confounders and year of dialysis start, patients were less likely to start dialysis in the winter versus the summer (OR: 0.86, 95% CI: 0.82, 0.90). Conversely, patients were more likely to "crash start" into dialysis in the winter versus the summer (OR: 1.14, 95% CI: 1.11, 1.17). Patients with a crash start were substantially less likely to initiate with home hemodialysis (OR: 0.16, 95% CI: 0.15, 0.16) and were less likely to ever use home dialysis in the first year (HR: 0.41, 95% CI: 0.40, 0.42). We observed seasonal heterogeneity in the admission diagnoses. Hospitalizations due to pneumonia, myocardial infarction, and congestive heart failure were 1.6, 1.4, and 1.3 times more likely to occur in the winter versus the summer, respectively. Hospitalizations due to diabetes, complications of devices, and chronic kidney disease were 1.05, 1.08, and 1.08 times more likely to occur in the winter, respectively.

Conclusions: We observed more dialysis crash starts in the winter and a subsequent decrease in home dialysis use in the first year. Winter hospitalizations were more often acute and due to cardiac and pulmonary etiologies. Clinicians should remain vigilant that patients may be prone to crash starts in the winter and should accelerate dialysis planning accordingly.

Funding: NIDDK Support

PO0958

Comorbidity Is Not Associated with Home Dialysis Choice

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Background: Over the past 15 years the proportion of Dutch home dialysis patients has decreased markedly. In addition, the rate of home dialysis varies significantly among centers. It is unclear whether this is the result of increased comorbidity, other patient characteristics or because dialysis centers perceive barriers for home dialysis differently. Our aim was to investigate the association between comorbidity and home dialysis.

Methods: The DOMESTICO study is a multicenter retrospective cohort study on home dialysis and randomly selected in-center hemodialysis patients. Comorbidity data was collected of patients who started dialysis between 2012 and 2017, including those who had previously received dialysis or obtained a kidney transplant. Patients who stopped dialysis or died within 30 days were excluded. Comorbidity was assessed with the Charlson comorbidity index (CCI). Home dialysis was defined as any peritoneal dialysis or home hemodialysis treatment during follow-up. Patients were followed until kidney transplantation, wish to stop dialysis, death or study end on 1 January 2017. Multivariable logistic regression analysis was used to assess the association between comorbidity and home dialysis, with a mixed model approach to adjust for dependency of patients within dialysis centers and for other patient characteristics including age, sex, and body mass index (BMI).

Results: Of 1358 included patients, 46% were treated with home dialysis. A high comorbidity score (CCI ≥5) was associated with a lower probability to receive home dialysis compared to patients without comorbidities (unadjusted OR 0.74, 95% CI 0.54–1.00). After adjustments for patient characteristics including age and BMI, there was no association between comorbidity and home dialysis. Only obese patients (BMI ≥30 kg/m^2) with comorbidities had a significant lower likelihood to receive home dialysis compared to obese patients without comorbidities (medium comorbidity score (CCI 3-4) adjusted OR 0.40, 95%CI 0.18–0.86 and high comorbidity score (CCI ≥5) adjusted OR 0.43, 95%CI 0.20–0.93).

Conclusions: Comorbidity is not associated with home dialysis, after adjustment for several confounding factors including age and BMI. Future studies should aim at unraveling the center-specific characteristics that play a role in dialysis treatment.

Funding: Commercial Support - Nierstichting/Dutch Kidney Foundation = non-profit organisation. Grant no: A2D4P02.

PO0959

Reducing Routine Bloodwork in Home Dialysis Patients: A Quality Improvement Initiative

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Background: There is a paucity of evidence for routine bloodwork frequency in maintenance dialysis patients to assess and manage complications such as anemia and mineral bone disease (MBD). Recent studies showed that decreasing the frequency in conventional in-center hemodialysis (ICHD) patients had no negative impacts. Given the strain on lab services from the COVID-19 pandemic, Alberta Kidney Care-South (AKC-S) decreased the frequency of routine labs from monthly to every 2 months in home hemodialysis (HHD) and peritoneal dialysis (PD) patients. We studied the effect of this change on patient outcomes.

Methods: We retrospectively compared prevalent home dialysis patients (>3 months) in AKC-S over two 6-month periods: a) Pre-pandemic May-Oct 2019 and b) Pandemic May-Oct 2020. Primary outcomes were number of routine bloodwork days and percentage of patients within target for anemia (hemoglobin, iron saturation) and MBD (calcium, phosphorus, parathyroid hormone). We also compared hospitalizations, mortality, technique failure (defined as transition to ICHD for >60days), and cost.

Results: There were 366 home dialysis patients in 2019 (270 PD, 96 HHD) and 400 in 2020 (296 PD, 104 HHD). The number of routine bloodwork days decreased in 2020 compared to 2019 ($p<0.01$) (Fig 1). The proportion of patients who achieved anemia (33% vs 35%, p=0.44) and MBD (34% vs 28%, p=0.1) targets was similar. There was no difference in the number of hospitalizations (155 vs 141, p=0.34), deaths (13 vs 17, p=0.71) or technique failure (8% vs 5%, p=0.06). Projected cost savings were $102 per patient year from reduced labs.

Conclusions: AKC-S reduced the frequency of routine labs during the pandemic in home dialysis without negative consequences on patient biomarkers or outcomes. Our study suggests that bloodwork frequency in home dialysis patients may be safely reduced.

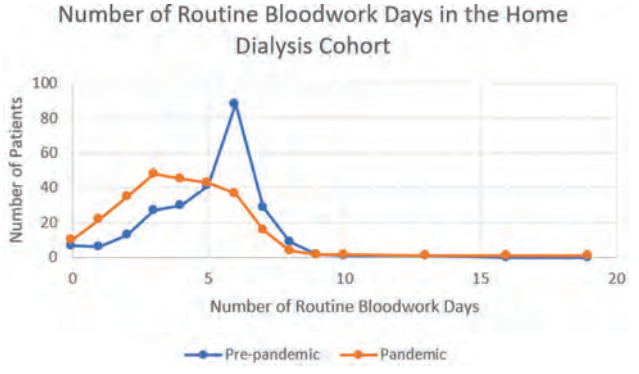

Figure 1. Distribution of the number of routine bloodwork days Home Dialysis patients had during the pre-pandemic (blue) and pandemic (orange) periods.

PO0960

On-Demand Automated Peritoneal Dialysis Solution Generation

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Background: While automated peritoneal dialysis (APD) is an effective treatment for kidney failure, ordering, delivery and storage of supplies can be challenging. The APD Solution Generation System (SGS) allows for dialysate solution generation using tap water in a patient's home with fewer supplies (Figure 1).

Methods: A 12-week single-arm, prospective, descriptive study was conducted with in-home APD patients. Patients were screened, trained and treated with the SGS. Endpoints included testing the final product against specifications for Dianeal and water purification ISO Standard 13959 and measuring PD adequacy. Adverse events and device deficiencies were collected.

Results: 22 patients were enrolled; 14 patients completed the study. Demographics are shown in Table 1. See Figure 1 for primary efficacy and safety endpoint results. All tested post-sterilization filter and final dialysis solution samples passed. Missing data for water purity attributed to only 56.9% of samples passing. Mean (SD) change from baseline for Kt/V was -0.15 (0.370). There were 2 peritonitis events (0.43 episodes per patient-year), 1 occurring in a patient with HIV. There were no safety signals.

Conclusions: The SGS has the technical capability to accurately and safely generate dialysate at home using tap water. Logistical challenges with lab sampling require further exploration to understand the impact in future trials and real-world settings. Lessons learned from the study allow for transition of the device to future development.

Table 1. Demographics (n=22)

Age (Mean ±SD)	61.9 ±13.7
Female (n(%))	14 (63.6)
Black (n(%))	7 (31.8)
Hispanic or Latino (n(%))	2 (9.1)
Baseline Kt/V_{urea} (Mean ±SD)	2.4 ±0.6

Figure 1. APD Solution Generation System and Main Results

PO0961

SmartPD™ Automated Peritoneal Dialysis System as a New Sophisticated Choice for Urgent Integration in Replacement Therapy for a Patient with ESRD

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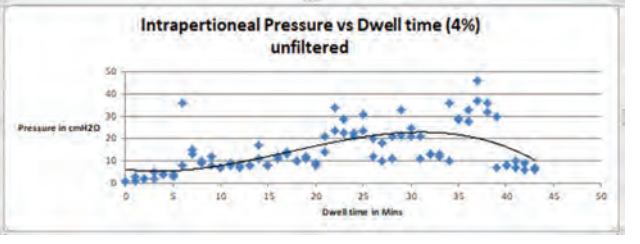
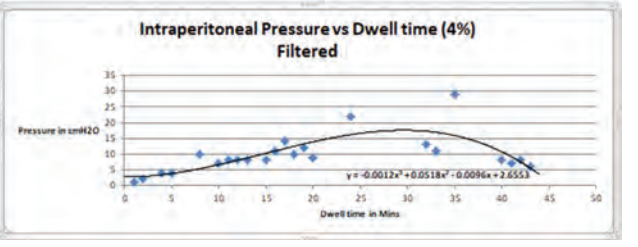
Introduction: Peritoneal dialysis (PD) is used to treat approximately 11% of dialysis patients globally despite wishes for 30%, due to Covid-19 pandemic. Expanded use of PD is impacted by clinician experience and confidence with "efficient", and "in home friendly" automated peritoneal dialysis (APD) system.

Case Description: A 60 years old lady presented from a remote island -under Covid-19 pandemic- with uremic features and started APD with *SmartPD*™ (Newsol technologies). *SmartPD*™ continuously monitors the intra-peritoneal pressure (IPP) during the Dwell. It can use this information to (a) determine optimal fill volume (b) automatically determining the optimal time to infuse or remove the dialysate from the peritoneum cavity (Fig 1a,b) and (c) records and provides UF transport characteristics (Fig 1a,b). From this composite data stream additional information can be evaluated or derive to determine the clinical health of the Peritoneal cavity. We noticed rapidly improvement in the metabolic profile and volume status (Bioimpedance measurement). Using the ability of SPD to independently adjust the dialysate concentration, number of exchanges and the dwell duration of each exchange we establish a best fit treatment time of typically 9-10 hours, with tidal volume 900 mils, 2% concentration over 9 cycles (40 mins a cycle). Our patient was under evaluation every month and today six months since starting APD with *SmartPD*™ she is in excellent condition, with no peritonitis episodes, zero incidence of overfill and minimal drain pain.

Discussion: *SmartPD*™ enables the formulation of prescribed dialysate at the point-of-care, maximizes dialysis performance, and optimizes treatment protocol. Remote monitoring capability by *SmartPD*™ allows remote supervision and management, an efficient choice especially in Covid-19 times.





PO0962

Animal Trial of Sorbent Cartridge for Portable Artificial Kidney (PAK)

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Background: The NextKidney/Dialyss HD Sorbent Cartridge (SC) uses a novel type of sodium-neutral sorbent to regenerate spent dialysate for standard hemodialysis (HD) therapies. The SC is intended to be used with the NextKidney sorbent HD device, where it produces fully physiological dialysate meeting today's industry standards. We tested the safety and efficacy of the sorbent system in a total kidney failure pig model. The animals were maintained exclusively on sorbent HD for up to 2 weeks.

Methods: Three highly uremic pigs (60–75Kg) underwent a total of 14 alternate-day, 4h sorbent HD therapy sessions. Total renal failure was induced via bilateral renal artery embolization (pig #1), or bilateral laparoscopic ligation of renal arteries (pigs #2 and 3). A palindrome catheter provided blood flow rates of 200 – 300mL/min. A hemoperfusion machine was used for the blood circuit, coupled with a prototype device controlling the dialysate circuit. Dialysate was continuously purified in the SC at a flow rate of 300 mL/min. Therapy efficacy and mass balances were calculated from blood and dialysate samples collected before and after the dialyzer at specific time points.

Results: The animals tolerated the therapies well. The incision site at the femoral artery of pig #1 re-opened on day 5 after surgery, resulting in internal bleeding and loss of the animal. Fourteen 4hr dialyses were averaged to calculate toxin removal efficacy and mass balances. The average clearances for urea, creatinine and phosphate were 139, 146 and 141mL/min, respectively. Dialysate sodium and bicarbonate concentrations remained within the permissible deviations of +/-5% and +/-25%, respectively.

Conclusions: The biocompatibility of the sorbent system has been confirmed in fourteen 4h HD therapies conducted on three highly uremic pigs. The sorbent system was able to maintain the highly uremic animals. There were no severe adverse events related to the sorbent HD therapy. We currently plan to proceed to a first-in-human trial to evaluate the safety and efficacy of the sorbent cartridge for human use.

Funding: Commercial Support - Dialyss Pte Ltd and Neokidney B.V.

Average Dialysate Concentrations

Solutes	Spent Dialysate [mmol/L]	Regenerated Dialysate [mmol/L]	Deviation [%]
Sodium	138.0	139.3	0.94
Bicarbonate	31.3	35.2	12.4
Chloride	102.6	103.8	1.24

PO0963

Thirty Days of Maintenance Peritoneal Dialysis Using a Sorbent-Based Automated Wearable Artificial Kidney (AWAK) PD Device in a Porcine Model

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Background: In sorbent-based PD, spent dialysate is processed and clean dialysate is re-introduced into the abdomen. Our aim was to determine if AWAK dialysis can maintain euvolemia and biochemistry for 30 days in a porcine model.

Methods: The study was conducted in a 5/6 nephrectomised pig (Sus Scrofa, male). Post nephrectomy, the animal was treated with CAPD (14 weeks) before commencing sorbent-based PD for 7 hour per day with initial fill of 2L 1.5% Dianeal for 30 consecutive days. Thereafter, the animal was maintained on standard of care (SOC) for 3 days (5x2L exchanges over 10 hour APD, with 1L last fill, 2.5% Dianeal).

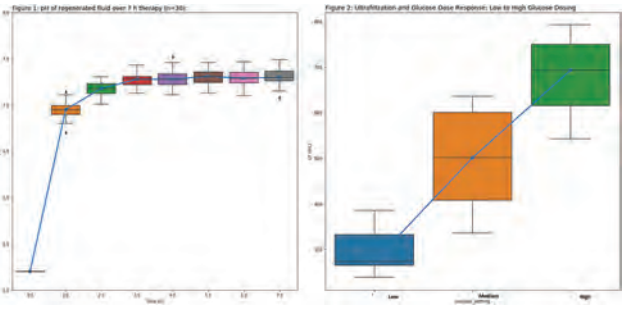
Results: Stable serum concentration of toxins, electrolytes and inflammatory markers were noted during AWAK therapy (Table); with no significant change after switch to SOC. pH of regenerated dialysate was consistent with biocompatible solutions (figure 1) and appropriate change in ultrafiltration was observed in response to glucose infusion (figure 2).

Conclusions: AWAK PD therapy successfully treated a CKD animal model for 30 days, without adverse impact on volume status or clinical parameters. Future long-term human studies are needed for device enhancement.

Funding: Commercial Support - AWAK Technologies Pte Ltd

	Day 1 [AWAK]	Day 30 [AWAK]	Mean (SD) [AWAK]	Median (IQR) [AWAK]	Mean (SD) [SOC]	p-value #
Urea (mmol/L)	7.5	7.9	8.5 (0.6)	8.6 (1)	8.9 (0.72)	0.29
Creatinine (µmol/L)	267.5	287.5	282.5 (9.9)	283 (14.4)	296.6 (4.8)	0.38
Phosphate (mmol/L)	2.57	2.72	2.6 (0.1)	2.6 (0.2)	2.6 (0.04)	0.83
B2M (µg/L)	317.5	266.5	293.6 (17)	297.5 (27.7)	285.3 (15.0)	0.24
Sodium (mmol/L)	142.5	145	144.6 (1.4)	144.8(1.5)	145.6 (1.52)	0.87
Potassium (mmol/L)	4.4	4.8	4.6 (0.18)	4.6 (0.36)	4.8 (0.2)	0.19
Chloride (mmol/L)	100	101	101.2 (1.0)	101 (1.4)	100.1 (0.2)	0.01
Bicarbonate (mmol/L)	34.6	34.1	34 (1.0)	34 (1.2)	34.8 (1.55)	0.97
Calcium (mmol/L)	2.41	2.45	2.4 (0.04)	2.4 (0.1)	2.47 (0.02)	0.19
Magnesium (mmol/L)	1.09	1.13	1.1 (0.05)	1.1 (0)	1.14 (0.04)	0.29
CRP	0.45	0.35	0.36 (0.08)	0.4 (0.1)	0.28 (0.05)	0.25
WBC (x10^9) g/L	13.3	8.8	9.6 (1.7)	9.4 (0.9)	8.85 (0.20)	0.84
Hb (g/dL)	8.4	11.4	10.7 (0.8)	10.9 (1.0)	11.2 (0.65)	0.93

#last 3 days data of AWAK and SOC compared



PO0964

Smartphone Application to Assist Peritoneal Dialysis Patients for Timely Detection of Peritonitis

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Background: Timely detection of peritonitis in patients undergoing peritoneal dialysis (PD) is critical to lower the risk of catheter loss, morbidity and mortality (Muthucumarana, 2016). Current practice of screening potential peritonitis events at home relies on patients' visual detection of turbid spent dialysate and symptoms recognition. To assist patients with the timely capture of a potential peritonitis episode, we developed a smartphone app, which uses light detection to quantitate cloudiness and estimate white blood cell (WBC) count in PD effluent (PDE).

Methods: The app uses the built-in light sensor and compares measurements taken from the ambient light ($L_{ambient}$) and light through PD bags (L_{bag}) to estimate dialysate cloudiness. PDE samples were obtained as part of two IRB-approved clinical studies over a period of 6 months. Cloudiness of each sample was measured 3x with the app. Cloudiness (in %) was calculated as $(1 - L_{bag} / L_{ambient}) * 100$. WBC were counted using a hematology analyzer (Horiba 80XL).

Results: Patients maintained a stable baseline cloudiness of 2-5% (Fig 1). A peritonitis episode (subject PDMET0002) increased the cloudiness to 40%, which is 32 percentage points over the patient's peritonitis-free baseline. One suspected peritonitis sample (albeit WBCs <100 cells/mL) showed slightly higher cloudiness than non-peritonitis samples (Fig 2).

Conclusions: Our smartphone app can distinguish peritonitis from normal PDE samples. Smartphone-enabled detection of cloudiness in PDE samples using light transmission is possible and has the potential to easily monitor and diagnose patients at risk for peritonitis. Studies to define diagnostic performance in a large patient cohort are underway.

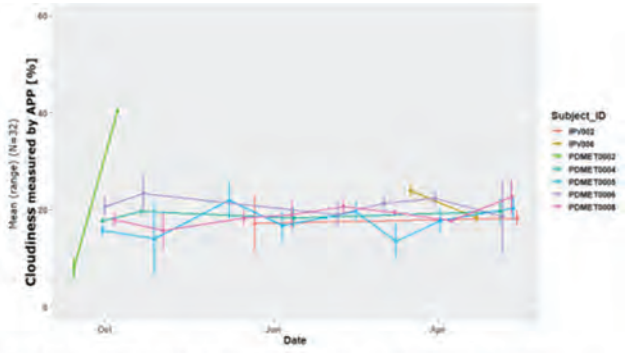

Figure 1: Mean (range) cloudiness for spent peritoneal dialysate collected repeatedly in 7 subjects over 6 months (N=32). Note the increased cloudiness during a peritonitis episode (subject PDMET0002).

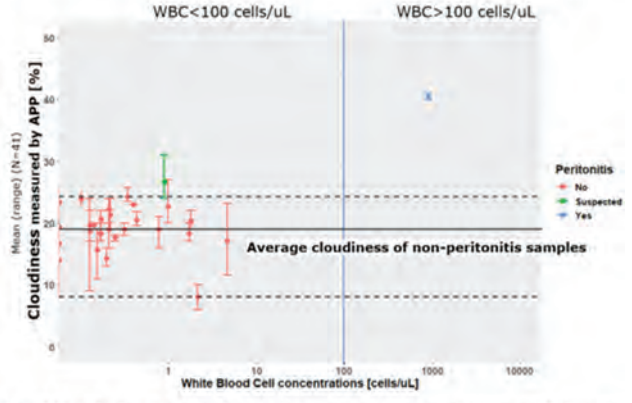

Figure 2: Mean cloudiness % measured by the smartphone app in spent peritoneal dialysate stratified according to white blood cell (WBC) concentration (N=41).

PO0965

Remote Monitoring of Patients with Automated Peritoneal Dialysis May Improve Clinical Outcomes: Analysis by Competing-Risk Regression Models

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Background: Current information technologies allow remote monitoring (RM) of patients on automatic peritoneal dialysis (APD) and the adoption of proactive behaviors to prevent complications and improve treatment quality. We analyzed the effect of RM-APD on survival and preventable complications through a controlled clinical trial.

Methods: In a two-branched cluster RCT, hospitals with >100 prevalent, >50 new patients per year, and >5 years APD experience were randomly assigned to perform RM-APD or conventional APD with equivalent APD-equipment in adults beginning APD. The primary outcome was a composite index (CI) of death, first adverse event (AE) or first hospitalization. Secondary outcomes were the same variables considered individually and for their specific causes. All-cause and cardiovascular disease (CVD) mortality risk and AEs were analyzed with competing-risk regression with transplantation as competing risk.

Results: Eleven hospitals per arm were included and 815 patients were followed-up by at least one year, 417 using RM-APD and 398 on APD. Patients in hospitals using APD reached earlier the CI as well as its individual components. Patients with APD as compared to RM-APD were older, more inflamed, and had higher all-cause and CVD mortality. In competing risk analysis, after adjusting for age, sex, presence of smoking, hypertension, CVD and diabetes, APD as compared with RM-APD associated with higher subdistribution hazard ratio (sHR) for *all-cause mortality* (sHR 1.79, 95%CI (1.15-2.81); p=0.01), *CVD-related mortality* (sHR 2.21, 95%CI (1.07-4.58); p=0.03), and *AE* (sHR 1.74, 95% (1.34-2.25); p=0.001).

Conclusions: Use of RM-APD may improve survival and prolong the time to first AE and hospitalization in comparison with APD, suggesting that RM-APD may improve clinical outcomes in APD patients.

Funding: Commercial Support - Baxter

PO0966

Peritoneal Dialysis Discontinuation: Trends and Risk Factors

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Background: Increasing use of dialysis home modalities among ESRD patients is a Centers for Medicare and Medicaid Services priority. This can be accomplished by increasing use of home dialysis among incident patients or by reducing PD discontinuation. We explore trends in PD persistence and risk factors associated with PD discontinuation.

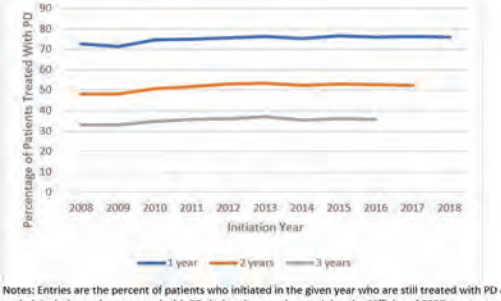
Methods: We identified incident ESRD patients from 2008 to 2018 who received peritoneal dialysis in their third month of ESRD treatment. We used data from CROWNWeb and Medicare claims to determine the patient's modality 1, 2, and 3 years after initiation of ESRD treatment. We summarize trends in share of incident PD patients who were treated with PD at each follow up and describe differences by patient and facility characteristics.

Results: From 2008 to 2017, approximately 70 percent of incident PD patients remained on PD after 1 year of dialysis, 50 percent after 2 years, and 30 percent after 3 years of dialysis (figure 1). Over these years the percentage of incident PD patients treated with PD after two years rose from 47.9 to 52.3 percent. The rate of two-year PD persistence has declined modestly since a peak of 53.1 percent in 2013. PD patients treated at DaVita facilities were more likely than those treated at FMC or independent facilities to remain on PD after two years. PD patients treated at facilities with a higher share of PD patients were more likely to remain on PD after two years. Among incident PD patients, the rate of peritonitis during the first year of dialysis declined from 33.5 to 21.7 between 2010 and 2018. Peritonitis was more common among dual eligible patients, Black and American Indian/Alaska Native patients, and overweight or obese patients.

Conclusions: Differences in PD discontinuation and peritonitis incidence across patient and facility subgroups represent opportunities for future quality improvement efforts.

Funding: Other U.S. Government Support

Figure 1. Percentage of Incident PD Patients Treated With PD at Follow-Up, 2008-2018



Notes: Entries are the percent of patients who initiated in the given year who are still treated with PD at the relevant follow-up period. Includes patients treated with PD during the month containing the 90th day of ESRD treatment.

PO0967

Peritoneal Dialysis Supplemental Telephone Support Program to Reduce 90-Day Drop-Out

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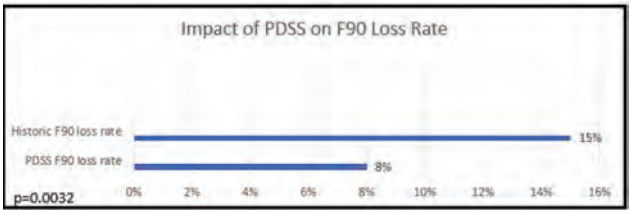
Background: Improving PD technique success is critical to meet Advancing American Kidney Health Initiative's (AAKHI) aggressive growth goal by 2025. Per results in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) 2017, the United States First 90-day (F90) dropout rate was 11.4% vs. 8.4% for all PDOPPS countries. Focused clinical intervention may lessen F90 dropout. The objective of this study is to evaluate the impact of a Peritoneal Dialysis Supplemental Support (PDSS) service to reduce F90 loss in Automated Peritoneal Dialysis (APD) patients utilizing remote monitoring. The PDSS service consists of telephone calls to patients and clinic nurses. PDSS provides pre-emptive technical support to patients and actionable clinical insights to clinicians.

Methods: A dialysis provider enrolled non-randomized, incident PD patients, who were being treated with a 2-way APD cycler enabled with a remote management system, into a PDSS program. The PDSS nurse reviews remote monitoring data and looks for trends in alerts and alarms that may lead to F90 dropout. For technical alerts and alarms, a member of the PDSS team proactively calls the patient to discuss technique and training reinforcement. For clinical alerts and alarms, the PDSS nurse contacts the clinic PD nurse (PDRN), who remains the only party in control of clinical care.

Results: The dialysis provider enrolled 202 incident patients from 23 clinics into the PDSS program. The dialysis provider's historical F90 loss within these clinics was 15.9%, N=69 for 2018-2020. PDSS began in November 2019 and continued through December 2020. Data revealed a decrease in F90 loss to 8.4%, N=17, for patients enrolled in PDSS, a 46.9% reduction in F90 loss (p=0.0032).

Conclusions: A supplemental PD telephone support service enhances the benefits of two-way remote patient monitoring. The patient benefits from timely support. The nurse benefits from additional analysis of clinical trends in the data. This enables the nurse to implement appropriate clinical interventions as needed. The result is a statistically significant reduction in F90 loss rate.

Funding: Commercial Support - Baxter Healthcare



PO0968

Contemporary Incidence of Peritoneal Dialysis Attrition and Variability Therein Among Age Strata

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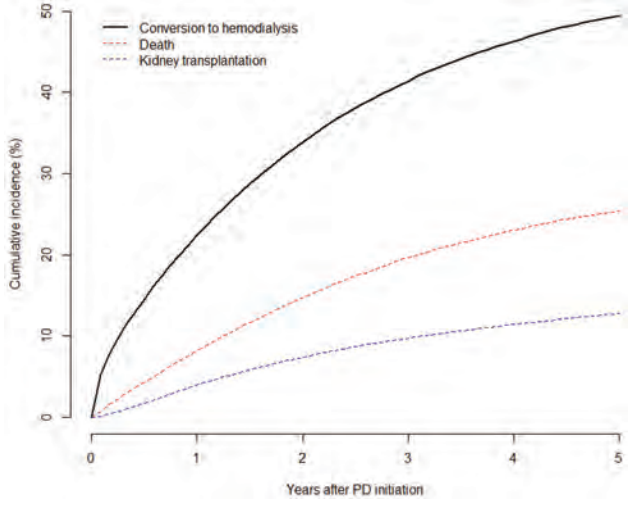
Background: With an increasing percentage of patients performing dialysis in the home setting, quality measurement systems should increase focus on home dialysis outcomes. Considering the central role of peritoneal dialysis (PD) in home dialysis, an important and readily estimable measure is the duration of PD before initiation of hemodialysis. We estimated the cumulative incidence of attrition due to initiation of hemodialysis among patients who recently initiated PD in the United States and assessed variability of incidence among age strata.

Methods: We analyzed United States Renal Data System Standard Analysis Files. We identified all patients who initiated PD in the home setting between January 1, 2011, and September 30, 2018, and within one year after diagnosis of end stage kidney disease (ESKD). We classified patients into cohorts of age 18-44, 45-64, 65-74, and ≥75 years. Overall and within age strata, we estimated the 5-year cumulative incidence of conversion to hemodialysis, with accounting for the competing risks of death and kidney transplantation.

Results: The cohort included 111,464 patients who initiated PD. The cumulative incidence of conversion to hemodialysis was 22.4% at 1 year, 33.9% at 2 years, 41.4% at 3 years, 46.3% at 4 years, and 49.4% at 5 years (figure). During those 5 years, 25.4% of patients died while receiving PD and 12.8% received a kidney transplant, thereby resulting in only 12.4% of patients still performing PD after 5 years. Among patients aged 18-44 years, 1-year (5-year) cumulative incidence of conversion to hemodialysis was 23.3% (51.1%); corresponding estimates were 22.3% (52.0%) among patients aged 45-64 years (48.3%), 21.9% among patients aged 65-74 years, and 22.5% (41.6%) among patients aged ≥75 years.

Conclusions: Regardless of age, between 22% and 23% of patients who initiated PD during the first year of ESKD transferred to hemodialysis within one year.

Funding: NIDDK Support



PO0969

Length of Peritoneal Dialysis Training and Risk of Early Treatment Attrition

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Background: Patient training is a critical component of the peritoneal dialysis (PD) program to ensure safe dialysis outcomes. However, there is a lack of clarity on how long patients should be trained before initiating PD at home. In this analysis, we evaluate the associations between the length of PD training and patient outcomes (early treatment attrition, peritonitis, and hospitalizations) among patients prescribed automated PD (APD).

Methods: Adult patients who initiated APD between 2017-2019 and received PD training at Fresenius Kidney Care facilities within 30 days of home treatments were included. Crude and case-mix adjusted risk of early PD attrition (discontinuation from PD within 3 months of enrollment due to switch to HD, death, or loss to follow-up) were compared between patients with a shorter (≤ 5 days), medium (6 to 10 days), and longer (>10 days) lengths of training. Early rates of peritonitis and hospitalizations were compared between patients with ≤ 10 days vs >10 days of training.

Results: 11,039 patients who received training ≤ 30 days prior to APD initiation were included. Compared to patients with a shorter PD training (n=3,333), patients with a medium length of training (n=6,310) had no significant difference in the risk of early attrition (Figure 1). Patients with longer PD training (n=1,396) had a lower risk of early attrition when compared to shorter PD training patients in the crude analysis, and no significant difference when controlled for case-mix variables (significant confounders: vintage, residual kidney function, and body surface area). There were no differences in the early rates of peritonitis and all-cause and peritonitis-related hospitalizations between patients receiving training for >10 days vs ≤10 days.

Conclusions: There were no significant associations between length of PD training and risk of early treatment attrition, hospitalizations, or peritonitis among automated PD patients.

Funding: Commercial Support - Fresenius Medical Care North America

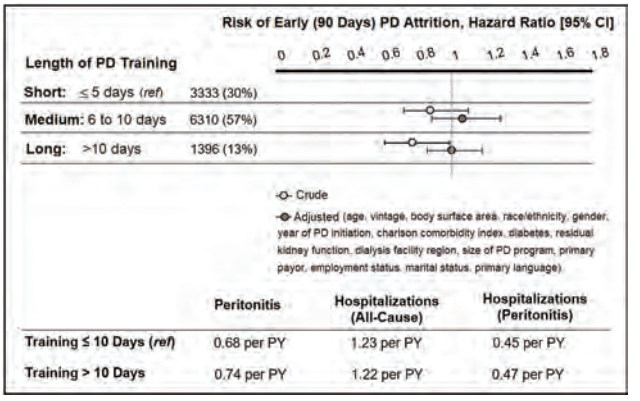

Figure 1

PO0970

Identifying Patients on Peritoneal Dialysis at High Risk of Transfer to Hemodialysis Using a Modified Surprise Question

Ayesha Anwaar,[1,2] Graham E. Abra,[2,1] Hatsumi Nielsen,[2] Sumi J. Sun,[2] Sai Liu,[1] Maria E. Montez-Rath,[1] Brigitte Schiller,[2,1] Wael F. Hussein.[2,1] *[1]Stanford University School of Medicine, Stanford, CA; [2]Satellite Healthcare, San Jose, CA.*

Background: Transfer from peritoneal dialysis (PD) to hemodialysis (HD) is associated with poor outcomes. Available prediction models of modality transfer are limited to the incident PD population. Simple predictive tools are needed to help guide risk stratification and subsequent clinical interventions to avoid unwanted modality transfer. We report on the correlates of nurse prediction of high risk using the question "Would you be surprised if this patient transfers to HD in the next 6 months?" (PD Surprise Question [PDSQ]).

Methods: This observational study included 1362 adults on PD receiving care at 35 centers in 3 states in the US, managed by a non-profit dialysis organization. A 'no' response to the PDSQ indicated high risk. Using multivariable logistic regression with backward elimination, we evaluated characteristics associated with being identified as high risk, including socio-demographic variables, BMI, primary kidney disease, vintage, comorbid conditions, renal and dialysate clearances, serum albumin, sodium, phosphorus, potassium, nPNA, last 3 months peritonitis and hospitalization, and insurance type. We used multiple imputations to handle missing data.

Results: Responses were obtained from 95/112 (85%) nurses for 1193/1362 (88%) patients. Mean age was 59 (SD: 16) years, 41% were female, median ESRD vintage 37 (IQR: 11 – 44) months and 46% had diabetes. 198 (17%) patients were identified as high risk. In the final model, patients were more likely to be identified as high risk if they were hospitalized in the last 3 months (odds ratio [OR]: 1.52, 95% confidence interval [CI] 1.30-1.74, p=0.0002). Having a higher serum sodium (for 1 meq/L: OR: 0.95, 95% CI 0.90-1.00, p=0.032), being married (OR: 0.76 95%CI 0.52-1.00, p=0.029), and longer PD vintage (for 1 month: OR: 0.99, 95%CI 0.0.98-1.00, p=0.013) were associated with lower odds of being identified as high risk.

Conclusions: The PD surprise question is a simple tool to assess the risk of transfer from PD to HD. Identified correlates of risk are consistent with high risk factors from the literature for transfer to HD. We are currently observing outcomes of included patients to examine the performance of the PDSQ to predict transfer to HD.

PO0971

Machine Learning-Driven Prediction of Peritoneal Dialysis Technique Failure

Caitlin Monaghan,[1] Joanna Willetts,[1] Hao Han,[1] Michael A. Kraus,[3,4] Dinesh K. Chatoth,[3,4] Len A. Usvyat,[1] Franklin W. Maddux.[2] *[1]Fresenius Medical Care, Global Medical Office, Waltham, MA; [2]Fresenius Medical Care AG und Co KGaA, Bad Homburg, Germany; [3]Fresenius Kidney Care, Waltham, MA; [4]Fresenius Medical Care North America, Waltham, MA.*

Background: Despite increased focus on starting and keeping dialysis patients on home therapy, Peritoneal Dialysis (PD) and Home Hemodialysis (HHD) rates are lower than desired. Two areas of opportunity are 1) keeping PD patients healthy so they can remain on PD longer and 2) transitioning PD patients to HHD when appropriate. To identify patients at risk of leaving PD in the short- (1-3 month) and long-term (3-6 month) timeframes, two machine learning (ML) models were developed. Along with risk scores, these models identify the factors driving increased risk to aid in prolonging time on PD while also allowing adequate notice to prepare for permanent access placement and HHD education.

Methods: Data were extracted for PD patients (n=53022) from 2016-2019; patients contributed one set of observations for each month they were on PD (n=823892 patient months). PD failure was defined as the first discharge from PD lasting over 30 days, and was coded as '1' if the patient changed modality in the next 1-3 or 3-6 months for the short- and long-term models, respectively. All other observations were coded as '0,' including censored events such as transplantation, loss to follow-up, or death. Two XGBoost ML models were trained using 80% of the dataset, with 20% used for evaluating model performance using 237 variables, derived from laboratory measurements, infection and hospitalization history, and other relevant clinical parameters.

Results: Evaluation of model performance on withheld data showed an area under the curve of 0.75 and 0.67 for the short- and long-term models, respectively. Patients were classified as High, Medium, or Low risk for each of their short- and long-term predictions. In the test dataset, 24% of high short-term risk patients dropped in the next 1-3 months, a rate almost 5 times higher than average and 12 times higher than low risk patients. For long-term predictions, 14% of high risk patients dropped in the next 3-6 months, 6% of medium risk, and 2% of low risk.

Conclusions: The two ML models showed good discrimination between patient risk categories for both short- and long-term timeframes. While further work is underway to gauge the clinical utility of these tools, these tools offer the potential to improve care of "failing" PD patients, reduce morbidity of transitions, and increase optimal starts with dialysis transitions.

Funding: Commercial Support - Fresenius Medical Care

PO0972

Technique Failure in the Dominican Republic National Peritoneal Dialysis Program

Erwin I. Campos,[1,2] Miguel A. Cuevas Budhart,[5] Elianny S. Polanco,[1] Jhanna H. Collado,[1] Mercedes Aquey,[1] Janny Guzman Chavez,[4] Alfonso Ramos.[3] Macrotech *[1]Macrotech, Santo Domingo, Dominican Republic; [2]Hospital Salvador B. Gautier, Santo Domingo, Dominican Republic; [3]Baxter Mexico, Ciudad de México, Mexico; [4]Baxter Colombia, Bogota, Colombia; [5]Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico.*

Background: Technique failure is a critical concern in peritoneal dialysis (PD), and it's associated with significant risk of patient lost. Technique failure is defined as transfer to HD 30 days after initiation of therapy or death within 30 days of transfer to HD.

Methods: This is a retrospective multicenter observational cohort study of incident Peritoneal Dialysis patients conducted between January 1st 2016 to December 31st 2020. Competing risk events were death and kidney transplantation, and patients were censored for recovery of kidney function, withdrawal or suspension of the therapy, and loss of a caregiver. Disease characteristics and baseline demographics were included. Data are expressed as mean ± standard deviation for continuous variables and as frequency counts and percentages for categorical variables. Incidence rates were performed for transfer to HD and finally, logistic regression analysis between the inferential type variables to determine the risk between having a history of diabetes mellitus and the variables of death and transfer to HD were calculated using an Odds Ratio analysis with 95% confidence intervals for parameters B.

Results: A total of 2326 patients were included, 59% men; the mean age was 57 ± 16 years, 53% had a diagnosis of Diabetes Mellitus (DM) and 65% had a basic educational level. 151 patients were censored (11%). Risk events were 1096 of which death accounts for 1084 (74%) and transplantation (0.8%). At the end of the first year, the cumulative incidence risk to HD transfer was 1%, the second year 4%, the third year 6%, the fourth 11%, and the fifth 16%. Based on the regression analysis between the variables of interest and the patients with a history of DM, there is a higher risk of death (p<0.001; OR. 2.123; CI 95% 1.781-2.532), however, for transfer to HD, no statistical significance was found (p=0.39; OR 1.14; CI 95% 0.838-1.564). The most frequent reason for technique failure was psychosocial and medical conditions 44%, followed by catheter malfunction 30%, peritonitis 13% and ultrafiltration failure 13%.

Conclusions: The technique failure rate is similar to the reported in RTS Colombian PD Program, but better than the mean of Latin American countries reports. Still, Improvement needs to be done in the catheter implant technique and mortality rates.

PO0973

Nurse-Based Educational Interventions in Patients with Peritoneal Dialysis: A Systematic Review and Meta-Analysis

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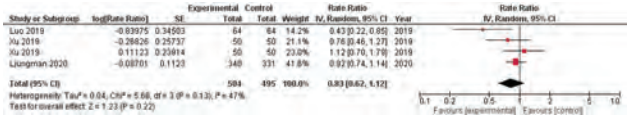
Background: Peritoneal dialysis (PD) is a major renal replacement therapy modality for patients with end-stage renal disease (ESRD) worldwide. As poor patient self-care could lead to serious complications, including peritonitis, exit-site infection, technique failure, and death; several nurse-based educational interventions have been introduced. However, these interventions varied and have been supported by small-scale studies so the effectiveness of nurse-based educational interventions on clinical outcomes of PD patients have been inconclusive.

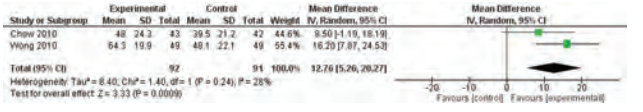
Methods: We performed a systematic search using PubMed, Embase, and CENTRAL. Selection criteria included Randomized Controlled Trials (RCTs) relevant to nurse-based education interventions in ESRD patients with PD in the English language up to February 20, 2020. The meta-analyses were conducted using a random-effects model to evaluate the summary outcomes of peritonitis, PD-related infection, mortality, transfer to hemodialysis, and quality of life (QOL).

Results: Of 7,240 potential studies, 61 theme-related abstracts were selected for further full-text articles screening against eligibility criteria. Ten studies (1,404 PD patients in seven countries) were included in the systematic review. Eight studies (1,363 PD patients in five countries) were included in the meta-analysis. Sleep QOL in the intervention group was significantly higher than control (mean difference 12.76, 95% CI 5.26–20.27). There was no difference between intervention and control groups on peritonitis, PD-related infection, transfer to hemodialysis, and overall QOL.

Conclusions: Nurse-based educational interventions could help reduce some PD complications, of which only the sleep QOL showed statistically significant improvement. High-quality evidence on the nurse-based educational interventions was limited and more RCTs are needed to provide more robust outcomes.



PD Peritonitis



Quality of Life (Sleep)

PO0974

Immediate Start PD: A Single-Center Experience

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Background: Peritoneal Dialysis catheters are felt to require a healing time prior to initial use. Concern for increased risk of leak, has led many to use supine intermittent low volume exchanges (<1000 mL) initially for earlier start peritoneal dialysis. We undertook a study to prospectively monitor and track peritoneal dialysis complications when catheter use was early (prior to 14 days post placement) and the nephrologist chose to start with higher volume dialysate (>= 1000mL) without regard to maintaining a supine position. Higher volume dialysis with earlier initiation should allow for better PD clearances when clinically warranted and more salt and water removal compared to supine intermittent low volume exchanges.

Methods: In this single center prospective observational study, peritoneal dialysis catheters were placed laparoscopically ensuring tunneling through the abdominal rectus muscle with the deep cuff placed just within or below the rectus abdominal muscle. Purse strings sutures were only used at the surgeons' discretion. Surgeons did undergo consistent education from two experienced surgeons prior to the study. Patients were included in the study if the nephrologist felt early start dialysis was indicated. Prescriptions were at the discretion of the nephrologist.

Results: Since January 2021, 23 PD catheters have been placed using this technique with only one adverse event. 8 patients (35%) initiated PD 24 – 72 hours post placement and 15 patients (65%) started dialysis between 73 hours and 2 weeks post catheter placement. All patients first exchanges were 1000 ml, and volumes were increased rapidly at the discretion of the nephrologist as patient condition warranted. In these 23 patients, 1 patient experienced a peritoneal leak which resolved with rest. That patient was in the > 72 hour group. No other catheter complications were noted.

Conclusions: In this single center observational study, peritoneal catheters placed laparoscopically with careful abdominal rectus tunnelling allowed for larger volume dialysis exchanges without concern for supine positioning or intermittent use. One leak was noted and no other complications for an acceptable leak rate of 4% in this small study. This study demonstrates that PD can be initiated sooner post dialysis and larger volumes are well tolerated.

PO0975

Converting ESKD Patients on Peritoneal Dialysis to Hemodialysis Post Cardiac Surgery: A Necessity or Comfort

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Background: End-stage kidney disease (EKSD) patients on peritoneal dialysis (PD) undergoing cardiac surgery are sometimes converted to hemodialysis (HD) post-surgery. The reasons for this conversion are not well defined in the literature. We sought to examine the reasons cited for converting PD patients to HD post operatively after undergoing major cardiac surgery.

Methods: We examined ESKD patients on PD undergoing cardiac surgery from 2009-2019 using an electronic health records (EHR)-based Cardio-Thoracic Surgery (CTS) registry at the Cleveland Clinic. We identified PD patients who were converted to HD perioperatively. We reviewed the EHR to identify the main causes for conversion.

Results: 62 ESKD patients on PD undergoing major cardiac surgery were identified. 16 patients, representing more than a quarter, were converted to HD post operatively. Out of those converted, 31.25% were converted for absolute indications (18.75% for PD catheter malfunction, 6.25% for gadolinium exposure and 6.25% for concern of pericardio-peritoneal communication). 68.75% were converted for less clear and relative indications (25% based on clinician preference, 43.75% for hemodynamic instability or requiring vasopressors). Results are displayed in (Table 1).

Conclusions: A small percentage of PD patients are converted to HD for absolute indications. Most patients are converted based on relative indications including lack of familiarity with PD and hemodynamic instability. As the number of ESKD patients on PD is expected to increase, a better understanding of the outcomes of PD patients post cardiac surgery is needed. In addition, more education is urgently needed to increase the comfort of practitioners managing PD patients in special situations that might be amenable to prescription alterations without premature transition to hemodialysis.

Reasons for PD to HD conversion post cardiac surgery

Absolute Indications (N=5)			Relative Indications (N=11)		
Reason Cited	N	Percentage	Reason Cited	N	Percentage
Catheter Malfunction	3	18.75%	Clinician Preference	4	25%
Gadolinium Exposure	1	6.25%	Hemodynamic Instability / Vasopressor requirement	7	43.75%
Pericardio-peritoneal shunt	1	6.25%			

Table 1

PO0976

Effect of Low-Dose PD in Elder Population on Protein Energy Wasting, Functionality, and Quality of Life

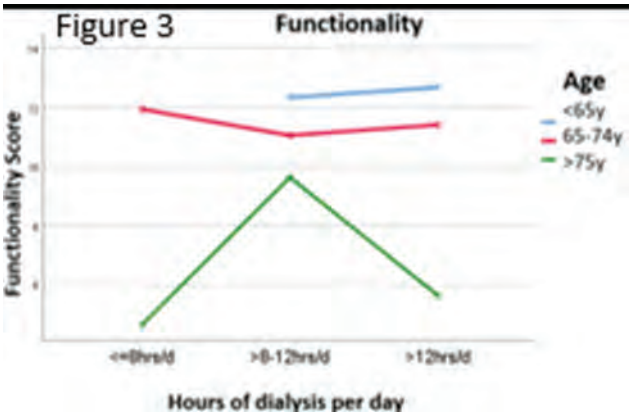
Gloria G. García Villalobos, L. M. Perez-Navarro, Rafael Valdez-Ortiz. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.*

Background: Elder population currently involves 55% of those who initiate dialysis. Age, comorbidities, functional status (FS), protein energy wasting (PEW) and quality of life (QoL) need to be considered. CAPD can cause PEW, loss of functionality and QoL decline, adjusting treatment to Intermittent Ambulatory PD (IAPD) (low-dose) has the intention to decrease disadvantages while maintaining the benefits. The aim of this study was to to evaluate the effect of low-dose PD on PEW, functionality and QoL.

Methods: A retrospective cohort of patients 60 years and older was analyzed. IAPD was defined as less than 16hrs of treatment per day. Clinical, biochemical data were collected. Katz, Lawton-Brody scales and EQ-5D-5L questionnaire were applied.

Results: 91 patients were on IAPD: Prescription of hrs/day of dialysis did not correlate with residual uresis (r -0.052, p 0.612). Questionnaires: **QoL.** EQ-5D-5L found the majority of patients were in the highest/positive scores for every category assessed. In the same way, 44% of the patients had 80 points or more in their perception of QoL (figure 1), and it was found to be associated with albumin and phosphorus (r.296, p 0.015; r .312, p 0.027). **Functionality.** 67% of patients were classified as independent (figure 2) and FS was associated with albumin, uresis and VAS QoL (r 0.462, p0.000; r 0.416, p0.000; r 0.407, p0.000 respectively). A model to identify the predictors of functionality was made. It was found that female, age >75y, uresis<500ml/d, albumin <3.5g/dl and hours of dialysis predict negatively scores. The interaction between hours of dialysis and age have the biggest effect size.

Conclusions: IAPD in this elder population does not mean suboptimal dialysis: there were found favorable results in regard to biochemical parameters; FS and QoL scores maintained despite the dialysis vintage. Of notice the group of 75years and older are more likely to be affected in a negative way by prescription of dialysis.



PO0977

A Uremic Pig Model for Peritoneal Dialysis Research

Joost C. de Vries,[1] Maaike K. van Gelder,[1] Anneke S. Monninkhof,[1] Sabbir Ahmed,[2] Diënty Hazenbrink,[1] Tri Q. Nguyen,[1] Koen Vaessen,[2] Jaap A. Joles,[1] Marianne C. Verhaar,[1] Karin G. Gerritsen.[1] *[1]University Medical Center Utrecht, Utrecht, Netherlands; [2]Utrecht University, Utrecht, Netherlands.*

Background: The renewed interest in home dialysis requires a translational uremic large animal model to evaluate innovations in peritoneal dialysis. Ideally, toxin plasma levels should be comparable to those in dialysis patients, without requiring maintenance dialysis for survival. To this end, we developed a pig model with stable moderate chronic kidney disease.

Methods: CKD was induced in five female pigs by bilateral subtotal renal artery embolization aiming for embolization of ~85-90% of total kidney tissue. Temporary aggravation of uremia was induced with gentamicin (10 mg/kg twice daily for 7 days). We hypothesized this approach would lead to stable CKD without the need for maintenance dialysis. Peritoneal transport was assessed with a standard peritoneal permeability assessment.

Results: After embolization, urea and creatinine levels increased from 1.6±0.2 to 7.5±1.0 mM and 103±12 to 338±60 μM, respectively, followed by stabilization within 2 weeks to 2.5±1.0 mM and 174±25 μM, respectively. GFR (iohexol clearance) decreased from 49 mL/min to 28 mL/min. Gentamicin induced temporary acute-on-chronic kidney injury with peak urea and creatinine concentrations of 17.0±6.1 mM and 932±504 μM, respectively (Figure 1), while potassium (range 4.1-4.7 mM) and phosphate (range 2.33-2.67 mM) remained stable. Peak indoxyl sulfate and hippuric acid levels were 10.5 ± 0.85 mg/L and 75.3 ± 81.5 mg/L respectively. Peritoneal dialysis, although complicated by peritonitis, could be successfully applied. Peritoneal transport assessment showed a low transport status (D/P creatinine (4h): 0.45±0.12) with an MTAC of 9.6±3.0, 4.6±2.5, 3.4±2.2 mL/min for urea, creatinine, and phosphate respectively.

Conclusions: We have established a pig model with stable moderate CKD without the need for maintenance dialysis. Temporary on-demand acute-on-chronic kidney injury, resulting in uremic solute levels representative for ESKD, allows evaluation of novel dialysis methods.

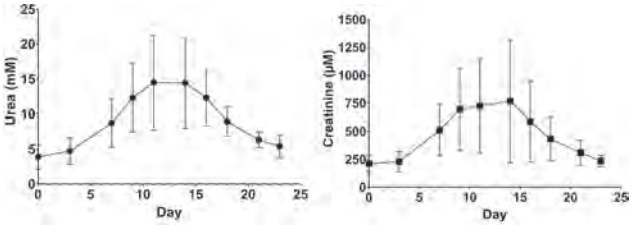


Figure 1. Urea (left) and creatinine (right) plasma levels after administration of gentamicin (day 0). Mean ± SD, n=10 administrations in n=5 pigs.

PO0978

Recurrent Abdominal Pain in a Patient on Peritoneal Dialysis

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Introduction: Abdominal pain can have many differentials in patients on peritoneal dialysis (PD). Some of them, including fungal peritonitis, requires PD catheter removal and a change in dialysis modalities. Here we present a case of recurrent abdominal pain in a patient on peritoneal dialysis which highlights the importance of prompt diagnosis.

Case Description: 40-year-old female with end stage renal disease secondary to systemic lupus erythematosus on PD for 3 years presented for urgent clinic appointment after her system was disconnected with leakage of PD fluid. PD effluent revealed white count of 300 with 2% neutrophils. She was treated empirically for peritonitis. 11 days later her fungal culture grew Candida famata and she was admitted with intermittent abdominal pain associated with vomiting and weakness. She was hemodynamically stable, and her exam was significant for epigastric tenderness with normal looking PD catheter site. Her white count was elevated to 13,000 with unremarkable metabolic panel. CT abdomen was unremarkable. A repeat PD effluent had white count of 40. Her PD catheter was removed the next day and she was switched to hemodialysis. She was treated with 10 days of oral fluconazole. On review, she had been having intermittent abdominal pain with PD effluent sometimes showing high white count for which she got multiple antibiotic courses for either presumed or culture positive bacterial peritonitis. She had also grown positive fungal culture about 18 months ago with Candida albicans and Stereum complicatum which went unnoticed.

Discussion: Fungal peritonitis can be catastrophic for patients on PD. Treatment involves prompt catheter removal and systemic antifungal treatment. Given its dire consequences, prevention is paramount. The ISPD recommends using anti-fungal prophylaxis when PD patients receive antibiotic courses. Risk factors include previous bacterial peritonitis and antibiotic use. This case demonstrates the need to follow cultures as fungal growth is slow and can take weeks. It is important to have a high index of suspicion for a fungal organism when cultures are negative. This patient received antibiotics on several occasions but only developed fungal peritonitis on 2 occasions which raises concern on antifungal prophylaxis. Further studies are indicated to determine number needed to treat to decide on need for antifungal prophylaxis.

PO0979

Micrococcus Peritonitis Complicating Peritoneal Dialysis

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Introduction: Peritonitis is one of the most common and consequential complications of peritoneal dialysis. *Micrococcus sp* are catalase-positive, coagulase-negative, gram-positive cocci that are increasingly recognized as opportunistic pathogens in patients with immunocompromise or indwelling catheters. These bacteria have been rarely implicated as causative in peritonitis. We present a case of peritonitis due to *Micrococcus sp* and review the pertinent literature.

Case Description: A 55-year-old female with history of ESKD due to diabetic kidney disease, CAD s/p CABG, and hypertension presented with a 1 day history of cloudy effluent. She had no prior peritonitis episodes. Vital signs were stable and exam was notable for a soft non-tender abdomen and clean and dry exit site without discharge or granulation tissue. Effluent was hazy in appearance. Administration of empiric vancomycin and gentamicin was initiated, resulting in clearing of effluent within 48 hours. Effluent leukocyte count was 204 cells/uL with 58% neutrophils. Intraperitoneal vancomycin was continued for 3 weeks due to intermittent low troughs. Further history revealed intermittent mask use while performing exchanges. After completion of treatment, there was a complete resolution of symptoms and peritoneal cell count. Cell count and culture were repeated 1 month later during evaluation of abdominal pain eventually found to be due to constipation. Leukocyte count was 6 cells/uL but culture again grew *Micrococcus sp*. After culture was repeated once more and remained persistently positive, repeat treatment to eradicate was attempted with 2 more weeks IP vancomycin but culture remained positive. Eventually the catheter was removed due to a change in living situation. After 5 months of hemodialysis, peritoneal catheter was replaced and the patient was restarted on peritoneal dialysis, after which time she has not had any peritonitis episodes.

Discussion: We present the 10th case of *Micrococcus sp.* Peritonitis in a peritoneal dialysis patient. Prior cases have been associated with breaks in technique and have shown a pattern of recurrence with resultant technique failure being very common. Attempted treatments have included vancomycin, cefazolin, ceftazidime, and teicoplanin. In the prior 9 published cases, 4 resulted in technique failure. This case and review of the literature can serve to inform future occurrences.

PO0980

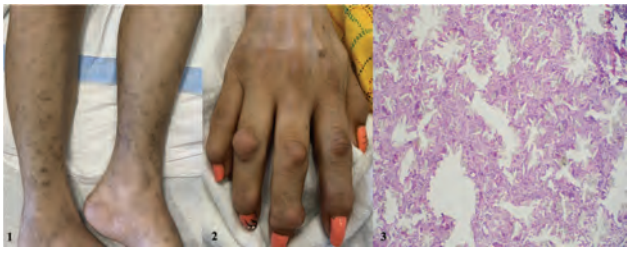
Cutaneous Oxalosis in a Patient on Peritoneal Dialysis

Stephanie Torres Rodriguez, Hunter Pyle, Audrey Rutherford, Arturo R. Dominguez, Shani Shastri. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Introduction: Oxalosis is the systemic deposition of calcium oxalate in multiple tissues and can be of primary or secondary etiology. Skin manifestations due to secondary hyperoxaluria (SH) attributable to renal insufficiency are rare. We present a case of cutaneous oxalosis in a patient with end stage renal disease (ESRD) receiving peritoneal dialysis (PD).

Case Description: A 45-year-old female with ESRD due to lupus nephritis (LN) on PD for 11 years presented with hypertensive encephalopathy. Dermatological evaluation revealed pseudoreticular hyperpigmented patches overlying firm, non-tender, subcutaneous nodules and plaques on bilateral lower extremities (Figure 1) and upper arms and firm nodules overlying the joints of her hands (Figure 2). With history of lupus, cutaneous findings were concerning for dystrophic calcinosis cutis. Skin biopsy showed radially arranged yellow-brown rhomboid crystals in the subcutis and deep dermis surrounded by histiocytes consistent with cutaneous oxalosis (Figure 3). Additional history revealed daily intake of Vitamin C 1g for past year and no prior gastrointestinal surgeries or chronic diarrhea. Non-obstructive bilateral nephrolithiasis were seen on imaging in 2020 but absent previously.

Discussion: Absence of early-age nephrolithiasis, negative family history & renal biopsy findings are inconsistent with primary hyperoxaluria (PH). SH is a result of excessive oxalate accumulation from increased intake, increased reabsorption due to small bowel disease, or decreased excretion in renal failure (retention oxalosis). Although dialysis patients may have high serum oxalate, clinical calcifications are rare. We speculate vitamin C supplementation and ESRD status contributed to the production of these deposits in our patient. Ascorbic acid is metabolized to oxalate; in long term dialysis patients doses of 500 mg daily may raise plasma oxalate by 50% to 100%. Management includes lowering serum calcium and oxalate levels by eliminating Vitamin C supplements or reducing dose < 100 mg daily, limiting dietary oxalate, increasing dialysis clearance and lowering dialysate calcium concentration if needed.



PO0981

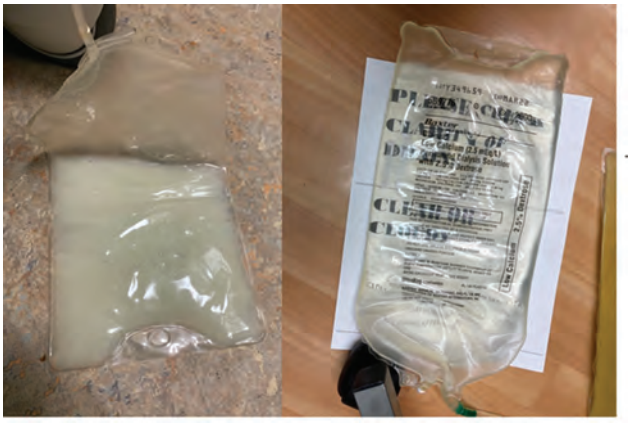
Chylous Peritoneal Fluid in a Patient on Peritoneal Dialysis Taking Nifedipine

Lauren E. Macaraeg, Dena E. Rifkin, Tyler Woodell, O. Alison Potok. *University of California San Diego, La Jolla, CA.*

Introduction: Chylous fluid in peritoneal dialysis (PD) patients may appear with lymphatic system disruption. This can be due to lymphatic obstruction, exudation through vessels, or via a lymphoperitoneal fistula.

Case Description: A 78 year-old man with ESKD due to diabetic nephropathy, transitioned five weeks prior from HD to PD, presented with newly cloudy PD fluid. His past medical history included hypertension, coronary artery disease, and monoclonal gammopathy of undetermined significance. He reported a newly cloudy white initial drain with lower abdominal pain, but denied fever, vomiting or diarrhea. He denied a breach in sterile technique. Medications included hydralazine, cinacalcet, furosemide, nifedipine, omeprazole, calcium acetate and darbepoietin. He was hemodynamically stable and had no abdominal tenderness. Laboratory results revealed a leukocytosis of 11.7 /cm3. Peritoneal fluid was milky (figure 1a) with 101 white blood cells (4% neutrophils); gram stain and culture were negative. Triglycerides were 96 and 62 mg/dL in the PD fluid and serum, respectively. Etiologic work-up was negative for malignancy, pancreatitis, cirrhosis, trauma and tuberculosis. Chylous nature of the PD fluid resolved within a day of nifedipine discontinuation (figure 1b). The patient self-resumed nifedipine weeks later and the milky fluid recurred the following day before again subsiding after its repeat cessation.

Discussion: This patient had the onset of chylous PD fluid 5 weeks after initiating PD, which resolved with cessation and recurred with reinitation of his long-term nifedipine. The mechanism of calcium channel blockers (CCB) – related chylous ascites is not well established. Some have suggested it may be related to the lipophilic nature of CCB. Patients on PD with higher peritoneal membrane transport may be at higher risk. Genetic factors may predispose to this phenomenon. Nephrologists should be aware of this rare complication of CCB use in PD patients. More research is needed to better understand the underlying pathophysiology of this rare condition.



PO0982

Severe Bleeding and Deep Inferior Epigastric Pseudoaneurysm After PD Catheter Removal

Nicola Matthews,[1] Tamara Glavinovic,[2] Bourne L. Auguste.[2] *[1]St. Michael's Hospital, Toronto, ON, Canada; [2]Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Introduction: In this case, the removal of a PD catheter with deep cuff calcification results in pseudoaneurysm formation with hemorrhage and hospitalization.

Case Description: A 24-year-old woman with end-stage kidney disease was switched from PD to HD due to worsening uremia and PD catheter removal was organized. At the time of catheter removal heavy calcification around the deep Dacron cuff embedded into the rectus muscle was seen. Upon catheter removal, the deep inferior epigastric perforating (DIEP) vessel was sheared, creating a pseudoaneurysm where urgent angiographic embolization to stop the bleeding was needed (Fig. 1). Intimate relationship between DIEP vessel and Dacron cuff was felt to be secondary to heavy calcification of these structures that developed during her time on PD (Table 1). The patient required an urgent transfusion and was admitted to hospital for monitoring. She was discharged the following day in stable condition.

Discussion: This is an important learning case in PD catheter removal and highiglights the following: -Poorly controlled bone mineral disease may lead to excessive calcification of the deep Dacron cuff and DIEP vessels. -When heavy calcification of the PD cuff is seen, catheter removal should be done in settings equipped with interventional radiology support in the event of complication.

Calcium-phosphate balance while on PD

	Month 1	Month 2	Month 3	Month 5	Month 7
Creatinine (mg/dL)	17.2	13.8	11.3	12.0	14.5
Urea (mg/dL)	75.1	78.1	67.2	66.7	85.7
Phosphate (mmol/L)	3.28	2.18	1.92	1.95	2.43
Calcium (mmol/L)	2.55	2.55	2.59	2.51	2.45
Albumin (g/L)	35	37	38	38	35
PTH (pmol/L)	175.3	100.4	88.5	106.8	103.6

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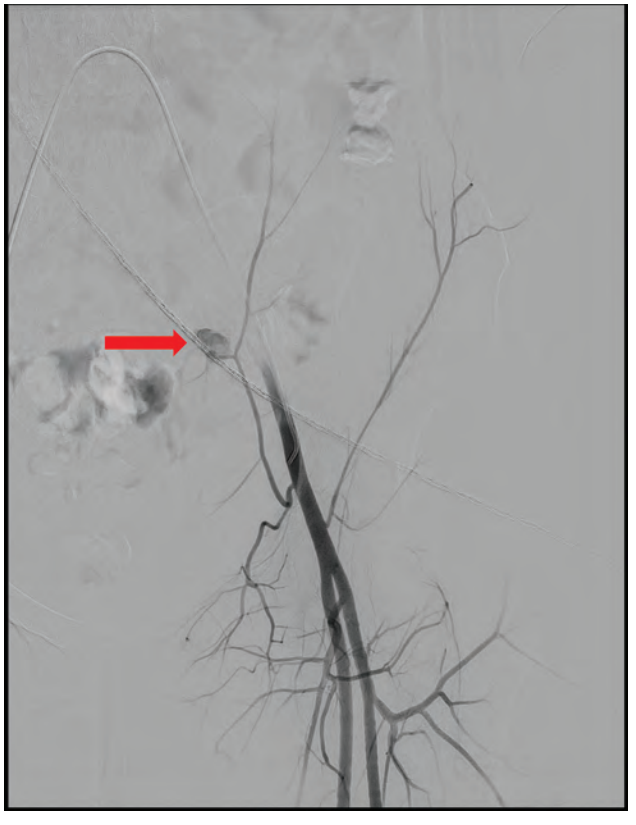

Pseudoaneurysm (red arrow) and hemorrhage of prominent DIEP vessel after PD catheter removal.

PO0983

A Case of Abdominal Wall Abscess Caused by Aeromonas hydrophila in Prior Peritoneal Catheter Site in an Immunocompromised Patient Post Kidney Transplant

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Introduction: *Aeromonas hydrophila* is a gram-negative rod-shaped bacterium found in aquatic ecosystems; it has been identified as the causative organism of different opportunistic infections in the immunocompromised and there is growing evidence of infection in the immunocompetent. This pathogen has been implicated in acute gastroenteritis, soft tissue infections, meningitis, peritonitis and sepsis among others.

Case Description: We report a case of a 56 year old woman with end stage kidney disease previously on peritoneal dialysis (PD) with subsequent live donor kidney transplant on immunosuppression, who presented with right lower quadrant abdominal cellulitis and deep abscess around the catheter site. Post transplant, her PD catheter was removed, however, the catheter site never healed completely. Although she did have multiple superficial skin infections in the past, those resolved with antibiotics. But this specific cellulitis, did not improve despite multiple antibiotic regimens, and further imaging studies revealed she had developed an abscess. The abscess was managed by surgical incision and drainage with debridement of the skin, subcutaneous tissue, fascia, and muscles around the whole catheter tract. *Aeromonas hydrophila* was found as the causative organism.

Discussion: To our knowledge, this is the first case of an *A. hydrophila* abscess associated with a peritoneal dialysis catheter. Firm association between aeromonads and the use of intravenous indwelling devices has already been demonstrated. We hypothesize that her deep seeded infection could be associated with the intrinsic ability of *A. hydrophila* to form biofilms upon detecting a suitable surface, making them more virulent. The formation of biofilm has been associated with exponential growth as the source of pathogenicity of this bacteria in pisciculture studies. This characteristic could be one of the factors contributing to reported cases of peritonitis and intravenous hemodialysis catheters by *A. hydrophila*. Further elucidation of *A. hydrophila* virulence factors in humans can provide insight on prevention of PD catheter associated infections by *A. hydrophila*.

PO0984

Mesenchymal Stem Cell Exosomes Protect Mouse Peritoneal Injury Induced by Human Peritonitis Dialysis Effluent

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Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but there are few effective therapies for it. The purpose of this study was to investigate the protective effect of exosomes secreted by mouse bone marrow mesenchymal stem cells(MSC) on peritoneal injury and to reveal the mechanism.

Methods: Forty-two male C57BL/6 mice were randomly divided into a normal group, a control group (2.5% glucose dialysate), a peritonitis-effluent group (The overnight 2.5% glucose dialysate of patients with peritonitis), a high glucose (4.25%) dialysate group, a peritonitis-dialysate+exosome group, and a high glucose dialysate+exosome group. The mouse model of peritoneal injury was constructed by intraperitoneal injection of human peritonitis dialysis effluent continuously for 42 days. The mice in the exosome treatment group received intraperitoneal injection of MSC-exosomes twice. The level of peritoneal structural and functional damage was detected. The effect of MSC-exosomes was validated in vitro.

Results: Peritoneal transport and structure was significantly impaired in the peritonitis-effluent group and the high glucose dialysate group after 42 days, and was significantly higher than control group. The results suggested that human peritonitis dialysis effluent could be used to construct a mouse model of peritoneal injury. Masson staining showed that fibrosis degree of exosome treatment group was significantly less than peritonitis-effluent group. Immunohistochemical analysis showed that expressions of mesothelial markers E-cadherin and ZO-1, neutrophil granulocytes (MPO) and macrophages (F4/80), and fibrosis markers (collagen I,a-SMA) in exosome treatment group were significantly lower than peritonitis-effluent group. Peritoneal ultrafiltration function of exosome treatment group was significantly improved than peritonitis-effluent group. In vitro experiments showed that exosomes could down-regulate the secretion of IL-1β, IL-6 and TGF-β1 by peritoneal mesothelial cells stimulated by high glucose dialysate, maintain expression of mesothelial cell marker (E-cadherin), and inhibit mesenchymal marker (a-SMA), suggesting that exosomes could inhibit the transdifferentiation of peritoneal mesenchymal cell-mesenchymal cells (MMT).

Conclusions: MSC-exosomes can alleviate peritoneal fibrosis by inhibiting peritoneal mesothelial cell-mesenchymal cell transdifferentiation.

PO0985

Dual Therapy with JAK1/2 Inhibitor and Losartan Attenuates Dialysate-Induced Angiogenesis in Polycystic Rats

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Background: Long term peritoneal dialysis (PD) is limited by reduced efficacy over time. Early peritoneal membrane (PM) injury is characterized by inflammation which progresses to hypervascularity and fibrosis. JAK/STAT signaling mediates inflammatory pathways, including angiotensin signaling. Our previous study showed dual therapy with JAK1/2 inhibitor (JAK1/2i) and an ARB maintains PM structure and function in rats with polycystic kidneys (PCK) chronically infused with 4.25% Dianeal x 16 wks. By using VEGFR2 as an endothelial marker, we further investigated if this dual therapy can attenuate chronic dialysate infusion induced hypervascularity in this rat model.

Methods: PCK rats were used. Dialysate infusions were performed BID via an implanted subcutaneous port in the neck tunneled to the intraperitoneal cavity. The following treatments were administered: **(1)** No surgery/infusions; **(2)** 4.25% Dianeal; **(3)** 4.25% Dianeal + JAK1/2i (5mg/kg BID); **(4)** 4.25% Dianeal + Losartan (5mg/kg BID); and **(5)** 4.25% Dianeal + Losartan +JAK1/2i (5mg/kg BID each). Parietal peritoneum was used for immunohistochemical staining of VGEFR2, which was digitally quantified by using Qu Path program. Data were analyzed by one-way-ANOVA followed by Tukey test. Results are mean ± SEM.

Results: VEGFR2 staining was significantly elevated after 16 weeks IP infusion of 4.25% Dianeal alone. JAK1/2i significantly reduced VEGFR2 expression; losartan tended to reduce VEGFR2, but this did not reach significance. Dual therapy with JAK1/2i and losartan resulted in the greatest reduction of VEGFR2

Conclusions: Long-term JAK1/2i, or JAK1/2i plus losartan intraperitoneal treatment reduces angiogenesis. Angiotensin inhibition is advocated to maintain residual renal function, by adding JAK1/2i, the combination also protects peritoneal structure/function by reducing angiogenesis.

PO0986

The Effect of Far-Infrared Therapy on the Peritoneal Expression of Glucose Degradation Products in Diabetic Patients on Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is a treatment modality for end-stage renal disease (ESRD) patients. Dextrose is a common osmotic agent used in PD solutions and its absorption may exacerbate diabetes mellitus. PD solutions also contain glucose degradation products (GDPs) that may lead to encapsulating peritoneal sclerosis (EPS). A previous study showed that far-infrared (FIR) therapy improved a patient's gastrointestinal symptoms due to EPS. Due to limited literature, this study aims to investigate dialysate GDPs and peritoneal function in diabetic patients on PD.

Methods: A prospective analysis conducted in a single center. The participants were recruited from the peritoneal dialysis outpatient department from November 25, 2016 to September 5, 2018. We included the patients who met the following criteria: (1) ESRD patients aged 20–90 years without receiving FIR therapy within 12 months; (2) receiving continuous ambulatory peritoneal dialysis or automated peritoneal dialysis; (3) no history of peritonitis, cerebrovascular accident, myocardial infarction, or receiving any cardiovascular intervention in the past 3 months. Patients were allocated to two groups based on their underlying DM history. Both groups of PD patients received FIR therapy for 6 months. We collected the last daily bag of peritoneal dialysate and compared the dialysate concentration of GDPs and clinical data in PD patients pre- and post-FIR therapy.

Results: Thirty-one PD patients were enrolled and underwent 40 min of FIR therapy twice daily for six months. We demonstrated the effect of FIR therapy on the following: (1) decrease of methylglyoxal ($p = 0.02$), furfural ($p = 0.005$), and 5-hydroxymethylfurfural ($p = 0.03$), (2) increase of D/D0 glucose ratio ($p = 0.03$), and (3) decrease of potassium levels ($p = 0.008$) in both DM and non-DM patients, as well as (4) maintenance and increase of peritoneal Kt/V in DM and non-DM patients, respectively ($p = 0.03$). FIR therapy is a non-invasive intervention that can decrease dialysate GDPs in PD patients by improving peritoneal transport rate and solute removal clearance, while also maintaining dialysis adequacy.

Conclusions: In conclusion, our study demonstrated that FIR therapy can decrease PD patients'dialysate GDPs by improving peritoneal transport rate and solute removal clearance, while also maintaining dialysis adequacy.

PO0987

Cumulative Dialysate Glucose Exposure Is a Risk Factor for Peritoneal Sclerosis in Pediatric Peritoneal Dialysis Patients Using Neutral-pH Fluids

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Background: The benefits of neutral-pH fluids for preventing peritoneal dialysis (PD)-related peritoneal sclerosis have been established, however, advanced peritoneal sclerosis still has been described in pediatric PD patients using neutral-pH fluids (Kidney Int 2018). The factors associated with peritoneal pathological changes after long-term use of neutral-pH fluids have not been elucidated.

Methods: Pediatric PD patients using only conventional acidic fluids (conventional group, n=31) and those using only neutral-pH fluids (neutral-pH group, n=33) for more than one year were analyzed. Propensity score matching was performed to compare the peritoneal pathological changes between groups. Clinical risk factors including PD duration and cumulative dialysate glucose exposure for peritoneal pathological changes in the neutral-pH group were analyzed using generalized linear model. Furthermore, immunofluorescence studies were performed on vascular endothelial growth factor-α (VEGF-α), cytokeratin; an epithelial marker, and α-smooth muscle actin (α-SMA); a myofibroblastic marker of epithelial-mesenchymal transition (EMT).

Results: Age at biopsy was 11.5 [8-17] years (median [IQR]) and duration of dialysis was 3.2 [1.7-5.3] years. The neutral-pH group showed less peritoneal deterioration except for higher submesothelial microvessel density (P <0.01) than conventional group. In the neutral-pH group, the cumulative dialysate glucose exposure was an independent risk factor for increased thickness of the submesothelial compact zone [OR, 1.004; 95%CI, 1.001, 1.007] and submesothelial microvessel density [OR, 1.003; 95%CI, 1.000-1.005]. Cumulative dialysate glucose exposure correlated with the proportion of VEGF-α positive areas (P<0.01, r=0.55). In immunofluorescence study, VEGF-α (+) cells comprised cytokeratin (+) cells and α-SMA (+) cells.

Conclusions: The neutral-pH fluids showed less deteriorations of the peritoneal membrane than acidic fluids except for increased angiogenesis. Cumulative dialysate glucose exposure was an independent risk factor for peritoneal fibrosis and angiogenesis in pediatric patients using neutral-pH fluids, which might be associated with increased VEGF-α production by mesothelial cells presenting EMT.

PO0988

Predicting Patient and Technique Survival in a Cohort of Incident Peritoneal Dialysis (PD) Patients According to Peritoneal Small Solutes Transport Rate (PSTR)

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Background: The association between PSTR and clinical outcomes in patients undergoing chronic peritoneal dialysis (PD) is uncertain. We explored the association of PSTR with mortality and technique survival in a large cohort of incident patients undergoing PD in Colombia.

Methods: In a cross-sectional study, 8170 PD patients, treated with APD (2705, 33.1%) and with CAPD (5465, 66.9%), who underwent peritoneal equilibration test to determine dialysate/plasma creatinine ratio at 4 hours were classified into slow (16.0%), slow average (35.4%), fast average (32.9%) and fast (15.7%) PSTR categories. Demographic, clinical and laboratory variables were evaluated. During median follow-up of two years, 2633 (32.2%) patients died, 1079 (13.2%) patients transferred to hemodialysis, and 661 (8.1%) patients underwent renal transplantation. All-cause and cardiovascular disease (CVD) mortality risk and technique survival were analyzed with competing-risk regression with transplantation as competing risk.

Results: Patients with fast as compared to slow PSTR were older, more often male or diabetic (DM), and had lower Hb and serum albumin levels. In competing risk analysis, after adjusting for age, sex, body mass index, residual kidney function, presence of diabetes and hypertension and circulating albumin, Hb, and phosphate levels, higher PSTR associated with greater risk (subdistribution hazard ratio, sHR) for *all-cause mortality* (fast average: sHR 1.13, 95%CI 1.00-1.26; p=0.04) and fast: sHR 1.19, 95% CI 1.04-1.36; p=0.01), and *CVD-related mortality* (fast average: sHR 1.18, 95%CI 0.99-1.41; p=0.05) and fast: sHR 1.19, 95%CI 0.97-1.46; p=0.08), and reduced *technique survival* (fast average: sHR 1.15, 95%CI 0.95-1.38; p=0.13) and fast: sHR 1.24, 95% CI 0.99-1.54; p=0.05).

Conclusions: These results suggest that fast and fast average PSTR associates with increased mortality risk and tendency towards reduced technique survival when analyzed using adjusted competing-risk regression models.

Funding: Commercial Support - Baxter Renal Care Services; Baxter Healthcare Corporation

PO0989

Multifrequency Bioimpedance Is a Useful Adjunct to Control Fluid Overload in PD Patients

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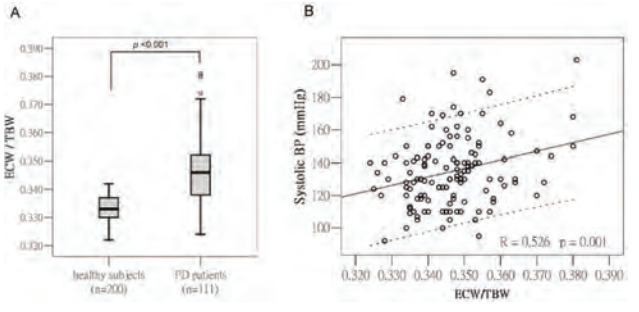
Background: Fluid overload is a well recognized phenomenon in many peritoneal dialysis (PD) patients, but a balance between reduction of dry weight and preservation of residual renal function (RRF) is mandatory. We hypothesize that, to achieve an ideal dry weight, adjustment by multi-frequency bioimpedance (MF-BIA) guide offers less adverse effect on residual renal function than that by clinical judgment alone.

Methods: The hydration status of various body compartments were measured using a MF-BIA device (Inbody 720, Biospace). The normalized hydration score was defined as extracellular water (ECW)/total body water (TBW). All patients were evaluated monthly for 6 months. The dry weight of study group was adjusted according to MF-BIA to avoid dehydration, and the dry weight of control group was determined clinically. Ambulatory blood pressure, anti-hypertension medication dosage, serum biochemical parameters, and RRF were recorded monthly. IL-6 and hs-CRP will be checked before and after the study.

Results: 93 stable PD patients (48 in study and 45 in control group) completed the study. ECW/TBW ratio was higher in PD patients than sex- and age- matched healthy subjects. (Figure 1). In PD patient, the ratio of ECW/TBW was positive correlated to age ($r = 0.534$), peritoneal D/P ratio ($r = 0.518$), systolic BP ($r = 0.526$) and negative correlated to urine volume ($r = -0.526$), serum albumin ($r = -0.658$). After 6 months intervention, study group decreased 1.2 kg and control group gained 0.2 kg. The study group had a better systolic and diastolic BP control and a higher serum albumin (3.75 ± 0.61 vs 3.48 ± 0.68 g/dl, $p = 0.047$). The RRF has no difference between two groups.

Conclusions: Our results showed that correction of fluid overload would improve blood pressure control. Being an objective tool to assess hydration status of various body compartments, MF-BIA is a useful adjunct to correct fluid overload without the loss of RRF in our short-term study.



PO0990

Associations Between Loop Diuretic Use and Outcomes Among Patients Treated with Peritoneal Dialysis

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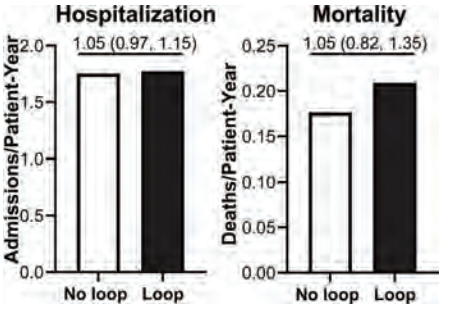
Background: Among hemodialysis patients, an active loop diuretic prescription at the time of dialysis initiation is associated with a lower hospitalization rate and other favorable outcomes, compared to no prescription. Whether this finding extends to patients initiating peritoneal dialysis (PD) is not known.

Methods: Data used for this retrospective study comprised electronic health records and US Renal Data System claims data merged through direct linkage. Included patients initiated PD at a large dialysis organization between 01 Jan 2006 and 30 June 2014, were nonoliguric at dialysis start (24-hour urine collection >200 cc), and had Medicare insurance. Exposure was determined on the basis of an active, filled supply for a loop diuretic spanning day 90 of PD. Outcomes were considered from day 91 of PD through the first of death, loss to follow-up, or study end (31 Dec 2014) and were compared across exposure groups using appropriate statistical models adjusted for imbalanced patient characteristics.

Results: Among patients initiating PD with a loop diuretic prescription (N=792), the hospitalization rate during follow-up was 1.77 admissions/patient-year (pt-yr), compared to 1.75/pt-year for those without (N=1363), corresponding to an adjusted incidence rate ratio (aIRR) of 1.05 (95% confidence interval [CI] 0.97-1.15). Mortality was likewise comparable between groups, with crude rates of 0.21 and 0.18 deaths/pt-yr, respectively (aIRR 1.05, 95% CI 0.82-1.35). No substantial differences were observed between exposure groups with respect to serum potassium, renal Kt/V, or time to transition to hemodialysis.

Conclusions: Among patients initiating PD, no beneficial associations were observed between loop diuretic use and any of the outcomes examined.



PO0991

Nationwide Standardized Peritonitis Reporting: Preliminary Results from the Optimizing the Prevention of Peritoneal Dialysis-Associated Peritonitis in the United States (OPPUS) Study

Jeffrey Perl,[1] Geoffrey A. Block,[4] Martin J. Schreiber,[8] Beth M. Piraino,[9] Suzanne Watnick,[3] Shweta Bansal,[7] Vesh Srivatana,[5] Tahsin Masud,[6] Leslie Garcia,[2] Lauren Kane,[2] Keith McCullough,[2] Isaac Teitelbaum,[10] Ronald L. Pisoni.[2] OPPUS Peritonitis Tracker Study consortium *[1]St. Michaels, Toronto, ON, Canada; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Northwest Kidney Centers, Seattle, WA; [4]US renal care, Plano, TX; [5]Rogosin Institute, New York, NY; [6]Emory University, Atlanta, GA; [7]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [8]DaVita Inc, Denver, CO; [9]University of Pittsburgh Medical Center, Pittsburgh, PA; [10]University of Colorado School of Medicine, Aurora, CO.*

Background: Peritoneal Dialysis (PD) associated peritonitis is the leading cause of transfer to hemodialysis (HD) in the US. No formal mechanism or surveillance system exists for nationwide peritonitis reporting. Our primary aim was to develop a uniform widescale peritonitis reporting mechanism and evaluate its implementation via a one-year pilot study.

Methods: Following literature review, stakeholder consultation, and ISPD guidelines review, a web-based peritonitis tracker tool (OPPUS-Link) was developed. Pilot sites for one-year data collection were selected based on geography and reported peritonitis rates, including 3 medium-large dialysis organizations. We provided formal training, central data review, and adjudication of all peritonitis episodes and outcomes.

Results: Initial data for 31/64 participating facilities includes 86 peritonitis episodes (rate of 0.26 episodes/year [326 patient years of follow-up]). PD catheter removal and hospitalization occurred in 14% and 41% of episodes respectively (see table). Ongoing challenges include high rates of culture-negative peritonitis (24% overall) and data retrieval for peritonitis episodes occurring during hospitalization.

Conclusions: Standardized, uniform peritonitis reporting is feasible, a first step in national PD-peritonitis surveillance, allowing for benchmarking, outbreak identification, and quality improvement initiative implementation. Further data validation is necessary and integrating routine peritonitis reporting in electronic health records with an overall goal of peritonitis reduction and improved outcomes for PD patients.

Funding: Other NIH Support - AHRQ

Preliminary results for 31/64 clinics

Measure/variable	Total
Total patient follow-up (patient-years)	325.8
Total peritonitis episodes reported*, no.	86
Peritonitis episode count (rate/patient-year) by organism type:	
Gram-positive	46 (0.14)
Gram-negative	9 (0.03)
Culture-negative	21 (0.06)
Polymicrobial	6 (0.02)
Yeast	3 (0.01)
Unknown to clinic	1 (0.00)
Peritonitis episodes after catheter insertion, but prior to or during PD training, no.	0
Patients with 1 peritonitis episode, no.	72
Patients with 2 peritonitis episodes, no.	7
Peritonitis rate, overall, event per patient-year	0.26
Peritonitis episodes associated with a hospitalization, no. (%)	35 (40.7%)
Hospitalizations with pre-existing peritonitis, (%)	85.1%
Peritonitis acquired in hospital [>24 hrs post-admission], (%)	14.9%
Peritonitis episodes associated with death (within 60 days), no. (%)	2 (2.3%)
Peritonitis episodes in which PD catheter was removed, no. (%)	12 (14.0%)
Peritonitis episodes associated with HD transfers, no. (%)	10 (11.6%)
Permanent HD transfer (%)	9.3%
Temporary HD transfer (%)	2.3%

*Total peritonitis episodes reported, excluding relapse episodes.

PO0992

Identifying Peritoneal Dialysis (PD)-Associated Peritonitis Using Medicare Claims

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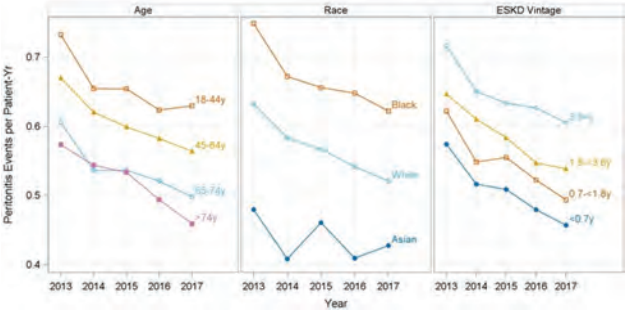
Background: Medicare fee-for-service (FFS) claims offer a population-based approach to PD-associated peritonitis that may offer valuable insights into predictors, trends and preferred practices.

Methods: We used United States Renal Data System (USRDS) standard analysis files for claims (inpatient, outpatient and physician-supplier), eligibility, modality and demographic information. The sample consisted of PD patient-months from 2013 through 2017 characterized by Medicare FFS coverage and paid claims for dialysis or hospital services. We identified ICD-9 and ICD-10 diagnosis codes for peritonitis, including those that do not clearly distinguish peritonitis from catheter infections/inflammation ("catheter codes"). A new peritonitis episode was defined as a peritonitis claim 30+ days from any prior peritonitis claim or 50+ days from the initial peritonitis claim for a prior episode.

Results: The sample included 88,396 adult patients (128,000 observed patient-years), yielding 510,000 peritonitis claims and 75,000 peritonitis episodes. Coding was heterogeneous with no single diagnosis code present on the majority of claims. Peritonitis episodes were inferred from aggregated claims (mean 6.3, median 2). Half of episodes were exclusively outpatient, 7% exclusively inpatient, and 16% exclusively comprised of catheter code claims. The overall peritonitis rate was 0.59 and 0.49 episodes per patient-year with and without inclusion of catheter codes respectively. Peritonitis rates declined by 4%/year from 2013-2017, and varied by age, race (Black > White >Asian), and ESKD vintage.

Conclusions: Coding heterogeneity indicates a lack of standardization and need for clearer coding guidance. We found differences between races, ages, and patient vintages, and declining rates from 2013-2017. These rates are 2-fold higher than reported in US-PDOPPS by Perl et al (AJKD 2020) which is not restricted to Medicare. Claims are an important data source for peritonitis, but more work is needed to validate these rates.

Funding: Other NIH Support - Agency for Healthcare Research and Quality



PO0993

Improving Peritoneal Dialysis Effluent Sample Collecting Techniques to Lower Culture-Negative Peritonitis Rate: A Single-Center Experience

Jie Ouyang, Shraddha Raghavan, Angelika C. Gruessner, Subodh J. Saggi. *SUNY Downstate Health Sciences University, New York City, NY.*

Background: The most common and severe complication of peritoneal dialysis (PD) is peritonitis. Patients usually present with abdominal pain and cloudy peritoneal effluent. An accurate diagnosis is critical to treatment and avoiding technique failure. Culture negative peritonitis (CNP) rate can be up to 20% with standard bedside collection. The rate among PD centers in the US was reported to be 13.4%-40%. The causes of CNP include recent antibiotic use, Gram-positive infections which fail to reach the threshold of detection, or technical imperfection. The culture techniques were highly variable across centers. Due to a high rate of CNP at our facility, we instituted a new policy of PD effluent culture techniques on 7/30/2013 that was recommended by ISPD guideline. We conducted a quality improvement analysis to examine the outcome of this intervention.

Methods: Data were collected for patients who received PD from 2009 to 2018. The new policy required that a 50 ml of PD effluent be collected and centrifuged prior to the sediment being cultured. Diagnosis of peritonitis was analyzed with culture results before and after the policy change.

Results: This study enrolled 38 patients and total 122 visits for potential peritonitis were observed. As shown in table1, our CNP rate prior to the policy change was 41.7%. After the implementation of the new culture strategy, the rate significantly decreased to 25%. However, the false positive rate increased from 4.9% to 23.1% with a drop of the true positive rate (sensitivity) from 95.1% to 76.9%, when the peritonitis rate in our facility declined from 0.43 to 0.09 /patient year.

Conclusions: This analysis showed that the new PD effluent culture policy effectively lowered the culture negative peritonitis rate in our PD center. However, constant reinforcement of this policy and proper sterilization is required for the purpose of due diligence.

Table 1

	1/1/2009-7/29/2013	7/30/2013-12/31/2018
- Peritonitis with no culture growth	58.3% (21/36)	75% (24/32)
+ Peritonitis with no culture growth	41.7% (15/36)	25% (8/32)
- Peritonitis with culture growth	4.9% (2/41)	23.1% (3/13)
+ Peritonitis with culture growth	95.1% (39/41)	76.9% (10/13)

PO0994

Protective Association Found Between Peritoneal Dialysis Patients Prescribed Home Antibiotics Kits and In-Center Hemodialysis Transition

Derek M. Blankenship,[1] Michelle Carver,[2] Dinesh K. Chatoth,[1] Chance Mysayphonh,[1] Debu Ray,[1] Patricia Mccarley,[1] Len A. Usvyat,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care, Global Medical Office, Waltham, MA; [2]Fresenius Medical Care North America, Waltham, MA.*

Background: Peritonitis is a complication of peritoneal dialysis (PD) and is likely associated with technique failure. To decrease time to peritonitis treatment, Fresenius Kidney Care (FKC) clinicians can prescribe broad-spectrum intraperitoneal and oral antibiotic kits. Kits are self-administered by home PD patients for suspected wet contamination or peritonitis per algorithm. The study purpose is to assess hemodialysis (HD) transition as well as peritonitis among PD patients receiving a home antibiotic kit.

Methods: This retrospective cohort study identified FKC PD patients prescribed home antibiotic kits between June 1st, 2019 and June 30th, 2020. Home FKC PD patients not receiving kit during same period composed the control pool. Patients are matched in a 1:4 ratio on clinical and demographic data using propensity scores. Patients were followed up to 6 months for transition to HD and first peritonitis event. Outcomes were analyzed with weighted competing risk Cox Proportional Hazards Models.

Results: 2,888 treatment and 10,613 controls were studied. Of the 2,888 treatment patients and weighted 1,921.2 matched controls, 11.9% and 13.5% transitioned to HD, respectively. A 0.88 hazard ratio (p=0.0448) determined treatment group is 12% less likely to transition to HD at any point during follow-up period. 10.4% treatment patients and 8.5% controls have at least one peritonitis event. The treatment group is 23% more likely to have a Peritonitis event (p=0.0019).

Conclusions: The study identified a protective association in HD attrition for home PD patients receiving peritonitis kits despite a positive association between patients receiving the kits and peritonitis. These findings may reflect residual confounding factors such as clinicians prescribing kits for patients at higher risk of peritonitis for uncontrolled or unmeasurable factors since kits do not prevent peritonitis but increase uniformity of treatment. The findings justify need for further research including prospective randomized studies.

Funding: Commercial Support - Fresenius Medical Care

PO0995

Assessing Physician Clinic Practices and Competencies in Performing Peritoneal Dialysis Catheter Flushes During the 10-Day Global Period

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Background: Early flushing of peritoneal dialysis (PD) catheters theoretically reduces the incidence of catheter obstruction by decreasing formation of fibrin strands or blood clots. Early flushing also enables timely identification of catheter dysfunction, creating an opportunity to revise the catheter prior to scheduled training and initiation of therapy. It is unknown how frequently PD access providers perform flushes in their clinics, but Centers for Medicare & Medicaid Services (CMS) has indicated that services performed within 10 days following catheter placement (global period) are the responsibility of PD access providers. Therefore, under existing regulations, dialysis organizations generally defer to access providers to perform catheter flushes during this global period. The purpose of this study is to assess current practices of PD access provider clinics (surgeon, interventional nephrologist or radiologist) in performing catheter flushes.

Methods: PD access providers placing catheters for a large dialysis organization in the southwestern United States during 2020 were surveyed. The 3-question survey asked 1) PD access provider specialty, 2) if the clinic performed catheter flushes, and 3) the background of the staff person assisting the physician with clinic procedures. Responses were acquired by direct or telephone contact with the physician or clinic staff.

Results: Survey responses were obtained for all 201 providers who placed PD catheters during 2020 (Table).

Conclusions: Significantly, none of the PD access provider clinics elected to perform catheter flushes. This lack of service may indicate a lack of expertise or readily accessible supplies. While PD nurses are trained and equipped by dialysis organizations to competently perform catheter flushes, current regulations generally prevent them from providing these services during the global period. The survey supports a re-examination of the CMS policy, suggesting a need for more flexibility for dialysis organizations to provide these services during the global period for patient safety and optimal patient outcomes.

Funding: Commercial Support - DaVita, Inc.

Survey Questions	Surgeon	Interventional Radiologist	Interventional Nephrologist
PD access provider specialty?, n (%)	186 (92.5)	12 (6)	3 (1.5)
Clinic performed catheter flushes?, n	0	0	0
Clinic staff background?, n (% of all clinic staff)			
Medical assistant, certified or not	132 (65.7)		
Licensed vocational nurse	6 (3)		
Radiology technician		12 (6)	
Registered nurse	34 (16.9)		3 (1.5)
Nurse practitioner	8 (4)		
Physician assistant	6 (3)		

PO0996

Peritoneal Dialysis Catheter Flushing Leading to Syncope from Vagal Nerve Stimulation

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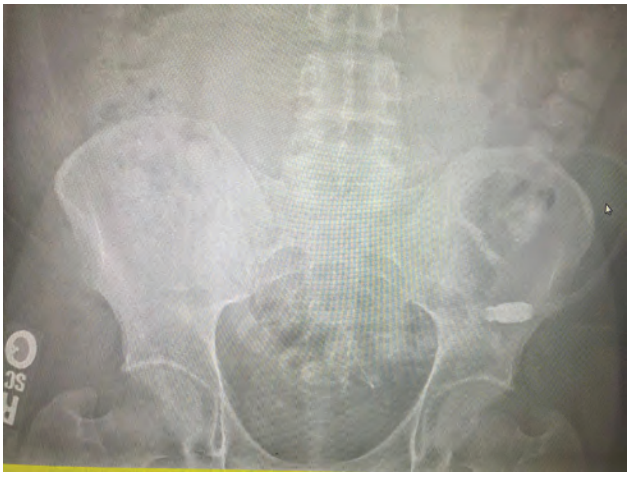
Introduction: Peritoneal dialysis is the most common form of home dialysis. Complications can arise however any time the peritoneum is invaded such as during surgery. The patient is a 37-year-old male on PD secondary to developing progressive IgA nephropathy. The patient suffered from an inguinal hernia which required open repair with mesh placement. This required the patient to be subsequently bridged with HD.

Case Description: After 6 weeks the patient was in the process of beginning to transition back to PD dialysis. The patient underwent flushing of his peritoneal catheter and subsequently developed hypotension, diaphoresis and near syncope. This process continued every time the patient's peritoneal catheter was flushed. 500 mL's of 2.5% warm dialysate was also attempted to fill the patient resulting in the same near syncopal episode. There was no problem with aspiration of the catheter. There was no resistance involved in aspiration or flushing. KUB was obtained showing the catheter placed in the left lower pelvis as well as a significant amount of stool burden. Despite aggressive regimen of laxatives the patient continued to suffer from hypotension and near syncope with catheter flushing. The patient was referred to surgery for catheter repositioning. Operative report identified that the tip of the catheter was caught in anterior abdominal adhesions. The catheter was repositioned to the right lower pelvis. After 2 weeks the patient was able to tolerate flushing of his dialysis catheter with progressively increasing fill volumes to the point that he was able to be completely converted back to peritoneal dialysis.

Discussion: It was theroized that catheter tip was uniquely postioned leading to vagal nerve stimulation when liquid was infused though the catheter. This case illustrates a unique complication of catheter malposition and adhesions resulting in near syncope secondary to vagal nerve stimulation. With repositioning of the patient's catheter the symptoms completely resolved.



PO0997

Pharmacokinetics of Intraperitoneal Vancomycin in Patients on Automated Peritoneal Dialysis

Edwin Lam,[1,2] Walter K. Kraft,[1] Douglas F. Stickle,[1] Beth M. Piraino,[3] JingJing Zhang.[1] *[1]Thomas Jefferson University, Philadelphia, PA; [2]National Institutes of Health, Bethesda, MD; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: It is unclear if the pharmacokinetics of vancomycin is the same during automated peritoneal dialysis (APD) where cycler exchanges may affect the systemic, peritoneal, and urinary disposition of drug.

Methods: This was a prospective pharmacokinetic study in peritonitis-negative patients on APD. A single dose of vancomycin (20 mg/kg) was administered through the peritoneum and allowed to dwell for at least 15 hours. Patients underwent four drug-free exchanges following the initial dwell period. Plasma, dialysate and urine were collected over the course of 7 days for pharmacokinetic analysis. A non-compartmental analysis was used to estimate vancomycin pharmacokinetic parameters.

Results: Four patients enrolled and completed the study with no adverse events. Three patients had residual renal function. Following a median (range) dwell of 14.6 (14.2 – 17.6 hours), the mean (± SD) observed maximum plasma concentration was 28.7 ± 4.9 mg/L with a mean (± SD) bioavailability of 98.5 ± 1.4% prior to starting the cycler. The overall mean plasma clearance estimated from study start to completion was was 7.3 ± 1.2 mL/min. In patients with residual renal function, the mean (± SD) vancomycin renal clearance was 3.1 ± 1.5 mL/min.

Conclusions: Despite the small sample size, this pilot study suggest that the dwell time has important implications for systemic vancomycin exposure, time to therapeutic plasma concentration, and dosing. Dose is driven by dwell time while the cycler determines the dosing interval. Rapid exchanges from APD will determine the frequency of dosing rather than the adequacy of absorption when vancomycin is given in the peritoneum.

Funding: Other NIH Support - Edwin Lam was supported by an NIH T32 training grant (GM008562) at the time of study conduct.

Plasma, dialysis, and urine pharmacokinetic parameters following a single intraperitoneal dose.

	T_{max} (hours)	C_{max} (mg/L)	$AUC_{0\text{-last}}$ (hr x mg/L)	CL/F (mL/min)§	CL_{renal} (mL/min)	CL_{APD} (mL/min)	CL/F (mL/min)*	V/F (L)	Plasma $t_{1/2}$ (hours)	Peritoneum-Plasma Transfer $t_{1/2}$ (hours)
Subject 1	13.8	34.4	3089.0	7.4	1.6	7.1	11.6	62.7	98.2	2.9
Subject 2	14.9	25.5	2635.8	5.5	-	6.5	6.5	62.8	132.4	3.3
Subject 3	14.0	23.8	2292.9	7.3	2.5	14.6	17.0	63.8	100.4	3.3
Subject 4	15.0	31.2	2341.9	8.6	5.1	16.2	19.2	49.2	66.0	4.0
Mean	14.4†	28.7	2589.9	7.2	3.1	11.1	13.6	59.6	99.3†	3.3†
SD	13.8 - 15.0‡	4.9	365.6	1.3	1.5	4.3	4.9	6.9	66.0 - 99.3‡	2.9 - 4.0‡

§ Represents the total plasma clearance for the duration of the study.

*Represents the total plasma clearance during the dialytic exchange period.

†Median value reported.

‡Min and Max range reported.

PO0998

Effect of Velphoro on Serum Phosphate and Albumin in Peritoneal Dialysis Patients

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Background: Hyperphosphatemia is common in patients on peritoneal dialysis (PD). Restricting phosphorus in the diet often leads to a decrease in protein intake, which may result in hypoalbuminemia. Hypoalbuminemia is associated with an increased risk of morbidity and mortality in PD patients. In observational studies, sucroferric oxyhydroxide (SO), an iron-based phosphate binder, was associated with improved phosphate control and higher serum albumin in hemodialysis patients. Whether SO improves phosphate control and nutritional status in PD patients is unknown.

Methods: We performed a prospective, open-label, 6-month, pilot study of 17 adult PD patients from the Denver Metro Area. Patients had to use automated peritoneal dialysis for at least 3 months, have a serum albumin ≤ 3.8 g/dL, and have serum phosphate ≥ 5.5 mg/dL or ≤5.5 mg/dL on a binder other than SO. Patients currently on phosphate binders underwent a 2-week washout period. Participants were started on SO at a dose of 1 tablet daily with meals. Serum phosphate was checked monthly and the dose of SO was titrated to a goal serum phosphate of < 5.5 mg/dL. The primary outcome was change in serum phosphate and serum albumin over 6 months.

Results: The mean (SD) age and dialysis vintage was 55 ± 13 years and 3.8 ± 2.7 years, respectively. The majority of patients were male (65%), white (82.4%) and non-Hispanic (64.7%). 88% of patients were on a phosphate binder at baseline and the majority were on sevelamer (73%). Twelve patients completed the study. Two patients withdrew due to side effects (diarrhea), 1 patient changed to hemodialysis and 2 patients died (unrelated to the study). Mild diarrhea and change in stool color were the most frequently reported side effects. Results are shown in Table 1. Serum phosphate decreased significantly from baseline but there was no significant change in serum albumin. Phosphate binder pill burden significantly decreased

Conclusions: Serum phosphate decreased significantly with fewer phosphate binder pills/day after switching to SO. There was no change in serum albumin.

Funding: Commercial Support - Fresenius Renal Therapies

	Prior to washout	Baseline	Month 3	Month 6	P-value
Phosphate mg/dL	6.72 ± 1.9	7.47 ± 1.76	5.63 ± 0.88	5.65 ± 1.81	0.001
Albumin g/L	3.51 ± 0.32	3.49 ± 0.37	3.58 ± 0.27	3.52 ± 0.28	0.46
PTH pg/mL	414 (143-613)	415 (292-630)	377 (128-504)	379 (237-540)	0.96
Phosphate binders (pills/day)	11.0 (9.0-12)			4.0 (3-5.50)	0.003

PO0999

Prognostic Significance of Plasma Vaspin and Adiponectin Levels in Peritoneal Dialysis Patients

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Background: Adiponectin and vaspin are key adipokines that play important roles in the physiology of adipose tissue and contribute to the pathogenesis of metabolic disturbance in chronic kidney disease (CKD). We explored the prognostic role of plasma adiponectin and vaspin levels in peritoneal dialysis (PD) patients – a population that metabolic syndrome, obesity, and cachexia are all common.

Methods: We measured plasma adiponectin and vaspin levels in a cohort of new PD patients and analyzed their relation with patient survival.

Results: We studied 152 patients. Their mean age was 58.38 ± 11.67 years; 102 (67.1%) were men, 92 (60.5%) were diabetic. The median plasma adiponectin level was 31.98 (Interquartile range [IQR]: 16.81-49.49) mg/ml; median vaspin level 0.18 (IQR: 0.11-0.32) ng/ml. There was no significant correlation between plasma adiponectin and vaspin levels. Plasma adiponectin level had modest correlations with Charlson's comorbidity score (r = -174, p = 0.039), triceps skin fold (r = -269, p = 0.001), and mass transfer area coefficient of peritoneum (r = 0.211; p = 0.015). In contrast, plasma vaspin level correlated with carotid-to-femoral pulse wave velocity (r = -240, p = 0.005), triceps skin fold (r = 0.198, p = 0.018), and extracellular to Intracellular fluid volume ratio (r = 170, p = 0.047). After adjusting for clinical confounders, plasma adiponectin and vaspin levels significantly predicted patient survival (adjusted hazard ratio [AHR] of adiponectin 1.018, 95% confidence interval [Cl] 1.004-1.031, p=0.010; AHR of vaspin 1.018, 95%Cl 1.008-1.029, p=0.001).

Conclusions: Plasma adiponectin level also correlated with peritoneal transport status, while plasma vaspin level correlated with the severity of fluid overload and atherosclerosis. Plasma levels of both adiponectin and vaspin are independent predictors of patient survival. Our results suggest that adiponectin and vaspin are involved in different pathways of metabolic disturbance in uremia.

PO1000

The Impact of Peritoneal and Urine Protein Losses on Nutritional Status in Peritoneal Dialysis Patients

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Background: The etiology of malnutrition in peritoneal dialysis (PD) patients is multifactorial, but the peritoneal protein losses (PPL) and proteinuria may be important contributing factors. We aimed to evaluate if the total protein losses (into urine and dialysate) in PD patients have an impact on their nutritional status.

Methods: A retrospective observational study of PD patients over the first year in PD. Demographic, clinical, and analytical data were collected at baseline (time of PD initiation), 6 and 12 months later. Nutritional status was assessed using normalized protein catabolic rate (nPCR), body mass index (BMI), lean body mass (LBM), and body fat mass (BFM). The total amount of 24h urine and dialysate protein losses (ProtUrDial) and delta (Δ) values (difference between the end of follow-up period and baseline) of continuous variables were also calculated.

Results: Twenty patients were enrolled (55.8±10.8 years; 65% male). Except for serum albumin (sAlb), which changed significantly from the baseline to the end of the follow-up period (p=0.001), there were no differences in protein loss into dialysate (ProtDial), proteinuria (ProtUrine), nPCR, BMI, LBM, and BFM over time. In the 3 time points there was a significative positive correlation between ProtUrine and nPCR (r=0.563, p=0.01; r=0.584, p=0.031; r=0.611, p=0.004, respectively). At the end of the follow-up period, we verified a negative correlation between sAlb and ProtUrDial (r=-0.477; p=0.033). There was no correlation between ΔProtDial and nutritional parameters status, however, there was a positive correlation between ΔProtUrine and ΔBMI (r=0.492; p=0.028). Regarding ΔProtUrDial, we verified a negative correlation with Δ%LBM (r=-0.664; p=0.026) and, although not significant, a positive correlation with Δ%BFM (r=0.573; p=0.066).

Conclusions: The PPL has already been linked to malnutrition in PD patients. However, we found that the total amount of protein losses daily (into urine and dialysate), and not each one individually, seems to influence the nutritional status of PD patients. Besides, proteinuria appeared to have a greater impact on nutritional changes than peritoneal losses. However, more studies with larger samples are needed to clarify this association.

PO1001

MMP-7 Affects Peritoneal Ultrafiltration Associated with Elevated Aquaporin-1 Expression via MAPK/ERK Pathway in Peritoneal Mesothelial Cells

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Background: Peritoneal membrane dysfunction and the resulting ultrafiltration failure are the major disadvantages of long-term peritoneal dialysis (PD). It becomes increasingly clear that mesothelial cells play a vital role in the pathophysiological changes of the peritoneal membrane. Matrix metalloproteinases (MMPs) function in the extracellular environment of cells and mediate extracellular matrix turnover during peritoneal membrane homeostasis. Aquaporin-1 (AQP-1), one of the water-specific channel proteins distributed in the endothelium lining the peritoneal capillaries, facilitates the osmotic transport of water across the capillary endothelium, thereby playing an essential role in ultrafiltration during PD.

Methods: Human peritoneal mesothelial cell (HPMCs)line (HMrSV5) strain was continuously cultured in vitro and stimulated with MMP-7. The concentration gradient and time gradient stimulated were set up respectively. HMrSV5 cells were incubated with the suggested volume of lenti-virus negative and lenti-virus MMP-7. Western Blot, RNA isolation, real time PCR and immunofluorescence assay were used to detect the expression of MMP-7, AQP-1 and mitogen-activated protein kinases (MAPKs) phosphorylation in HMrSV5 cells, to verify that MMP-7 affects peritoneal ultrafiltration associated with elevated aquaporin-1 expression via MAPK/ERK pathway in peritoneal mesothelial cells.

Results: We showed that dialysate MMP-7 levels markedly increased in the patients with PD, and the elevated MMP-7 level was negatively associated with peritoneal ultrafiltration volume. Interestingly, MMP-7 could regulate the cell osmotic pressure and volume of human peritoneal mesothelial cells. Moreover, we provided the evidence that MMP-7 activated mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinase 1/2 (ERK) pathway and subsequently promoted the expression of aquaporin-1 (AQP-1) resulting in the change of cell osmotic pressure. Using a specific inhibitor of ERK pathway abrogated the MMP-7-mediating AQP-1 upregulation and cellular homeostasis.

Conclusions: In summary, all the findings indicate that MMP-7 could modulate the activity of peritoneal cavity during PD, and dialysate MMP-7 might be a noninvasive biomarker and an alternative therapeutic target for PD patients with ultrafiltration failure.

Funding: Clinical Revenue Support

PO1002

Psychosocial Impact of COVID-19 Pandemic on Patients with ESKD on Peritoneal Dialysis

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Background: The mortality rate from COVID-19 is remarkably high in elderly patients and those with chronic conditions. Increases in physical and mental stress among patients with chronic conditions, especially end-stage kidney disease, were expected to have occurred in response to the COVID-19 pandemic. This study reports that the psychosocial impact of the COVID-19 pandemic on patients receiving peritoneal dialysis.

Methods: During the pandemic, we surveyed the mental health of patients with end-stage kidney disease on peritoneal dialysis at a single center. Depression using with BDI scoring was evaluated and then compared in peritoneal dialysis patients between before and the pandemic declaration. We also surveyed patient satisfaction with the self-care services associated with peritoneal dialysis under the pandemic period.

Results: One-third of the survey respondents (n=176) were moderately to extremely worried about their physical health being impacted by the pandemic, while 20% moderately to extremely worried about their mental and emotional health being impacted. About half of participant reported feeling that they were unable to handle their personal problems and that things were out of their control. However, most felt that they could retain control over the important things and overcome their difficulties. Despite COVID-19 pandemic, no significant changes in depression scores were apparent between before and during the pandemic. Most participants were satisfied with the in-home self-care services delivered by either telephone or remote monitoring.

Conclusions: Many participants reported that they were afraid of COVID-19, but most patients with PD felt that they could overcome the crisis. The COVID-19 pandemic did not affect the depression of patients receiving peritoneal dialysis.

PO1003

Peritoneal-Mediastinal Communication Complication in Peritoneal Dialysis

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Introduction: Increased intra-abdominal pressure is a well-recognized non-infectious complication of peritoneal dialysis (PD) resulting from instillation of dialysate fluid into the peritoneal cavity. Peritoneal-pleural communication causing hydrothorax is well-described in the literature, but cases of peritoneal-mediastinal communication are scarce.

Case Description: A 36-year old Caucasian man with end-stage kidney disease secondary to calcineurin inhibitor nephrotoxicity and BK virus nephropathy transitioned to continuous cycler peritoneal dialysis (CCPD) after one year of intermittent hemodialysis (iHD). He presented to our institution nine months after starting CCPD primarily because of complications related to prior heart transplantation. He underwent cardiac surgery and did not have any problem with his CCPD in the immediate post-operative period and was discharged. One month later, however, he presented with increased serous drainage from his sternal incision site and reduced ultrafiltration. A chest CT scan revealed a partially loculated anterior chest wall subcutaneous fluid collection. He was taken to the operating room and was found to have a peritoneal-mediastinal communication. He was successfully managed with "low-pressure" PD by using reduced fill volumes for all his exchanges, which also allowed optimal healing of the muscle flap closing the communication. Transition to iHD was considered, but he had no vascular access options because of multiple prior thromboses. He was able to subsequently return to his outpatient CCPD prescription about two months after his surgery by doing very gentle uptitration of his fill volumes. Unfortunately, one and a half months after his last hospitalization, he succumbed to septic shock secondary to trans-lumbar PICC-associated Candida glabrata fungemia.

Discussion: A peritoneal-mediastinal communication should be suspected in an otherwise asymptomatic patient on PD with reduced ultrafiltration who underwent any form of chest surgery. Clinical suspicion can be confirmed either through CT peritoneography or intraoperatively. Management with a trial of "low-pressure" PD is feasible and can be successful, particularly if iHD is not an option. A multi-disciplinary approach involving our surgical colleagues is also crucial to ensure appropriate patient care.

PO1004

Sweet Pleural Effusion in a Peritoneal Dialysis Patient

Karla G. Carias Martinez,[1] Nityasree Srialluri,[1] Jose M. Monroy-Trujillo.[2] *[1]Johns Hopkins Medicine, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD.*

Introduction: Pleural Effusions are frequently seen in dialysis patients with an incidence as high as 80%, with a variety of possible differential etiologies

Case Description: A 62-year-old female with HFpEF, DM and ESRD due to biopsy proven diabetic nephropathy recently started on nightly continuous cyclic PD with a prescription of 4 exchanges of 2.5% Dextrose solution with 2 liters fill volumes with a dwell time of 1h40 min for a total time of 8.5 hrs with no day dwells presented with dyspnea. She had missed 2 sessions of dialysis and noted increasing weight as declining ultrafiltration volumes. On exam tachypneic on 4L of oxygen and saturating 100%, had decreased breath sounds on the right pulmonary base, no JVD or lower extremity edema. Laboratory showed creatinine 4.19 mg/dl, BUN 41 mg/dl, proBNP 30,186 pg/ml, Hemoglobin 11 gm/dl and WBC 5.91 mg/dl. Chest X- Ray revealed small to moderate right pleural effusion and opacities in the right mid and lower lung. CT Chest showed a large right sided pleural effusion. With her unilateral pleural effusion and recent start of PD the presence of a peritoneal pleural fistula was suspected. A therapeutic thoracentesis was done draining 1 liter of fluid consistent with a transudate, no microorganism or malignant cells were isolated. Pleural fluid glucose was 274 mg/dL compared to a serum glucose of 155 mg/dL. A peritoneal perfusion scan was done detecting radiotracer uptake in right hemithorax Image 1 confirming a peritoneal pleural communication. She was transitioned to HD and maintained on it per the patient's preference

Discussion: A pleuroperitoneal leak is a rare but important cause of pleural effusion in patients on PD and should be considered in any patient presenting with a unilateral effusion. Incidence is less than 2%. The diagnosis is made by measuring the ratio between the pleural to serum glucose which usually is > 1. Other tests include technetium-99m labeled peritoneal scintigraphy. Treatment usually requires cessation of PD for 4-6 weeks and transition to HD. For patients willing to return to PD, a diaphragmatic repair is usually required

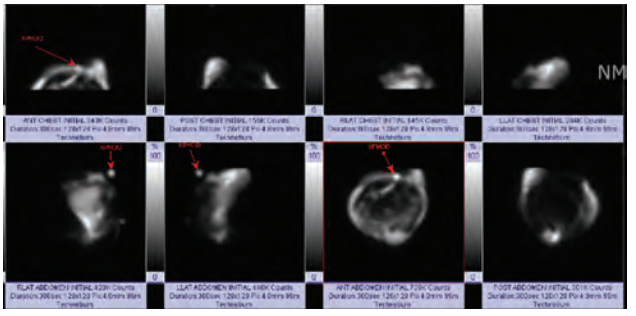

Image 1

PO1005

Progression of Left Ventricular Mass Index After Peritoneal Dialysis Initiation: A Potential Killer

Yun Chen, Shuqi Dai, Chuan-Ming Hao, Tongying Zhu. *Huashan Hospital Fudan University, Shanghai, China.*

Background: Left ventricular hypertrophy (LVH), defined by the left ventricular mass index (LVMI), is highly prevalent in dialysis patients. LVMI has been widely accepted as a strong predictor of cardiovascular events. However, the dynamic changes of LVMI are rarely discussed, especially among peritoneal dialysis (PD) patients. The study aimed to investigate the prognostic significance of LVMI-progression in PD patients, and explore risks factors for LVMI-progression.

Methods: It was designed as a prospective, observational study. Incident PD patients between February 2008 and July 2018 were recruited. Echocardiography was performed yearly to collect LVMI and evaluate its progression. Participants were divided into two subgroups: group with LVMI-progression and group without LVMI-progression. The end points include all-cause mortality, cardiovascular mortality and cardiovascular events. Cox regression models were performed to identify the associations between LVMI-progression and these endpoints. Multivariate logistic regression was conducted to identify factors associated with LVMI-progression.

Results: A total of 216 PD patients (130 men,60.2%) with a mean age of 54.3±16.7 years were recruited. LVMI-progression was identified in 65 patients (30%) after PD initiation. The cohort was followed for a median duration of 65.9 months. Multivariable Cox regression analysis revealed that LVMI-progression was an independent predictor of all-cause mortality (HR, 2.111; 95%CI, 1.148–3.881; p = 0.016), cardiovascular mortality (HR, 2.785; 95%CI, 1.151–6.741; p = 0.023), and cardiovascular events (HR, 1.869; 95% CI, 1.016–3.439; p = 0.044). Multivariable logistic regression showed that hemoglobin (OR, 0.967; 95% CI, 0.939–0.996; p = 0.027), ferritin (OR, 0.995; 95% CI, 0.992–0.999; p = 0.007) and mean arterial pressure (MAP) (OR, 1.048; 95% CI, 1.001–1.097; p = 0.043) were significantly associated with LVMI-progression.

Conclusions: LVMI-progression after PD initiation was independently associated with all-cause mortality and cardiovascular outcomes in PD patients. The dynamic monitoring of LVMI might therefore help identify high-risk patients early. Further studies are needed to clarify whether treatment interventions for factors such as anemia could improve patient outcomes.

PO1006

Estimation of Residual Kidney Function with Serum Levels of β2-Microglobulin in Peritoneal Dialysis

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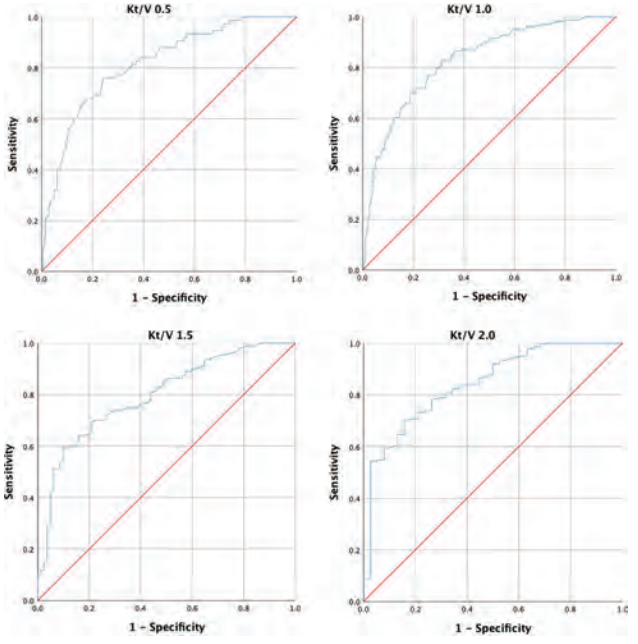
Background: Residual kidney function (RKF) is defined as the kidney function in patients with end-stage renal disease (ESRD) who are receiving dialysis. The ideal method to evaluate and measure RKF is still uncertain and the estimated glomerular filtration rate (eGFR) and urea clearance may over- and underestimate RFK, respectively. ß2-microglobulin (ß2M) is a 11818 Da protein freely filtered and metabolized in kidney

tubules, thus its accumulation reflects an impaired RKF. Our study aimed to evaluate if serum levels of ß2MG could be used as a complementary tool for evaluating RKF in peritoneal dialysis (PD) patients.

Methods: For this retrospective cohort study, we evaluated 423 urine samples of 166 patients who were in the PD program of Hospital das Clínicas, HCFMUSP, Universidade de Sao Paulo, Brazil from January first of 2014 up to August 10th of 2020. We correlated serum ß2M levels with the urea renal Kt/V (urea clearance adjusted by the total body water (TBW), measured with bioimpedance), serum creatinine and urinary volume.

Results: We found a correlation between renal Kt/V and ß2 microglobulin (r= -0.656, p<0.0001), serum creatinine (r= -0.603, p<0.0001), and urinary volume (r= -0.682, p<0.0001). ROC curve revealed that ß2 microglobulin had a high performance to predict renal Kt/V, with a sensitivity of 70 to 81.7% according to the best cutoff. The specificity varied from 71.5% to 84.2%for Kt/V cutoff 0.5, 1.0, 1.5 and 2.0.

Conclusions: Based on the good correlation between serum ß2M and urea renal Kt/V, we suggest that ß2M can be a useful tool to estimate the RFK. This findings can be particularly useful in patients who have difficulties in storing or collecting a 24-hour urine sample.



PO1007

A Rare Case of Roseomonas gilardii Peritonitis in a Peritoneal Dialysis Patient

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Introduction: We report a case of *Roseomonas gilardii* peritonitis in a continuous ambulatory peritoneal dialysis patient.

Case Description: A 71-year-old woman with end stage renal disease (ESRD) on continuous ambulatory peritoneal dialysis (CAPD) for 5 years presented with cloudy effluent without abdominal pain or fever. Laboratory studies revealed a fluid cell count of 800 wbcs/mm^3 with 87% neutrophils. She was started on empiric antibiotic therapy with intraperitoneal vancomycin and ceftazadime. Effluent remained cloudy with elevated WBC despite a 2-week course of antibiotics. Eventually culture grew *Roseomonas gilardii*, a slow growing gram-negative bacillus sensitive to aminoglycosides. Her antibiotic was changed to IP gentamycin and her effluent cleared by day three. Gentamycin was continued for three weeks to ensure she didn't have a relapse as per prior described experience in a similar case.

Discussion: Peritoneal dialysis peritonitis is known to be caused mainly by gram positive and occasionally gram-negative organisms, the usual culprits being pseudomonas, Klebsiella etc. Roseomonas has recently been implicated as a rare cause of bacterial peritonitis with only six reports between 1997 till date. It was first described in 1993 as a cause of bacteremia in humans. *Roseomonas gilardii* is a pink-pigmented, oxidized, gram-negative coccobacillus genus of Roseomonas associated with contaminated water source and soil. Our patient was unaware of being in contact with contaminated water or soil however this could not be ruled out as she did endorse having plants. Of the six cases reported, ours is the third case of R. *gilardii* reported till date. Although the incidence of peritoneal dialysis peritonitis caused by *Roseomonas gilardii* is rare, it is causative agent to be considered by physicians and laboratory staff in the differential diagnosis of refractory bacterial peritonitis in peritoneal dialysis patients. It also serves as a point to emphasize when educating PD patients on the hand-washing techniques and ensuring sterility of water source used for this.

PO1008

Unusual Cause of Recurrent Shortness of Breath in a Peritoneal Dialysis Patient

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Introduction: Pleuroperitoneal leak (PPL) is an unusual cause of recurrent pleural effusion in patients on peritoneal dialysis (PD). It is a rare complication and occur in less than 2% of cases. Diagnosis is challenging and requires high clinical suspicion and awareness of this life threatening complication. Pleural fluid to serum glucose ratio of >50 mg/dl is highly specific for detecting leak of high glucose dialysate into pleural cavity, however this needs to be interpreted in relation with the last dialysis session.

Case Description: A 72 year-old-female with history of end stage renal disease due to biopsy proven focal segmental glomerular sclerosis thought to be secondary to obesity started on CCPD one-month prior presented with worsening shortness of breath of 1 week duration. Workup was unremarkable except for chest X-ray that showed right side pleural effusion. A non-contrast CT chest did not show a diaphragmatic defect. She continued to have worsening SOB prompting an emergent thoracentesis that drained 1.6 L transudate pleural fluid. Pleural fluid to serum glucose gradient was normal at 5 mg/dl but pleural fluid to serum glucose ratio was >1. However, last PD session was 2 days prior to thoracentesis, which could explain this lower ratio. Due to inconclusive[NL1] results, it was decided to instill 300 ml gastrografin in 6L of 2.5% dialysate bags and repeat CT chest. It showed interval re-accumulation of high-density pleural effusion, suggesting trans-diaphragmatic communication. Cardiothoracic surgery was consulted for repair of diaphragmatic defect; however, patient opted for hemodialysis instead.

Discussion: It is important to maintain high clinical index of suspicion in PD patients presenting with hydrothorax. Although high pleural fluid to serum glucose gradient is specific for PPL, pleural to serum glucose ratio >1 is another index that should be considered in addition to post- gastrografin imaging or technetium 99 peritoneal scintigraphy, especially if the last dialysis session was not recent and could potentially alter the biochemical assay results as happened in our case Most cases of PPL occur soon after PD initiation, common on right side. For those who wish to continue PD, surgical repair is often required while transitioning to HD temporarily or doing low volume recumbent PD. Some case series have noted the defect to close spontaneously after holding PD.

PO1009

The Association Between Lower Serum Potassium Level and Increased Cardiovascular Death Among Patients Undergoing Peritoneal Dialysis

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Background: In patients undergoing peritoneal dialysis (PD), lower serum potassium concentration has been related to low nutrition status and suggested as a risk factor for all-cause and cardiovascular mortality. However, the risk of lower serum potassium concentration for cardiovascular death in patients using renin-angiotensin system (RAS) inhibitors or β-blockers is not clear. This study investigated the relationship between lower serum potassium concentration and cardiovascular death among Japanese patients undergoing PD.

Methods: We retrospectively included the 549 patients from our previous multicenter cohort study (Fukuoka Peritoneal Dialysis Database Study). The participants who had undergone PD for at least 90 days were registered from 1 January 2006 to 31 December 2016 and followed until they were transferred to hemodialysis, received a kidney transplantation, died during PD, or were lost to follow-up, or until 31 December 2017. The patients were divided into three groups according to the baseline serum potassium concentration (T1 ≤ 4.0, 4.0 <T2 ≤ 4.5, T3> 4.5 mEq/L). We estimated the relationship between serum potassium concentration and cardiovascular mortality using a Cox proportional hazards model.

Results: During the median observation period of 2.3 years, 111 patients died of any cause, and 38 died of cardiovascular. After multivariable adjustment in the Cox proportional hazard model, lower serum potassium concentration was shown to be an independent risk factor for cardiovascular death; (hazard ratio 95% confidence intervals) T2 and T1 vs. T3 were 2.21 (0.77–6.27) and 2.67 (1.01–7.07), respectively. Stratified-analysis according to the use of RAS inhibitors, β-blockers, or a combination of both drugs showed that this relation was not modified by the use of these drugs.

Conclusions: This study showed that lower serum potassium concentration was associated with increased cardiovascular mortality in PD patients. There was no difference in the risk of lower serum potassium concentration for cardiovascular death according to the use of the RAS inhibitors and/or β-blockers in PD patients.

PO1010

Higher Serum Total Cholesterol to High-Density Lipoprotein Cholesterol Ratio Was Associated with Increased Mortality Among Incident Peritoneal Dialysis Patients

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Background: A few studies have shown that serum total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C) was a risk factor for cardiovascular mortality in the general populations. This study aimed to evaluate the association of TC/HDL-C with mortality in incident peritoneal dialysis patients.

Methods: We enrolled Total of 630 incident peritoneal dialysis patients from 2008 to 2015 in a multi-center, prospective cohort study of Korea. Participants were stratified into quintiles according to the baseline TC, HDL-C, or TC/HDL-C. The association between all-cause mortality and each lipid profile was evaluated using multivariate Cox regression analysis.

Results: During a median follow-up period of 70.3 ± 25.2 months, 185 deaths were recorded. The median TC/HDL-C was 4.54 ± 2.51. Highest TC/HDL-C group showed highest body mass index, percentage of diabetes, and serum albumin level. Multivariate analysis revealed that the highest quintile of the TC/HDL-C (>5.60) was associated with increased risk of all-cause mortality (hazard ratio 1.69, 95% confidence interval 1.04 to 2.76; P = 0.036), whereas neither of TC and HDL were associated with mortality. Increased serum TC/HDL-C was also independent risk factor for mortality in the patients with old age over 50 years, non-diabetes, and any cardiovascular disease.

Conclusions: The single lipid marker of TC or HDL-C could not predict mortality in PD patients. However, non-traditional lipid profile such as increased serum TC/HDL-C ratio was independently associated with an increased risk of all-cause mortality in PD patients.

	Quintile 1 (N =126)		Quintile 2 (N =125)		Quintile 4 (N =127)		Quintile 5 (N =125)	
	HR(95% CI)	P-value	HR(95% CI)	P-value	HR(95% CI)	P-value	HR(95% CI)	P-value
All cause mortality								
Model 1	1.27 (0.77-2.08)	0.347	1.40 (0.87-2.27)	0.180	1.36 (0.84-2.21)	0.208	1.74 (1.09-2.76)	0.020
Model 2	1.17 (0.71-1.95)	0.535	1.22 (0.75-2.00)	0.420	1.30 (0.80-2.11)	0.286	1.65 (1.04-2.64)	0.035
Model 3	1.27 (0.76-2.13)	0.366	1.29 (0.79-2.12)	0.315	1.46 (0.88-2.40)	0.141	1.70 (1.04-2.76)	0.034
Model 4	1.27 (0.75-2.13)	0.374	1.29 (0.78-2.12)	0.319	1.45 (0.88-2.34)	0.148	1.69 (1.04-2.76)	0.036

HR, hazard ratio. Reference group was Quintile 3
Model 1: Unadjusted
Model 2: Model 1 plus age, sex and body mass index.
Model 3: Model 2 plus laboratory data and MCCI.
Model 4: Model 3 plus 24hour urine volume.

PO1011

Peritoneal Dialysis Caregiver Scope and Functions: A Systematic Scoping Review

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Background: Caregivers play important roles in peritoneal dialysis (PD) care. Classifying PD self-care tasks is important for determining the PD caregiver roles. As the scope and functions of PD caregiver in published literature have been inconsistent, we aimed to systematically explore the variations of the term caregiver in high-quality PD studies.

Methods: We performed a systematic search using PubMed, Embase, and CENTRAL for randomized controlled trials and observational studies relevant to a caregiver in ESRD (end-stage renal disease) patients with PD in the English language up to February 20th, 2020. Outcomes were choice of words used in articles for "caregiver," the definition of "caregiver," persons defined as caregiver, and detailed functions of caregivers.

Results: Of 2,514 potential studies relevant to a caregiver in ESRD patients with PD, 299 theme-related abstracts were selected for further full-text articles screening against eligibility criteria, and 111 were included in the systematic review (72,101 patients in 34 countries). In terms of word choice, "caregiver(s)" was used in 86.4%, "carer(s)" in 20.7% and other words were used in 13.5% of included studies. Only 8.1% of studies gave the explicit definitions of those words. The most referred person is the parents (40.5%), followed by a spouse (37.8%), other family members (37.8%), children (34.2%), non-relative non-healthcare workers (25.2%), friends (20.7%), and healthcare workers (19.8%). The explanation of functions for each word comprises 41.4%, with the PD-specific functions by 32.4%, instrumental activities of daily living by 9.9%, and basic activities of daily living by 5.4%.

Conclusions: PD caregiver has been broadly defined and vary across studies. PD-specific functions should be used for making the definition of PD caregiver clearer.

PO1012

Autophagy Response and Arteriovenous Fistula Maturation

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Background: Arteriovenous fistula (AVF) are the preferred vascular access for hemodialysis. AVF creation results in disturbed blood flow within the AVF anastomosis. The objectives of this study were to: 1. Characterize autophagy flux after AVF creation, and during the remodeling process, 2. Use an in vitro model to evaluate autophagy status during the laminar and turbulent flow.

Methods: Femoral AVFs were created in male rats. Yorkshire pigs were used to create carotid artery-jugular vein AVF. Autophagy flux was evaluated after 1 hour and 7 days. AVF and contralateral vessels were harvested for histology and Western blot (WB). Autophagy-related proteins were analyzed in the AVF human vein samples. Effects of hemodynamic changes were investigated by utilizing an in vitro model. Human umbilical vein smooth muscle cells and endothelial cells were co-cultured in the vessel-like system under laminar or disturbed flow conditions. After 24 hours, cells were harvested for histology and WB.

Results: In the rat model impaired autophagy flux was observed in the vein 1 hour after AVF creation. At day 7 expression of ATG3 and ATG7 protein was significantly higher ($p<0.003$) in the AVF vein compare to contralateral control. Significant increases in p62 expression was detected in 7 days AVF vein ($p<0.001$) in both in vivo models. Disturbed autophagy flux also observed in human vein samples collected during new AVF creation. In vitro model showed dysregulation of autophagy flux in disturbed flow, as compared to laminar flow.

Conclusions: Our in vitro and in vivo studies both demonstrated that autophagy response may play an important role in vessel remodeling in the setting of disturbed flow as seen in AVFs. Autophagy may be a potential target to improve AVF maturation.

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

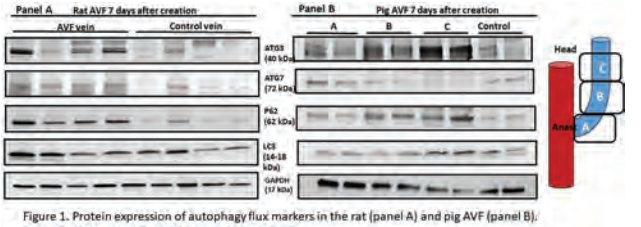

Figure 1. Protein expression of autophagy flux markers in the rat (panel A) and pig AVF (panel B). Control veins were collected from contralateral side.

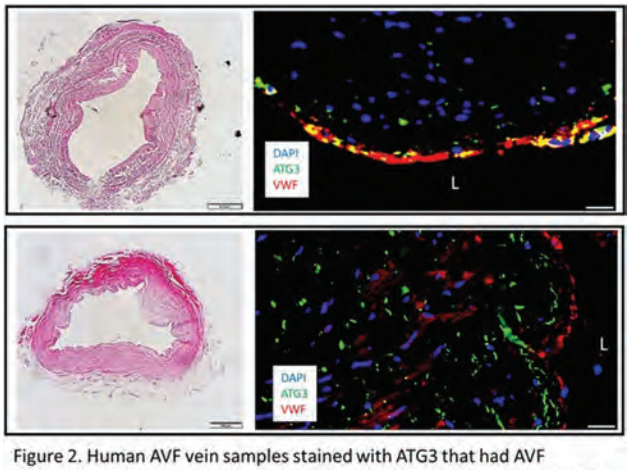

Figure 2. Human AVF vein samples stained with ATG3 that had AVF maturation failure (lower panel) and successful AVF use (upper panel). Co-localization (yellow stain) of ATG3 (red) with VWF (an EC marker) was observed in endothelium in AVF with successful use. L=vein lumen.

PO1013

The Rat Arteriovenous Fistula in the Setting of CKD Displays a Senescence Phenotype

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Background: We previously demonstrated that the murine arteriovenous fistula model in the setting of CKD (AVF-CKD) exhibits a senescence phenotype including increased expression of hallmark cell cycle inhibitors, senescence-associated β-galactosidase (SA-β-Gal) and senescence-associated secretory phenotype (SASP) factors, along with evidence of telomere erosion [Am J Physiol Renal Physiol. 315(5):F1493-F1499, 2018]. In the present study, we questioned whether this senescence phenotype exists in an AVF created in another species, namely the femoral AVF in the rat.

Methods: An end-vein to side-artery AVF was surgically created in the femoral vessels of rats which had previously been subjected to uremia via subtotal nephrectomy. At 1 and 2 weeks after AVF formation the arterial and venous limbs of the AVF were harvested for the assessment of gene and protein expression and the assay of SA-β-Gal activity. Femoral veins and arteries from rats subjected to sham surgery were used as controls.

Results: At 1 week after AVF creation mRNA levels of senescence drivers p16 and p21 were markedly elevated in AVF veins compared to sham veins, as were p21 protein levels; the AVF artery also displayed elevated p21 protein levels at this time point. At 2 weeks, p21 protein was again upregulated in both the vein and artery of the AVF, and protein levels of an upstream mediator in the p21 senescence pathway, p53, were significantly increased in the AVF artery; p53 levels did not achieve significance ($p=0.083$) in the AVF vein at this time point. Upregulation of SASP factors was also observed in the AVF vein at 1 week: mRNA expression of PAI-1, IL-6, TNF-α and MCP-1 was robustly increased as compared to sham veins at 1 week after AVF creation. Additionally, miR21, which has been associated with vascular senescence, was markedly elevated in the AVF vein at 1 week post AVF placement. Finally, SA-β-Gal activity, an established marker of senescence was significantly increased in both the artery and vein compared to their sham counterparts at both 1 and 2 weeks post AVF surgery.

Conclusions: Using established criteria, this study demonstrates that the rat femoral AVF in the setting of CKD has a senescence phenotype similar to the murine AVF-CKD model. These findings thus demonstrate the development of senescence in another species subjected to an AVF in the presence of uremia.

Funding: NIDDK Support

PO1014

The Adaptive Response of the Vein to CKD: A Transcriptomics Perspective

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Background: The impact of CKD on gene expression in the vascular wall remains unknown, particularly in veins, despite their fundamental role as conduits for hemodialysis.

Methods: In this study, we investigated the CKD fingerprint on the transcriptome of basilic veins by analyzing 48 pre-access veins from end-stage renal disease patients and 20 veins from non-CKD trauma donors by bulk RNA sequencing.

Results: We uncovered 16,893 differentially expressed genes (DEG) between CKD and control individuals ($\log_2$FoldChange>1, FDR<0.05). The presence of kidney disease caused a noticeable decrease in transcriptional activity in veins, with the downregulation of >97% of DEG transcripts. These included 6,081 non-coding RNAs, 3,826 protein-coding genes, and other miscellaneous transcripts. In contrast, a unique set of 462 genes was upregulated in CKD veins vs. controls, 161 of which corresponded to non-coding RNAs, 201 to protein-coding genes, and the rest to minor RNA biotypes. Gene set enrichment analysis (GSEA) identified a suppression of pathways related to vascular maintenance, cell morphogenesis, cell metabolism, and microtubule-based cytoskeletal functions. Interestingly, the protein-coding genes upregulated in CKD veins belonged to processes related to gas transport and detoxification of oxidative stress byproducts.

Conclusions: In conclusion, we have uncovered a profound suppressive effect of CKD on the venous transcriptome, likely affecting basic cell functions such as metabolism, cell division, and migration. We also identified a transcriptomic signature of upregulated genes in response to oxidative stress which may play a fundamental role in cell survival in the CKD environment.

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

PO1015

Gender-Specific Risk Genes in Arteriovenous Fistula Failure

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Background: Gender is known to play a role in arteriovenous fistula remodeling and risk of failure. However, the clinical and molecular mechanisms behind this phenomenon have not been elucidated.

Methods: To address this question, 48 pre-access veins obtained at the time of two-stage AVF creation (24 matured and 24 failed postoperatively) and 40 postoperative transposition samples (20 matured and 20 failed) were randomly selected from the University of Miami Vascular Biorepository and submitted for bulk RNA sequencing. Females and males were equally represented in both outcome groups and were similar in demographics and baseline characteristics. We searched for common and sex-specific differentially expressed genes (DEG) in pre-access veins and postoperative samples in association with failure.

Results: In the pre-access vein, we found 28 DEG between veins that matured or failed postoperatively ($\log_2$FoldChange>1, FDR<0.05) and in common between both sexes. In male veins, 1180 transcripts were differentially expressed between both outcomes, whereas no female-specific DEG were detected in the same number of individuals. Principal component analyses demonstrated more transcriptional variability in both outcome groups in females, decreasing our power to identify female-specific genes in the vein. In postoperative samples, we found 156 DEG between fistulas that matured or failed and in common between both sexes. In addition, 143 female-specific and 153 male-specific genes were differentially expressed between outcomes, indicating gender relevant processes of postoperative remodeling. Both sexes showed a downregulation of genes related to responses to external stimuli and stress. However, gene set enrichment analysis (GSEA) revealed a suppression of cell-surface receptor signaling and cell adhesion mechanisms in males but not in females, suggesting a sex-specific effect in cell migration.

Conclusions: In conclusions, these analyses uncover potential differences in postoperative remodeling between females and males in relation to AVF failure. They also indicate a more complex transcriptional landscape in female tissues which may affect our ability to predict remodeling in this group of patients. These data may open the door to personalized medicine in preventing or treating vascular access complications.

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

PO1016

Inhibition of Phosphodiesterase Type 5A Prevents Pathological Cardiac Remodeling Following Arteriovenous Fistula Creation

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Background: Cardiac events are the most common etiology of mortality in hemodialysis patients. The gold standard of vascular access, the arteriovenous fistula (AVF), may adversely affect cardiac structural and functional remodeling leading to heart failure. We hypothesize that inhibition of cGMP catabolism with a selective phosphodiesterase type 5A (PDE5A) inhibitor, sildenafil, may induce more favorable cardiac remodeling following AVF creation

Methods: Sildenafil was administered to 12-16 weeks old Sprague-Dawley rats two weeks prior to AVF creation and continued until sacrifice at 28 days. Cardiac structural and functional changes were evaluated by 1) 2D-echocardiography 2) measurement of collagen volume and oxidative stress and 3) evaluation of cardiomyocyte cytoskeletal-mitochondrial architecture

Results: Sildenafil treatment significantly improve pathological collagen degradation, reduces HNE4 expression, reverse desmin degradation and focal mitochondrial clustering following AVF creation, as compared to the control. We also observed a significant increase in cardiac output and stroke volume without reversing LV dilation which may suggest improvement in cardiac contractility.

Conclusions: PDE5A inhibition may provide a new treatment strategy for pathological cardiac remodeling following AVF creation

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

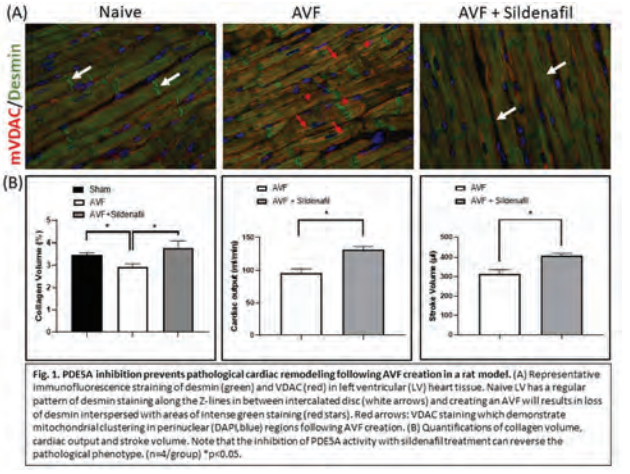

Fig. 1. PDE5A inhibition prevents pathological cardiac remodeling following AVF creation in a rat model. (A) Representative immunofluorescence straining of desmin (green) and VDAC (red) in left ventricular (LV) heart tissue. Naive LV has a regular pattern of desmin staining along the Z-lines in between intercalated disc (white arrows) and creating an AVF will results in loss of desmin interspersed with areas of intense green staining (red stars). Red arrows: VDAC staining which demonstrate mitochondrial clustering in perinuclear (DAPI,blue) regions following AVF creation. (B) Quantifications of collagen volume, cardiac output and stroke volume. Note that the inhibition of PDE5A activity with sildenafil treatment can reverse the pathological phenotype. (n=4/group) *p<0.05.

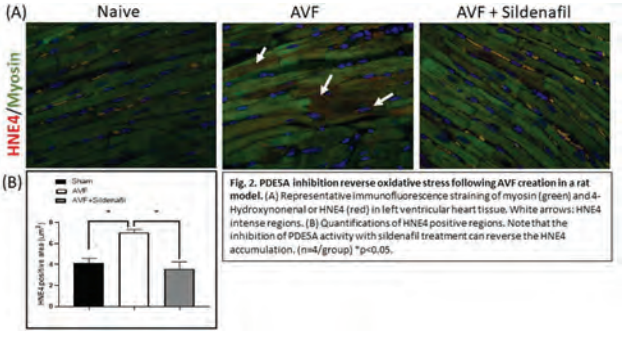

Fig. 2. PDE5A inhibition reverse oxidative stress following AVF creation in a rat model. (A) Representative immunofluorescence straining of myosin (green) and 4-Hydroxynonenal or HNE4 (red) in left ventricular heart tissue. White arrows: HNE4 intense regions. (B) Quantifications of HNE4 positive regions. Note that the inhibition of PDE5A activity with sildenafil treatment can reverse the HNE4 accumulation. (n=4/group) *p<0.05.

PO1017

Pre-Access Vein Transcriptomics as a Predictor of Arteriovenous Fistula Failure: A Machine Learning Approach

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Background: As the number of patients with end-stage renal disease continues to rise, the creation of a robust and efficient hemodialysis access is more important than ever. A mature arteriovenous fistula (AVF) is the preferred method for long-term hemodialysis. However, the nationwide maturation rate continues to be as low as 50-60%, and we currently lack an effective risk stratifying method to identify patients at higher risk of AVF failure.

Methods: To address this clinical need we developed a predictive model based on supervised machine learning from transcriptomics of the pre-access vein. Forty-eight pre-access veins obtained at the time of AVF creation (24 matured and 24 failed postoperatively) were randomly selected from the University of Miami Vascular Biorepository and submitted for bulk RNA sequencing. Both outcome groups were matched by age, sex, demographics, and baseline clinical characteristics. The highest expressing genes (normalized gene expression counts >200) were used as input in KNN, SVM, XGBoost, and other machine learning algorithms. Area under the curve (AUC) and receiver-operating characteristic (ROC) plots were used to compare the performance of the models relative to each other. The best performing algorithm, XGBoost, was optimized with the following hyperparameters {gamma=0.25, learning_rate=0.001, max_depth=4, reg_lambda=10, scale_pos_weight=3}. The SHapley Additive exPlanations (SHAP) analysis was then used to evaluate the highest contributing features to the XGBoost model.

Results: Ten highly predictive and abundantly expressed genes were identified using this methodology (RIC1, CLIC5, DNAL1, FOXO4, TIMMDC1, GALNT11, CDH13, KLHDC10, ZNF8, and DBT). Using these transcripts, the AUC in the logistic regression model is 97.6%.

Conclusions: In conclusion, this study has identified 10 potential pre-access gene predictors of postoperative AVF failure, which could be used clinically as a stratifying or risk management tool in vascular access patients.

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

PO1018

Arteriovenous Fistula Non-Maturation: Does the Immune System Play a Role?

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Background: Arteriovenous fistula (AVF) non-maturation is a persistent problem, particularly among female and Black patients. The immune system promotes several vascular disease processes, but its contribution to AVF non-maturation has not been well-studied. We evaluated the association of serum panel reactive antibodies (PRA), a measure of immune system reactivity assessed in patients undergoing kidney transplant evaluation, with AVF non-maturation.

Methods: We identified 132 patients at our institution who underwent surgical AVF creation between 2010-2019 and had PRA testing within one year of AVF creation. Multivariable logistic regression was used to determine the association of patient demographic, clinical, and vascular factors with AVF maturation. Receiver operator characteristic (ROC) curves were generated to determine the predictive value of key variables on AVF non-maturation.

Results: AVF non-maturation was more common in females than males (44% vs 20%, p=0.003) and in Black than white patients (40% vs 13%, p=0.001). Class II PRA was higher in females than males (12% +/- 23% vs 4% +/- 13%, p=0.02), but did not differ by race. In the multivariable model, AVF non-maturation was associated with class II PRA (adjusted odds ratio [aOR] 1.34 per absolute 10% increase; 95% confidence interval [CI], 1.04 to 1.82, p=0.02) and Black race (aOR 3.34; 95% CI, 1.02 to 10.89, p=0.03). An ROC curve using seven key variables (Table 1 and Figure 1) showed an area under the curve of 0.73 (95% CI, 0.63 to 0.82, p<0.0001)

Conclusions: The novel association of elevated class II PRA with AVF non-maturation suggests a role for the immune system in AVF maturation outcomes, especially for female patients.

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Age, per 10 yr increase	1.09	0.76 to 1.56	0.64
Sex, female	1.96	0.80 to 4.81	0.14
Race, Black or African American	3.34	1.02 to 10.89	0.03
Preoperative arterial diameter, per 1 mm increase	0.72	0.44 to 1.15	0.17
Preoperative venous diameter, per 1 mm increase	0.82	0.45 to 1.47	0.51
Class I PRA, per 10% increase	0.91	0.72 to 1.14	0.42
Class II PRA, per 10% increase	1.34	1.04 to 1.82	0.02

Table 1. AOR of 7 key variables for AVF non-maturation.

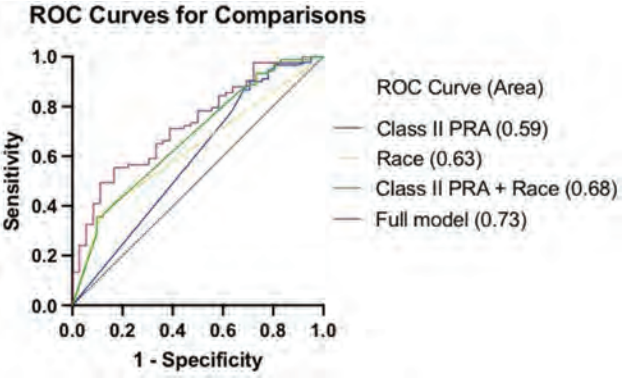

Figure 1. ROC curves.

PO1019

Functioning Tailor-Made 3D-Printed Vascular Graft for Hemodialysis: A Proof-of-Concept In Vivo Study

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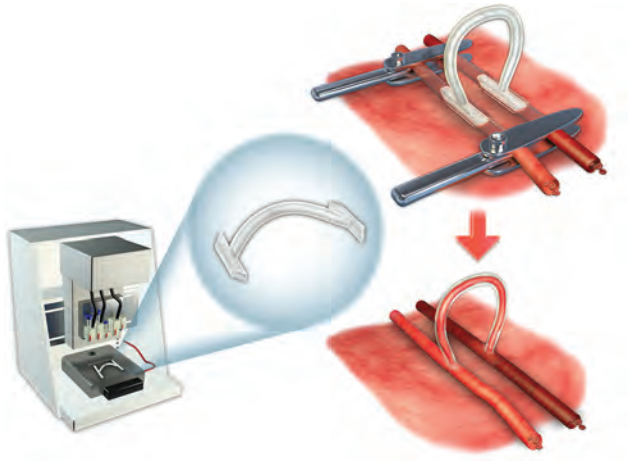
Background: The two ends of arteriovenous graft (AVG) are anastomosed to the upper limb vessels by surgery for hemodialysis therapy. However, the size of upper limb vessels varies to a large extent among different individuals. With advances in three-dimensional (3D) printing technology, it is now possible to realize tailor-made AVG for personalized surgery. In this study, we aim to investigate the function of 3D-printed AVGs *in vivo*.

Methods: The computed tomography angiographic scan of the rabbit neck was performed before the surgery. According to the shape and size of neck vessels, an H-shape AVG was produced by the 3D printer and then sterilized. The 3D-printed AVG was trimmed and inserted in the rabbit's common carotid artery and common jugular vein.

Results: The tailor-made 3D-printed AVGs can be implanted in the rabbit's neck vessels with ease and function *in vivo*. The surgical procedure was quick, and no suture was required. The blood loss was minimal, and no hematoma was noted at least one week after the surgery. The blood flow velocity within the implanted AVG was 14.9 ± 3.7 cm/sec.

Conclusions: Through the 3D printing technology, the AVG can be tailored to fit the specific vessel size. This kind of 3D-printed AVG is functioning *in vivo*, and our results realize personalized vascular implants. Further studies conducted in large animal models are warranted to validate our promising results.

Funding: Government Support - Non-U.S.



Graphical Abstract. The schematic diagram of the three-dimensional (3D)-printed vascular graft implantation. After surgically free of the rabbit's common carotid artery and common jugular vein, the 3D-printed vascular graft was trimmed and inserted into the blood vessels. The blood recirculates at once after releasing the vascular clamps.

PO1020

Far Infrared Radiation on the Arteriovenous Fistula Induces Changes in VCAM and ICAM in Patients on Hemodialysis

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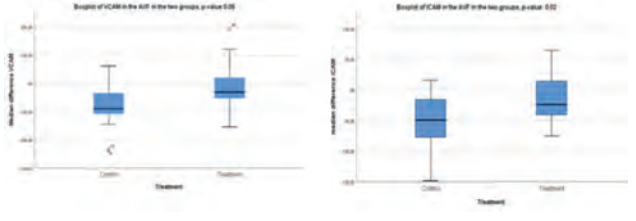
Background: The risk of stenosis in the arteriovenous fistula (AVF) in hemodialysis patients is substantial. Development of an AVF stenosis is due to neointimal hyperplasia. Far infrared radiation (FIR) is a non-invasive intervention with a potentially beneficial effect on AVF patency and survival, although the mechanism is not fully understood. The aim of this study was to investigate the effect of a single FIR treatment on inflammatory and vasodilating factors

Methods: Forty hemodialysis patients with an AVF from the Faith-in-Fistula-Trial were included in the study. Each patient was randomized to receive either FIR (FIR group) or no FIR (control group). Blood samples were drawn from the AVF arm and the non-AVF arm before (T0) and after (T40) treatment in both groups during a hemodialysis session. The changes (median [interquatile range]) in several inflammatory and vasodilating factors during FIR were explored in both groups.

Results: In the FIR group 19 patients were included, 21 patients in the control group. No differences in baseline characteristics between the groups were seen. After one FIR treatment, both Vascular Cell adhesion molecule (VCAM) and Intercellular adhesion molecule (ICAM) changed, although the change was significantly lower in the AVF arm compared to the control group. VCAM: -31.55 (-54.33;22.1) vs. -89.87 (-121.55;-29.31), p:0.005 and ICAM: -24.19 (-43.53;25.26) vs. -49 (-79.91;-11.58), p:0.02. Other factors, such as interleukines, nitric oxide and tumor-necrosis-factor 1 also declined, but with no significant differences related to FIR

Conclusions: A single FIR treatment attenuated the decrease in VCAM and ICAM in the AVF arm compared to a control group. These findings do not support the hypothesis of FIRs beneficial effects on the endothelium, although the long term effects of FIR on these factors and their beneficial effects are unknown.

Funding: Private Foundation Support



PO1021

The Association of Transition-to-Dialysis Planning and Healthcare Resource Use and Mortality in Patients with ESRD

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Background: The onset of ESRD is associated with poor outcomes and high mortality, and the role of transition-to-dialysis planning is not well understood. We evaluated the association between dialysis transition planning factors such as nephrologist care, vascular access placement, and place of index dialysis, with inpatient (IP) stays, emergency department (ED) visits, and mortality.

Methods: This retrospective study used the Humana Research Database to identify 7,026 patients, 19-89 years of age, diagnosed with ESRD between 1/1/17 and 12/31/17, enrolled in a Medicare Advantage Prescription Drug plan, with ≥12 months of continuous enrollment pre- and post-index date (i.e., first evidence of ESRD). Patients with a kidney transplant indication, hospice election, or dialysis pre-index were excluded. Transition-to-dialysis planning was defined as optimal, partial, or unplanned (Table 1). IP stays, ED visits, and mortality were evaluated within 12 months post-index.

Results: The cohort was 41% female, 66% White, with an average age of 70 years. An optimally planned, partially planned, and unplanned transition to dialysis occurred for 15%, 34%, and 44% of the ESRD cohort, respectively. Among patients with pre-index CKD stages 3a and 3b, 64%, and 55%, respectively, had an unplanned dialysis transition. For patients with pre-index CKD stages 4 and 5, 68% and 84%, respectively, experienced planning prior to dialysis initiation. In adjusted models, patients with partially or optimally planned transition to dialysis were 57% to 72% less likely to die, 20% to 37% less likely to experience an IP stay, and 80% to 100% more likely to experience an ED visit than patients with an unplanned transition. Higher ED utilization with planned transition was attributed to longer time to mortality, allowing more time for healthcare utilization.

Conclusions: A planned transition to dialysis was associated with improved outcomes and lower mortality. Targeting care coordination for patients with CKD stages 3a/3b may help slow disease progression and ensure a planned, safer transition to dialysis.

Table 1. Transition-to-Dialysis Planning Definitions

Optimal: Vascular access placed
Partial: Nephrologist care but no vascular access
Unplanned: Dialysis in IP stay or ED visit

PO1022

Prediction of Stenosis in Arteriovenous Fistula Using Video Image Analysis

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Background: We developed a video image processing (VIP) technique with frequency domain analysis to predict stenosis in AVF. The study aimed to evaluate whether the degree of stenosis can be assessed using parameters from frequency domain signal analysis.

Methods: We employed VIP in 100 hemodialysis patients (age 63.3 ±14.1 years, 47 females) prior to endovascular arterio-venous fistula (AVF) interventions. A 1-minute video of the AVF area was recorded using a smartphone (Fig 1). We constructed time series based on pixel changes between two consecutive video frames (Fig 2-A) and used Fast Fourier Transform (FFT) to transform the time domain signals into the frequency domain (Fig 2-B). Parameters in the frequency domain included maximal (Max) and minimum (Min) amplitude, and frequency (F_{Max} and F_{Min}). ΔF was defined as F_{Min} - F_{Max}. M2 was calculated by the squared ratio of the Max-to-median magnitude. The degree of AVF stenosis (%ST) was determined by angiography, the access flow (AF) by thermodilution (HVT100; Transonic Systems Inc., Ithaca, NY, USA).

Results: Data from 98 patients were analyzed. %ST was categorized into three groups: 60% stenosis (n=8), 70-80% (n=76), and 90% (n=14). AF correlated with %ST. Max, F_{Max}, F_{Min} and ΔF were associated with %ST (Table 1). An algorithm was developed to predict degree of %ST based on patient characteristics and parameters of frequency domain analysis. In the respective three %ST groups the sensitivities to detect AVF stenoses were 88%, 86% and 100%, and the specificities 99%, 82% and 98% (Table 1).

Conclusions: VIP applied to videos taken with a smartphone may provide a contact-free method to estimate the degree of AVF stenosis. Validation studies in independent cohorts are needed to further assess the diagnostic capability of the proposed method.

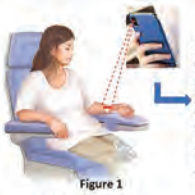

Figure 1

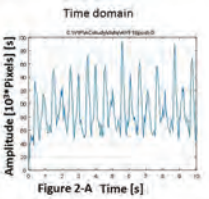

Figure 2-A Time [s]

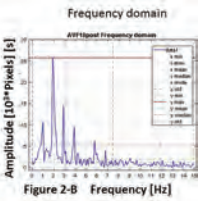

Figure 2-B Frequency [Hz]

Table 1

	%ST 90% (n=14)	%ST 70-80% (n=76)	%ST 60% (n=8)
Max (10^{34}*Pixels)	2057±1697	2916±2277	2436±2520
F_{Min} (Hz)	5.95±1.8	6.44±1.76	7.23±1.35
ΔF (Hz)	3.62±2.34	4.10±1.82	5.07±2.17
M2	38.68±17.25	63.91±70.51	46.54±37.97
AF (ml/min)	912±400	1432±706	1341±440*
Sensitivity (%)	86	88	100
Specificity (%)	99	82	98

PO1023

Catheter-Related Bloodstream Infection Incidence and Associated Mortality Risk: Analysis of Merged USRDS-Medicare Claims

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Background: Despite policy and provider initiatives, nearly 80% of end-stage-renal-disease (ESRD) patients initiate hemodialysis (HD) with a central venous catheter (CVC). However, CVCs may elevate risk of catheter hub contamination resulting in catheter-related blood stream infections (CRBSIs) and potentially serious consequences. This analysis aims to estimate the incidence, risk, and associated mortality of CRBSIs among CVC-dependent HD patients in the US.

Methods: A propensity score matched case-control analysis of 2013-2017 linked data from the United States Renal Data System (USRDS), dialysis organizations (i.e., CROWNWeb), and Medicare claims was conducted. Occurrence of CRBSI and associated mortality among incident CVC-dependent HD patients between 2014-2016 with a 1-year pre- and ≥1-year post-index were assessed. CRBSI case group index date was the first date of occurrence of any of the following post CVC insertion: ICD-9/10-CM 999.32, T80211x; 999.31, T80219x, T80218x and sepsis/bacteremia diagnosis within ±3 days of hospitalization; sepsis/bacteremia diagnosis without occurrence for pneumonia, gangrene, or urinary tract infections within ±3 days of hospitalization. Non-CRBSI control group was identified by an assigned index date (i.e., CVC insertion date + median days to CRBSI reported in CRBSI-case group). Frequency, mean, median, and chi-square and *t*-tests assessed group differences. Adjusted cox proportional hazards models examined time to CRBSI and time to mortality post CRBSI.

Results: Of the 55,727 CVC-dependent HD patients (mean age 67.8, 45% female), nearly 29% (n=15,882) developed a CRBSI (median time, 69 days); 54% (n=8,393), 67% (n= 10,327), and 80% (n=12,705) occurred within 90, 180 and 365 days of CVC insertion, respectively. After CRBSI occurrence, 40% and 50% died within 60 days and 180 days, respectively. CRBSI patients also had a significantly lower median survival (25.1 vs. 37.3 months) compared to non-CRBSI patients [hazard ratio: 0.74, 95% CI: 0.71-0.76].

Conclusions: CRBSIs occur in a third of CVC-dependent HD patients, with over half of the initial infections occurring within 90 days of CVC insertion. Patients with CRBSI had a higher risk of death compared to patients without CRBSI; with a 40% mortality within 60 days post-CRBSI.

Funding: Commercial Support - Cormedix

PO1024

The Association of Incremental Hemodialysis with Complications of Arteriovenous Access

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Background: Protection of arteriovenous vascular access by incremental hemodialysis was not examined. We conducted a historical cohort study to investigate the association of incremental hemodialysis with complications of arteriovenous access among incident hemodialysis patients.

Methods: Incident hemodialysis patients from Huashan hospital in Shanghai, China, over the period of 2012 to 2019 were enrolled and followed every three months. Complications of arteriovenous access included surgical interventions for failure, stenosis, or thrombosis. The risks of time to first complication of arteriovenous access for incremental versus conventional hemodialysis were examined by cox proportional hazards models. The risk of time to recurrent complications of arteriovenous access was examined by Andersen-Gill model (AG model) and Prentice, Williams and Peterson model (PWP-TT model).

Results: Of the 113 patients enrolled in the study, 45 patients underwent incremental and 68 conventional hemodialysis. The incidence rates of arteriovenous access complications between groups were 8.5 and 29.8 per 100 person-years, respectively. A decrease in risk for having an arteriovenous access complication was also observed for incremental hemodialysis by Cox models with an adjusted HR of 0.26 (95% CI, 0.08-0.82). Moreover, the adjusted risk of recurrent complications of arteriovenous access for incremental hemodialysis decreased in AG model (HR, 0.27; 95% CI, 0.10 – 0.74; $P = 0.01$) and in PWP-TT model (HR, 0.31; 95% CI, 0.12 – 0.80; $P = 0.02$) after multiple adjustments.

Conclusions: Incremental hemodialysis was significantly associated with reduced complications of arteriovenous access.

Unadjusted and adjusted Hazard Ratio of Arteriovenous access complications by hemodialysis regimens

Model	Hazard Ratio	95% Confidential Interval	P
Cox Model			
Univariate	0.36	0.13, 0.98	0.04
Model 1	0.27	0.09, 0.81	0.02
Model 2	0.26	0.08, 0.82	0.02
AG Model			
Univariate	0.29	0.11, 0.79	0.02
Model 1	0.25	0.10, 0.63	0.003
Model 2	0.27	0.10, 0.74	0.01
PWP-TT Model			
Univariate	0.37	0.16, 0.86	0.02
Model 1	0.30	0.14, 0.66	0.003
Model 2	0.31	0.12, 0.80	0.02

PO1025

Vascular Access in Kidney Transplant Patients with Allograft Failure Returning to Hemodialysis

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Background: Central vein catheters (CVC) are the predominant vascular access (VA) in incident hemodialysis (HD) patients and are associated with worse outcomes compared to arteriovenous (AV) access. Limited data exist on VA type and association with outcomes in kidney transplant recipients (KTR) with allograft failure. We aimed to determine factors associated with VA type among KTR with allograft failure who return to HD.

Methods: We performed a retrospective study of 147 KTR >18 years with allograft failure between 2010-2021 at an academic hospital in the Bronx, NY. KTR with immediate allograft failure or <1 month of HD following allograft failure were excluded. Data was collected on pre-transplant dialysis modality, vintage, and VA type. Data at allograft failure included sociodemographics, comorbidities, clinic visits, VA type. Descriptive analyses and logistic regression were performed to evaluate factors associated with VA among KTR who return to HD.

Results: At allograft failure, mean age was 53 years (SD 15), 62% were men and 46% were of Black race. Pre-transplant, 91.8% patients were on HD, 2.7% were on peritoneal dialysis (PD), and 5.5% were not on dialysis. Mean vintage was 4.6 years (SD 4.4). Pre-transplant VA included AV access in 87.7% and CVC in 4.1% of patients. At allograft failure, 82.3% and 17.7% KTR initiated HD with an AV access and CVC, respectively. Compared to pre-transplant HD patients, those on PD or who received a preemptive transplant were less likely to initiate HD with an AV access at time of allograft failure (80.6% vs 50% vs 12.5%, p<0.001). KTR were 19% less likely to initiate HD with an AV access for each year increase between the time of transplant and allograft failure (OR 0.81, 95% CI 0.69-0.94). Sociodemographics, comorbidities and number of clinic visits 1 year prior to allograft failure were not associated with VA. One year mortality was 10.7% in KTR initiating HD with a CVC vs 3.4% in those with an AV access (p=0.12).

Conclusions: The majority of KTR with allograft failure returned to HD with an AV access. CVC use was higher in those with longer allograft survival, previously on PD or who received a preemptive transplant, highlighting a need for transition of care optimization. Larger studies are needed to determine if VA type is associated with mortality in this population.

PO1026

Abstract Withdrawn

PO1027

Reusing Occluded Veins: Inside-Out Central Venous Access for Hemodialysis, Our Institutional Experience

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Background: Central venous occlusion is a challenge in end-stage renal disease (ESRD) patients dependent on hemodialysis. The inside-out central venous access (IOCVA) procedure is an established method of re-using occluded veins.

Methods: Retrospective single-center study examining characteristics of patients with ESRD who underwent IOCVA between 01/01/2017 – 05/01/2021. All procedures were performed with moderate conscious sedation by an interventional cardiologist or nephrologist.

Results: 46 IOCVA procedures were performed in 39 ESRD patients. All procedures were performed to re-use the occluded right internal jugular vein (RIJ) for tunneled dialysis catheter placement. Mean patient age was 58 ± 14.6 years. 20 (51.3%) patients were male. Hypertension and diabetes were comorbid conditions in 29 (74.4%) and 20 (51.3%) patients, respectively. A total of 7 (17.9%) patients had prior kidney transplant.

The average number of prior vascular accesses (defined as venous access or arteriovenous fistula/graft) in patients prior to IOCVA was 2.6 ± 1.7 (range 1-9). 9 (23.1%) had two prior accesses, and 30 (76.9%) had >3 prior accesses. 5 (12.8%) patients had >1 prior IOCVA procedure. 5 (12.8%) patients had complete superior vena cava occlusion. 17 (43.6%) patients had failed AVF/AVG and 2 (5.1%) had failed translumbar venous access. Technical success rate was 100% with no complications.

Conclusions: The RIJ vein is the most effective and durable site for long-term hemodialysis access. Occlusion, stenosis of this vein can lead to a downward spiral of access crisis with venous exhaustion resulting in trans-lumbar or trans-hepatic catheter placement for dialysis. These approaches are associated with high rates of dysfunction as well as infection, catheter migration and thrombosis. The transhepatic approach can also cause life-threatening intraperitoneal hemorrhage. The use of IOCVA alleviates the need to sacrifice subsequent veins and allows for the occluded RIJ to be re-accessed as many times as needed via the femoral vein. Our data provides further evidence in support of the safety and efficacy of IOCVA for long-term hemodialysis access in ESRD patients.

PO1028

Real-World Efficacy of Paclitaxel-Coated Balloons (P-DCB) in the Treatment of Initial and Recurrent Arteriovenous Fistula (AVF) Stenosis

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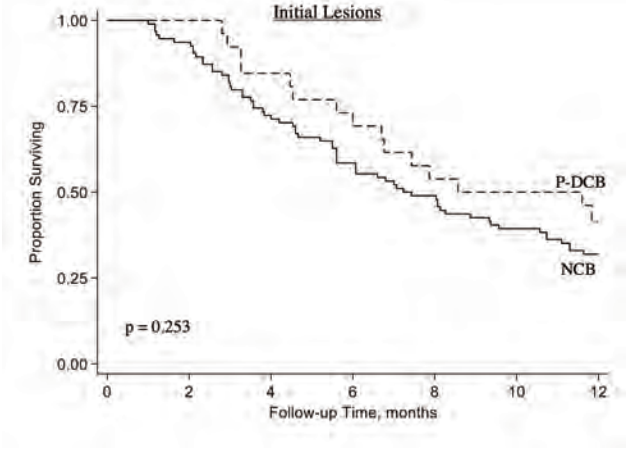
Background: A 2-year randomized trial has shown variable efficacy of P-DCB in AVF angioplasty when compared to non coated balloons (NCB). A subsequent study at our center showed the average time to lesion recurrence after P-DCB AVF angioplasty to be significantly shorter than NCB. Selection bias of using P-DCB more often in frequently recurring lesions was attributed to this observation. Our study was conducted to evaluate if use of P-DCB has better outcomes in initial lesions.

Methods: We retrospectively reviewed charts of 277 AVF balloon angioplasties performed over a 19 month period (July 2018 through January 2020). Patients were stratified into 4 groups: P-DCB initial lesions (n=26), NCB initial lesions (n=95), P-DCB recurrent lesions (n=46), NCB recurrent lesions (n=110). Patients were followed until recurrence or until January 2021 for lesions that did not recur.

Results: Groups were similar in terms of baseline characteristics. In the initial lesion group, 15 of 26 patients (57.69 %) treated with P-DCB and 64 of 95 patients (67.3 %) treated with NCB had recurrence during the follow up period of 1 year. There was a trend toward less recurrence in the P-DCB group but it did not reach statistical significance. (p=0.358). In the recurrent lesion group, 34 of 46 patients (73.9 %) treated with P-DCB and 71 of 110 patients (64.5 %) treated with NCB had recurrence during follow up. The difference was not statistically significant. (p=0.255).

Conclusions: There is no significant difference in recurrence rates for initial or recurrent lesions between the 2 balloons. However, there is a trend towards lower recurrence rates with P-DCB in initial lesions. There may be more benefit in treating initial lesions with P-DCB compared to recurrent lesions but further studies with larger number of patients are needed to substantiate these findings.



PO1029

Machine Learning for Prediction of Arteriovenous Fistula Failure

Suman K. Lama,[1] Rishi Razdan,[2] Murat Sor,[2] Eyal Barzel,[2] Caitlin Monaghan,[1] Joanna Willetts,[1] Sheetal Chaudhuri,[1] Nancy Mclaughlin,[2] Hanjie Zhang,[3] Peter Kotanko,[3] Jeffrey L. Hymes,[1] John W. Larkin,[1] Len A. Usvyat,[1] Franklin W. Maddux.[4] *[1]Fresenius Medical Care, Waltham, MA; [2]Azura Vascular Care, Malvern, PA; [3]Renal Research Institute, New York, NY; [4]Fresenius Medical Care AG und Co KGaA, Bad Homburg, Germany.*

Background: Over 23% of primary arteriovenous fistula (AVF) placements fail for patients on chronic hemodialysis (HD); interventional procedures can be performed to prevent fistulas from failing completely or to correct the malfunction of fistulas (Al-Jaishi AJKD 2014). We developed a Machine Learning (ML) model to predict the likelihood of an AVF failure within 30 days.

Methods: We used data from a cohort of HD patients with a functioning AVF treated at an integrated kidney disease company from Jan-Dec 2018 to develop an ML model (XGBoost) that predicts AVF failure within 30 days from the last use. AVF failure was defined as a status change (active to permanently/temporarily unusable), or if an interventional procedure (IP) was performed for the first time. Model used approximately 2400 variables, which included baseline and derived lab values, treatment data, clinical notes entered by physicians and dialysis staff, and care providers. The cohort was randomly split into 60% training, 20% validation, and 20% test datasets.

Results: We identified a cohort of 15,449 HD patients actively using an AVF to develop the ML model. We achieved area under the receiver operating characteristic curve as 0.76 in the test dataset. When using a 0.5 probability threshold for classifying predictions as positive or negative for AVF failure in the next 30 days, the model showed suitable performance with precision as 0.57, and recall as 0.29. Variables such as prediction score from clinical notes, days since last treatment, and days since fistula was placed had a positive relationship with the fistula failure prediction whereas comorbidity counts had a negative relationship with the failure of fistula (**Figure 1**).

Conclusions: Our AVF failure prediction model appears to have the potential to provide an early identification of an access that is likely to malfunction. Further evaluation and clinical testing is warranted to validate the ML model.

Funding: Commercial Support - Fresenius Medical Care

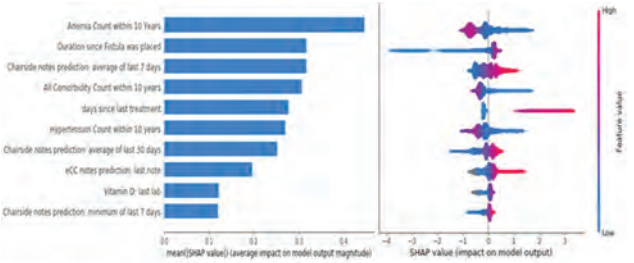


Figure 1: SHAP value plots for ML model showing the extent each predictor contributes (positively or negatively) to each individual prediction. (Left panel) Bar plot of the mean absolute SHAP values for the top 10 predictors in descending order. (Right panel) SHAP value plot for the degree of the positive or negative effect of each individual measurement on the prediction (x-axis), with warmer colors representing higher observed values for that measurement, cooler colors indicating lower values for that measurement, and gray representing a missing value for that measurement.

PO1030

Artificial Intelligence to Evaluate Vascular Access Aneurysms in Hemodialysis Patients

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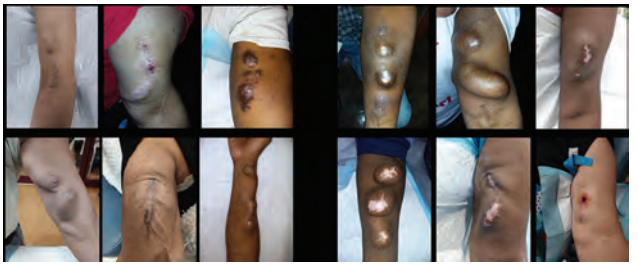
Background: Vascular access aneurysms are a frequent finding in hemodialysis patients with arterio-venous (AV) fistulas and grafts. Of great concern is aneurysm rupture that may result in fatal hemorrhage. To that end we used artificial intelligence (AI) to automatically evaluate vascular access aneurysms.

Methods: We collected images of a diverse range of AV vascular accesses using mobile devices. Vascular access experts adjudicated the images and diagnosed the severity of AV fistula and graft aneurysms. We then randomized the images for training (70%) and validation (30%). We trained a convolutional neural network (CNN) utilizing Amazon SageMaker platform. CNN performance was measured by the area under the receiver operating characteristics (ROC) curve in the validation images.

Results: We collected 1,341 AV access images in patients dialyzed in 20 Renal Research Institute clinics in six U.S. states. The adjudication of images identified 1,093 not advanced and 248 advanced aneurysms; examples are shown in Figure 1. With the validation images, we achieved an area under the ROC curve of 0.96. Considering different probability threshold for advanced aneurysm, if threshold is 0.37, we achieved sensitivity of 80%, specificity of 95%, false positive rate of 5%, precision of 79%, if threshold is 0.7, sensitivity of 66%, specificity of 99%, false positive rate of 1%, precision of 92%.

Conclusions: Our solution of applying advanced AI technologies achieved very high sensitivity, specificity, precision, and a low false positive rate. The CNN could assist the clinical staff with actionable information and improve clinical outcomes.

Funding: Commercial Support - Fresenius Medical Care North America



Severity of AV access aneurysms. Panel A shows the images from 6 patients with not advanced AV aneurysms. Panel B shows images from 6 patients with advanced AV aneurysm.

PO1031

Evaluation of a Wearable Device for Continuous, Noninvasive Monitoring of Hematocrit Levels in Hemodialysis Patients

David J. Kuraguntla, Forrest Miller. *Alio, San Francisco, CA.*

Background: Maintenance of euvolemia is a major challenge for hemodialysis patients, who account for a combined 6.5M annual hospital days. Clinical outcomes could be improved, and healthcare costs lowered, by enabling better management of fluid status and anemia, which is common among ESRD patients. This study presents a novel wearable device, SmartPatch, that uses multi-wavelength photoplethysmography (PPG) and other sensors to measure blood hematocrit (Hct), a key metric for monitoring fluid status and anemia. The SmartPatch is a component of a novel Remote Monitoring System (RMS) that facilitates secure data transmission and analysis and generates actionable alerts. Data demonstrating the feasibility of the RMS were previously presented at Kidney Week 2019 (Kuraguntla et al.). The aim of this study was to evaluate the system's ability to accurately and precisely measure Hct in a real-world dialysis setting.

Methods: 14 ESRD patients with arteriovenous fistulae currently undergoing dialysis were recruited to participate in this study. Each of these patients had a SmartPatch device placed on the skin over their fistula at each of three dialysis sessions two weeks apart. Reference Hct measurements were taken immediately before and after the session, timed to coincide with SmartPatch data recordings. A total of 83 sets of multi-channel PPG data were recorded and analyzed to determine the accuracy and precision of Hct measurement.

Results: The RMS measured Hct with root-mean-square error (RMSE) of 2.13 Hct compared to reference values obtained from a Sysmex XN-1000 blood analyzer. The standard deviations for each read on the same patient–with the same device–were computed and averaged, weighted by group size, as a measure of precision. The RMS measured Hct with a mean standard deviation of 1.15 Hct. These error and standard deviation values compare favorably to available point-of-care devices like the HemoCue Hb 201+, which has been reported to measure Hct with a mean of 4.32-4.81 Hct and standard deviation of 1.56-3.88 Hct.

Conclusions: The results of this study illustrate the ability of the wearable SmartPatch to non-invasively measure blood Hct in ESRD patients with AV fistulae, to a degree of accuracy and precision that may outperform available point-of-care methods. This study also demonstrated the efficacy of the end-to-end Remote Monitoring System.

Funding: Commercial Support - Alio, Inc.

PO1032

Impact of a Change in Vascular Access Flow Volume After Percutaneous Transluminal Angioplasty on Cardiac Function

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Background: Vascular access (VA) is necessary for patients on hemodialysis, and percutaneous transluminal angioplasty (PTA) is a useful treatment for maintaining VA function. PTA immediately increases the VA flow volume, which can affect cardiac function. We investigated the relationship between changes in VA flow volume and cardiac function in patients who underwent PTA.

Methods: This was a single-center retrospective observational study, including patients who underwent PTA between June 2016 and August 2016. VA flow volume and cardiac function were measured by sonography before and 1 hour after PTA.

Results: This study included 50 PTA procedures in 50 cases. PTA significantly increased the median VA flow volume from 445 (range, 150–1229) to 725 (350–1268) mL/min. Although the ejection fraction and diameter of the inferior vena cava were unchanged, the cardiac output (CO) and cardiac index increased significantly in most cases. Surprisingly, the CO was obviously decreased in 18% of cases despite the increased VA flow volume. In this atypical group, a high CO before PTA was found to be a significant factor for the decrease in CO by PTA.

Conclusions: In most cases, both VA flow volume and CO were increased by PTA, whereas in some cases, the CO was decreased despite increase in VA flow volume. This atypical phenomenon may be due to the insufficient adaptive response in the peripheral artery and heart and could predict risks for future cardiac events. Therefore, it is important that such patients are carefully followed up.

PO1033

Predicting Arteriovenous Graft Failure with Sound Signatures in Patients on Hemodialysis

Tiffany W. Shien,[1,2] Juan-Wei Xu,[3] Yi-Ren Yeh,[3] Hugo Y. Lin.[1,2] *[1]Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Medical University, Kaohsiung, Taiwan; [3]National Kaohsiung Normal University - Yanchao Campus, Kaohsiung, Taiwan.*

Background: The fast-growing prevalence of end stage renal disease leads to an increasing burden of population requiring dialysis worldwide. Specifically, patients on hemodialysis face the problem of maintaining their vascular accesses. Unfortunately, occurrence of stenosis and clots is not uncommon, especially in arteriovenous grafts (AVG). Graft longevity can be improved by effectively detecting and preventing these circumstances. The aim of this study is to develop a portable recording device that detects stenosis by extracting information from blood flow sounds.

Methods: Blood flow sounds were collected at four different locations on the arm, including venous and arterial ends of arteriovenous access. Measurements were conducted weekly, with four one-minute recordings per patient. A logistic regression model is used to analyze sound data. Recordings obtained prior to percutaneous transluminal angioplasty (PTA) procedures were labeled abnormal and those after PTA were labeled normal. Extracted features from each labeled recording include energy, spectrum, mel-frequency cepstrum, and chroma, as shown in Figure 1.

Results: In total, we have 109 labels, 25 of which are abnormal cases. Note that each case contains 4 separate recordings. For evaluation purposes, we randomly chose 75% of the labels as training cases and used the rest as testing cases. Each random trial compares single-location detection models to one integrated model, which combines data from all four locations. The trial was repeated 100 times. Our results in Table 1 indicate that arterial sounds are more informative than venous sounds in detecting stenosis. Note that the integrated model also significantly outperforms the other single-location models.

Conclusions: Our proposed model shows excellent performance in screening for AVG failure. This algorithm has potential to provide reliable and reproducible detection of vascular access abnormalities, optimizing AVG outcome and management for clinicians and patients.

Funding: Clinical Revenue Support

Type I and Type II error rate of detection models

Model	Venous end	Arterial end	Graft (v)	Graft (a)	Integrated model
Type I error rate	0.516	0.279	0.513	0.298	0.124
Type II error rate	0.278	0.118	0.267	0.161	0.060

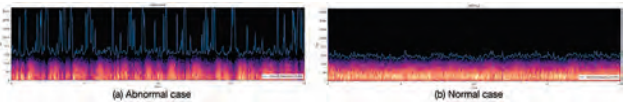


Figure 1: Spectrum and roll-off frequency of (a) abnormal and (b) normal cases

PO1034

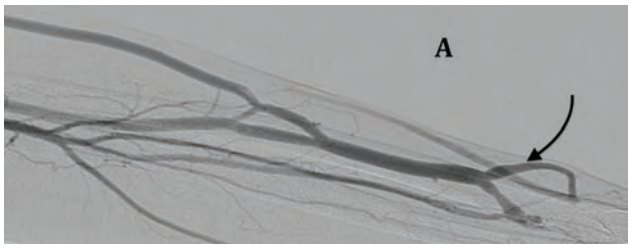
A Novel Method for Ligation of Accessory Veins: A Case Series of Eight Patients

Khaled Boubes,[1] Nabil J. Haddad,[1] Anil K. Agarwal.[2] *[1]The Ohio State University, Columbus, OH; [2]VA Central California Health Care System, Fresno, CA.*

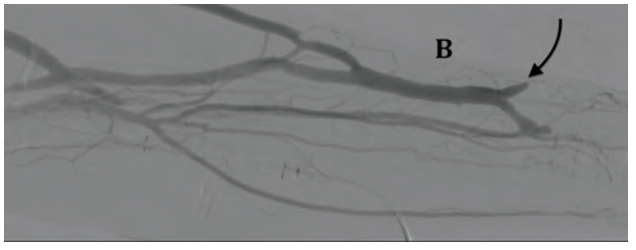
Introduction: Accessory veins are a common cause for decreased blood flow through the body of arteriovenous fistulae (AVF). A common practice is to have these ligated surgically through a cut-down procedure. Alternatively, these can be blocked by coiling, embolization, or by percutaneous ligation. We present a case series where accessory veins were ligated percutaneously under direct ultrasound (US) visualization.

Case Description: A total of 8 patients underwent percutaneous accessory vein ligation from Dec 2020 through May 2021. None had any immediate complications. Cessation of blood flow through the accessory vein was confirmed by color doppler ultrasonography and by angiography. Technique description: After identifying the accessory vein on angiography and its impact on the flow through the AVF, the vein is then identified using the US. The location to ligate the vein is then chosen as close as possible to the vein "take-off". Using a 4-0 absorbable suture and under direct US visualization, the needle is inserted from one side of the vein and passed underneath to come out from the other side. Then, the needle is flipped and inserted back subcutaneously, passing above the vein to come out eventually next to the initial insertion site. The suture is then tied firmly. Depending on the size and location of the vein, another suture can be done in a similar fashion a few millimeters away. Color doppler is then used to detect any flow through the vein. Confirmation of the cessation of flow can also be achieved by repeat angiography.

Discussion: Percutaneous ligation of the accessory veins is a technique that saves the patients from undergoing an open surgical intervention. Utilizing the US for direct visualization of the needle during the procedure enhances its safety and efficiency.



Flow through the accessory vein before the ligation.



Cessation of the blood flow through the accessory vein after the ligation.

PO1035

Feasibility of Treating Stenotic Fistula Lesions with a Drug-Coated Balloon Prior to Using a Standard High Pressure Balloon

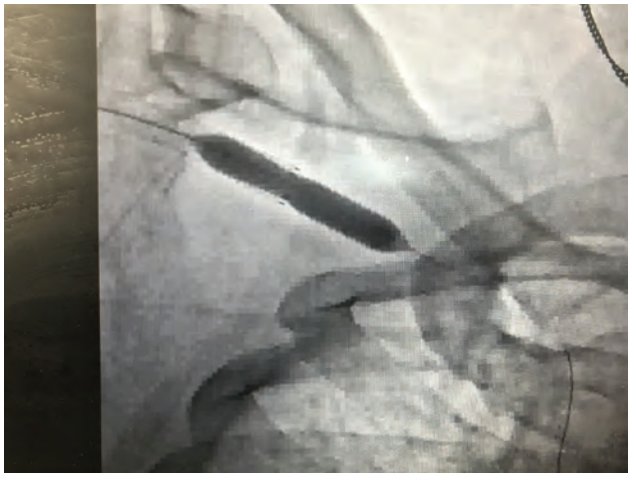
Sylvester Barnes.[1,2] *[1]Edward Hines Junior VA Hospital, Hines, IL; [2]Loyola University Chicago, Chicago, IL.*

Background: Hemodialysis access maintenance is a major cost expenditure for dialysis care. Patients often require multiple procedures per year, often treating the same access lesion in a AVF / AVG. A large proportion of stenotic lesions develop secondary to neointimal hyperplasia. Standard treatment has been angioplasty using high pressure non-compliant balloons. Recently drug coated balloons (DCB), coated with the medication paclitaxel; to help decrease neointimal hyperplasia, have been used in dialysis access treatment. The safety profile and efficacy have been proven to decrease lesion reoccurrence at 6 months when compared to regular angioplasty. Traditionally the recommendation for use of DCB is to follow after the lesion has been primarily dilated with a high-pressure balloon (HPB).

Methods: For DCB use the manufacture recommends pretreatment of the lesion with a HPB followed by secondary DCB treatment. This Arthur decided to modify the technique and treat lesions needing angioplasty with DCB first (example in figure 1) and only secondary treatment with HPB if there was not sufficient resolution of the lesion / ballon inflation to acheive less than 30% residual stenosis. Observational data is being tracked for patients undergoing fistulograms to provide a single center observational prospective cohort to look into this issue.

Results: Currently 11 patients with 15 total lesions have undergone this modification of treatment in the past 9 months, with 3 of the 11 patients having repeat fistulograms post treatment. Nine of the 11 patients required no HPB follow up. One of the 11 patients suffered a cephalic arch rupture and required stent graft placement.

Conclusions: Early data from this observational study shows that treatment of a stenotic lesion using a DCB as the only treatment is effective in the majority of cases to achive full lesion angioplasty. Preliminary results indicate no change in long term efficacy in the DCB lesion treatment.



PO1036

Predictors of Vascular Access Thrombosis in Maintenance Hemodialysis Patients: An Historic Cohort Study

Rita Veríssimo,[1,2] Luís Leite de sousa,[1,3] Tiago J. Carvalho,[1,4] Artur P. Mendes.[1,2] *[1]DaVita Vascular Access Center - Lisbon, Lisbon, Portugal; [2]DaVita Sacavém Hemodialysis Unit, Lisbon, Portugal; [3]DaVita Sintra Hemodialysis Unit, Lisbon, Portugal; [4]DaVita Cascais Hemodialysis Unit, Lisbon, Portugal.*

Background: Vascular access (VA) thrombosis is a known complication in patients with end-stage kidney disease on hemodialysis (HD), but its risk factors are not completely established. We performed a study with the aim of ascertaining risk factors for VA thrombosis.

Methods: A multicenter retrospective cohort study was performed in three HD units to determine VA thrombosis rate and associated risk factors in maintenance HD patients, from July 2019 to April 2021. Descriptive statistics were calculated and expressed as median (IQR) or count (%). Univariate and multivariate logistic regression was used to calculate the adjusted odds ratio (aOR) with 95% CI for the variables associated with VA thrombosis.

Results: From a total of 178 maintenance HD patients, there were 30 (16.9%) VA thrombosis during follow-up. Our cohort had a median of 71 years (61-80), 59,6% (n=106) were male, were on HD for a median of 63.52 months (37.58-98.87), 37.6% (n=67) had diabetes, 60.1% (n=107) cardiovascular disease and 55.6% were on anticoagulant or antiplatelet agents. As to the VA, 87.1% (n=155) had arteriovenous fistulas (AVFs) and 28.1% (n=50) had history of previous percutaneous or surgical interventions. When comparing cases that led to thrombosis to VAs that maintained patency, thrombosis was more likely in arteriovenous grafts (AVGs) versus AVFs (60.9% vs 19.3%, p< 0.001), in VAs that had previous percutaneous or surgical interventions (34% vs 10.2%, p<0.001), had a VA flow (Qa) slope ≥ 25% or Qa value < 500ml/min, excluding radiocephalic AVFs (30.4% vs 11.7%, <0.001) and those with spKt/V < 1.4 (40% vs 11.2%, p<0.001). Multivariate analysis risk factors independently associated with VA thrombosis were AVGs [aOR 13.35 (4.38-40.74), p<0.001], Qa slope ≥ 25% or Qa < 500ml/min, excluding radiocephalic AVFs [aOR 5.00 (1.76-14.18), p=0.003], and spKt/V <1.4 [aOR 8.23 (2.90- 23.35), p<0.001]. The model had a Nagelkerke R2 of 42.1%, Hosmer-Lemeshow goodness-of-fit test performed well ($\chi 2$= 0.215, df=3, p=0.975) and showed very good discriminative ability [AUROC (95% CI) 0.85 (0.77-0.94)].

Conclusions: Our study showed AVGs, Qa slope ≥ 25% or Qa < 500ml/min, excluding radiocephalic AVFs, and spKt/V < 1.4 were independent predictors of VA thrombosis. Interestingly, patients' demographic characteristics and comorbidities were not associated with VA thrombosis.

PO1037

Efficacy and Safety of Plastic Cannulae Compared with Metal Needles in the Initial Use of an Arteriovenous Fistulae in Incident Hemodialysis Patients: A Randomized Controlled Study

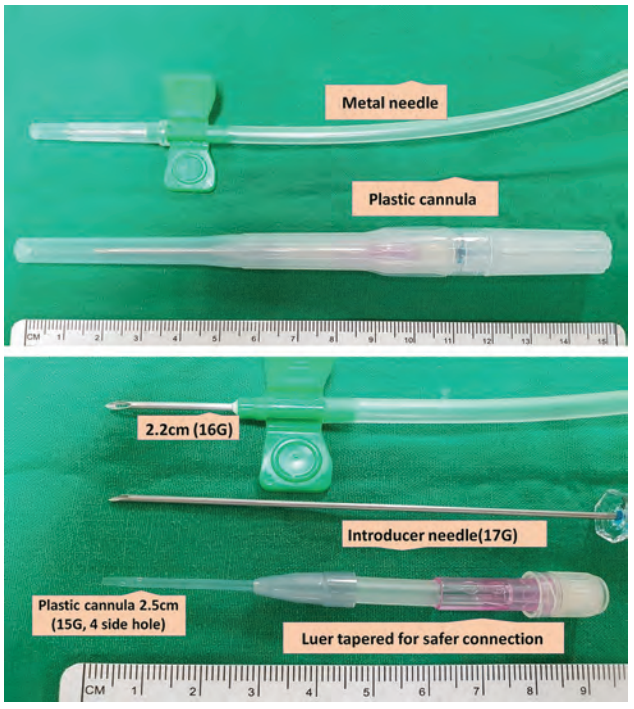
Sung gyun Kim, Hoi Woul Lee, Jwa-kyung Kim. *Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.*

Background: Successful cannulation of an arteriovenous fistula (AVF) is important in patients starting hemodialysis (HD). Metal needles have been used for decades, but the usefulness of plastic cannulae has recently been demonstrated as a new technique.

Methods: As a prospective, randomized study, eligible patients were randomized into two groups in a 1:1 ratio (n=45/group). Maturation of the AVF was confirmed using Doppler ultrasound. The primary endpoint was the initial cannulation failure rate, defined as the failure of successful completion of three consecutive dialysis sessions. The secondary endpoints were time for hemostasis at the end of HD, degree of patients' pain, degree of cannulation difficulty felt by the nursing staffs, and achieving optimal HD adequacy.

Results: The mean time from AVF creation to the first cannulation was 48.1±16.7 days. A total of 17 cases of cannulation failure occurred, and the failure risk tended to be higher in the metal needle group than the plastic cannula group (HR 2.6, 95% CI 0.95-7.41) after adjusting for age, gender, comorbidities, and location. The overall incidence of vessel injury was higher and time for hemostasis was significantly longer in the metal group than the plastic group. The use of plastic cannula was associated with better HD adequacy compared to metal needle. However, the patients' pain score (*P*=0.004) and nursing staff's cannulation difficulty score (*P*=0.084) were higher in the plastic group, emphasizing the great importance of practice using plastic cannulae.

Conclusions: The vascular outcomes of plastic cannulae were much favorable compared to metal needles in incident HD patients. The use of plastic cannulae could be a new and innovative way to improve the quality of dialysis.



PO1038

Alignment Between Patient and Provider Perspectives on Hemodialysis Vascular Access Decision-Making: A Qualitative Study

Angela R. Schneider,[1] Pietro Ravani,[1] Kathryn M. King--Shier,[1] Robert R. Quinn,[1] Jennifer M. MacRae,[1] Matthew J. Oliver,[3] Swapnil Hiremath,[2] Matthew T. James,[1] Meghan J. Elliott.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]University of Ottawa, Ottawa, ON, Canada; [3]University of Toronto, Toronto, ON, Canada.*

Background: Recent updates to the KDOQI Clinical Practice Guideline for Vascular Access emphasize attaining the "right access, in the right patient, at the right time, for the right reasons". Yet, how patients, their caregivers, and healthcare providers integrate medical factors with care preferences in patient-centered vascular access decision making is unknown. We sought to explore the extent to which these diverse perspectives align in hemodialysis vascular access selection.

Methods: In this qualitative descriptive study, we purposively sampled patients receiving maintenance hemodialysis via an arteriovenous fistula or catheter, their informal caregivers, and healthcare providers. We conducted semi-structured interviews in person or by telephone with 19 patients, 2 caregivers, and 21 healthcare providers (7 hemodialysis nurses, 6 vascular access nurses, 8 nephrologists). We coded transcripts in duplicate and generated themes through an inductive, content analysis approach.

Results: While participants across roles shared perspectives related to vascular access decision making, we identified several areas where views diverged. Participants acknowledged the importance of decisional timing and readiness, the iterative nature of decision making, and a desire for vascular access selection to be a shared decision. Perspectives differed in the following key aspects: 1) priorities for vascular access type – providers' preferences for fistulas and physiological optimization contrasted with patients' focus on quality of life; 2) provider involvement in the decision – patients desired guidance from their trusted providers, whereas care providers tried to avoid unduly influencing the decision; 3) informational needs – tools and resources offered by the care team may not meet patients' need for pragmatic, experiential knowledge about vascular access options.

Conclusions: While patients and providers identified common perspectives related to the nature and timing of the vascular access decision, conflicting priorities and preferences may impact the decisional outcome. This study highlights opportunities to address decisional conflicts and enable shared decision making in vascular access selection.

PO1039

Vascular Access Selection Among People Receiving Hemodialysis: A Qualitative Study of Shared Decision-Making

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Background: The vascular access decision process for people receiving maintenance hemodialysis involves weighing the likelihood of having a functional access with its associated risks. How patient and clinician preferences are integrated alongside best evidence to make joint vascular access decisions is unclear. We aimed to explore how such decisions are made from the perspectives of patients, their caregivers, and their kidney care providers.

Methods: In this qualitative descriptive study, we purposively sampled patients receiving in-centre hemodialysis for >3 months via either an arteriovenous fistula or a central venous catheter, their informal caregivers, and their hemodialysis care providers. We conducted semi-structured interviews by telephone or in person with 19 patients, 2 caregivers, and 21 healthcare providers (8 nephrologists, 7 hemodialysis nurses, 6 vascular access nurses). We coded transcripts in duplicate and generated themes through an inductive, thematic analysis approach.

Results: Participants described a decisional hierarchy, whereby decisions regarding vascular access were predicated on upstream decisions (i.e., dialysis initiation, transplantation, home dialysis) that were preference sensitive and prioritized over vascular access type. Upon reaching a decision for hemodialysis, vascular access decision making was influenced by the following: 1) preferences for kidney replacement therapy, including anticipated timeline to transplantation or transition to home dialysis modalities; 2) urgency and timing of dialysis need, where urgent starts undermined expressed preferences; 3) limitations of individualized decisions, as when preferences and practicalities diverged; 4) occasions to re-visit the vascular access selection; and 5) availability of support for vascular access decision making and the decisional outcome.

Conclusions: Although patients and care providers prioritized upstream decisions, several influences on vascular access decision making were identified once the decision for hemodialysis was made. These findings can inform approaches to integrating shared decision making in dialysis and vascular access selection.

PO1040

Racial Disparities in Arteriovenous Fistula Use Among Hemodialysis Patients: The Role of Vascular Surgeon Availability

Yi Zhang,[1] Mae Thamer,[1] Timmy C. Lee,[2] Deidra C. Crews,[3] Michael Allon.[2] *[1]Medical Technology and Practice Patterns Institute, Bethesda, MD; [2]The University of Alabama at Birmingham School of Medicine, Birmingham, AL; [3]Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Factors contributing to persistent racial disparities in the use of arteriovenous fistulas (AVF) among HD patients are unclear. A recent study reported significant geographic variation in the availability or supply of vascular access (VA) surgeons. We examined whether racial disparity in AVF use is affected by VA surgeon availability.

Methods: Using CROWNWeb and Medicare claims data from the US Renal Data System (USRDS), longitudinal competing risk analyses of all adult outpatients initiating HD with a central venous catheter (CVC) in 2016 and 2017 (n=103,286) were performed. Likelihood of successful AVF use was compared between Black and White patients after adjusting for VA surgeons supply, calculated as the number of surgeons normalized by the number of HD patients in each hospital referral region (HRR).

Results: Patient, facility, and area characteristics varied significantly among different levels of surgeon supply. At month 12 of hemodialysis, 40% of patients who initiated with a CVC had successful AVF use. Compared to the 1st quartile of surgeon supply, higher supply levels were associated with modestly increased likelihood of AVF use: 3% (95% CI 0.4-6.1%), 4% (95% CI 0.7-6.9%, and 3% (0.0-6.1%) for 2nd, 3rd, and 4th quartiles, respectively. However, residing in areas with a greater surgeon availability was not associated with less racial disparity in likelihood of AVF use (Figure 1). Specifically, compared to White patients, Black patients were 10% (95% CI 7 to 13%) and 8% (95% CI 5 to 11%) less likely to have successful AVF use in low and high surgeon supply areas, respectively.

Conclusions: VA surgeon supply was not associated with racial disparities in AVF use among patients initiating with a CVC. Additional studies of patient, provider, practice, and regional factors are needed to identify relevant factors to mitigate lower rates of AVF use among Black HD patients.

Funding: Other NIH Support - NIMHD

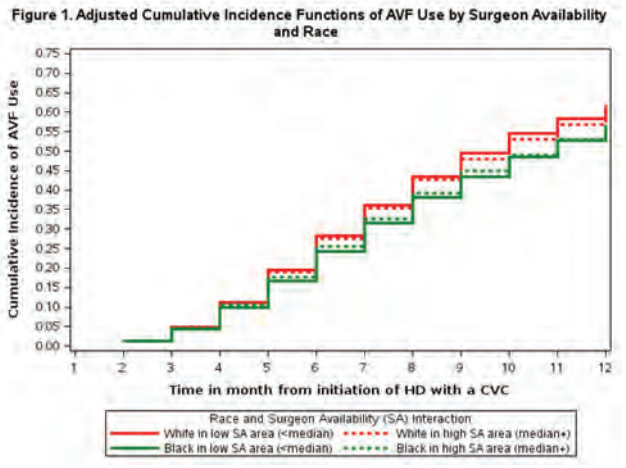

Figure 1

PO1041

Feasibility of Creation of an Endovascular Arteriovenous Fistula in Patients Undergoing Preoperative Vascular Mapping

Alian Albalas, Salam Madi, Ammar Almehmi, Michelle L. Robbin, Michael Allon. *The University of Alabama at Birmingham, Birmingham, AL.*

Background: The endovascular arteriovenous fistula (endoAVF), a novel percutaneous technique of AVF creation, was approved by the Food and Drug Administration in 2018, and has been placed in a small number of U.S. hemodialysis patients. It is unknown how often patients with advanced chronic kidney disease have vascular anatomy suitable for endoAVF creation. The goal of the present study was to determine the proportion of patients with a vascular anatomy suitable for endoAVF creation, and to assess patient characteristics associated with such suitability.

Methods: All patients referred for vascular access placement at a large academic medical center underwent standardized preoperative sonographic vascular mapping to assess suitability for an AVF. During a two-year period (March 2019 to March 2021), we assessed the suitability of the vessels for creation of an endoAVF. We then compared the demographic characteristics, comorbidities, and vascular mapping measurements between patients who were or were not suitable for an endoAVF.

Results: During the study period, 223 patients had preoperative vascular mapping results suitable for creation of a surgical AVF. Of these, 140 patients (63%) were also suitable for an endoAVF. Patients with a vascular anatomy suitable for an endoAVF were younger (age 55±15 vs 60±14 years, p=0.01), but similar in sex, race, diabetes, hypertension, coronary artery disease, and peripheral artery disease.

Conclusions: Among patients with chronic kidney disease with vascular anatomy suitable for a surgical AVF, 63% are also suitable for an endoAVF. Older patients are less frequently suitable for an endoAVF.

Funding: NIDDK Support

PO1042

Endovascular Arteriovenous Fistula Closure with Covered Stent Placement

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Introduction: WaveLinQ™ endovascular arteriovenous fistula (EndoAVF) system is a new technique that uses radiofrequency energy to create AVF. It has been gaining popularity as it avoids major surgery, has less recovery time and better success rates than surgical AVF creation. Pseudoaneurysm, dissection of brachial artery, intra-procedure brachial artery thrombosis, device embolization, and steal syndrome are described complications of the procedure. We present a case of EndoAVF creation complicated with forearm swelling and its successful management.

Case Description: Patient is a 45 y/o male with End-Stage Renal Disease due to Hypertensive Nephrosclerosis and obstructive uropathy, now s/p failed kidney transplant, currently on Peritoneal Dialysis (PD). PD was failing and decision was made to transition patient to hemodialysis (HD). In preparation of HD, AVF using WavelinQ EndoAVF system was placed in right forearm between intraosseous artery and vein with coiling of the medial brachial vein. A week after fistula creation, patient developed right forearm swelling with numbness and tingling. Fistulogram demonstrated stenosis in the perforator vein with poorly developed cephalic vein and diversion of blood flow to multiple superficial collateral veins in the forearm causing swelling. Multiple attempts at balloon assisted maturation of the cephalic outflow were unsuccessful. Due to persistent forearm swelling with discomfort a decision was made to close the fistula. A 5 x 15 mm self-expanding ViaBahn™ stent was deployed in interosseus vein across the anastomosis to close the fistula. Post fistula closure, arm swelling resolved completely.

Discussion: Covered stents have been used in the maintenance of hemodialysis AVF for various purposes including dialysis access stenosis, central vein stenosis, pseudoaneurysm exclusion and angioplasty associated vascular rupture that cannot be repaired using balloon catheter. This is the first reported case of successful use of covered stent graft to occlude anastomosis to close EndoAVF. As these fistulae are created more often, more novel complications will be encountered. It will be imperative for interventionalists to find creative solutions as well as actively report the successful management of complications.

PO1043

Long-Term Prognosis of Vascular Access in Hemodialysis Patients with Systemic Lupus Erythematosus

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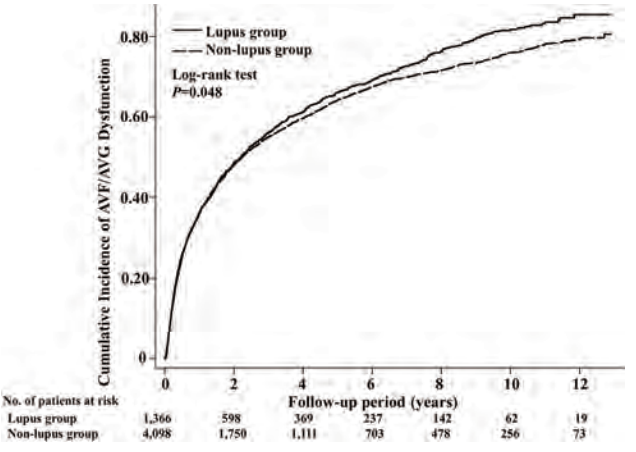
Background: Patients with systemic lupus erythematosus (SLE) have a higher risk of vascular complications.

Methods: This retrospective cohort study is aimed to analyze the differences in the risk of arteriovenous fistula or graft (AVF/AVG) dysfunction in hemodialysis (HD) patients with and without SLE from Taiwan Nationwide Health Insurance Database over a 10-year period. AVF/AVG dysfunction is defined as occurrence of the first episode of intervention after vascular access creation. This retrospective cohort study is aimed to analyze the differences in the risk of arteriovenous fistula or graft (AVF/AVG) dysfunction in hemodialysis (HD) patients with and without SLE from Taiwan Nationwide Health Insurance Database over a 10-year period. AVF/AVG dysfunction is defined as occurrence of the first episode of intervention after vascular access creation.

Results: Totally, 1366 HD patients with SLE had higher incidence rates of AVF/AVG dysfunction than 4098 non-SLE HD patients in the following 4 periods, (1) after 1 year (incidence rates were 15.21% and 13.01% respectively; subdistribution hazard ratio (SHR) = 1.16; P = 0.007), (2) 1st-to-10th-year period (15.36% and 13.25%; SHR = 1.16; P = 0.007), (3) 5th-to-10th-year period (11.91% and 8.1%; SHR = 1.42; P = 0.003), and (4) overall period (23.53% and 21.66%; SHR = 1.09; P = 0.027). There were significantly higher incidence rates of AVF/AVG dysfunction in SLE patients during the long-term follow-up period.

Conclusions: In conclusion, regular surveillance of vascular access function by clinical examination after 1 year, especially during 5 to 10 years, is needed to improve vascular access patency and dialysis adequacy in SLE patients undergoing maintenance hemodialysis.



PO1044

Arteriovenous Access Creation and Re-Intervention Before Starting Hemodialysis

Epiphane E. Kolla,[1] Raphael Coscas,[3,1] Cécile Couchoud,[4] Ziad Massy,[2,1] Benedicte Stengel,[1] Marie Metzger,[1] Natalia Alencar de Pinho.[1] [1]*Paris-Saclay University, UVSQ, Inserm, Center for Research in Epidemiology and Population Health, Villejuif, France;* [2]*Div. Nephrology, Ambroise Paré University Hospital, APHP, Boulogne Billancourt, France;* [3]*Div. Vascular Surgery, Ambroise Paré University Hospital, APHP, Boulogne Billancourt, France;* [4]*Biomedicine Agency, La Plaine Saint Denis, France.*

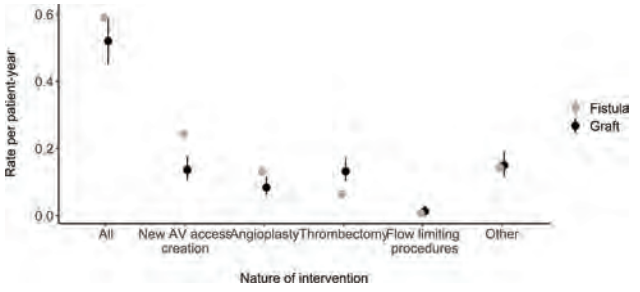
Background: Arteriovenous fistulae and grafts are preferred to catheters for patients undergoing maintenance hemodialysis. They require early creation to be functional at time of hemodialysis initiation, but may need re-interventions to mature and remain functional.

Methods: Using data from the French REIN Registry linked to the national healthcare system database (Système National des Données de Santé - SNDS), we assessed: A) the timing of first arteriovenous access creation before hemodialysis initiation; B) vascular access re-intervention rates before hemodialysis initiation; and C) the frequency of catheter use at hemodialysis initiation in 43,495 matched incident patients from 2010 through 2015.

Results: Median age was 71 years, 64% were men, 43% had diabetes, and 33% started hemodialysis urgently. Half (51%) underwent a first arteriovenous access creation: a fistula in 21,240 patients, created a median of 5 months (IQR, 2-12), and a graft, in 741 patients, 3 (1-8) months before hemodialysis initiation. Among patients with a first fistula attempt, 30% underwent at least one vascular access re-intervention before hemodialysis initiation, versus 21% among those with a first graft attempt (p<0.001). The types of intervention substantially differed according to vascular access (Figure). When dialysis start was urgent, catheter was used in 43% of patients in both access groups (p=0.86); when it was not, catheter was used in 12 and 14% of patients with a first fistula or graft attempt, respectively (p=0.15).

Conclusions: In incident hemodialysis patients in France, fistula is typically the first attempted arteriovenous access. Early arteriovenous access creation prevents from using catheter at dialysis initiation in a majority of patients, but requires close monitoring of potential complications.

Funding: Government Support - Non-U.S.



PO1045

Incidence of De Novo Central Vein Stenosis in Hemodialysis Patients Following Their First Tunneled Central Vein Catheter (CVC) Placement

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Background: Central vein stenosis is a common complication in hemodialysis patients following tunneled CVC insertion. Little is known about its incidence, association with patient characteristics, or relationship with duration of CVC placement. We systematically evaluated central vein stenosis in hemodialysis patients receiving their first CVC at a large medical center.

Methods: All new hemodialysis patients underwent an ultrasound prior to their internal jugular tunneled CVC placement, to exclude venous stenosis or thrombosis. If they were subsequently referred for CVC exchange, a catheterogram/venogram was performed to assess for hemodynamically significant (≥50%) central vein stenosis. During a five-year period (January 2016 to January 2021), we quantified the incidence of central vein stenosis in patients undergoing CVC exchange. We also evaluated the association of central vein stenosis with patient demographics, comorbidities, and duration of CVC dependence prior to exchange.

Results: During the study period, 273 patients underwent exchange of a tunneled internal jugular vein CVC preceded by a catheterogram/venogram. Of these, hemodynamically significant central vein stenosis was observed in 36 patients (13%). Central vein stenosis was not associated with patient age, sex, race, diabetes, hypertension, coronary artery disease, peripheral artery disease or CVC laterality (**Table 1**). The frequency of central vein stenosis was progressively higher with greater duration of CVC dependence, being 10%, 12%, 24%, and 28% in patients with <3 months, 3 to 6 months, 6 to 9 months and >9 months of catheter dependence, respectively (p=0.025).

Conclusions: Among incident hemodialysis patients receiving their first tunneled internal jugular CVC, the overall incidence of hemodynamically significant central vein stenosis was 13%. The likelihood of central vein stenosis was directly associated with the duration of CVC dependence.

Funding: NIDDK Support

PO1046

Hospitalization Risk and Long-Term Complications Associated with Catheter-Related Bloodstream Infection Among Hemodialysis Patients

Krithika Rajagopalan,[1] Kenneth Massey,[2] Srinivasan Rajagopalan,[1] Stephen Imperiale-Hagerman,[1] Paul Chew.[2] *[1]Anlitiks Inc, Dover, MA; [2]Cormedix, Berkeley Heights, MA.*

Background: Central venous catheters (CVC) are frequently required for vascular access in hemodialysis (HD) and are commonly associated with catheter-related bloodstream infections (CRBSIs). CRBSIs may have devastating consequences leading to increased hospitalizations, and long-term complications such as stroke, myocardial infarction (MI), heart failure (HF), and endocarditis, among others. This analysis explores the risk of CRBSI-associated hospitalizations and long-term complications among HD patients.

Methods: A 1:1 propensity score matched case-control analysis was conducted using merged data from United States Renal Data System (USRDS), CROWNWeb (dialysis organizations), and Medicare claims database (2013-2017). All CVC-dependent HD patients from 2014-2016 with a 1-year pre- and ≥ 1-year post-index period were included. CRBSI was defined as a composite measure of its ICD codes or sepsis/bacteremia diagnosis with hospitalization or without occurring pneumonia, gangrene, or urinary tract infections and hospitalization. An assigned index date (i.e., CVC insertion date + median days to CRBSI reported in CRBSI-case group) was used to identify non-CRBSI patients. CRBSI/non-CRBSI group differences were described using frequency, mean, median, chi-square, and t-tests. At 1-year post CRBSI, adjusted differences in hospitalizations and hospital days and time to long-term complications were modeled using generalized linear models cox proportional hazard models, respectively.

Results: CRBSIs result in higher 1-year incremental rates of: stroke (6.6%), MI (9.2%), HF (13.4%), PVD (13.6%), and endocarditis (9.4%). Mean number of hospitalizations and hospital days were 3.79 and 25.0 days for CRBSI, and 1.96 and 5.86 days for non-CRBSI patients, respectively. Mean hospitalizations and hospital days were significantly higher for CRBSI vs. non-CRBSI patients (p<0.05) at 1-year post-CRBSI. Hazard ratios for CRBSI patients were: stroke (1.64, 95% CI 1.53-1.75), MI (2.56, 95% CI 2.37-2.78), HF (2.01, 95% CI 1.88-2.14), and endocarditis (13.42, 95% CI 10.97-16.42).

Conclusions: Results show HD patients with CRBSIs incur a significant morbidity burden due to increased hospitalizations, hospital days, and long-term complications such as stroke, MI, HF, PVD, and endocarditis.

Funding: Commercial Support - Cormedix

PO1047

Hemorrhagic Shock due to Cutting of the Tunneled Dialysis Catheter

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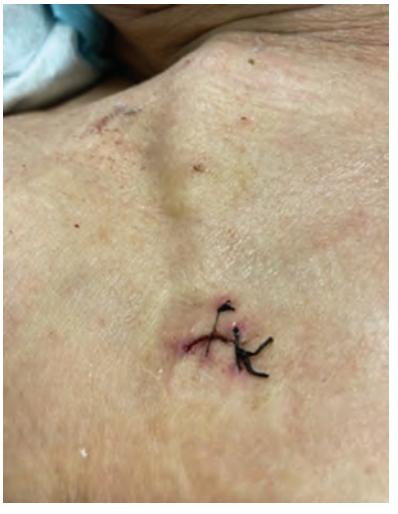
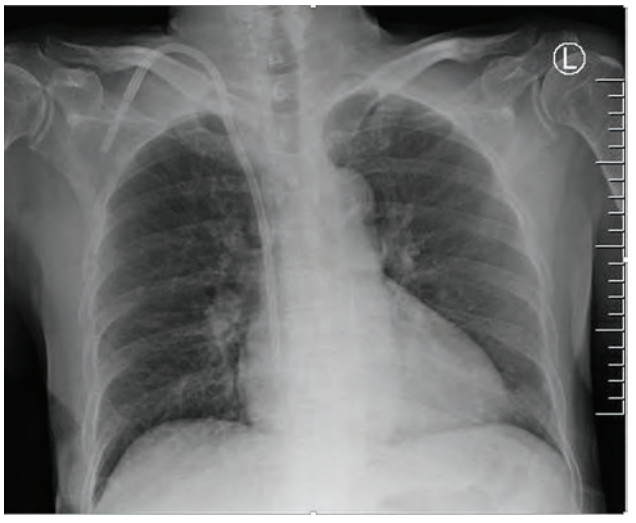
Introduction: Bleeding is a relatively rare complication of dialysis CVC overall.

Case Description: We describe the case of a 68-year-old non English speaking dementia patient with ESRD on HD. While in hospital, he had tried to cut the tape that was causing itching, but accidentally cut CVC. He was found in shock, bleeding from the exit site, which required aggressive resuscitation and compression to stop bleeding. After stabilisation examination revealed a palpable, well retracted catheter that was not visible (Fig 1). X ray showed the catheter in situ, but the Y along with the arterial and venous ports were absent (Fig 2). In retrospect, bleeding was particularly difficult to control because the cuff at this location is rigid and not compressible. This places the patient at increased risk for exsanguination leading to hemorrhagic shock, air embolism and mortality.

Discussion: To our knowledge, this is the first report of a cut tunnelled CVC proximal to the Y. This case demonstrates the risk of significant hemorrhage when a tunnelled CVC is damaged at this location and need for early recognition and control of bleeding. It also highlights important patient safety considerations given the risk of self-inflicted trauma in patients with dementia and language barrier for communication.



Catheter palpable, but not seen.



X Ray showing the retained tunnelled catheter proximal to Y

PO1048

Facial Swelling: Angioedema or Superior Vena Cava (SVC) Syndrome

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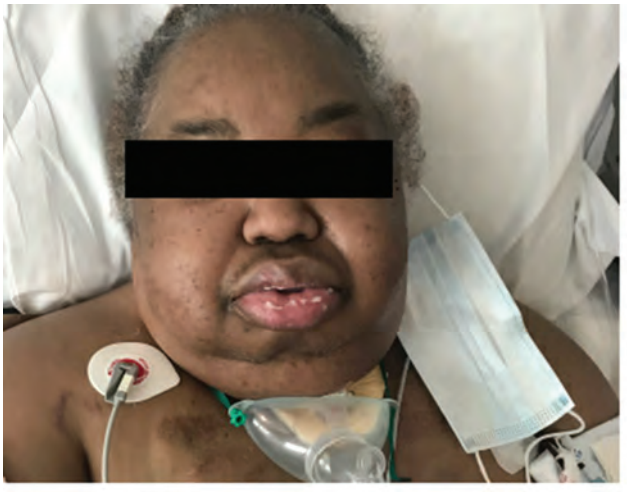
Introduction: Central venous stenosis is a common complication of recurrent central venous catheters (CVCs). Diagnosis can be challenging given its versatile presentation. Facial, unilateral breast or upper extremity swelling and signs of congestion mimicking pulmonary edema can be subtle clues. We describe a case of SVC syndrome that eluded clinicians as angioedema.

Case Description: 55-year-old female with history of morbid obesity, CKD 4, recurrent bacteremia, endocarditis and anemia presented with 1-day history of facial and oropharyngeal swelling, requiring intubation for airway protection. She was unsuccessfully treated for presumed angioedema with steroids, H2 blocker and C1 esterase inhibitor. She deteriorated, requiring tracheostomy tube, dialysis and then transferred to our hospital. She had episodes of worsening facial swelling, drooling and dyspnea with dialysis. Her medical records revealed multiple infections of her more than 10 CVCs placed in the past 12 years for frequent IV draws, iron infusions and antibiotics. Six portacaths were on the right side including 3 in subclavian, 1 in internal jugular vein and 2 peripherally inserted central catheters. A CO2 angiogram revealed stenosis of the right internal jugular, subclavian and brachiocephalic veins. The left internal jugular had the dialysis catheter with some narrowing around it. Endovascular interventions were unsuccessful at recanalization. Surgical bypass was not an option given her comorbidities. She was being evaluated for sharp or radiofrequency recanalization and/or inside-out device intervention. Unfortunately, devastated with failures, she opted for hospice.

Discussion: A high index of suspicion is crucial in patients with prior CV accesses and frequent access clotting, poor flows and facial or upper extremity swelling. The number, duration and infections of CVCs increase the risk of CV stenosis. Dialysis related dyspnea, drooling or treatment resistant angioedema should be evaluated with a venogram urgently. Prompt use of advanced treatments like endovascular recanalization can be lifesaving.



SVC syndrome

PO1049

Rare Cause of Pleural Effusion in a Dialysis Patient

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Introduction: The most common causes of pleural effusion in dialysis patients are congestive heart failure, infections, and tumors. However, in some dialysis patients, identifying the rare cause of pleural effusion requires careful consideration.

Case Description: A 29-year-old African American female with ESRD secondary to Lupus Nephritis (LN) s/p deceased donor kidney transplant, developed allograft failure and restarted dialysis. Upon initiating dialysis and weaning of immunosuppression she had episodes of fever, myalgias, synovitis and pleural effusions thought to be manifestations of lupus flare. Despite restarting immunosuppression, she presented frequently with dyspnea and recurrent bilateral transudative pleural effusions requiring repeat thoracenteses. Her physical exam was notable for swelling of bilateral upper extremities and face with minimal lower extremity edema. Lupus serologies were normal. Echo was unrevealing. CT angiogram (CTA) revealed complete occlusion of the distal superior vena cava (SVC) with extensive collateralization in the chest and abdominal wall.

Discussion: Her initial symptoms were attributed to volume overload and lupus serositis. However, inactive serologies, ongoing immunosuppression, and the transudative nature of the effusion were not consistent with lupus flare. Aggressive UF also failed to prevent recurrent pleural effusion. Given CTA and clinical findings, we concluded that the persistent pleural effusion is a manifestation of the SVC syndrome in our patient. The occlusion of the SVC was below the junction of the arch of the azygos vein. Venous blood flow from the upper body and extremities was shunted into the azygos system and flowed counter-current, returning to the right heart through the inferior vena cava. This results in increased hydrostatic pressure in the intercostal veins, contributing to the development of edema of the head, upper chest, bilateral upper extremities, and pleural effusions. Our patient had multiple central venous catheters increasing her risk for SVC syndrome. Clinicians should consider SVC stenosis as a potential cause of recurrent pleural effusions in a dialysis patient.

PO1050

Innovative Care Model for Vascular Access Strategy in AKI in Critically Ill Patients

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Background: Central venous catheter (CVC) is the preferred vascular access in critically-ill patients needing kidney replacement therapy (KRT). Non-tunneled CVC (NT-CVC) is frequently selected for bedside placement and provider familiarity. With hemodynamic instability, tunneled CVC (T-CVC), despite its known advantages of lower infection risk, lower mechanical complications, better blood flow rates and patient comfort, is infrequently considered due to competing demands for central vein access, and provider inexperience. We report our early experience of building a collaborative training program to improve vascular access approach in the critically-ill patients.

Methods: A single center retrospective study of T-CVC placed in an adult medical ICU between March 1, 2020 and December 31, 2020 by a nephrologist or an intensivist. The T-CVCs were placed in hemodynamically unstable patients for KRT and other medical therapies. Statistical analysis was limited to assess feasibility and safety of implementing a collaborative procedural service in an academic medical ICU.

Results: A total of 120 CVC related procedures were completed during the study period. 106 were T-CVC placements (68 for KRT, 38 small bore non-KRT), seven T-CVC removals, one difficult NT-CVC for KRT, one T-CVC exchange, one fluoroscopy guided repositioning of NT-CVC, four aborted for suspected central vein occlusion. Twenty-seven T-CVC (23 in COVID-19 positive and 4 for other compelling reasons) were placed at bedside with ultrasound guidance and anatomical landmarks without fluoroscopy. A safety pre-procedure checklist was developed for eligibility based on this experience. A minimum of 48-hr sterile blood culture report was essential to proceed. Complex comorbidities included coagulopathic patients. A minimum training competency was established and 2 critical care staff physicians were credentialed during this period. No major complications were encountered.

Conclusions: A collaborative care model between nephrology and medical ICU for T-CVC focused strategy is feasible. T-CVC can be placed safely in a carefully selected critically-ill patient population. Training intensivists with basic procedural skills for T-CVC procedure is achievable over a short period.

PO1051

Acute Atypical Chest Pain from Hemodialysis Access as a Culprit

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Introduction: Cardiovascular mortality is a well-known fact in CKD and ESKD patients specially in patients who are experiencing a cardiovascular event. There is an increased rate of cardiovascular complications and death. Frequent causes of acute chest pain in patients with ESKD include myocardial infarction, pericarditis, air embolism, acid reflux and complications from catheters but is rare to have complications from functional AVF.

Case Description: 40-year-old male with history of ESKD and was on hemodialysis via left brachial- brachial arteriovenous fistula with graft extension, DDKT in 02/2020, HTN and HIV who presented to the ED 1 year after transplant with a week history of

worsening sharp, non-radiating chest pain localized at the left hemithorax. Patient referred nausea and vomiting for 2 days. Emesis was as thick mucus possibly blood-streaked; however, no coffee-grounds. Stated he had never experienced this chest pain before. He reported not taking any medication at home for pain. On examination there was no cardiac murmurs, no lung abnormalities on auscultation and he had a patent arteriovenous fistula with good thrill and bruit and no signs of stenosis. Had 2 negative troponin levels with serial EKGs without ischemic changes. An echocardiogram that was negative for wall motion abnormalities or any changes in ejection fraction, ruling out an acute coronary syndrome. He had CXR showing curvilinear density projecting over the left lung base with a CT chest that reported a small curvilinear metallic density at the right ventricular apex. He was not on hemodialysis but before his transplant, he had multiple endovascular procedures including a stent placement to keep a patent AV access. A left upper extremity xray showed a left AV access stent fracture; findings were consistent with an embolized fragment from AVG stent. He underwent explant of the stent from AVG, but embolized fragment was not removed by CT surgery. Currently patient is chest pain free and asymptomatic.

Discussion: Stent fractures are commonly seen when they are in arteries, however this is an uncommon event in venous system specially in hemodialysis vascular access. Some of the complication associated with stent fracture are related to in-stent stenosis and central vein stenosis, but this is the first report of chest pain from stent fracture migrated to the left ventricle.

PO1052

Agitated Saline Bubble-Enhanced Ultrasound to Visualize Appropriated Position of Hemodialysis Catheter: Does Catheter Venous Site Matter?

Gessica Sabrine Braga Barbosa, Rayra G. Ribeiro, Jorge L. Espinosa Armijos, Lucia Andrade, Igor Smolentzov, Camila E. Rodrigues. *Universidade de Sao Paulo Hospital das Clinicas, Sao Paulo, Brazil.*

Background: The hemodialysis non tunneled catheter (HDC) is the most common access of starting renal replacement therapy. Malposition of catheter is associated with delays in treatment. Agitated saline bubble-enhanced ultrasound (SBUS) has become a new method to visualize the HDC position. Delayed appearance of microbubbles (≥ 2-second) in the right atrium indicates malposition. Our objective is to analyze the accuracy of SBUS between right and left internal jugular vein (IJV) HDC insertion, comparing to chest radiography (standard method).

Methods: From December 2019 to May 2021, we evaluated 145 hospitalized patients submitted to HDC insertion in IJV. We compared SBUS with chest radiography (CR); the time spent to perform the CR; complications; patient characteristics; catheter blood flow and quality of dialysis.

Results: Total of 145 patients were analyzed, the median age was 62 years old [50.5-70], and there was no statistical difference between the site of insertion. In RIJV, 91% catheters were placed. AKI was more frequent than CKD (75% vs 25%), except when the site was LIJV (46% vs 54%, p<0.05). AKI-related COVID-19 was the most common etiology (54%). The confirmation of catheter placement by SBUS was correlated with position by CR (All: r=0.6603, p<0.0001; RIJV: r=0.7044, p<0.0001; LIJV: r=0.6396, p=0.0769). SBUS was highly accurate in identifying adequate location of HDC, especially in RIJV (All: 97.9%; RIJV: 99.2%; LIJV: 84.6%, p< 0.05). The time of the catheter insertion to perform radiography was 191 minutes [83.5-287]. Adequate syringe blood flow and an effective hemodialysis session was more frequent in RIJV catheter (99.2% vs 53.8%, p<0.05; 96.8% vs 72.7%, p <0.05, respectively). Complications occurred only in 4.2%, without statistical difference between catheter sites.

Conclusions: Comparing with chest radiography, agitated saline bubble-enhanced ultrasound was more accurate in identifying adequate placement of RIJV than LIJV hemodialysis catheters.

Funding: Government Support - Non-U.S.

PO1053

Using the Seraph® 100 Microbind® Affinity Blood Filter Under Slow Flow Conditions Through a Normal Central Line

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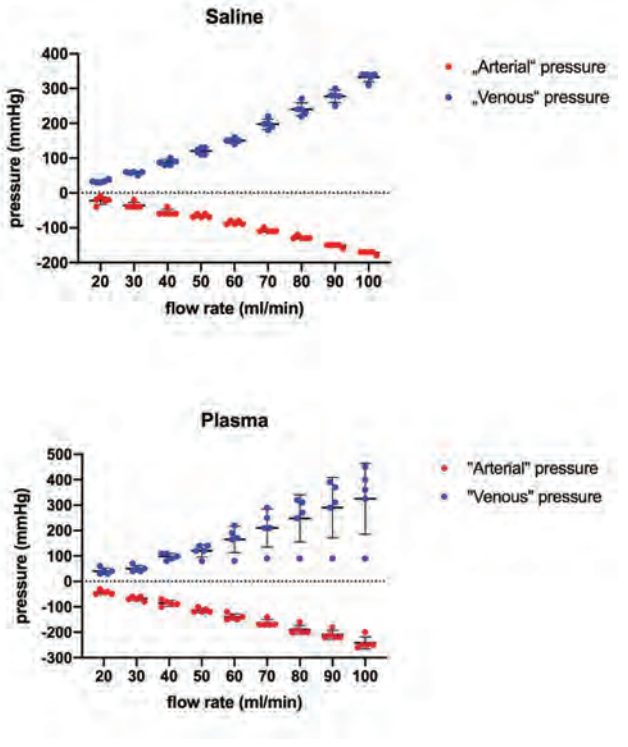
Background: The Seraph® 100 Microbind® Affinity blood filter has been in use since 2019 for the treatment of difficult to treat blood stream infections.and since 2020 for the treatment of critically ill COVID-19 patients. It is operated under blood flow rates of 100 – 350 mL/min, which requires a large bore central line a dialysis catheter. The aim of our study was to evaluate to evaluate the usability of the Seraph® 100 under slow flow conditions through a normal central line (in clinical practice).

Methods: A standard hemoperfusion blood tubing system as well as the Seraph® 100 (Exthera Medical, CA, USA) was used. Vascular access was a 20 cm trillumen central venous line (2 x 18 G and 1 x 16 G) that was inserted into a reservoir. The Multifiltrate (Fresenius Medical Care) was used to pump normal saline (n=5) or human plasma (n=5) through the Seraph® 100. Pressures were recored at any given flows (Qb). In two patients connected to a five lumen 20 cm catheter (Certofix Safety Quinto S1220, B. Braun, Melsungen, Germany - 1 x 12 G, 1 x 16 G, 3 x 18 G) blood flow as well as arterial and venous pressure were recorded through the 24 h treatment.

Results: Using saline or human plasma the Seraph® 100 Microbind®Affinity Blood Filter can be operatied at blood flow rates of up to 100 mL/min even through a 16 & 18 G lumen at tolerable arterial and venous pressures. In men using either the 12 G or the 16 G lumen as "arterial line" blood a blood flow rate of 50 mL/mon could be onbtained for 24 hours without problems.

Conclusions: The Seraph® 100 Microbind®Affinity Blood Filter can be operated at blood flow rates of 50 mL/min even through 16 & 18 G catheters.



"Arterial" and "venous" pressures depending on the flow (Qb) during hemoperfusion with the Seraph® 100 Microbind® Affinity Blood Filter.

PO1054

Keeping the Vascular Access Alive During the COVID-19 Pandemic

Min S. Cho, Cesar F. Hernandez-Arroyo, Muhammad Sohaib Karim, Micah R. Chan, Brad C. Astor, Ali I. Gardezi. *University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI.*

Background: Delay in care of suspected stenosis or thrombosis can increase the chance of losing hemodialysis access. Many procedures were canceled or postponed at the start of the COVID-19 pandemic. We have done a study to determine if the COVID-19 pandemic affected dialysis access care.

Methods: We performed a retrospective chart review to evaluate the incidence of both fistula and graft thrombectomies between April 1, 2020, and March 31, 2021, designated as the COVID-19 group and compared it with an incidence between April 1, 2019, and March 31, 2020, designated as the pre-COVID-19 group. Unsuccessful thrombectomy was defined as subsequent tunneled hemodialysis catheter placement within 48 hours after thrombectomy due to clotted access.

Results: There was no significant difference in the total fistula and graft thrombectomies between the two time periods: 44 cases in the pre-COVID-19 era, the incidence rate of 0.12 per patient-year; 54 cases in the COVID-19 era, the incidence rate of 0.14 per patient-year (HR=1.23, 95% CI= 0.81-1.89, p=0.31). However, there was a significant increase in the fistula thrombectomy in the COVID-19 era: 9 cases in the pre-COVID-19 era, the incidence rate of 0.024 per patient-year; 21 cases in the COVID-19 era, the incidence rate of 0.057 per patient-year (HR=2.38, 95% CI= 1.03-5.88, p=0.02). In addition, the incidence of unsuccessful fistula thrombectomy also increased significantly: 2 cases in the pre-COVID-19 era, the incidence rate of 0.005 per patient-year; 9 cases in the COVID-19 era, the incidence rate of 0.024 per patient-year (HR=4.54, 95% CI= 1.01-50, p=0.03). There was no significant difference in total as well as unsuccessful graft thrombectomy between the two eras.

Conclusions: We noticed a significant increase in fistula thrombosis and unsuccessful fistula thrombectomy in 1-year of the COVID-19 pandemic. This could be due to a delay in referring the patients for treatment of fistula stenosis. Even though the dialysis access procedures were considered essential, there might have been hesitancy on part of patients and referring dialysis center which led to this result. However, we did not notice this trend in AV graft. Timely referral for intervention is important to prevent vascular access thrombosis and loss.

PO1055

Virtual Interviewing in the COVID-19 Era: What Have We Learned?

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Background: The COVID-19 pandemic forced institutions across the US to switch to virtual interviewing. While some institutions were already offering virtual interviews on a limited basis, this was the first time all interviews were conducted using a virtual platform. Herein, we describe the experience of the nephrology fellowship interviewees at the University of North Carolina (UNC).

Methods: We distributed an anonymous Qualtrics survey to all the nephrology fellowship interviewees (N=80) at UNC. The survey included questions on quality of virtual interviews and was completed after the match to avoid bias related to the matching process.

Results: Thirty-one candidates completed the survey (39%), although not all questions were answered by everyone. The total number of interviewees increased from 41 in 2019-20 to 80 in 2020-21. 95% were satisfied with their virtual experience. 82% indicated that the virtual interview process enabled an informed decision about the fellowship program. Everyone was satisfied with the organization of the interview day (N=22). 28% responders (5/18) identified as underrepresented minority (URM). In 2019-20, 6/41 interviewees identified as URM as compared to 14/80 in 2020-21. The most common reasons for not ranking our program amongst the top three included limited job opportunities for partners, inability to visit the area, and lack of family in the area. Candidates valued the people they met and were able to get a good feel for the program despite virtual interviews. They were particularly satisfied with the opportunity to meet fellows one on one. Interviewees specified lower cost and time efficiency as advantages of virtual interviews.

Conclusions: This is the first report of the virtual interview experience for nephrology fellowship applicants. The virtual interview process increased the applications to our program although the number of URM applications were similar compared to previous years. There was uniform satisfaction with the virtual format and interviewees were able to appreciate the culture of the division. Most applicants found the virtual interview format favorable because of reduced cost and time expenditure, enabling them to interview at more programs. Our data suggest that serious consideration should be given to a virtual format in future years to provide opportunity and flexibility to the applicant pool and improve geographical diversity.

PO1056

"Breaking Bad News" During the COVID-19 Epidemic: A Virtual Objective Structured Clinical Examination (OSCE) for Nephrology Fellows

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Background: The "Breaking Bad News" OSCE assesses fellow counselling/communication skills in 20-minute simulation scenarios: kidney replacement therapy (KRT) in ESKD, urgent KRT in AKI, and kidney biopsy. In-person simulation was impractical during the COVID epidemic, so we adapted the OSCE to a virtual platform.

Methods: The AKI scenario was audio only. Fellows called a simulated patient (SP) surrogate for urgent KRT consent. The ESKD and kidney biopsy scenarios were video encounters between fellows and SPs. Faculty observed while muted/video off. After each scenario, fellows received feedback from SPs and faculty (unmuted/video on). Fellows from 3 programs at 2 centers completed the OSCE in May 2021. Post-OSCE, fellows were anonymously surveyed about each scenario, the OSCE overall, and their estimate of the percent of outpatient encounters and inpatient KRT counseling they had done virtually in the past year.

Results: 15 fellows did the OSCE; 14 completed the survey (93% response rate). 93% rated the OSCE overall as a good/very good approximation of a telemedicine experience. 100% were satisfied/very satisfied with the AKI scenario, 79% with the ESKD, and 77% with the kidney biopsy scenarios. Several commented that the AKI scenario was most realistic—they often counseled surrogates by telephone for urgent KRT. Fellows estimated that about 25% (median 27.5%; IQR 16-50%) of counseling for acute inpatient KRT was done virtually in the past year. They estimated about 50% (median 52.5%; IQR 36-70%) of outpatient encounters were done virtually in the past year, but several (dissatisfied with the ESKD and kidney biopsy scenarios) indicated they would not have counseled similar outpatients using telemedicine.

Conclusions: Overall, fellows felt the OSCE well-approximated virtual encounters. All were satisfied with the AKI scenario. The majority were satisfied with the ESKD and Kidney Biopsy scenarios, but some did not feel they were consistent with normal practice. The OSCE allows fellows to practice telemedicine communication skills that will remain relevant post-pandemic. *The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Defense or U.S. Government.*

Funding: Other U.S. Government Support

PO1057

Well-Being of Nephrology Fellows: Evolution over the Course of a Pandemic Year

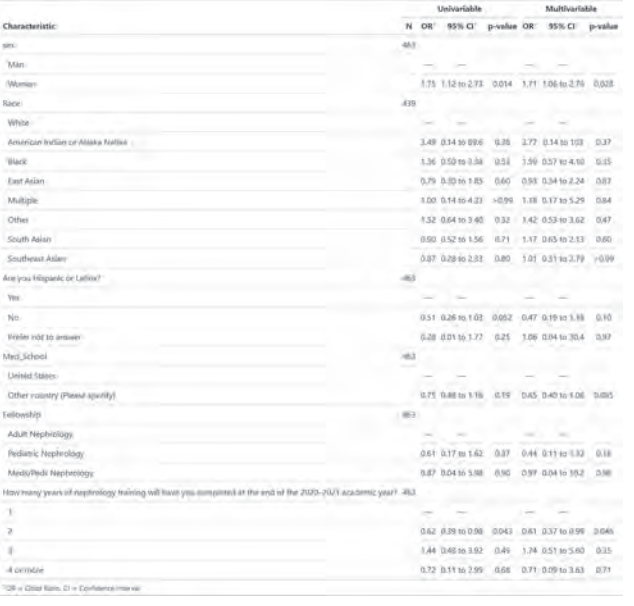
Hitesh H. Shah,[1] Kurtis Pivert,[2] Susan M. Halbach,[3] Anna M. Burgner,[4] Benjamin S. Ko,[5] Lili Chan,[6] Suzanne Boyle,[7] Joshua S. Waitzman,[8] Stephen M. Sozio.[9] *[1]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [2]American Society of Nephrology, Washington, DC; [3]Seattle Children's Hospital, Seattle, WA; [4]Vanderbilt University Medical Center, Nashville, TN; [5]University of Chicago, Chicago, IL; [6]Icahn School of Medicine at Mount Sinai, New York, NY; [7]Lewis Katz School of Medicine at Temple University, Philadelphia, PA; [8]Beth Israel Deaconess Medical Center, Boston, MA; [9]Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: We sought to assess changes in well-being of nephrology fellows over the first year of the COVID-19 pandemic in the U.S.

Methods: The Resident Well-Being Index (RWBI), a validated tool assessing physician distress, was distributed as part of ASN's annual nephrology fellow survey to 920 current adult, pediatric, and adult/pediatric fellows. An RWBI ≥ 5 (range 0–7) indicated distress. Demographic and fellowship factors associated with meeting the distress threshold were evaluated in univariable and multivariable logistic regression.

Results: A total of 511 fellows participated (56% response), of whom 463 completed the RWBI instrument. After 1 year of the COVID-19 pandemic, there were a higher proportion of nephrology fellows meeting the RWBI distress threshold—22% in 2021 versus 15% in 2020. Female nephrology fellows had higher RWBI scores (median 3 [IQR 5]) than their male colleagues (median 1 [IQR 3]). Higher proportions of 1st-year fellows (50% vs 42% for 2nd years, OR 0.61 for 2nd years [95% CI 037–0.99], p=0.046) and women (27% vs 18% of men, OR 1.71 [95%CI 1.06–2.76], p=0.028) met the distress threshold (Figure 1). There were no significant differences by race, ethnicity, medical school location, or adult vs pediatric fellowship. Despite the higher proportion of distress overall, 88% of respondents would recommend nephrology to medical students and residents.

Conclusions: Our follow-up assessment of nephrology fellows' well-being after the first year of the COVID-19 pandemic indicate the continued need for supportive measures to ensure the health of the future nephrology workforce, especially among 1st year and women trainees.



Characteristic	N	Univariable OR*	Univariable 95% CI*	Univariable p-value	Multivariable OR*	Multivariable 95% CI*	Multivariable p-value
sex	463						
Man	—	—	—		—	—	
Women		1.75	1.12 to 2.73	0.014	1.71	1.06 to 2.76	0.028
Race	439						
White	—	—	—		—	—	
American Indian or Alaska Native		3.49	0.14 to 89.6	0.46	2.72	0.14 to 103	0.57
Black		1.36	0.59 to 3.08	0.51	1.59	0.57 to 4.10	0.15
East Asian		0.79	0.30 to 1.83	0.60	0.93	0.34 to 2.24	0.87
Multiple		1.00	0.14 to 4.23	>0.99	1.18	0.17 to 5.29	0.84
Other		1.52	0.64 to 3.40	0.32	1.42	0.53 to 3.62	0.47
South Asian		0.90	0.52 to 1.56	0.71	1.17	0.65 to 2.13	0.60
Southeast Asian		0.87	0.28 to 2.32	0.80	1.01	0.31 to 2.79	>0.99
Are you Hispanic or Latinx?	463						
Yes	—	—	—		—	—	
No		0.51	0.26 to 1.02	0.052	0.47	0.19 to 1.18	0.10
Prefer not to answer		0.28	0.01 to 1.77	0.25	1.06	0.04 to 30.4	0.97
Med_School	463						
United States	—	—	—		—	—	
Other country (Please specify)		0.75	0.48 to 1.16	0.19	0.45	0.40 to 1.06	0.085
Fellowship	463						
Adult Nephrology	—	—	—		—	—	
Pediatric Nephrology		0.61	0.17 to 1.62	0.37	0.44	0.11 to 1.32	0.18
Medy/Pedi Nephrology		0.87	0.04 to 5.98	0.90	0.97	0.04 to 10.2	0.98
How many years of nephrology training will have you completed at the end of the 2020–20/1 academic year?	463						
1	—	—	—		—	—	
2		0.62	0.39 to 0.98	0.043	0.61	0.37 to 0.99	0.046
3		1.44	0.48 to 3.92	0.49	1.74	0.51 to 5.60	0.35
4 or more		0.72	0.11 to 2.99	0.68	0.71	0.09 to 3.63	0.71

*OR = Odds Ratio, CI = Confidence Interval

Figure 1: Association of Distress with Demographic Varaibles on Univariable and Multivariable Logistic Regression

PO1058

The Battle Between Home Call and Fellows Well-Being

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Background: Night call is traditionally taken by nephrology fellows to provide exposure to after-hour care. Lack of physician wellness and development of burnout are being seen more frequently and may have been enhanced during the COVID-19 pandemic. In an attempt to quantify the burden of call, nephrology fellows at the University of Wisconsin tracked home call activities and aimed to identify areas for improvement.

Methods: Each of the 6 nephrology fellows filled out a daily survey between November 9, 2020 and January 31, 2021, which was the peak of the COVID-19 pandemic in Wisconsin to address: 1) the total amount of sleep hours 2) quality of sleep (restful or fragmented) and 3) whether on-call fellow reported to hospital from home. Responses were collected the following morning to decrease recall bias.

Results: Over the 3-month study period, 100% of the call night data was recorded. The average amount of sleep per night was 5.3 hours. When necessary to report, the average hours of sleep dropped to 4.3 hours. However, if not called in, sleep increased to 5.8 hours per night. The percentage of nights requiring patient evaluation by coming to the hospital overnight was 50% during the study period, with a range of 48% of nights in December and 61% in January. Sleep during night call was described as 55% restful vs. 45% fragmented.

Conclusions: This survey has generated discussion amongst fellowship leadership and current fellows regarding novel ways to improve the night call experience to maximize education and clinical experience during training as well as improve fellow wellness. It was determined that the burden of call did not detract from the fellow education enough to warrant a change to a night float system. However, it did identify changes in management processes such as the timing of labs, implementation of dot phrases, and a sleep expert discussion to improve duration and quality of sleep.

Fellows Home Call Data

	November (11/9/20 - 11/30/20)	December (12/1/20 - 12/31/20)	January (1/1/21 - 1/31/21)	Total Average
Average Hours of Sleep (n)	5.3	5.1	5.5	5.3
Average Hours of Sleep if Called in (n)	4.4	3.9	4.6	4.3
Average Hours of Sleep if Not Called in (n)	5.9	5.8	5.8	5.8
Total Number of Frequency Called In per Month (n)	10	19	13	14
Percent of Nights Called in (%)	45	61	42	49
Percent of Nights with Restful Sleep (%)	55	48	61	55
Percent of Nights with Fragmented Sleep (%)	45	52	39	45

PO1059

Integrating Healthcare Education for Nephrology Best Practice – Topic Tagging and What Is "Deemed" Clinically Relevant Context: A Quantitative Perspective

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Background: Technology has allowed patients with Long-Term Conditions (LTCs) to access information through websites, portals, and Patient-centred organisations. 1) To understand, retrospectively, whether there has been an education neglect as part of healthcare delivery and 2) To understand if technology can help join up education.

Methods: Fourteen (14) topic tags were applied over 1-month (March and April 2020) between groups the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support (KDARs) (est.2014) for Kids platforms. Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection.

Results: 2,560 threads were topic tagged between two groups. For adults, educational gaps surround Renal Replacement Therapy (166 tags, 12.66%); Lab Tests and Biomarkers (137 tags, 10.50%) and Medication and Pharmacy (135 tags, 10.29%). For paediatrics and young people, educational gaps include Medication and Pharmacy (148 tags, 11.85%); Renal Replacement Therapy (133 tags, 10.65%); Peer Support (125 tags, 10.01%) and Nursing (115 tags, 9.20%).

Conclusions: Online educational modules should complement CKD pathways, and be delivered by wider Allied Health Professionals. This is the first UK retrospective study that examines clinically relevant educational gaps between online paediatric and adult renal cohorts close to two decades. Education is where healthcare requires investment.

PO1060

Nephrology Education Needs Assessment: Five Years and a Pandemic Later

Benjamin S. Ko,[1] Rob Rope,[3] Kurtis Pivert,[2] Anna M. Burgner,[5] Joshua S. Waitzman,[4] Susan M. Halbach,[6] Suzanne Boyle,[7] Lili Chan,[8] Hitesh H. Shah,[9] Stephen M. Sozio.[10] *[1]University of Chicago, Chicago, IL; [2]American Society of Nephrology, Washington, DC; [3]Oregon Health & Science University, Portland, OR; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Vanderbilt University Medical Center, Nashville, TN; [6]Seattle Children's Hospital, Seattle, WA; [7]Temple University, Philadelphia, PA; [8]Icahn School of Medicine at Mount Sinai, New York, NY; [9]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [10]Johns Hopkins Medicine, Baltimore, MD.*

Background: We sought to identify how educational tools utilized in nephrology training had evolved in the past 5 years and through the COVID-19 pandemic.

Methods: Questions about educational tools were distributed as part of ASN's annual nephrology fellow survey to 920 current adult/pediatric fellows.

Results: 511 fellows participated in 2021 (56% response rate), compared with 377 fellows in 2016 (31% response rate). Fellows indicated that UpToDate was still the most used (82%) and most effective educational tool (66% rated it "Very Effective"); however, ASN KSAP increased in popularity (27% in 2016, 58% 2021) and was also highly rated (65% Very Effective). Use of online resource and social media increased, including both new opportunities and prior available ones such as NephJC (7% to 32%, with 46% rated Very Effective) (Figure 1). A majority of fellows (84%) rated their education as good or excellent in 2021, a percentage similar to 2016 (81%).

Conclusions: Our follow-up assessment of nephrology fellows' educational tools found an increase in the adoption of online resources with similar effectiveness ratings as traditional resources.

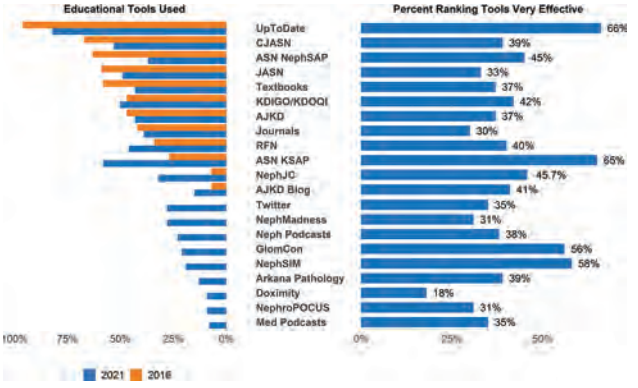

Figure 1: Educational Tools Used by Nephrology Fellows in 2016 and 2021 *(left)* and Percentage 2021 Nephrology Fellows Ranking Tools as Very Effective *(right).*

PO1061

Curriculum-Based Online Education Improves Nephrologists' Ability to Manage Hyperkalemia in Practice

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape Education, New York, NY.*

Background: The goal of continuing medical education (CME) is professional growth and improved patient care. We sought to determine if series of online continuing medical education (CME) activities will improve the clinical knowledge, competence, and confidence of nephrologists related to hyperkalemia management.

Methods: The online CME curriculum consisted of 5 online activities housed on a dedicated collection page. All used repeated pairs pre-/post-assessment study design was used and McNemar's test ($P < .05$ is considered significant) to assess educational effect. The last activity was a medical patient simulation that utilized tailored clinical guidance (CG), based on current evidence and expert recommendation, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions using a McNemar's test to determine *P* values. The activities launched between March and October, 2020 and data were collected for up to 12 weeks.

Results: The education reached over 15,000 physicians, including over 1,706 nephrologists. Overall, knowledge improved by 24% (P<.001) and competence by 4% (P=NS) (all relative improvements) by nephrologists. Specific improvements: 40% relative increase in knowledge related to impact of hyperkalemia (P<.001) 31% relative increase in knowledge related to clinical use of potassium binders (P<.001) 24% relative increase in knowledge related to optimizing RAAS inhibitors in patients with hyperkalemia (P<.05) 7% relative increase in competence related to clinical use of potassium binders (P=NS) Of the nephrologists who were included, 30% (P<.001) had a measurable increase in confidence in hyperkalemia management.

Conclusions: This curriculum demonstrates that a curriculum is effective at moving learners on the continuum for knowledge improvements to competence improvements. Some gaps remain after education. Among these learners, 49% need knowledge improvements related to optimizing RAAS inhibitors in patients with hyperkalemia and 41% related to clinical use of potassium binders. As such, further education needed in these areas.

Funding: Commercial Support - Astrazeneca

PO1062

Level of Confidence, Knowledge, and Literacy in Genetics Among US Nephrologists

Hila Milo Rasouly, Olivia Balderes, Maddalena Marasa, Hilda E. Fernandez, Marissa Lipton, Fangming Lin, Ali G. Gharavi, Maya Sabatello. *Columbia University Irving Medical Center, New York, NY.*

Background: Increased availability of genetic tests in nephrology and at reduced costs are promising for improved patient diagnostic and clinical care. Nephrologists' confidence, knowledge and genetic literacy are likely to impact the utilization of genetic testing (GT). Identifying gaps in nephrologists' knowledge and confidence and preferred methods of learning are needed to develop tailored approaches to improving it.

Methods: An online survey assessing genetic confidence, knowledge, and genetic literacy measured using GeneLiFT, a rapid word recognition screening test, was administered between January-May 2021 to nephrologists working in the US (self-identification).

Results: 201 nephrologists completed the survey, 67% working in an academic setting. All clinicians reported treating patients with genetic forms of kidney disease, but only 32% have to date referred >20 patients to GT. We observed limited genetic knowledge in 32% of respondents (Table), and 68% did not recognize the word "actionability" as real. Only 20% reported high confidence in all aspects of GT (ordering, discussing risks and benefits, results' interpretation, and using results to guide clinical care), and high level of confidence was significantly associated with working in an academic setting ($p= 2.6x10^{-5}$). Preferred methods for continued genetic education were "conferences" (70%), "self-directed methods" (45%) and "workshops" (40%). Methods used were mostly "reading specialty texts" (65%) and "internal specialty seminars and conferences" (55%).

Conclusions: There is a need to improve nephrologists' genetic literacy, knowledge, and confidence in genetics to ensure to ensure broad adoption of genetic testing in nephrology. Employing diverse educational methods will prevent widening the gap between the adoption of genetic testing in different clinical settings.

Funding: NIDDK Support

Table 1: Genetic knowledge amongst surveyed nephrologists (n=201)

Do you think the following statements are correct or incorrect? (5-point Likert scale from 'Definitely incorrect' to 'Definitely correct')		
Concept	Sentence	Incorrect answer
Genetic risk	Genetic testing may find genetic mutations that increase a person	42 (21%)
Panels/ exome	Genetic testing may give a person information about their chance of developing several different genetic conditions.	31 (16%)
Pharmaco-genomics	Genetic testing may find genetic variants that determine how a person responds to certain medicines.	21 (11%)
Heritability	Genetic testing may find genetic variants that a person can pass on to his/her children.	9 (5%)
Inheritance	Healthy parents can have a child with a genetic condition.	9 (5%)
Penetrance	Some people with a genetic mutation may not develop the genetic condition.	9 (5%)

PO1063

Mind Map, an Educational Tool for Teaching Clinical Reasoning in Nephrology: A Mixed-Method Study

Aghiles Hamroun,[1] Eléonore Lepers,[2] Aurélie Dupré,[2] Patrick Truffert,[1] François Glowacki.[1] *[1]Centre Hospitalier Universitaire de Lille, Lille, France; [2]Universite de Lille Faculte de Medecine, Lille, France.*

Background: Nephrology is commonly considered as one of the most complex disciplines for medical students, justifying the implementation of new educational tools. Although its relevance has been well-established, the mind map is still marginally used in medical education. The objective of this study is to assess the contribution of mind map for teaching clinical reasoning in nephrology.

Methods: Between November 2020 and April 2021, three groups of med students (4th to 6th year) were provided with a teaching program of 5 weekly sessions of 30-45 minutes focused on three topics (serum creatinine elevation/AKI, glomerular syndromes, dysnatremia), each developed through a specific mind map. The contribution of this program was evaluated by a mixed method: 1. quantitative assessment: comparison of three quiz scores respectively the day before, day after and two weeks after each learning session (paired Wilcoxon tests); 2. qualitative assessment: focus group interviews with each group at the end of the teaching program.

Results: In total, 12 med students took part in this educational experience (respectively four in 4th, 5th and 6th years). Quiz scores were significantly higher after each teaching session and overall (28.0 [26.0; 31.4], 33.0 [31.2; 36.1], 34.4 [32.4; 37.0] respectively at baseline, immediately after and after two weeks, $p < 0.001$) (Fig1). Moreover, focus group interviews highlighted several themes about the specific contribution of mind map (in addition to previous standard lessons): logical and intuitive tool, effective for quick knowledge transmission, promoting long-term memorization and providing a global/ integrated vision of clinical reasoning in nephrology.

Conclusions: Mind map appears to be an interesting educational tool in teaching clinical nephrology reasoning to medical students.

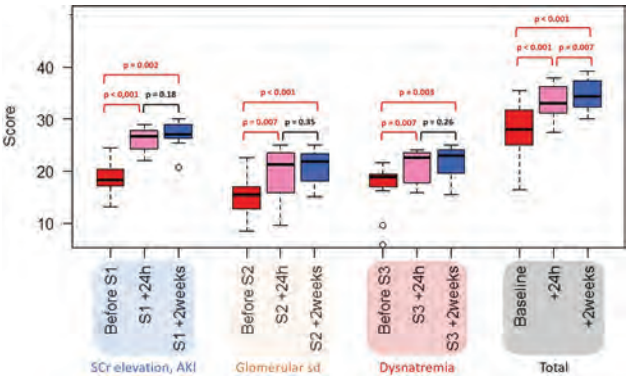

Figure 1. Quiz scores at three assessment times (day before, day after and two weeks after each session) and by topic. On the right, global results pooling the scores of all topical sessions.

PO1064

Improving the Management of Gout in Patients with CKD or Kidney Transplant: Effect of Online Education

Nimish Mehta, John Maeglin, Karen Badal. *Medscape LLC, New York, NY.*

Background: Gout is a chronic condition with a considerable effect on patient health and quality of life. Hyperuricemia and gout are associated with declining renal function, and recent studies have shown that renal dysfunction and kidney transplant are risk factors for gout. A study was conducted to determine if online, segmented education could improve knowledge, competence, and confidence of nephrologists regarding the management of gout in patients with chronic kidney disease (CKD) or kidney transplant (KT).

Methods: Educational design included a 45-minute video activity with slides, segmented into a series of 5 mini-lectures by different faculty covering various aspects of gout in patients with or without CKD and KT. Educational effectiveness was assessed with a repeated-pairs pre-/post-assessment study design with 3 knowledge questions and 1 confidence question, in which each individual served as his/her own control. A chi-squared test assessed statistical significance at the P <.05 level. The activity launched 9/25/2020, with data collected through 12/4/2020.

Results: The analysis set consisted of responses from nephrologists (n=89) who answered all assessment questions during the study period. Analysis of pre- vs post-intervention responses demonstrated a significant improvement in overall knowledge; average correct responses increased from 52% pre to 76% post education. Specific areas of improvement include: Treat-to-target strategy with a target of serum UA level < 6 mg/dL in patients taking urate lowering therapy (20% relative improvement, P<.05) Starting low-dose allopurinol in a patient previously diagnosed with gout and stage 3 CKD, presenting with painful subcutaneous tophi (25% relative improvement, P<.01) Recommending pegloticase without dose adjustment for the management of refractory gout in patients with stage 4 or 5 CKD (222% relative improvement, P<.001) Post-education, 48% of nephrologists had a measurable increase in confidence in their ability to manage patients with CKD who may develop gout.

Conclusions: This study demonstrated the success of online, segmented, mini-lectures on improving the evidence-based knowledge, competence, and confidence of nephrologists in appropriately managing gout in patients with CKD or kidney transplant.

Funding: Commercial Support - Horizon pharma

PO1065

Development and Implementation of an Immune Suppression Toolkit to Guide Nephrology Fellow Medication Prescribing and Monitoring

Lauren Lamie, Panduranga S. Rao, Laura H. Mariani, Andrea L. Oliverio, Julie A. Wright Nunes, Markus Bitzer. *University of Michigan, Ann Arbor, MI.*

Background: There are many important considerations when prescribing high risk medications like immune suppression (IS). Informed by surveys administered to nephrology faculty and fellows, we developed a training curriculum and a concise, clinically applicable guide for IS prescription and monitoring.

Methods: A cross sectional survey was administered to nephrology faculty and fellows in November 2017 to assess perceptions, self-efficacy, and knowledge about prescribing, monitoring, and adjusting IS (12 questions with item-responses from 1=strongly agree to 4=strongly disagree). Informed by this survey we developed and implemented a toolkit (one-time training curriculum and IS reference guide) for fellows and assessed their perceptions of the toolkit using pre-and post-surveys. Results are reported using mean (SD) or N (%), with associations examined using linear regression.

Results: Twenty-eight nephrology faculty and fellows completed the baseline survey; 19 (68%) were attending physicians and 9 (32%) fellows. Twenty (71%) were men, 16 (59%) Caucasian, 11 (41%) Asian. Collectively, 19 (77%) reported prescribing IS ranging from 1 to 40 times yearly. Attending physicians exhibited higher self-efficacy in prescribing IS (1.7 (0.6) compared to 3.3 (0.8) p=0.02) and both attendings and fellows strongly agreed there was a need for IS guides 1.4 (0.8) and would use them if available 1.4 (0.6). In particular, fellows strongly disagreed they understood all steps needed to use

IS (3.3 (0.8) compared to 2.3 (.07) for attending physicians). In May 2021, 5 nephrology fellows received the IS toolkit and completed the surveys. Self-efficacy improved post intervention from mean (SD) 3.0 (1.2) to 2.2 (1.6). All 5 fellows (100%) strongly agreed that the toolkit added value to training, provided a guide they would use and recommended the toolkit for future fellows.

Conclusions: Nephrology faculty and fellows strongly agreed that there is a need for guides and protocols for prescribing and monitoring IS medications. Our pilot IS toolkit incorporated into nephrology fellow training was well received and improved fellow self-efficacy.

Funding: Veterans Affairs Support

PO1066

Quality Improvement Study on Dialysis Education for Residents in an Outpatient Nephrology Clinic

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Background: In a large safety net hospital outpatient nephrology clinic in Southern California, resident physicians provide a significant portion of care to patients who have chronic kidney disease (CKD) stages III to V. Many of these patients eventually require initiation of long-term renal replacement therapy (RRT). However, there are many barriers to a timely and safe initiation of RRT in this patient population. One such barrier is a deficiency in education regarding dialysis between residents and patients in nephrology clinic. We attempted to identify barriers of resident education with patients regarding the topic of RRT and assess the effects of our educational intervention. Objectives: 1. Increase resident's knowledge regarding RRT based on pre and post intervention questionnaire 2. Increase resident's subjective preparedness/comfort level regarding discussions of RRT 3. Increase the frequency with which residents discuss RRT with patients

Methods: We created and distributed a pre-assessment survey to all Internal Medicine and Internal Medicine+Pediatrics residents at a large teaching hospital and received an approximately 50% response rate. Residents overwhelmingly responded that they do not feel patients have an adequate understanding of dialysis by the time they are deemed to require renal replacement therapy, nor did residents feel that they were adequately prepared or knowledgeable about the nuances of dialysis in order to counsel patients with CKD. We created a short teaching presentation with video reviewing dialysis topics and strategies to approach discussions with patients for residents who rotate through nephrology clinic, after which a post-survey was administered. Results are currently being collected.

Results: Results are currently being collected. We expect resident physicians will demonstrate increased knowledge regarding RRT based on pre- and post-intervention questionnaire, feel more comfortable discussing RRT with patients, and will discuss RRT more often with patients in clinic.

Conclusions: We expect to be able to conclude that resident education is a vital aspect in increasing patient understanding and comfort in regards to their disease process and dialysis at similar teaching centers where residents represent the majority of patient-physician interface in renal subspecialty clinic.

PO1067

The Impact of Electronic Sign-Out Dot-Phrase and Simulation Exercises on Inpatient Nephrology Transitions of Care

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Background: A fellow-led QI project was initiated in 2018 after division surveys indicated a need for change in the ongoing division transitions of care (TOC) practice.

Methods: We developed a standardized "sign-out score" to objectively assess TOC on the EMR sign-out. We next developed and implemented a standardized electronic medical record (EMR) dot-phrase as our first QI intervention. Case-based simulation sessions highlighting TOC pearls were conducted as the second QI intervention. Pre- and Post-intervention data for sign-out score was evaluated.

Results: A total of 647 patient EMR sign outs were assessed between 2018-2021. Overall sign-out accuracy score (0-2) significantly improved with QI interventions (pre-intervention mean 0.9 [95% CI: 0.9-1; N=298] to 1.6 post-dot phrase [1.5-1.6; N=220] to 1.7 post-simulation [1.6-1.8; N=129]; p<0.001). Table 1 provides details on the results of sign-out score. After adjustment for level of training, improvement in overall accuracy was independently associated with both dot-phrase (adjusted odds ratio (aOR) 7.6 [95% CI: 4.9-11.9]; p<0.001) and simulation (aOR 1.88 [1.1-3.16]; p=0.01). Although 2 sign-out score measures which were high performing pre-intervention worsened with dot-phrase implementation: anticipated changes and non-RRT management (aOR 0.15 [0.1-0.23]; p<0.001 and 0.07 [0.02-0.23]; p<0.001, respectively), improvement was seen following simulation (aOR 1.36 [0.84-2.2]; p=0.21 and 4.6 [1.74-14.5]; p=0.002).

Conclusions: A standardized EMR sign out dot-phrase and simulation exercises both improved the overall accuracy of TOC practiced for inpatient Nephrology consult service. The impact of dot-phrase alone on previously high performing TOC measures suggests the need for further optimization of dot-phrase and continuing simulation to enhance provider self-realization of important components of TOC.

Table1: Frequency of best possible "sign-out score" before and after QI interventions

Sign-out score measures:	Pre- intervention (N=298)	Post-dot phrase (N=220)	Post- simulation (N=129)	Overall p-value
Renal Diagnosis (% [N])	14 (41)	72 (159)	90 (116)	<0.001
Baseline serum creatinine (% [N])	41 (123)	81 (178)	82 (106)	<0.001
Renal replacement treatment (RRT) details (% [N])	66 (112/170)	80 (90/112	89 (67/75)	<0.001
Non-RRT treatment details (% [N])	97 (83/86)	67 (70/104)	91 (51/56)	<0.001
Overall accuracy (% [N])	18 (55)	67 (147)	76 (98)	<0.001
Anticipated Changes (% [N])	67 (199)	30 (66)	35 (45)	<0.001

PO1068

Point-of-Care Ultrasound Training for Nephrologists: A National Survey of Nephrology Fellows

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Background: Despite many potential applications of PoCUS in nephrology, nephrologists have been slow to adopt this technology. The past five years have seen an increase in ultrasound training within nephrology fellowship programs, although the scope of training is unknown. We conducted a national survey of nephrology fellows in United States-based training programs. The main objective of this survey was to identify the current landscape and clinical use of POCUS in US nephrology training programs.

Methods: We surveyed post-graduate year (PGY) 4-8 trainees in US nephrology fellowship programs. Survey items were included in a broader trainee survey disseminated to all programs by the American Society of Nephrology in April, 2021. The six-item survey instrument probed attitudes toward POCUS, current use, preferred instruction format, and perceived competence.

Results: Out of 822 US nephrology fellows surveyed, 631 (76.8 %) responded. A majority of respondents were 30-34 years of age with the majority of participants graduating from international medical schools. The majority of fellows (64.6%) indicated interest in PoCUS education, with highest interest in procedural ultrasound and diagnostic kidney imaging. Only 240 (38%) of fellows reported receiving PoCUS education during training. Of the fellows who received PoCUS training, 112 of 227 (49%) reported incorporation of PoCUS at a frequency of less than monthly, with only 62 of 227 (27%) incorporating PoCUS once per week or more. 83 of 226 (36%) fellows reported receiving adequate instruction to independently perform P0CUS, and 74 of 224 (33%) reported that they expect to be competent to independently perform PoCUS by the end of training. Hands-on training, particularly with an instructor, was highly valued as a teaching technique.

Conclusions: Despite high trainee interest in POCUS, the majority of current nephrology fellows are not receiving training in this domain and do not feel competent to independently perform PoCUS procedures. Hands-on training guided by a skilled instructor is a highly valued PoCUS teaching technique. This survey identifies a need for the development of PoCUS programs within nephrology fellowships that incorporate hands-on teaching techniques.

PO1069

Point-of-Care Ultrasound Education in Nephrology During the COVID-19 Pandemic

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Background: The COVID-19 pandemic led to changes in the way people taught and learned, with higher reliance on online learning. Unfortunately, point of care ultrasound is a difficult topic to teach without hands-on practice. Here we discuss the implementation of a novel ultrasound curriculum during the COVID-19 pandemic.

Methods: The curriculum was based on published curriculum on point of care ultrasound for the nephrologist, with focus on four fundamental exams: kidney, lung, cardiac, and volume status. We employed a flip the classroom approach with pre-reading and videos, a pre-session quiz, followed by hands on application of skills. Standardized patients or volunteers would have been used for the hands-on session, but this was eschewed for safety concerns. The fellows and instructors themselves modeled, with proper sanitation and PPE. The hands-on sessions were well received and attended by all fellows. The skills were then applied on the wards.

Results: As the restrictions lifted and vaccines were available, standardized patients were available in small groups. The learners were scheduled for two hour-long sessions with standardized patients, for practice of the skills acquired as well as the Objective structured clinical examination (OSCE). After the first session with all learners, we added a third session focused on OSCEs, as well as line placement as requested by the learners. By the end of the third session, all learners felt more confident in their skills and had passed their OSCEs.

Conclusions: Given the positive reception, this course is planned to continue as currently structured as well as expanded upon by rising fellows. The use of flipped classroom helped maximize the time of supervised scanning by learners. The use of ultrasound by fellows has risen and will continue to climb with further development of this important curriculum.

Osce Station 1: Focused Renal Ultrasound

Instruction to the Candidate:

1. Introduce yourself to the patient, your role, and explain, in brief, what you will be doing today
2. Access the correct probe and materials within the room
3. Access the correct views in a timely manner
4. Give the patient a brief overview of your findings
5. Clean and sterilize equipment
6. Document your findings

Instructions to the Assessor

1. Indicate that this is a practical skill session. Instruct them to speak out loud all of their actions so they can be credited appropriately
2. Help locate any materials that may not be obviously accessible when asked
3. Instruct them to perform a focused renal ultrasound
4. Instruct them to perform a quick bladder scan

Equipment:

1. Hand sanitizer
2. Butterfly iQ and iPhone
3. Ultrasound gel
4. Drapes
5. Tissues
6. PDI purple wipes

Checklist

Action/Response	Maximum	Actual
Proper Hand hygiene, introduces self to patient and explains role and procedure coherently	1	
Drapes patient appropriately	1	
Chooses correct probe setting (abdominal) and adjusts depth and gain if needed	1	
Obtains Coronal image of L Kidney, fans to view whole kidney, Saves image	1	
Obtains Sagittal image of L Kidney, fans to view whole kidney, Saves image	1	
Obtains Coronal image of R Kidney, fans to view whole kidney, Saves image	1	
Obtains Sagittal image of R Kidney, fans to view whole kidney, Saves image	1	
Obtains image of bladder, attempts to visualize ureteral jets on both side	1	
Wipes patient off, ensures comfort	1	
Explains findings	1	
Sterilizes Probe and phone prior to returning to document	1	
Documents procedure and finding	1	
Total Marks	12	

PO1070

Teaching Application of Ultrasound in Nephrology Practice in Medical Schools Using Student Peer Teaching: A Prospective, Randomized Pediatric Trial

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Background: Ultrasound has become the leading diagnostic technology in pediatrics due to its high sensitivity, easy applicability and lack of invasiveness and plays critical roles in many aspects of nephrology practice. However, it is associated with a higher examiner dependent variance. Teaching ultrasound in medical schools has grown in importance over the past years, while pediatric aspects are mainly reserved for postgraduate education. Student peer teachers take on the task of lecturers at many faculties with promising results in ultrasound education.

Methods: We designed a prospective, randomized trial in a pre-/post-test design for 257 4th year medical students in our pediatric classes to investigate the effectiveness of peer teaching in pediatric ultrasound. Besides a mandatory theoretical training by a student peer teacher prior to the course for all students (group A and B), half of the participants received a supporting manual (group B). All students had to measure the right kidney volume of their partners in advance to test pre-existing practical skills and a multiple choice progress test was performed prior and after the course. Afterwards, students were spitted in smaller groups and received a standardized practical training by a student peer teacher in our skills lab using similar ultrasound machines. The success was examined using an objective structured clinical examination (OSCE) at the end of semester using a pediatric-nephrologic case vignette.

Results: All students (groups A and B) showed an impressive increase of knowledge and the course and clinical trial was well received. Over 95% of students presented the renal topography sonographically well with no significant differences between both groups. However, we also observed a high interindividual variance in the volumetric results. The use of a supporting pediatric ultrasound manual did not show any significant benefit.

Conclusions: The concept of student peer teaching seems to work very well also in specific disciplines such as pediatric ultrasound and pediatric nephrology education. Therefore peer teaching seems to be of value in medical schools also in teaching complex learning contents.

Funding: Private Foundation Support

PO1071

Patient Navigators and Study Coordinators: A Team Approach Towards Patient Support in Decentralized Clinical Trials

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Background: COVID-19 related restrictions have accelerated adoption of decentralized clinical trials(DCT). DCTs offer increased patient flexibility via online study platforms, telemedicine and home-based nursing. DCTs reduce travel, hospitalization and in-person interactions, all problematic under COVID. Potential drawbacks exist for both patients and study coordinators, however. In DCTs, removal of study-site visits may leave patients feeling confused, unsafe, disempowered and disengaged, potentially increasing drop-out risk. While DCTs may mean increased enrollment for sites, management of novel patient pathways may prove more time-consuming for study coordinators. Crucial protocol driven events or patient concerns/questions may be missed due to complex patient tracking.

Methods: The role of the patient navigator(PN) was developed to support both patients and study coordinators in DCTs. PNs will provide culturally-appropriate psychosocial education to ensure patients feel safe, informed, and supported. PNs serve as conduits between the patient and the study site, ensuring bi-directional communication of patient progress. This unique approach is being trialed in ARENA2, a pediatric Phase III study in primary distal renal tubular acidosis, a rare renal disease.

Results: A multi-lingual team with unique educational and counseling experience was recruited and trained on the protocol and disease. The team will provide weekly check-ins with patients to foster engagement as well as identify any concerns the patient may be having in home healthcare. This role will offer around the clock patient support which will increase accessibility and decrease burden experienced by study coordinators with heavy caseloads. PNs have also developed educational videos in target languages using lay-friendly terminology to ensure patient understanding. Topics include clinical trials, ARENA2 and research in rare diseases. The study website contains additional resources including written articles that help set expectations and provide subjects with strategies for success as they go through ARENA2.

Conclusions: The concept of sponsor-driven PN team services in DCTs will offer both patients and study sites the added benefits of support.

Funding: Commercial Support - Advicenne Inc.

PO1072

Do Undergraduates Know "Nephrology?"– A Single-Site Survey of College Students

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Background: Over the past decade, Nephrology has experienced a 43% decline in fellowship applicants. A factor to choosing Nephrology could be a lack of early exposure. While studies have been conducted to explain why residents choose a specific fellowship program, none have surveyed the undergraduate student population to inquire whether the name "Nephrology" was even a recognizable medical specialty compared to other medical specialties. To this end, we conducted a survey of undergraduate students at the College of Charleston (CofC) to test the hypothesis that Nephrology will rank amongst the least recognizable specialties.

Methods: 274 undergraduates at CofC responded to a survey where they were asked to select every medical specialty they recognized by name (15 real specialties/1fictious). Demographic questions regarding sex, race, collegiate level, high school location, pre-med track, and household income were included. Differences were considered by comparing 95% confidence intervals or Chi-Square test. Spearman-Rank test was used to examine whether the number of applicants per specialty fellowship position was correlated with the proportion of responses.

Results: Out of 15 medical specialties, Nephrology ranked lowest (29%); whereas, Pediatrics (97%) and Surgery (97%) ranked highest. The fictious specialty, "diasymptomology" was recognized least (4%). Sex, race, collegiate level, and household income were not different between those students that recognized the word Nephrology versus those that did not. Pre-med students were about twice as likely ($p<0.001$) to have recognized Nephrology versus non pre-med students (49% vs. 22%, respectively). There was no correlation between the proportion of undergraduate students who recognized a specific medical specialty and the number of applicants per fellowship position in 2019 ($r=0.2$, $p=0.7$).

Conclusions: Nephrology was the least recognized, non-fictional, specialty amongst undergraduates. Lack of correlation between student responses and fellowship applications, suggest that name recognition alone will not predict fellowship applicant number. The discrepancy between Nephrology and other specialties highlights a gap in name recognition at an early career stage, even amongst premedical students.

Funding: NIDDK Support

PO1073

The Information Dilemma

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Background: The Internet has changed search. The amount of searchable information is growing as more bytes are added/modified than deleted and the criteria by which search results are obtained has also changed. Results are not exclusively obtained by their relevance to the query. Social media search uses predictive algorithms to display results with which the learner is most likely to engage (retweets, likes, replies, clicks). Results that promote engagement are valued more than those pertinent to the query. Known as customized search, this strategy is obvious when 2 individuals make an identical query and receive different search results and in a different order. Customized search protocols increase engagement but at the cost of creating an information dilemma. In this dilemma, each learner is exposed to a different set of facts upon which scientific discussions are started. In order to establish a common set of facts, I created a search engine based on a standard search protocol.

Methods: NephTwitterArchive.com is a non-commercial search engine that identifies scientific tweets from various NephTwitter communities. I coded 51 algorithms to identify scientific tweets at 15-minute intervals. Scientific tweets have informative text and a slide, URL to a scientific resource, or both. The engine uses a standard search protocol in which search results are based only on the query. All searches are anonymous. I measured learner-affinity for the engine by number of completed searches. Four elements are required for a single completed search to be recorded: query is made & executed, results are displayed, and a link to the primary scientific tweet is clicked.

Results: From 11/2011 to 4/2021, the engine identified 341742 tweets from 517 NephTwitter communities. A third of these were scientific tweets. From 10/2019-4/2021 learners completed 28313 searches (monthly median 1368, IQR 1264-1580). From 2019 to 2020, median monthly completed searches changed +12%; from 2020 to 4/2021, a +38% change. Nearly half of all learners used the engine immediately after visiting Twitter or Facebook; 37% visited the engine directly.

Conclusions: Scientific discourse is valuable if all participants start the conversation with a common set of facts. Social media search tools do not support this goal. A search engine that uses standard search protocol can mitigate the information dilemma and restore search to its primary function of providing results based on query alone.

PO1074

Understanding Healthcare Education for Nephrology Best Practice – A Question of Which Health Professionals: A Quantitative Investigation

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Background: Technology has allowed patients with Long-Term Conditions (LTCs) to access information through websites, portals, and Patient-centred organisations. 1) To understand, whether, retrospectively, there has been an education neglect as part of healthcare delivery and 2) To understand if technology can help join up education.

Methods: Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection. Fourteen (14) topic tags were applied over 1-month (March and April 2020) between the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support Group (KDARs) for Kids (est.2014) platforms. Two surveys were developed with several themes and implemented via online Qualtrics Software., one for health professionals, and one for CKD patients. Participants only had to complete once.

Results: 19 surveys completed from Health Professionals and 45 completed from CKD patient cohort. Descriptive statistics was used to analyse quantitative data and inform results. Relating Health Professionals, highest responses included Female (57.14%) vs. Males (42.86%). Relating CKD Patients, highest responses included Females (55.00%) vs. Males (38.89%). 2,560 threads were topic tagged between two groups. Health professionals who contributed highest included Healthcare Scientists (47 %), second were Nephrologists, other Allied Health Professionals (AHPs) and other (all 17.65 %), and GPs (5.88 %). CKD patients who contributed highest included Transplant patients (60.53%), second were ESRD (Haemodialysis) (13.16%), and CKD patients (stages 3-5) (10.53%). AHPs will increasingly work with GPs to provide laboratory screening, and POCT advice and/ or education (16.67%). CKD patients who contributed relating Appropriate Support Surrounding Healthcare, highest response included I have ability to communicate with a health professional about blood tests and investigations (25.49%).

Conclusions: Online educational modules should complement CKD care, and be delivered by broader Allied Health Professionals. This is the first UK retrospective study that examines clinically relevant educational gaps between online paediatric and adult renal cohorts close to two decades. Education is where healthcare requires investment.

PO1075

A Survey of Current Trends in Urinary Extracellular Vesicle Research

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Background: The Urine Task Force of the International Society of Extracellular Vesicles (ISEV) was created to advocate for best practices in this emerging area of research. Here we present the results of a survey, conducted using SurveyMonkey by the Urine Task Force, to better understand current research practices in the study of urinary extracellular vesicles (uEVs).

Methods: Two separate, identical surveys were administered: one directed to Urine Task Force members (28 respondents at the time of reporting) and one directed to the ISEV community (42 respondents).

Results: The mean time studying uEVs was 7.8 years for task force members and 5.4 years for community respondents. For task force members: 48.3% of respondents primarily focus on kidney, 44.8% prostate and 6.9% bladder. For the community focus was 29.4% kidney, 21.5% prostate, 19.6% bladder and 29.4% "other". Both communities largely collect spot urines compared with timed collection (Task force: 78.6% spot vs 21.4% timed, Community: 75.8% spot vs 24.2% timed). Urine storage was a significant focus of the survey. For the Task Force: 92.9% of respondents studied samples stored >3 months, 57.1% samples stored <3 months, and 50% studied fresh samples. The community studied less often fresh samples. Both groups predominantly stored samples as "cell-free urine": 85.7% for task force and 65.6% for community. All task force respondents study samples frozen at -80 °C with 10.7% of respondents also studying samples stored at 4 °C. By contrast, 93.8% -of community respondents stored samples at 80 °C, 9.4% at -20 °C and 6.3% at 4 °C. The task force ranked the following isolation methods in order of priority 1) centrifugation, 2) size exclusion chromatography, and 3) filtration. For the community survey this was similar. Both surveys prioritized the same downstream applications: 1) protein analysis, 2) RNA analysis, 3) functional assays. The urine task force identified "understanding of approaches to normalization" while the community identified "Impact of renal disease and comorbidities on EV analysis" as key knowledge gaps.

Conclusions: In summary, the present survey identified key similarities and differences between current practices for the Urine Task Force and the urinary EV research community. Such information will be used to help guide future efforts to address key knowledge gaps.

PO1076

A Potential Novel Variant of Slc4a4 Can Regulate the Functional Activity of the Electrogenic Na/HCO3 Cotransporter NBCe1-B

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Background: The electrogenic Na/HCO_3 cotransporter (NBCe1) regulates intracellular pH in many tissues and elicits vectorial HCO_3^- flow across many epithelia. Five variants of NBCe1 have been identified: -A, mainly in kidneys; -B, ubiquitous; -C, in brain; -D/E, in mouse reproductive organs. Because the A/D and B/C/E variants are transcribed from two distinct promoters, they have different NH_2-termini (Nt). The Romero Lab developed an isoform-specific knockout (KO) mouse of NBCe1-A/D by causing a frameshift mutation in the A/D variants' unique Nt region (Chen et al, *JASN* 25:71A, 2014). Fang et al found that NBCe1-B (e1B) is expressed in kidneys of both WT and KO mice, and that e1B expression increases with metabolic acidosis in KOs (*AJP Renal*, 2018). They reached this conclusion by RT-PCR-amplification of B-variant–specific bands from KO kidneys. However, these amplifications generated several unidentified bands. Intrigued by these additional bands, we repeated the RT-PCR in an attempt to identify them.

Methods: Using TA cloning, we determined the sequences of two of the unidentified bands: (1) partial *Slc4a4* product missing exon 4, which would lead to a frameshift, and (2) partial *Slc4a4* product missing exons 4 & 5, but remaining in-frame. Because Fang et al confirmed lack of C/D/E variants, we introduced mutations (1) and (2) in e1B and studied functional activity by two-electrode voltage-clamping in *Xenopus* oocytes. We also determined protein abundance/interaction by surface protein biotinylation. Inasmuch as e1B has low activity, we co-expressed WT e1B and/or mutant e1B with super-IRBIT (which lacks PP1 binding site).

Results: We found that neither mutant, alone, has activity even though Δexon 4/5-e1B interacts with super-IRBIT. However, Δexon 4/5-e1B has a dominant-negative (DN) effect on WT e1B. To test if these mutants are specific for KO mice, we inspected other WT tissues.

Conclusions: Contrary to our hypothesis, we found that e1B mutants (1) and (2) exist at least in kidneys, brain, and pancreas, leading us to conclude that cells could in principle regulate NBCe1-B activity by adjusting the amount of the novel DN variant Δexon 4/5-e1B.

Funding: NIDDK Support, Other U.S. Government Support

PO1077

A Novel I551F Variant of Na+/HCO3- Cotransporter NBCe1 Shows Reduced Cell Surface Expression and May Exert a Dominant Negative Activity

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Background: Homozygous mutations in *SLC4A4*, encoding the electrogenic Na^+/HCO_3^- cotransporter NBCe1, cause proximal renal tubular acidosis (pRTA) associated with extrarenal symptoms. Although 17 mutated sites in *SLC4A4* have thus far been identified among pRTA patients, physiological significance of other nonsynonymous single nucleotide variants (SNVs) in this gene remains largely undetermined.

Methods: We investigated the functional properties of SNVs in NBCe1 using immunocytochemical, western blotting, and electrophysiological assays. From NCBI data base, we identified 13 SNVs that have not previously been characterized in highly conserved, transmembrane domains of NBCe1-A.

Results: Immunocytochemical analysis revealed that I551F variant was present predominantly in the cytoplasm in HEK293 cells, whereas all other SNVs did not show obvious changes in subcellular distribution. Western blot analysis in HEK293 cells demonstrated that the I551F variant showed impaired glycosylation and a 69% reduction in cell surface levels. To determine the role of Ile551 in more detail, we examined the significance of various artificial mutants both in non-polarized HEK293 cells and polarized MDCK cells, which indicated that only I551F substitution resulted in cytoplasmic retention. Moreover, functional analysis using *Xenopus* oocytes demonstrated that the I551F variant had a significantly reduced activity corresponding to 39% of that of wild-type, whereas any other SNVs and artificial I551 mutants did not show significant changes in activity. Finally, immunofluorescence study in HEK293 cells indicated that the I551F variant retains wild-type NBCe1-A in the cytoplasm.

Conclusions: These data demonstrate that I551F-NBCe1-A shows impaired transport activity predominantly through cytoplasmic retention, and suggest that the variant can have a dominant-negative effect by forming complexes with wild-type NBCe1-A.

Funding: Government Support - Non-U.S.

PO1078

Diacidic Motif Is Required for Efficient Transport of NKCC2 to the Plasma Membrane

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Background: Mutations in the apical Na-K-2Cl cotransporter, NKCC2, cause type I Bartter syndrome (BS1), a life-threatening kidney disease. We have previously demonstrated that BS1 nonsense mutation Y998X, which interferes with the highly conserved dileucine like motifs of NKCC2 C-terminus, compromises NKCC2 surface delivery through ER retention mechanisms. However, whether these dileucine like motifs are sufficient for anterograde trafficking of NKCC2 remained to be determined. Consequently, the aim of the present study was to investigate whether additional motifs are required for NKCC2 efficient transport to the plasma membrane.

Methods: NKCC2 protein expression was monitored in transiently transfected OKP and HEK cells, using immunoblot and confocal imaging. NKCC2 surface expression was assessed by cell surface biotinylation assay. NKCC2 stability and maturation was monitored by cycloheximide chase assay.

Results: Among the motifs identified as ER export signals in ion channels are the diacidic D/E-X-D/E motifs, which have been shown to promote interaction of cargo with the coat complex II (COPII) budding machinery. Interestingly, sequence analysis of NKCC2 C-terminus revealed the presence of two di-acidic motifs, ^{949}EEE^{951} and ^{1019}DAE^{1021}, located upstream and downstream of BS1 mutation Y998X, respectively. Importantly, mutation of ^{1019}DAE^{1021} to ^{1019}AAA^{1021} disrupted glycosylation and cell surface expression of NKCC2, whereas mutation of ^{949}EEE^{951} had no effect. Cycloheximide chase analysis demonstrated that the absence of the terminally glycosylated form of ^{1019}AAA^{1021} was not due to increased rates of degradation of mutant co-transporters, but was instead caused by defect in maturation. Accordinglty, co-immunolocalization experiments showed that ^{1019}AAA^{1021} was trapped in the ER. Finally, overexpression of dominant negative mutant of Sar1 GTPase completely abolished NKCC2 maturation, clearly indicating that NKCC2 exit from the ER is COPII dependent.

Conclusions: Our data indicate that in addition to highly conserved dileucine like motifs of NKCC2 C-terminus, the cotransporter uses also a di-acidic exit code for export from the ER and targeting to the cell surface. Elucidating the molecular mechanisms of the motif-facilitated ER export may help to develop therapeutic strategies targeting NKCC2 transport from the ER to the cell surface.

Funding: Government Support - Non-U.S.

PO1079

Furosemide Alleviates Hypercalciuria and Hypomagnesemia in Claudin 16-Deficient Mice

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Background: Loss-of-function mutations in the CLDN16 gene encoding for claudin-16 lead to Familial Hypomagnesaemia with Hypercalciuria and Nephrocalcinosis (*FHHNC*) in human. Claudin-16 resides in tight junctions of the thick ascending limb (TAL) and mediates paracellular reabsorption of divalent cations. The ensuing distal convoluted tubule (DCT), connecting tubule (CNT) and cortical collecting duct (CCD) perform transcellular Ca^{2+} and Mg^{2+} reabsorption via the transient receptor potential (TRP) channels, TRPV5 and TRPM6. DCT, CNT, and CCD exhibit unique functional and structural plasticity enabling them to compensate for defects of proximal salt reabsorption. Using claudin-16-deficient (*Cldn16*-/-) mice as a FHHNC model, we tested the hypothesis that enforcement of distal nephron function using a loop diuretic furosemide may enhance the transcellular reabsorption of Ca^{2+} and Mg^{2+} thus compensating for the paracellular TAL defect.

Methods: Wild-type (WT) vs. Cldn16-/- mice were treated with furosemide (50 mg/kg body weight) for 7 days followed by physiological, morphological and biochemical evaluation of kidneys.

Results: Compared to WT, *Cldn16*-/- mice showed significantly increased urinary excretion of Ca^{2+} and Mg^{2+} and hypomagnesemia at baseline. Furosemide enhanced urinary Ca^{2+} excretion without concomitant increase of urinary Mg^{2+} levels in WT. In contrast, *Cldn16*-deficient mice responded to the diuretic with a marked reduction of urinary Ca^{2+} levels and normalization of plasma Mg^{2+} levels. Evaluation of distal Ca^{2+} and Mg^{2+} transport proteins by immunoblotting and immunofluorescence showed furosemide-dependent increases of TRPV5 and calbindin levels in *Cldn16*-/- kidneys along with signs of hyperthrophy of the distal nephron.

Conclusions: The present results suggest that loop diuretics bear potential to alleviate symptoms of Cldn16-deficiency due to compensatory stimulation of electrolyte reabsorption in DCT, CNT, and CCD.

Funding: Government Support - Non-U.S.

PO1080

Cholesterol Efflux on Sodium-Sensitive Blood Pressure

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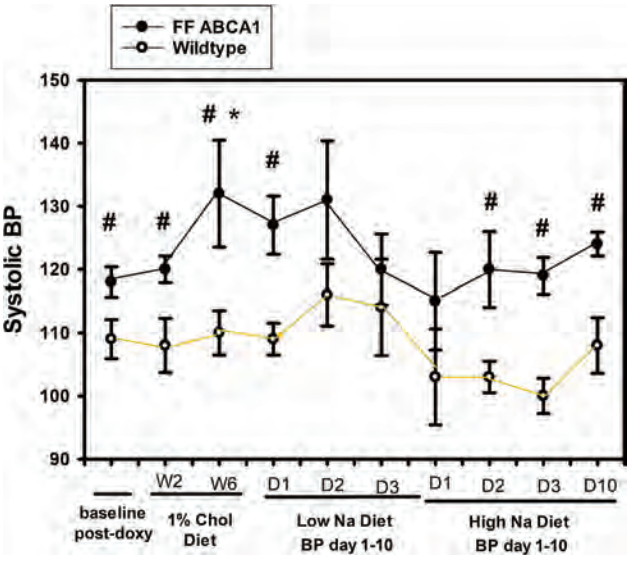
Background: Na sensitive BP is linked to greater mortality than Na resistant hypertension. Dyslipidemia and changes in plasma membrane (PM) lipid composition contribute to Na sensitivity. In addition, diets enriched in cholesterol (chol) (1) raise cortical collecting duct (CCD) chol, (2) stimulate ENaC, and (3) repress natriuretic factors. Renal ABCA1, a chol efflux protein, increases in chol fed mice to mitigate cellular chol integration. Therefore, we hypothesize renal tubular ABCA1 ablation will lead to Na dependent changes in BP.

Methods: Transgenic mice ($Tg^{PAX8rtTA;tetO\text{-}Cre/+}$), which express CRE recombinase in tubular epithelia when fed doxycycline (dox), were bred with mice expressing floxed ABCA1 to generate a model deficient in tubular ABCA1 (FF). Tail cuff systolic BP (SBP; Visitech) and urine volume after diuretic administration was measured in mice. Immunoblotting was performed on kidney protein lysate.

Results: Immunoblotting of renal PM showed reduced ABCA1 (50±11%; n=6, $p<0.05$) in FF compared to littermate wildtypes (WTs; 100±7% (n=5)) mice. The SBP of FF (n=11) mice was greater immediately post-dox and during chol or high Na feeding (Fig.1; #, $p<0.05$ vs WT) compared to WTs (n=15). Low Na diet abolished SBP differences between mice, while 6 weeks (W) of 1% chol diet raised the SBP in ABCA1 FF vs FF mice post-dox feeding (Fig. 1; *, $p<0.05$ vs. FF post-dox). No difference NKCC2, NCC or α-ENaC protein abundance was noted in whole kidney lysate; however, γ-ENaC 83 kD and cleaved 70 kD subunits were increased in FF compared to WT kidney. Furosemide injection induced a greater diuretic effect in FF (n=4; 1.35±0.08 mL) vs WT (n=4; 0.88±0.08 mL; $p<0.05$).

Conclusions: Tubular ABCA1 deficiency stimulates Na dependent SBP which we speculate is related to enhanced Na dependent ENaC and NKCC2 activity.

Funding: Veterans Affairs Support, Private Foundation Support



SBP of FF and WT mice in days (D) and weeks (W) of diet

PO1081

WNK4 Is a Transductor of V2 Receptor Signaling in the Thick Ascending Limbs and Distal Convoluted Tubules

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Background: Vasopressin (AVP) is essential for water and Na^+ homeostasis. In the kidney, its actions are mediated by the V2 receptor (V2R), which signals through protein kinase A (PKA). The phosphorylation of the Na^+-Cl^- cotransporter (NCC) and the Na^+-K^+-Cl^- cotransporter 2 (NKCC2) by the WNK-SPAK signaling pathway upregulates their activity and increases in response to AVP. WNK4 can be regulated by PKA through the phosphorylation of its RRxS motifs in *in vitro* models. Thus, we hypothesized that WNK4 mediates the activation of NCC and NKCC2 in response to AVP.

Methods: We transfected HEK293 cells with NKCC2 or the V2R with SPAK and either WNK1, WNK3, WT WNK4 or WNK4 with Ala instead of Ser in its 5 RRxS motifs. Cells were stimulated with 30 nM forskolin or 1 nM desmopressin (dDAVP). We cross-bred our WNK4$^{-/-}$ strain (in a C57BL/6 background) with 129Sv mice while selecting for the full-length allele of NKCC2 to evaluate the phosphorylation status of NKCC2. dDAVP (5 ng/h) was administered in miniosmotic pumps for 3 days. Protein extracts were subjected to immunoblot. qRT-PCR of *Wnk4*, *Slc12a3*, and 18S was carried out with Taqman probes. 12 h urine collections were conducted and water intake between the groups was equalized using gelled diets.

Results: In HEK293 cells, we found that an increase in phosphorylation of SPAK and of NKCC2 at T100 and T105 (SPAK regulated sites) with forskolin requires of WT WNK4. In contrast, phosphorylation of S130 of NKCC2 was WNK-independent. Only cells with WT WNK4 and the V2R showed an increase in SPAK phosphorylation when stimulated by dDAVP. dDAVP also increased WNK4's phosphorylation at S1196. dDAVP-infused WT mice increased their total and phosphorylated WNK4, NCC, and NKCC2, as well as phosphorylated SPAK and *Slc12a3* mRNA levels. These effects were absent in WNK4$^{-/-}$ animals. In contrast, WNK4$^{-/-}$ mice did respond to dDAVP by increasing AQP2 protein levels. In addition, WNK4$^{-/-}$ mice had increased water consumption at baseline and an increased urine output when water-restricted, with a tendency towards lower total kidney osmolality.

Conclusions: Our data suggest that WNK4 is a transductor of AVP signaling in the TAL and DCT, modulating NKCC2 and NCC. This might contribute to the anti-natriuretic effects of this hormone and the increase in medullary osmolality that occurs with antidiuresis.

Funding: Government Support - Non-U.S.

PO1083

Upregulation of NCC by Hypokalemia Involves Additional Mechanisms to Direct Cl- Sensing by WNK4

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Background: Cl^--sensitive WNK4 kinase plays an important role in the modulation NaCl reabsorption in the distal convoluted tubule (DCT). WNK4 activates the NaCl cotransporter (NCC) in response to hypokalemia, promoting its phosphorylation. Low plasma $[K^+]$ decreases intracellular $[Cl^-]$ ($[Cl^-]_i$) and thus Cl^- binding to WNK4's active site, leading to its activation. We have previously shown that hypokalemia and low $[Cl^-]_i$ increase WNK4 phosphorylation at S64 and S1196. Hypokalemia also promotes phosphorylation of KLHL3, the substrate adaptor of the Cullin-Ring ligase that regulates WNK degradation, at a site that is similar to S64 and S1196 of WNK4. Thus, we wondered if KLHL3-mediated modulation of WNK abundance in the DCT is also regulated by $[Cl^-]_i$.

Methods: Transient transfection of HEK293 cells and incubation with media with varying electrolyte concentrations. Hydrochlorothiazide (HCTZ) administration in the diet to WT mice for 12 hrs. Generation of WNK4-L319F mice with CRISPR/Cas9, which were fed with normal or low K+ diets for 7 days. Immunoblot assays of cell and kidney lysates. Immunofluorescence (IF) of kidney slices.

Results: Co-expression of WNK4 and KLHL3 in HEK293 cells promoted a decrease in WNK4 abundance, which was partially prevented by incubation with a low K^+ medium or a hypotonic low Cl^- medium. Next, HCTZ-treated mice showed no changes in plasma $[K^+]$, but increased pNCC and KS-WNK1 protein levels were observed by immunoblot, possibly due to decreased $[Cl^-]_i$. In addition, WNK1- and WNK4- positive cytoplasmatic puncta were observed in the DCTs by immunostaining. In WNK4-KO mice, which might also have decreased $[Cl^-]_i$ in their DCT, we also observed increased KS-WNK1 levels as well as WNK1-positive cytoplasmic puncta. Finally, WNK4-L319F mice were capable of upregulating pNCC, despite having a Cl^--insensitive WNK4. We also observed an increase in WNK4 protein levels and its phosphorylation at Ser64 and Ser1196 in WNK4-L319F mice on low K^+ diet.

Conclusions: Our work shows that low K^+ mediated upregulation of NCC does not solely depend on the Cl^--sensing capability of WNK4. A yet unidentified Cl^--regulated mechanism can regulate WNK4 phosphorylation and KS-WNK1 and WNK4 abundance, which converges in the increase of the WNK4-NCC pathway in the DCT.

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

PO1084

Calcium-Sensing Receptor-Mediated Activation of the WNK4-SPAK-NCC Pathway by Glucose/Fructose In Vivo and Ex Vivo

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Background: NCC is activated via the CaSR-WNK4-SPAK pathway. Glucose and other sugars act as positive allosteric modulators of the CaSR. In vitro data from our lab (ASN 2019-2020) showed that extracellular glucose or fructose increases activity of the WNK4-SPAK-NCC pathway via the CaSR. Since glucose reabsorption occurs proximally in the nephron, delivery to the distal convoluted tubule (DCT) is negligible. Fructose delivery depends largely on intake. Thus, sugars delivery to DCT could result in NCC activation via CaSR-WNK4-SPAK pathway.

Methods: We used wild-type mice treated with vehicle, oral fructose +/- calcilytic NPS2143, or a single dose of dapagliflozin 1mg/kg ip to induce transient glycosuria +/- NPS2143. Kidneys were extracted after 3 hours to assess activation of the WNK4-SPAK-NCC pathway by immunoblotting. To rule out an effect of dapagliflozin in the WNK4-SPAK-NCC by angiotensin II, we pre-treated mice with losartan. The response to a thiazide challenge in vehicle, fructose or dapagliflozin treated mice was assessed. Finally, we used an ex vivo Langerhans rat kidney preparation to evaluate the effect of different concentrations of glucose infusion in the renal artery.

Results: In WT mice, we observed increased activity of the WNK4-SPAK-NCC pathway in the kidney after exposure to 20% fructose or administration of dapagliflozin ($p<0.01$). These effects were abrogated by NPS2143 ($p<0.01$) and was not observed in WNK4-KO mice ($p<0.001$). Additionally, the effect of dapagliflozin was present in mice pre-treated with losartan ($p<0.01$). Natriuresis induced by a thiazide challenge was significantly higher in fructose or dapagliflozin, than in vehicle treated mice, suggesting activation of NCC. Finally, we observed increased NCC and SPAK phosphorylation by infusing glucose above proximal tubule reabsorption threshold levels to ex vivo rat kidney preparations ($p<0.001$); notably, this effect was prevented by NPS2143.

Conclusions: Glycosuria or fructosuria increases NCC, SPAK and WNK4 phosphorylation in a CaSR-dependent fashion. Our data thus suggest a calcimimetic-like behavior for sugars in the DCT. This effect may have implications for salt-retention mechanisms induced by disorders of glucose metabolism and increased dietary fructose intake.

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

PO1085

Kidney-Specific WNK1 Amplifies NCC Responsiveness to Potassium Imbalance

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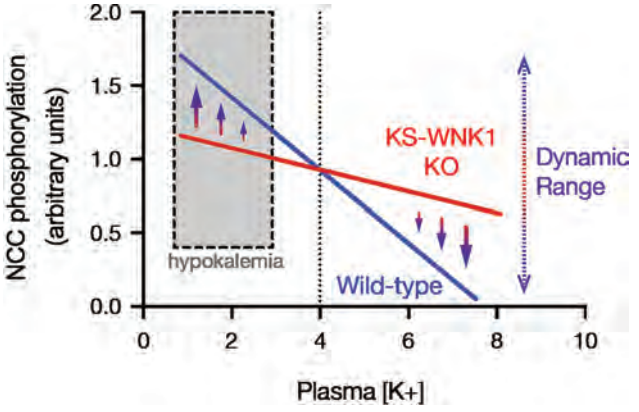
Background: The distal convoluted tubule (DCT) NaCl cotransporter NCC is activated by phosphorylation, a process that is potassium (K+)-regulated and dependent on With-No-Lysine (WNK) kinases. KS-WNK1, a kidney-specific WNK1 isoform lacking the kinase domain, controls WNK signaling pathway localization in the DCT. Its role in NCC regulation, however, is unresolved: while early studies proposed that KS-WNK1 functions as an NCC inhibitor, recent work suggests that it activates NCC.

Methods: To evaluate the role of KS-WNK1 on K+-dependent NCC regulation, we studied KS-WNK1$^{-/-}$ mice across a wide range of plasma K+ (2.0-9.0 mmol/L), induced by dietary maneuvers and diuretic challenges.

Results: K+-restricted KS-WNK1$^{-/-}$ mice exhibited blunted NCC phosphorylation compared to littermates, indicating that KS-WNK1 activates NCC during K+ deficiency. In contrast, NCC phosphorylation was augmented in K+-loaded KS-WNK1$^{-/-}$ mice relative to controls, consistent with KS-WNK1-mediating NCC inhibition during hyperkalemia. Focusing on K+-restricted mice: 1) KS-WNK1$^{-/-}$ mice had mislocalized WNK-SPAK proteins, 2) KS-WNK1$^{-/-}$ mice had blunted activation of the WNK-SPAK/OSR1 kinase cascade, 3) KS-WNK1$^{-/-}$ mice had sex-specific alterations to K+ and Ca2+ plasma levels, 4) KS-WNK1$^{-/-}$ mice had no change to blood pressure, but were less sensitive to thiazide diuretics compared to littermates.

Conclusions: KS-WNK1 has a bimodal effect on NCC, activating NCC during K+ restriction and inhibiting NCC during high K+, thus expanding the inverse relationship between NCC phosphorylation and plasma [K+]. During K+ deprivation, KS-WNK1 facilities the localization and activation of the WNK-SPAK/OSR1 pathway. Mice that lack KS-WNK1 have sex-specific differences in electrolytes, as well as thiazide resistance. These observations clarify the role of KS-WNK1 on NCC, and identify a novel mechanism that contributes to sexual dimorphism in the mammalian nephron.

Funding: NIDDK Support, Other NIH Support - NIDDK R01D098145, NIDDK K08DK118211, NHLBI R01HL152680



PO1086

High Dietary Potassium Increases Blood Pressure in a Rat Model of CKD

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Background: Potassium dephosphorylates the sodium chloride cotransporter (pNCC) thereby increasing natriuresis and reducing blood pressure. However, it is unclear if this response is intact in chronic kidney disease (CKD).

Methods: To address this, CKD was induced by 5/6th nephrectomy in rats which were fed a low KCl diet (0.03%), normal KCl diet (0.1%), modestly high KCl diet (0.8%), high KCl diet (2.5%) or high KCitrate diet (2.5%). The latter group was included to analyze the effect of the accompanying anion. All diets contained 0.16% Na^+. The effects of these diets on telemetric blood pressure, plasma potassium (K^+), plasma aldosterone, plasma bicarbonate, and pNCC were analyzed.

Results: Both the low and the high KCl diets increased blood pressure compared to the normal KCl diet, although the effect of the high KCl diets was more pronounced (**Table**). Higher dietary K^+ intake caused higher plasma aldosterone levels, and high KCitrate further increased plasma aldosterone. pNCC was significantly increased by the low KCl diet and decreased by the moderately high KCl diet. The effect of dietary KCl on pNCC, however, was lost with the high KCl diet. The high KCitrate diet attenuated the rise in blood pressure despite the highest plasma aldosterone and pNCC levels.

Conclusions: Although the inverse relationship between potassium and pNCC is intact in experimental CKD, high potassium diets cause hypertension possibly mediated by aldosterone. This rise in blood pressure is attenuated when potassium is given with citrate, despite high aldosterone and pNCC levels.

	Low KCl diet	Normal KCl diet	Moderately high KCl diet	High KCl diet	High KCitrate diet
Δ Systolic BP, mmHg	3*	Ref.	9*	21*	8*
Plasma K^+, mEq/L	2.3*	3.8	4.5	5.2	5.0
Plasma aldosterone, ng/L	N.M.	33	186*	577*	1144*
Plasma bicarbonate, mEq/L	18.9	22.0	19.7	18.8	35.2*
Urine K^+, mEq/24h	0.2	0.3	3.1*	9.8*	9.7*
Urine Na^+, mEq/24h	1.0	1.0	1.6*	1.7*	1.6*
pNCC expression, A.U	2.9*	1	0.3*	0.9	15*

* $P < 0.01$ compared to normal KCl diet (ANOVA with post-hoc testing).

A.U., arbitrary units; BP, blood pressure; N.M., not measured.

PO1087

Rescuing Low Blood Pressure in Amiloride-Treated Mice by Low-Potassium Diet Relies on NCC Activation

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Background: NCC activity has been widely recognized to impact on blood pressure levels, as Gitelman syndrome, caused by inactivating mutations in the Slc12a3 gene, features arterial hypotension. In contrast, Familial Hyperkalemic Hypertension (FHHt) is a mendelian disease mainly driven by NCC overactivation. NCC activity is exquisitely regulated by changes in extracellular [K^+], and it has been shown that this regulation might be at least in part responsible for the inverse relationship observed between dietary K^+ consumption and blood pressure levels in animal models and in human populations. It has been shown that amiloride-induced hyperkalemia results in NCC inhibition, which can be prevented with administration of a low K^+ diet. Thus, we decided to evaluate the role of NCC inhibition in the volume depletion and hypotension induced by amiloride treatment.

Methods: We treated 12-week-old C57Bl/6 male mice with amiloride at 25mg/L in the drinking water. During treatment, mice were kept on normal chow (0.4% NaCl, 0.8% K^+) for 4 days, then switched to low K^+ diet (0.1% K^+), and at the 4th day of low K^+ diet hydrochlorothiazide (HCTZ, 60 mg/kg/d, in the diet) treatment was started in a subset of mice.

Results: Amiloride-treated mice developed a PHA1-like syndrome (a severe hyperkalemic, salt losing nephropathy, with marked hypotension). Hyperkalemia and hypotension were prevented by low K^+ diet. Basal blood pressure levels were re-established by day 4 on low K^+ diet, while further treatment with HCTZ produced a steep drop in the blood pressure of these animals. Immunoblot analysis of whole kidney lysates from amiloride-treated mice showed decreased levels of NCC and pNCC that were reversed by low K^+ diet.

Conclusions: We show that the salt losing hyperkalemic phenotype induced by amiloride can be fully recovered by low K^+ diet and that this recovery is mediated by the increased activity of NCC.

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

PO1088

SALL3 Is a Salt-Responsive Distal Convoluted Tubule-Specific Transcription Factor Induced in Distal Nephron Remodeling

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Background: Adaptive remodeling of the distal nephron provides a physiological mechanism to control electrolyte transport and body fluid homeostasis. Activation of the sodium chloride cotransporter (NCC, Slc12a3) in the DCT is paralleled by an increase in DCT mass as an adaptive response to intravascular volume depletion or hypokalemia. The downstream regulatory factors that induce structural expansion of DCT are unknown.

Methods: Mice were genetically engineered to constitutively activate the SPAK kinase (CA-SPAK) in the DCT, causing constitutive NCC activation, and DCT hypertrophy and hyperplasia. Genome-wide RNA-Seq transcriptomic analysis was performed in renal cortical tissue. Differential gene expression analysis was performed to compare 1) CA-SPAK vs wild type (WT-CT) on control diet and 2) CA-SPAK on high salt diet (CS-HS) and WT on high salt diet (WT-HS). Bioinformatic approaches were applied to identify the DCT-specific transcription factors (TFs) that are dependent on the NCC activation. TF protein localization and expression was evaluated by immunofluorescence and confocal microscopy, and image analysis tools.

Results: Differential expression analysis and cell deconvolution of the bulk RNA-Seq, using kidney single-cell transcriptome datasets, revealed 10 TFs (Camta1, Emx1, Hoxd8, Hoxd9, Hoxd10, Tfap2b, Tfcp2l1, Tsc22d2, Sall3 and Zfp467) that were significantly induced in DCT of the CA-SPAK mice with high salt diet. Among 10 TF candidates, Spalt like transcription factor 3 (Sall3) was the only DCT-specific TF that was induced by CA-SPAK, and further increased by high salt diet. Network analysis revealed that Sall3 interacts with eight of the other induced TFs (Emx1, Hoxd10, Tfcp2l1, Hoxd9, Hoxd8, Camta1, Tfap2b and Zfp467). Microscopy confirmed Sall3 is specifically expressed in DCT cells, where it localizes predominately to the nucleus and is significantly increased in the CA-SPAK mice, and increased further upon dietary salt loading.

Conclusions: In summary, Sall3 is the predominate DCT-specific TF that is activated during DCT expansion, suggesting that it is a key component of the core transcriptional regulatory circuit maintaining DCT cell identity as the DCT expands.

Funding: Private Foundation Support

PO1089

Chemogenetic Activation of the Distal Convoluted Tubule Enhances Sodium Excretion Through Rapid Dephosphorylation of the Sodium-Chloride Cotransporter

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Background: The distal convoluted tubule (DCT) plays a crucial role in the regulation of sodium and potassium balance, predominantly through its apical sodium chloride entry pathway, NCC, which is activated by N-terminal phosphorylation. This nephron segment is rich in G protein-coupled receptors (GPCR), including *ptgfr* (prostacyclin F), *avpr2* (arginine vasopressin), and others. The role that these GPCRs play regulating DCT function has been a challenge to investigate as they are expressed within multiple cell types that alter kidney physiology. Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology can be used to explore the physiological role of GPCR activation.

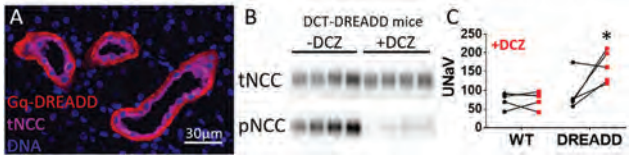
Methods: To explore the role of Gq-coupled GPCRs along the DCT, we bred DCT-specific inducible Cre Recombinase mice (NCC-cre^{ERT2}) to Gq-coupled DREADD mice to create DCT-DREADD mice. We verified the localization of the Gq DREADD protein using immunohistochemistry. We then activated Gq signaling in DCT cells with i.p. injection of DREADD-specific agonist deschloroclozapine (DCZ) and determined the abundance of phosphorylated NCC by Western blot. Lastly, we measured sodium excretion in metabolic cages for 4 hours following DCZ administration in WT compared to DCT-DREADD mice.

Results: We found that the Gq-DREADD protein was specifically expressed within the basolateral membrane of the DCT (**Figure A**). DCZ injection caused rapid dephosphorylation of NCC within 30 minutes to 15% of the abundance observed in DCT-

DREADD mice not treated with DCZ (**Figure B**, 100 ± 15 vs. 15 ± 3, t-test: p<.001). Injection of DCZ increased sodium excretion (UNaV) by 215% in DCT-DREADD mice compared to wildtype controls (**Figure C**, 100 ± 13 vs. 215 ± 24, t-test: p<.001).

Conclusions: We conclude that chemogenetic activation of the DCT enhances sodium excretion through rapid dephosphorylation of NCC. These findings support a role for Gq GPCR-mediated regulation of NCC. The DCT-DREADD mouse is a novel model for exploring the molecular mechanisms that underlie the regulation of NCC activity by GPCRs absent the confounding effects of other epithelial cells along the nephron.

Funding: NIDDK Support, Private Foundation Support



PO1090

Mechanistic Importance of Reduced KLHL3 and CUL3 Expression in CUL3-Δ9-Mediated Familial Hyperkalemic Hypertension

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Background: Mutations in the ubiquitin ligase scaffold protein Cullin 3 (CUL3) cause the disease familial hyperkalemic hypertension (FHHt). In the kidney, mutant CUL3 (CUL3-Δ9) cannot interact with COP9 signalosome subunit JAB1 that negatively regulates CUL3 activity. This leads to CUL3-Δ9 autodegradation, and increased abundance of With-No-Lysine [K] Kinase 4 (WNK4), which inappropriately activates the downstream kinase SPAK, which then phosphorylates and hyperactivates the Na^+-Cl^- cotransporter (NCC). We showed lower that CUL3 alone does not increase WNK4, so the precise mechanism by which CUL3-Δ9 causes FHHt is unclear. We hypothesized CUL3-Δ9 degrades Kelch-like 3 (KLHL3), the CUL3 substrate adaptor for WNK4; thus reduced abundance of KLHL3 combined with reduced CUL3 are mechanistically important in CUL3-Δ9-mediated FHHt.

Methods: We studied *Cul3* KO (*Cul3*$^{-/-}$) mice, *Cul3* KO mice expressing CUL3-Δ9 (*Cul3*$^{-/-/\Delta 9}$), *Cul3* heterozygotes expressing CUL3-Δ9 (*Cul3*$^{+/-/\Delta 9}$), compound *Cul3* and *Klhl3* heterozygotes (*Cul3*$^{+/-}$*Klhl3*$^{+/-}$), and *Jab1* KO (*Jab1*$^{-/-}$) mice. All mouse lines were inducible and renal tubule-specific.

Results: CUL3-Δ9 did not promote degradation of CUL3 targets that accumulate in *Cul3*$^{-/-}$ kidney: WNK4, cyclin E, or NQO1 (a surrogate for the CUL3 substrate Nrf2). In *Cul3*$^{-/-/\Delta 9}$ mice, CUL3-Δ9 prevented KLHL3 accumulation seen in *Cul3*$^{-/-}$ kidney and promoted KLHL3 degradation in *Cul3*$^{+/-/\Delta 9}$ mice. Higher NQO1 and lower cyclin E abundances were observed in *Cul3*$^{+/-/\Delta 9}$ mice compared to control mice. *Cul3*$^{+/-}$*Klhl3*$^{+/-}$ mice displayed increased WNK4-SPAK activation and phospho-NCC abundance, and FHHt-like phenotype with increased plasma [K^+] and salt-sensitive blood pressure. Similarly, reduced CUL3 and KLHL3 abundances and increased abundances of WNK4 and phsopho-NCC were observed in *Jab1*$^{-/-}$ mice.

Conclusions: Together, these data provide evidence for a mechanism of reduced KLHL3 and reduced CUL3 in CUL3-Δ9-mediated FHHt. CUL3-Δ9 potently degrades KLHL3, but also exerts modest effects on other CUL3 targets, raising the possibility of unidentified renal phenotypes in the human disease.

Funding: NIDDK Support, Private Foundation Support

PO1091

Non-Reabsorbable Anions Enhance Potassium Excretion by Multiple Mechanisms

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Background: Potassium (K^+) secretion in the distal nephron (DN) is governed, in part, by the lumen-negative transepithelial potential (Vte), created by ENaC-mediated sodium reabsorption, and partially attenuated by paracellular chloride (Cl^-) reabsorption. K^+ secretion increases when nonreabsorbable anions (NRA), such as $HCO3^-$ or beta-hydroxybutyrate, replace luminal Cl^-. Although this allows an appropriate response to alkaline-ash rich diets, it can drive exaggerated K^+ secretion in alkalosis. According to textbook views, NRA facilitates K^+ secretion solely by increasing the lumen-negative Vte. However, the effects of NRA on the potassium secretory machinery have not been determined.

Methods: Wild-type C57BL6J mice were randomized to control (1%K^+), potassium chloride (KCl:5%K^+) or potassium bicarbonate (KHCO3:5%K^+) diets for 10 days. Physiological, molecular and imaging analysis were performed. Pendrin-KO mice were examined to assess the specific role of pendrin in NRA-mediated potassium excretion.

Results: Consumption of the high KHCO3 diet increased urinary potassium K^+ excretion and the trans-tubular K^+ gradient (TTKG) significantly more than with the high KCl diet, consistent with an NRA response. Both diets increased aldosterone to the same extent, correlating with similar increases in ENaC expression and proteolytic activation. Surprisingly, the high KHCO3 diet significantly enhanced ROMK protein expression and apical localization in the late distal convoluted tubule and CNT more than the high KCl diet. The diets also induced opposite changes in Pendrin protein and apical membrane localization; Pendrin decreased with the high KCl diet but increased in the high HKCO3 diet. The high KHCO3 diet also uniquely induced a remodeling of the intercalated cells in the late DCT and CNT, whereby the number of pendrin-positive cells increased without change in principal cells. Pendrin-KO mice excrete the high dietary KHCO3 load to the same extent as WT mice but develop metabolic alkalosis.

Conclusions: In summary, NRA stimulates potassium excretion beyond a Vte effect. By increasing apical membrane ROMK and Pendrin expression, and remodeling the DN, mice increase the capacity to adapt to alkaline-ash rich diets, preventing hyperkalemia and alkalosis.

Funding: NIDDK Support

PO1092

The Effect of Epidermal Growth Factor Inhibition on Distal Nephron Sodium Reabsorption in Mice

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Background: Studies have shown that the epidermal growth factor (EGF) decreases the activity of ENaC while the influence of EGF on renal Na^+ transport via NCC is unknown. Previous investigations in mDCT-15 cells showed that EGF increases endocytosis of NCC. Using radio-telemetry, we found that EGF inhibition increases systolic blood pressure in response to increasing the dietary Na^+ intake. Our results in consolidation with other researchers, suggest that EGF affects BP by influencing the activity of ENaC and NCC. Our goal is to determine whether EGF inhibition increases BP via alterations in Na^+ reabsorption.

Methods: Using metabolic cages, we collected urine samples at three time points over 24 hours in 7 week old male mice. Normal salt (LS) diet (0.4% Na chow) was given for baseline collections and high salt (HS) diet (4% Na chow) for experimental collections. Only the experimental (E) group, n=4 received gefitinib (an EGF receptor tyrosine kinase inhibitor) orally at 100 mg/kg/d and the control (C) group, n=4 received placebo. Hydrochlorothiazide (HCTZ) 2.4mg per 10g BW orally and amiloride 1.45 μg/g via IP injection were administered. Following a washout period, HCTZ and amiloride were given simultaneously to assess the total effect on NCC and ENaC.

Results: There was no difference in the average urinary Na^+ excretion over 24 hours for baseline measurements between the groups when receiving the LS diet (experimental (E) group: 105 ± 13 mmol vs. control (C) group: 82 ± 23 mmol, N.S.). However, when giving the HS diet and HCTZ, the E group had a higher average urinary Na^+ excretion over 24 hours in response to a higher dietary Na^+ intake (E group: 966 ± 108 vs. C group: 517 ± 139 mmHg, p<0.05). For amiloride with HS diet there was no difference in average urinary Na^+ excretion between the groups (E group: 1130 ± 127 vs. C group: 920 ± 48 mmol, N.S.). When giving both HCTZ and amiloride to the mice while receiving the HS diet, the E group had a higher urinary Na^+ excretion compared to the C group (E group: 997 ± 66 vs. C group: 777 ± 48 mmol, p<0.05).

Conclusions: Therefore, our data suggests that inhibition of EGF increases Na^+ reabsorption via NCC. As previously suggested, this may indicate that EGFR ligands act as tonic inhibitors of NCC tubular sodium reabsorption. Future experiments will explore the in vivo effects of EGFR inhibition on sodium excretion along other components of the nephron.

Funding: NIDDK Support, Veterans Affairs Support

PO1093

Role of mTORC2/SGK1 Signaling in Rapid Response to Acute K Load to Maintain K+ Homeostasis

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Background: The kinase mTORC2 phosphorylates SGK1 and is required for normal K^+ secretion in the aldosterone-sensitive distal nephron. Aldosterone is known to play a role in mediating a sustained response through effects on SGK1 gene transcription, however, it is unknown how rapid responses are mediated. Here we have explored the role of mTORC2 and ENaC activity in the early response to an acute K^+ load to regulate K secretion.

Methods: Inducible tubule-specific Rictor (a core component of mTORC2) knockout mice (TRKO) were generated (Pax8-rtTA/LC-1/Rictorflox/flox). Both WT and TRKO mice received control or 2% KCl via gavage following intraperitoneal vehicle or Benzamil (ENaC inhibitor) injection. Spot urine was collected. ENaC and ROMK activity were measured in split open tubules by apical membrane patch clamp 3h post gavage. Membrane and cytoplasmic proteins were extracted from kidneys for immunoblot analysis.

Results: Adult TRKO mice on normal diet displayed no abnormality except significantly elevated aldosterone. K^+ administration by gavage triggered markedly greater Na^+ excretion and lower K^+ excretion in TRKO than WT mice, with differences detectable within 1 h of gavage. Benzamil induced a greater natriuresis in WT than in TRKO mice, and more strongly suppressed kaliuresis, consistent with greater ENaC activation in WT than in TRKO. The response of WT occurred rapidly, before significant change in aldosterone. In benzamil-treated mice, the natriuresis and kaliuresis of WT and TRKO mice were comparable, strongly supporting the idea that KCl induced

ENaC-dependent K^+ secretion in WT, and that this response is defective in TRKO. Patch clamp measurement demonstrated increased ENaC activity in WT but not in TRKO mice and no change in ROMK activity in WT or TRKO by KCl gavage. Membrane expression of cleaved α- and gENaC were significantly increased in WT but not in TRKO mice receiving KCl gavage. No significant increase in membrane expression of ROMK was observed in WT or TRKO post gavage. Finally, both SGK1 and Nedd4-2 phosphorylation were increased in WT but not TRKO mice receiving KCl gavage.

Conclusions: Overall, the data strongly suggest that an acute K^+ load acts through mTORC2/SGK1 to rapidly stimulate ENaC but not ROMK to promote K^+ secretion. These effects are primarily due to local renal tubular K^+ sensing.

Funding: NIDDK Support, Private Foundation Support

PO1094

Structural Determinants of mTORC2 Substrate Specificity and SGK1 Phosphorylation Revealed by Cryogenic Electron Microscopy

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Background: mTORC2 is a multi-subunit kinase complex central to multiple essential signaling pathways. Notably, it responds to hormonal signals and local electrolyte concentrations to phosphorylate SGK1 and regulate K+ secretion in the renal tubules. Two core subunits, Rictor and mSin1 distinguish mTORC2 from its much better characterized relative, mTORC1. Two other subunits, mTOR itself and a small scaffold, mLST8, complete the core complex. Previous mTORC2 reconstructions have lacked key regions of the > 1 MDa complex, particularly determinants of specificity.

Methods: Core mTORC2 subunits were expressed in Expi293F cells and purified using new methods for on grid purification. cryo-EM was peformed using Krios at SLAC for high energy electrons for density maps of human mTORC2. Structures were solved for apo-complex at overall 3.23 Å resolution, and for co-complexes with substrates, SGK1 and Akt, at 3.38 and 3.44 Å, respectively.

Results: The apo-complex reveals architectural features of functionally important domains, including specific side chain positions and interactions, which are visualized for the first time. In particular Rictor/Ser-1624 and Ser-1625 were observed to engage in hydrogen bond interactions with mTOR/Thr-2098, in a manner that provides steric hindrance to binding of Rapamycin, and explains mTORC2 resistance to the effects of this clinically important mTORC1 inhibitor. In addition, mSin1, the other defining subunit of mTORC2, is seen to form extensive contacts with Rictor, including an extended strand, which makes multiple weak contacts with a Rictor helical cluster. Most notably for the role mTORC2 plays in renal electrolyte handling, in the co-complex structure with SGK1—but not the Akt co-complex, we see a marked change in the conformation of the mSin1 N-terminal extended strand in a manner consistent with previous functional data identifying this region as required for phosphorylation of SGK1, but not Akt, thus providing a structural basis for differential regulation.

Conclusions: These findings provide new structural insight into mTORC2 specificity and context-dependent activities, and foundation for further mechanistic studies. Further, these findings provide a potential avenue toward highly selective mTOR modulators with potential clinical utility.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences, Private Foundation Support

PO1095

In Vivo Influence of a Protease-Resistant Epithelial Sodium Channel Gamma Subunit on Fluid Homeostasis

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Background: Extracellular fluid depletion promotes proteolytic processing of ENaC's γ subunit. Removal of the subunit's inhibitory tract enhances channel open probability. Although several cleavage sites exist distal to the γ subunit's inhibitory tract, only one known site resides proximal to the inhibitory tract: a furin cleavage site ($RKRK^{143}$). We hypothesized that a mouse expressing a protease-resistant ENaC γ subunit would exhibit signs consistent with reduced renal tubular ENaC activity, such as attenuated ability to adapt to dietary Na restriction.

Methods: We used TEV in Xenopus oocytes to confirm the ability of disruption of the γ subunit's furin cleavage site ($RKRK^{143}$ to $QQQQ^{143}$, or "Q4") to reduce ENaC activity. In 129sv mice, we used CRISPR-Cas9 to introduce this amino acid substitution into ENaC's γ subunit. Altered cleavage of ENaC's γ subunit was confirmed by Western blot of tissues from mice on a low (0.04%) Na diet (LSD). Lysates of kidneys from these animals were digested in PNGase to deglycosylate proteins, facilitating interpretation of molecular weights. Blood electrolytes were evaluated by iSTAT at sacrifice. Animal body fluid was assessed in live animals using quantitative magnetic resonance (Echo-MRI).

Results: Expression of the protease prostasin in oocytes, along with ENaC (N = 15), increased amiloride-sensitive currents, compared to oocytes with ENaC but no prostasin (N = 15; $p < 0.0001$). In oocytes expressing a Q4 gamma subunit (N = 15), prostasin no longer increased currents (N =15). Western blot of PNGase-digested tissue lysates revealed a full-length (~60 kDa) γ subunit and two shorter proteins, consistent with subunits either cleaved at the furin site (~53 kDa) or at a more distal site. Tissues from Q4 mice lacked the 53 kDa band, suggesting impaired Furin site cleavage. Blood K+ was normal in Q4 mice (N ≥ 7 for each sex and genotype). On a LSD, Q4 male mice exhibited greater loss of body water than control males ($p = 0.04$; N = 6-7), but females exhibited no difference in body water (N = 7-8).

Conclusions: These findings support a role for proteolytic activation of ENaC in male mice maintaining total body fluid in response to dietary Na depletion. Females did not show a impaired body fluid retention, suggesting additional compensatory mechanisms.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO1096

A Rare Case of Acquired 11-Beta-Hydroxysteroid Dehydrogenase Deficiency

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Introduction: 11-Beta Hydroxysteroid Dehydrogenase (HSD11B) is an enzyme that is involved in steroid hormone physiology. HSD11B enzyme exists in two isoforms, HSD11B-type 1 and type 2. Type 2 isozyme is responsible for converting cortisol to inactive cortisone. Plasma concentration of cortisol is approximately 100-fold higher than aldosterone and activation of mineralocorticoid receptors by cortisol is normally limited due to its conversion to inactive cortisone at the sites of aldosterone action by the enzyme HSD11B-type 2. We are presenting a rare case of HSD11B deficiency in a patient taking herbal supplementation.

Case Description: A 73-year-old female with PMH of hypertension, hyperlipidemia and chronic pain was admitted to the hospital with fatigue and shortness of breath. She denied any history of diarrhea or recent use of diuretics or laxatives. She has a history of using some herbal supplements in large quantities for pain control. Initial blood pressure was 140/80 mmHg. EKG showed sinus bradycardia with PVCs and bigeminy. The lab results are summarized in **table A**. She received aggressive potassium supplementation and spironolactone with subsequent improvement of her condition.

Discussion: HSD11B deficiency is either congenital or acquired by ingestion of licorice or its derivatives (glycyrrhizic and glycyrrhetinic acids). The deficiency results in a decreased conversion to cortisone and accumulation of cortisol. The effect of cortisol on the mineralocorticoid receptor results in hypokalemia, metabolic alkalosis, and low aldosterone and renin activity. The diagnosis requires careful history and identification of specific clinical features and biochemical abnormalities.

Blood work	
Sodium	142 mmol/L
Potassium	1.5 mmol/L
Bicarbonate	43 mmol/L
Creatinine	0.68 mg/dl
Serum cortisone	< 0.1 ug/dL
Renin	0.1 ng/mL/hr
Aldosterone	<3.0 ng/dL
Aldosterone Renin Ratio	30

Table A: Lab Results

PO1097

New Method to Discriminate Function of A and B Type of Intercalated Cells in Split-Opened Collecting Ducts

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Background: The collecting duct (CD) is a highly adaptive terminal part of the nephron, which is essential for maintaining systemic homeostasis. Electrically uncoupled principal and intercalated cells (PCs and ICs) perform different physiological tasks and exhibit rather distinctive morphology. However, acid-secreting A- and base secreting B-type of ICs cannot be easily separated in functional studies despite virtually mirrored localization of their transport acid-base systems. Thus, there is no consensus of whether and how systemic pH stimuli affect function and A/B cell type ratio in the CD. The technique of split-opening isolated CD allows unambiguous monitoring of alterations in function in many individual cells within the split-opened area. However, it is not possible to specifically change the driving force for Cl- at luminal or basolateral sides, which is used in perfused tubule studies to identify IC types of certain cells on periphery.

Methods: We used BCECF-sensitive intracellular pH (pH_i) measurements in split-opened CDs followed by immunofluorescent (IF) detection of AQP2 and pendrin from WT and ClC-K2-/- mice to demonstrate that inhibition of this Cl- channel enables sorting out signals from A- and B- types of ICs.

Results: We show that ClC-K2 Cl- channel is exclusively expressed on the basolateral side of AQP2-negative ICs, where it likely participates in Cl-dependent H+/HCO3- transport. Indeed, ClC-K2 blocker, NPPB, had no effect on pHi in PCs, whereas it caused acidification or alkalization in different subpopulations of ICs in WT but not ClC-K2-/- mice. IF assay of the same CDs revealed that NPPB decreased pHi in pendrin-positive B-type and increased pHi in A-type of ICs. Induction of metabolic acidosis markedly increased A/B cell ratio from 74% to 145%. Furthermore, dietary acidification also resulted in significantly augmented H+ secretion (assessed as recovery after acidification) in A-type and decreased pH transport in B-type of ICs.

Conclusions: We show that inhibition of ClC-K2 can be employed to discriminate between A- and B-type of ICs in split-opened CD preparations. Using this method, we found that metabolic acidosis leads to augmented transport rate and increased total population of A-type in the CD.

PO1098

Piezo1 in Intercalated Cells (ICs) Mediates Flow-Induced [Ca2+]i Transients in Mouse Cortical Collecting Duct (CCD)

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Background: Within the CCD, an acute increase in tubular fluid flow rate (TFFR) exposes principal cells (PCs) and ICs therein to hydrodynamic forces. In response, a biphasic increase in $[Ca^{2+}]_i$ is observed, with an immediate high amplitude increase due to release of IP3-sensitive internal Ca^{2+} stores coupled to extracellular Ca^{2+} entry at the basolateral membrane. This is followed by a decay to a plateau level that is higher than baseline and sustained by luminal Ca^{2+} entry (Liu et al., 2003; 2005; 2007). This increase in $[Ca^{2+}]_i$ is necessary for BK channel-mediated flow induced K^+ secretion (FIKS) in the microperfused mammalian CCD. We have recently reported that PIEZO1, a mechanosensitive, Ca^{2+} permeable channel, is expressed on the basolateral membranes of PCs and ICs in the mouse CCD (Dalghi et al., 2019).

Methods: To examine whether IC *Piezo1* expression contributes to the increase in $[Ca^{2+}]_i$ triggered by TFFR, we generated a mouse with targeted deletion of *Piezo1* in ICs (IC-Piezo1-KO).

Results: Immunofluorescence analyses of kidneys harvested from mice (C57BL/6) expressing PIEZO1-tdTomato revealed a significant increase of PIEZO1 expression in ICs from mice fed a high K (HK, 5% K^+, n=4) vs. standard K (SK, 1% K^+, n=4) diet for 10 days. Fluorescence intensity ratios (FIRs; ratio of the Ca^{2+} indicator Fura-2 emission signals measured at excitation wavelengths of 340 nm and 380 nm), corresponding to $[Ca^{2+}]_i$, were measured in individually identified PCs and ICs in CCDs isolated from (i) HK-fed IC-*Piezo1*-KO (n=3), (ii) SK-fed littermate control (n=3), and (iii) HK-fed control (n=3) mice and then exposed to the PIEZO1-activator Yoda1 (1 μM). PCs and ICs from HK-fed control mice exhibited a greater increase in $[Ca^{2+}]$i in response to Yoda1 than SK-fed control mice ($p \leq 0.001$). However, ICs from HK-fed IC-Piezo1-KO mice exhibited a reduced or absent increase in $[Ca^{2+}]_i$ in response to Yoda1 vs. SK-fed control mice ($p \leq 0.001$). In microperfused CCDs isolated from IC-*Piezo1*-KO mice, an increase in TFFR did not elicit a typical increase in $[Ca^{2+}]_i$ in ICs ($p \leq 0.001$, n=3 controls and n=4 KOs).

Conclusions: We conclude that *Piezo1* is upregulated in the CCD by a HK diet and contributes to the TFFR-induced increase in $[Ca^{2+}]_i$ in ICs necessary for FIKS.

Funding: NIDDK Support, Other NIH Support - R01 DK038470, R01 HL147818, R01 DK119183, P30 DK079307

PO1099

An Extremely Rare Interaction Between Two Commonly Used Drugs

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Introduction: The use of Paracetamol and Flucloxacillin can result in an elevated anion gap metabolic acidosis. Interaction between these drugs is a rare disorder that results from accumulation of pyroglutamic acid. Affected patients are usually women with chronic illness, sepsis, and malnutrition.

Case Description: We present the case of a 79 year-old hypertensive and diabetic woman with a past medical history of chronic kidney disease (baseline creatine of 1.6 mg/dl). She was admitted to the hospital due to a Methicillin-Sensitive Staphylococcus Aureus spondylodiscitis and she underwent surgical decompression with postoperative severe pain complaints. In that context, she was started on opioids, NSAIs and high-dose paracetamol (4 g daily), and Flucloxacillin (12 g daily). After 10 days she presented with dyspnea and generalized weakness. Blood gas analysis revealed metabolic acidosis (pH 7.35; pCO2 16 mmHg; pO2 102 mmHg; HCO3 8 mmol/L; anion gap 22 mmol/L; lactate 0.4 mmol/L). Laboratory tests showed hypoalbuminemia of 1g/dl in the context of severe malnutrition, and no worsening of kidney function. The patient was screened for lactic acidosis, ketoacidosis, toxic alcohol ingestion and salicylate poisoning with no positive findings. Finally, we concluded accumulation of pyroglutamic acid secondary to concomitant use of flucloxacillin and paracetamol in high doses as the leading cause of elevated anion gap metabolic acidosis. Despite these drugs were immediately stopped and sodium bicarbonate was started, the patient showed no clinical improvement and presented with respiratory exhaustion. Hemodialysis was started to correct the acid-base disorder.

Discussion: Despite being extremely rare, metabolic acidosis induced by drug interaction between Paracetamol and Flucloxacillin is a severe and potentially life-threatening disorder. We recognize the relevance of this case since these drugs are commonly prescribed together.

PO1100

Dietary Ammonium Exacerbates Pyelonephritis in Mice Prone to Vesicoureteral Reflux

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Background: In a mouse model of urinary tract infection with Uropathogenic E. Coli (UPEC-UTI) dietary NH_4Cl (AC) induces metabolic acidosis and increases UPEC burden in reflux prone C3H-HeN, but not Tlr4 deficient, C3H-HeJ mice[2]. We have confirmed and extended these studies by comparing the inflammatory response in C3H-HeN mice fed AC-diet vs. standard chow (SC), and by examining the effect of HCl-acidosis.

Methods: Female C3H-HeN mice were fed: standard chow (SC), NH_4Cl (2% w/w; AC), or 1g/ml 0.4 N HCl supplemented chow (HCl-A). Acid-base state was assessed by blood /gas analysis using an iSTAT® G3+ and urine pH. UPEC-UTI: Urinary Tract Infection of mice (6-8 wks) with Uropathogenic E. Coli (UPEC strain CFT073; 10^7-10^8 cfu/50 μl) was induced via transurethral inoculation. UPEC burden (cfu/g) was determined by culture of tissue homogenates. NOS2 mRNA in bladder and kidney cells was quantitated by qRT-PCR. Ly6G+ kidney neutrophil infiltrates, phagocytosis of UPEC-GFP (GFP mean fluorescent intensity, MFI, in Ly6G+ neutrophils) and oxidative burst (DHR123 fluorescence, MFI) were quantitated by flow cytometry. Statistics: Two-tailed T-test or Mann-Whitney U-Test $p<0.05$.

Results: Consistent with higher UPEC burden in bladder and kidney and increased chemokine/cytokine production[2], Ly6G+ neutrophil infiltrates were 4.5±0.6 fold higher in kidneys from AC vs. SC-infected mice (N=3; $p<0.01$)[2], and NOS2 (iNOS) mRNA was increased 8.7±1.8 vs. SC-infected bladder and 10.5±2.5 fold vs uninfected kidney (N=10; $p<0.002$). The % double (GFP^+Ly6G^+) neutrophils (Mean±SE: SC= 66.6±3.6%, N=5; AC= 69.1±7.5%, N=4), UPEC-GFP MFI in Ly6G+ neutrophils (SC=4.6E3±756, N=5; AC = 6.3E3±2.8E3, N=4), and DHR123 fluorescence of Ly6G+ cells (DHR123 MFI: SC =5E3±712; AC=8.1E3±107) were not significantly different between groups ($p>0.5$) indicating that neutrophil phagocytosis and oxidative burst were unaffected by dietary ammonium. HCl-acidosis (s[HCO3-]: HCl-A=16.3±0.1 vs. SC=23.2±0.6, N=4; $p<0.01$) did not increase UPEC burden (Kidney cfu/g: SC: 4E3±2E3 vs. HCL-A: 2E3±8E2, $p>0.05$) indicating that acidosis per se does not impair UPEC-UTI clearance. [2]Purkerson et al. (2020) Physiolog.Rep. 8(19)e14525.

Conclusions: Dietary ammonium chloride impairs clearance of UPEC-UTI and exacerbates pyelonephritis. The effect of dietary ammonium is unrelated to acidosis and neutrophil function.

Funding: Private Foundation Support

PO1101

Molecular Insights into the Structural and Dynamical Changes of Calcium Channel TRPV6 Induced by Its Interaction with Phosphatidylinositol 4,5-Bisphosphate

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Background: Transient receptor potential vanilloid subfamily member 6 (TRPV6) is a Ca^{2+}-selective channel that mediates Ca^{2+} entry into epithelial cells as the first step of the transcellular Ca^{2+} transport pathway. TRPV6 is expressed in the kidney, intestine, and other epithelial tissues, and the dysregulation of this channel has been implicated in cancers. TRPV6 and its close homologue TRPV5 are activated by phosphatidylinositol 4,5-bisphosphate (PIP_2); however, it is less clear how PIP_2 activates TRPV6 at the molecular level.

Methods: Recently, a structure of rabbit TRPV5 in complex with dioctanoyl (diC8) PIP_2, a soluble form of PIP_2, was determined by cryo-electron microscopy. Based on this structure, a structural model of human TRPV6 with PIP_2 was set up. This model was then embedded in a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipid bilayer with water molecules added on both sides of the bilayer using CHARMM-GUI. Using the AMBER18 software, three 500-ns molecular dynamics simulations were performed for the two systems of TRPV6 with and without PIP_2.

Results: Interaction energy analyses show that the positively charged residues K300, R302, R305, K484, and R584 of TRPV6 play important roles in the binding of PIP_2, which is consistent with the structural data that residues R302 and K484 in TRPV5 are responsible for the binding of diC8 PIP_2. The binding of PIP_2 to TRPV6 increases the distance between the diagonally opposed residues D542 in the selectivity filter as well as the distance between the diagonally opposed residues M578 in the lower gate. Secondary structure and density analyses show that residue M578 in TRPV6 in the presence of PIP_2 undergoes structural and position changes, suggesting the opening of the lower gate. Principal component analysis also indicates that the binding of PIP_2 increases the dynamic motion of both the selectivity filter and the lower gate of TRPV6.

Conclusions: Simulation results indicate that PIP_2 increases the fluctuation of the key residues in both the selectivity filter and the lower gate of TRPV6. In addition, PIP_2 reduces the helix occupancy of a key residue in the lower gate. Furthermore, the diameters of both the selectivity filter and the lower gate are increased by PIP_2. These changes likely contribute to the opening of the TRPV6 channel.

Funding: NIDDK Support

PO1102

Lithium Treatment Induces Changes in E-Cadherin, β-Catenin, and Na+/K+-ATPase β1 in Rat Inner Medullary Collecting Duct in a Time-Dependent Manner

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Background: Lithium (Li)-induced Nephrogenic Diabetes Insipidus (NDI) develops in around 40% of psychiatric patients receiving Li treatment. NDI is characterized by the inability of the kidney to concentrate urine due to insufficient water reabsorption in the kidney collecting duct (CD). Studies in rats have shown that Li induces a cellular compositional change of the CD with a fractional decrease in the ratio of principal-to-intercalated cells after 4 weeks of Li. This cellular remodeling is reversible in rats undergoing recovery for 19 days following 4 weeks of Li treatment. We aimed to investigate if regulation of the cell-contacts E-cadherin and β-catenin have a role in the cellular remodeling. The Na^+/K^+-ATPase was also investigated due to previously shown influences on cell polarity and cell-contact formation in kidney cells (Rajasekaran et al, Mol Biol Cell, 2001).

Methods: Immunohistochemistry (IHC) was performed on rat kidney sections used in previously published studies (Christensen et al, AJP, 2006; Trepiccione et al, AJP, 2013). Sections from rats treated with Li for 4, 10 and 15 days and 4 weeks were stained using antibodies against the cytoplasmic domain of E-cadherin, β-catenin and Na^+/K^+-ATPase β1-subunit. Sections from rats that had undergone recovery for 6 and 12 days following 4 weeks of Li treatment were stained for β-catenin.

Results: E-cadherin and β-catenin labeled basal and lateral plasma membrane domains in the inner medullary CD (IMCD). In the proximal part of IMCD, the labeling was absent from the basal plasma membrane domains of multiple cells after 4 and 10 days of Li treatment and was present again after 4 weeks of Li. In addition, the basal labeling of β-catenin was absent from some cells after 12 days of recovery. IHC of the Na^+/K^+-ATPase β1-subunit revealed a similar subcellular localization, and the protein was not present in the basal plasma membrane domains of multiple cells in the proximal part of the IMCD already after 4 days of Li.

Conclusions: The subcellular localization of the adherens junction proteins E-cadherin, β-catenin and Na^+, K^+-ATPase b1 is affected by Li treatment in the proximal part of the IMCD. In addition, the absence of labeling from the basal plasma membrane domains appears to occur prior to the cellular remodeling.

Funding: Private Foundation Support

PO1103

Deletion of the EP3 Receptor in the Kidney Tubule of Adult Mice Has No Impact on the Major Channels and Transporters Involved in Kidney Water Handling

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Background: Prostaglandin E2 (PGE2) is an important lipid mediator modulating various aspects of kidney function. PGE2 exerts its effects via four PGE2 receptors, EP1-EP4, but it is unclear which PGE2 effects are mediated through which receptor. The EP3 receptor is expressed in the thick ascending limb (TAL) and the collecting duct, where it is proposed to inhibit cAMP generation and NaCl and water reabsorption. However, EP3 is also expressed in endothelial cells of arteries and arterioles, that also play a role in kidney function.

Methods: To assess the tubular role of EP3 in adult mice we generated a mouse model based on the Pax8Cre system with doxycycline-dependent deletion of EP3 along the renal tubule and assessed their renal phenotype in respect to water handling. qPCR and RNAscope confirmed that EP3 was highly expressed in cortical and medullary TAL and collecting ducts, but it was not detected in proximal tubule and thin limbs.

Results: Two weeks after treatment with doxycycline, EP3 mRNA expression was reduced by >80% in whole kidney (RT-q-PCR) and non-detectable (RNAscope) in tubules of knockout mice compared to control mice. The other EP receptors expression remained unchanged in the kidney except for a slightly increase in EP4 expression. Under basal conditions, there were no significant differences in food and water intake, bodyweight, urinary output or plasma and urine biochemistries in both male and female control and knockout mice. There were no differences between genotypes in their kidney handling of water during an acute water load, or in their response to the vasopressin V2 receptor agonist dDAVP. Moreover, the expression levels of the main channels and transporters involved in kidney water handling, including AQP2, AQP3, AQP4, NKCC2, αENaC, UT-A1, ROMK and NaK-ATPase remained similar to the control mice.

Conclusions: This new model provides a novel tool for examination of the role of EP3 in other aspects of kidney function or kidney disease independently of potential developmental abnormalities or systemic effects.

PO1104

Bayesian Identification of Transcription Factors That Regulate Aqp2 Transcription

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Background: Renal collecting duct and connecting tubule cells selectively express the water channel aquaporin-2 (AQP2) and *Aqp2* gene transcription is strongly regulated by vasopressin. However, the transcription factors (TFs) responsible for regulation of expression of AQP2 remain largely unknown. Here, we used Bayesian data integration techniques to identify these TFs.

Methods: The general strategy is to use Bayes' Rule to integrate several -omic datasets to stratify a curated list of 1344 TFs present in the mouse genome with regard to probability of regulating *Aqp2* gene transcription. To prioritize TFs, existing proteomic and transcriptomic data, ATAC-Seq, histone H3K27-acetylation ChIP-Seq, and RNA-polymerase II ChIP-Seq data are used. Beyond this, we use additional -omic datasets to prioritize TFs that are regulated by vasopressin. Finally, we carried out new RNA-Seq experiments mapping the time course of vasopressin induced changes in the transcriptome of mouse mpkCCD cells to further prioritize TFs that change in tandem with AQP2.

Results: The analysis identified 17 TFs out of 1344 in the mouse genome that are most likely to be involved in regulation of *Aqp2* gene transcription. These TFs included eight that have been proposed in prior studies to play a role in Aqp2 regulation, viz. Cebpb, Elf1, Elf3, Ets1, Jun, Junb, Nfkb1, and Sp1. The remaining nine represent new candidates for future studies (Atf1, Irf3, Klf5, Klf6, Mef2d, Nfyb, Nr2f6, Stat3, Nr4a1). The RNA-Seq time course experiments in mpkCCD cells showed a rapid increase in Aqp2 mRNA, within 3 hour of vasopressin exposure. This response was matched by an equally rapid increase in the abundance of the mRNA coding for Cebpb, which we have shown by ChIP-seq studies to bind downstream from the *Aqp2* gene.

Conclusions: The Bayesian analysis has identified the TFs most likely to bind to Aqp2 cis-regulatory elements and likely to be regulated by vasopressin stimulation, providing a roadmap for future studies to understand regulation of *Aqp2* gene expression.

Funding: Other NIH Support - Division of Intramural Research, National Heart, Lung, and Blood Institute (project ZIA-HL001285 and ZIA-HL006129, M.A.K.)

PO1105

The Enhanced Expression of AQP4 in Cerebral Ischemia Is Attenuated in AQP11 Heterologous Knockout Mice

Yasuko Tanaka, Kenichi Ishibashi. *Meiji Yakka Daigaku, Kiyose, Japan.*

Background: The role of aquaporins (AQPs) in the brain edema needs to be clarified to advance its treatment. Since the importance of AQP4 for the formation of brain edema has been shown, AQP11, expressed in the brain capillary, may also be important for the regulation of brain edema. In fact, we recently reported the associated expression of AQP4 and AQP11 in osmotically challenged AQP11 heterologous knockout mice (HKM) (Koike S et al. Biochimie. 2021).

Methods: Both common cervical arteries were ligated for 15 min or 60 min to produce an ischemic-reperfusion model of brain infarction. On one or two days after the reperfusion, total RNA in the brain between Bregma and Lambda was isolated from wild mice and HKM. A real-time RT-qPCR was employed to examine the expression levels of several genes including AQP1, AQP4, AQP11, Iba1 (microglial marker), GFAP (astrocyte marker), Lamp2 (pro-autophagic factor), Bax (pro-apoptotic factor).

Results: Gene expression profiles were similar between wild mice and HKM in Iba1 (increase), Lamp2 (increase) with more severity in 60 min ligation and in the second day. A similar profile was also observed with slightly decreased AQP1 by 5-22%. In contrast, the expression profiles of AQP4 and GFAP were outstanding in that both were more highly induced in wild mice than HKM, by 56% vs. 21% and by 570% vs. 335%, respectively, with further increases in 60 min ligation and in the second day. The results suggested the activation of astrocytes expressing AQP4 by the reperfusion, which might be attenuated in HKM. In agreement with this, the expression of Bax was increased in wild mice by 18% with 60-min ligation while it was decreased by 12% in HKM, suggesting a smaller brain damage in HKM. Interestingly, AQP11 expression was decreased after reperfusion by 13-25% in wild mice while it was decreased more in HKM by 25-30%. The results suggest that this further AQP11 decrease in HKM may have attenuated the increasing AQP4 expression after reperfusion.

Conclusions: The decreased AQP11 expression in HKM attenuated the enhanced expression of AQP4 and Bax in a mouse ischemia-reperfusion brain model. Thus, the inhibition of AQP11 may alleviate the brain edema by attenuating the expression of detrimental AQP4 in brain infarction.

Funding: Government Support - Non-U.S.

PO1106

Acute Hemoglobin Level Drop Based on Body Volume Gained

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Background: Hemoglobin (Hb) changes with blood transfusions have been widely studied, but to our knowledge, Hb drop associated with volume gained have not been studied. High fluid volume infusion in critically ill patients always result in Hb drop, but the acceptable extent of Hb drop is generally a clinical guess. We herein started a pilot study to assess Hb changes based on daily volume gained among anuric hemodialysis patients.

Methods: Chronic anuric hemodialysis (HD) patients without active bleed admitted to our institution for reasons other than dialysis were included. Strict input/output measurements and Hb levels peri-HD were obtained. Post-HD levels were measured at least 12h post treatment to allow for equilibrated fluid comparmentalization. Changes in Hb per L of body volume gained were calculated.

Results: 10 consecutive HD individuals were included. Average age 60.7±7.2 years, 6 males, 4 females, estimated fat free mass (FFM) 49.3±5 Kg, pre-HD Hb 9.74±1.28, post-HD Hb 9.36±1.28 g/dL, positive fluid balance per patient 1182±775 mL. Average Hb drop was -0.19±0.58 g/dL per L of fluid gained, or 0.004±0.12 g/dL/L of fluid gained/Kg of FFM.

Conclusions: Hemoglobin drop with large fluid infusion may be studied in the anuric HD population. Our pilot study indicates thus far that Hb drop may be ~0.2 g/dL/L on average or a maximum of ~0.8 g/dL per liter of positive fluid balance. Additional data are being collected. Our study may help clinicians gauge for possible blood loss during large fluid infusion required for hemodynamically unstable patients.

PO1107

A Salty Goodbye to Diuretic Resistance: Hypertonic Saline

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Introduction: Understanding the complex interplay of Cardiorenal physiology and pathophysiology in diuretic resistance requires a deep understanding of RAAS, ADH, and virtually all segments of the nephron. To treat, requires not only understanding but also the ability to investigate and differentiate. However, a treatment that can inhibit RAAS (directly and indirectly), stimulate Cardiac Output, improve GFR, and increase natriuesis could be the universal answer. 3% Saline has the ability to improve Cardiac Output and decrease SVR, increase GFR, increase natriuresis, inhibit RAAS and ADH (directly and indirectly), *and stimulate ANP.* **Therefore, the answer to Diuretic Resistance is 3% Saline.**

Case Description: A 55 y.o. AAF presented to the hospital for severe edema and shortness of breath. PMHx of HFpEF, DM, HTN, CKDg3a3 (non-nephrotic). She presented with AKI III, severe hyponatremia, and anasarca. Echo revealed EF 40%, biatrial enlargement, RV overload and reduced RV function. She was initially treated with high dose furosemide but did not improve. She was given Metolazone which caused worsening hyponatremia which was treated with 100mL of 3% Saline. This caused an immediate increase in urine output and sodium. She was then changed to a bumex drip and high dose spironolactone (200mg) with some improvement (via objective urine electrolyte assessment) she was still inadequately diuresed. She was then treated with 3% + Loop pulse dosing and sustained a robust diuresis of >3L of urine and maintained urinary sodium >50.

Discussion: The potential causes of diuretic resistance arise from the RAAS system *and* the individual nephron segments. The RAAS system however is the most universal target (when inhibited). While DCT, ASDN, CD and CCT. are involved, regardless of which segment is primary, targetting the RAAS system would likely have significant benefits in all diuretic resistance. 3% Saline works as a potent IVF to improve Cardiac Output, decrease SVR, improve renal blood flow, inhibit RAAS, inhibit ADH, and stimulate ANP. Using 100mL of 3% saline to augment diuresis (or alone) causes improvement in virtually all Cardiorenal parameters. The NaCl load directly inhibiting RAAS through distal NaCl delivery (salt load also increases salt wasting), this causes decreased afferent arteriolar constriction and thus further improving GFR. It also stimulates ANP in the RA to inhibit RAAS and ADH indirectly.

PO1108

Enhanced Diuresis with Sequential Nephron Blockade

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Introduction: Achieving volume control in patients with severe edema can be challenging, as diuretic resistance may occur. In such cases, sequential nephron blockade (SNB), a targeted multi-diuretic use strategy should be considered.

Case Description: A 60-year-old woman with HIV and Dilated Cardiomyopathy s/p CRT-D presented with dyspnea and anasarca despite torsemide and losartan. In the ED she weighed 370 Lbs., had stable hemodynamic parameters, hypoxemia, diffuse lung infiltrates and low CD4 count. Oxygen, IV loop diuretics and Bactrim were initiated for concerns of PCP and HF. Despite an average UO of 3 L/day she had no meaningful weight loss, protracted lung congestion, hyponatremia and developed radiocontrast nephropathy after CTA. Fluid restriction and SNB with IV thiazide and loop agents were instituted. Tolvaptan was added intermittently and led to an impressive diuresis of 8-11 L/day, restored normonatremia and was hemodynamically and metabolically well tolerated. Within 12 days, weight loss of 154 Lbs. was achieved with major clinical improvement.

Discussion: Loop agents are a mainstay for diuresis in patients with volume overload. However, diuretic resistance can occur through various mechanisms, including hypertrophy of the distal nephron and loss of function due to AKI. SNB provides a unique approach by strategically targeting ultrafiltrate dynamics in a stepwise manner and interfering with fluid reabsorption within various tubular segments. Central to this premise is the ability to maximize drug bioavailability and parenteral administration is initially necessary. Close hemodynamic and metabolic surveillance are mandatory as the mobilization of vast amounts of extracellular fluid may result in significant complications. Remarkably, in this case, while her eGFR was 25% she achieved 11 L diuresis (30% of UF) safely. This underscores the enormous capacity for fluid sequestration in the extracellular space and the crucial role of trans-compartmental fluid shifts in HF. SNB has been available for years and various diuretics combinations are plausible. This case exemplifies the effectiveness of a novel regimen with vaptans in promoting voluminous diuresis and aquaresis, improving outcomes and decreasing length of stay.

PO1109

Functional Sodium Magnetic Resonance Imaging of Human Kidney

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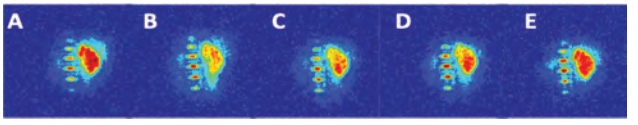
Background: Maintenance of a cortico-medullary concentration gradient (CMG) is required for urine concentration. We explored the ability of ^{23}NaMRI in measuring 1) the dynamics of CMG for the first time compared to urinary osmolarity after a water load and 2) the CMG in kidney disease.

Methods: We conducted an exploratory pilot study for 10 healthy controls following water load then 5 cardiorenal patients with kidney disease. 1) Fasting healthy controls provided urine samples to measure osmolarity and baseline ^{23}NaMRI scans were performed. They were instructed to ingest water (15 mL/kg) within 15 minutes. Four subsequent sodium images and urine samples were acquired at 15 min intervals starting one hour after water ingestion. 2) Cardiorenal patients underwent an MRI scan, provided a blood and urine sample, but no water loading.

Results: Mean age of the 10 healthy controls was 41.8 ± 15.3 years. In the morning fasting, medulla/cortex ratio was 1.55 ± 0.11 with concurrent urinary osmolarity measured at 814 ± 121 mOsm/L. Mean ± SD fasting urinary osmolarity dropped significantly to 73 ± 14 mOsm/L, p=0.001. Mean medulla/cortex ratio dropped significantly to 1.31 ± 0.09 mOsm/L for maximal dilution, p=0.002. Figure 1 displays changes of ^{23}NaMRI pictures before (A) then 1h (B), 1H15 (C), 1h30 (D) and 1h45 (E) after a water load. Urinary osmolarity and medulla/cortex ratio are significantly correlated, r=0.54, p=0.0001. Mean age of the 5 cardiorenal patients was 76.6 ± 12.2 years, eGFR was 54 ± 37 mL/min/1.73m^2. Urinary osmolarity was 498 ± 145 mOsm/L and medulla/cortex ratio was 1.35 ± 0.11. We measured corticomedullary gradient in cardiorenal patient with different level of eGFR to show the ability and feasibility to measure this gradient in pathological settings.

Conclusions: We explored CMG dynamically every 15 min in healthy controls and demonstrated significant changes after a water load. We were also able to acquire ^{23}NaMRI pictures in cardiorenal patients with kidney disease with plans for future analyses.



PO1110

Validity of a Simple Equation to Estimate Urine Output in Outpatients with Suspected Nephrolithiasis

Luke Webster,[1] Alexander Bullen,[1] John R. Asplin,[2] Michael Shlipak,[3] Seth Bechis,[1] Manoj Monga,[1] Joachim H. Ix.[4,1] *[1]University of California San Diego, La Jolla, CA; [2]LithoLink Corp, Chicago, IL; [3]University of California San Francisco, San Francisco, CA; [4]VA San Diego Healthcare System, San Diego, CA.*

Background: We previously developed and validated an equation to estimate urine volume from spot urine creatinine, demographic variables, and body weight in patients with kidney disease. We hypothesized this equation could accurately estimate daily urine output in outpatients with nephrolithiasis.

Methods: Among persons submitting specimens to Litholink Laboratories between May 2013 and January 2016, we identified 19,884 individuals who had two 24 hour urine collections on consecutive days, with creatinine excretion rates ±10%. We used Pearson correlations and Bland-Altman analysis to evaluate equation estimated with measured urine volume on the first of the two 24 hour urine collections. We also tested the equation's test characteristics to accurately identify producers >2L/day; a guideline directed urine output goal among stone formers.

Results: Estimated and measured urine volumes were strongly correlated (r=0.76, p < 0.001). The estimated urine flow rate was 195 ml/day (8.7%) higher than measured. Overall, 78% of individuals had an estimated urine volume within 30% of measured. Performance was similar in men and women, across strata of body weight, in those with and without CKD, and when evaluating the second day measured urine volume. An estimated urine volume ≥ 2L/day had 86% sensitivity, 83% specificity, 76% PPV and 91% NPV for identifying individuals with measured urine volumes > 2L/day **(Figure 1).**

Conclusions: A simple equation using urine creatinine, demographics and body weight can predict urine flow rate among patients with nephrolithiasis. The equation may provide a tool to enhance diagnostic accuracy in the urinary risk factors for stones, and to identify patients among whom efforts to increase hydration could be targeted to diminish risk of stone recurrence.

Funding: NIDDK Support

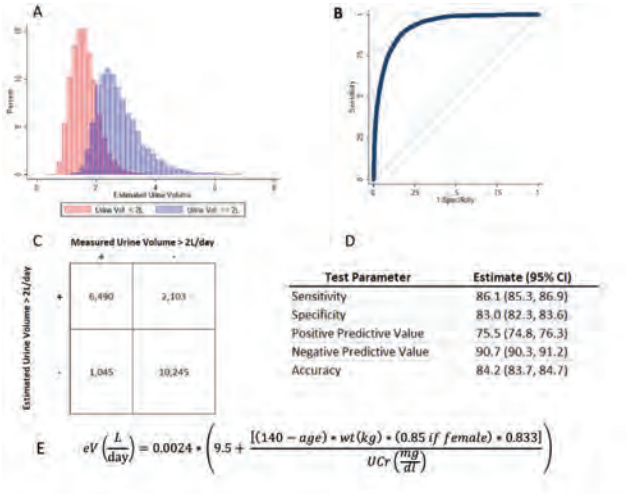


Figure 1. Test Characteristics of Estimated Urine Volume Equation to Predict Measured Urine Volume > 2L/Day.

Panel A depicts overlaying histograms showing estimated urine volume among those who had measured urine volume ≤ vs. ≥ 2L/day. **Panel B** shows the area under the receiver operator curve (AUC) when estimated urine flow rate is used to predict whether a patient has a measured urine volume ≥ 2L/day (AUC 0.845). **Panel C** depicts the 2 X 2 table comparing estimated vs. measured urine volume ≥ 2L/day, and **Panel D** provides the corresponding sensitivity, specificity, positive and negative predictive values, and overall accuracy, along with 95% confidence intervals of these estimate. **Panel E** depicts the estimated flow equation (eV) used for this analysis.

PO1111

Attenuated Urinary Sodium and Volume in Response to Saline Load in Heart Failure with Preserved Ejection Fraction

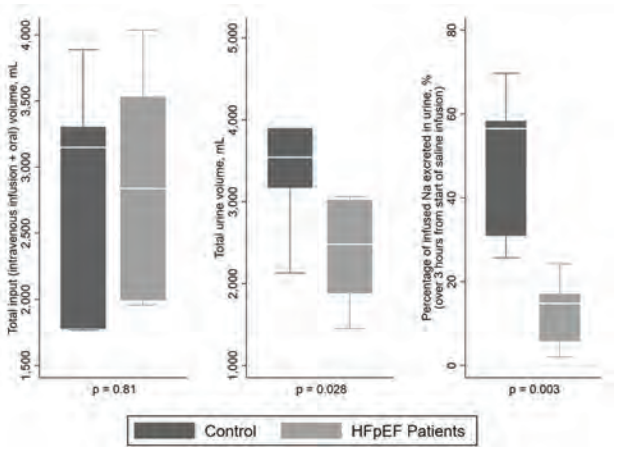
Adhish Agarwal, Srinivasan Beddhu, Robert E. Boucher, Aylin R. Rodan, Habeeb Mohammad, Guo Wei, Kevin S. Shah, James C. Fang, Alfred K. Cheung. *University of Utah Health, Salt Lake City, UT.*

Background: Heart failure (HF) is characterized by fluid overload due to impaired sodium (Na) excretion. Impaired urinary Na excretion in response to intravenous Na load has been demonstrated in HF with *reduced* ejection fraction (HFrEF). We hypothesized that patients with HF with *preserved* ejection fraction (HFpEF) also have impaired urinary sodium excretion and volume in response to intravenous Na load.

Methods: All participants were instructed to follow a low (2-3 g/d) sodium diet for one week prior to the study and held their diuretic (if prescribed) the morning of the study. After obtaining approval from our center's institutional review board, saline was infused intravenously at 0.25 ml/kg/min for 60 minutes in 9 patients with HFpEF and 5 controls (no known renal or cardiac disease). Urine output was measured throughout, and blood and urine samples were collected at baseline and 2 hours after ending the infusion. Urine volume and urinary sodium excretion between the groups were compared using Wilcoxon rank-sum tests.

Results: Mean age (yrs) and body mass index (kg/sqm) were 62+/-12 and 36.3+/-8.5 respectively in the HFpEF participants, and 47+/-18 and 24.6+/-3.7 in controls. The fraction of intravenous sodium that was excreted in the urine over 3 hours was significantly lower in cases (12% versus 46%, p=0.003). Mean urine output was significantly lower in cases (2480 versus 3541 ml; p=0.028), even though the total fluid intake (intravenous + oral) during the same time period was similar (2839 versus 3149 ml; p=0.81).

Conclusions: In this rigorous, controlled human pilot study, patients with HFpEF had lower urinary volume and attenuated urinary sodium excretion compared to controls after intravenous sodium and volume load. Data and biospecimens collected in this study should inform the pathogenesis of sodium retention in HFpEF.



PO1112

Attenuated Renal Response to Endogenous Natriuretic Peptides in Heart Failure with Preserved Ejection Fraction

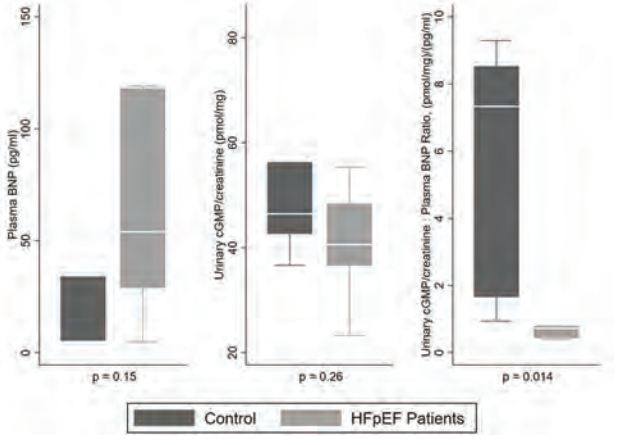
Adhish Agarwal,[1] Srinivasan Beddhu,[1] Robert E. Boucher,[1] Nirupama Ramkumar,[1] Aylin R. Rodan,[1] Veena Rao,[2] Habeeb Mohammad,[1] Elizabeth Dranow,[1] Guo Wei,[1] Kevin S. Shah,[1] James C. Fang,[1] Alfred K. Cheung.[1] *[1]University of Utah Health, Salt Lake City, UT; [2]Yale University, New Haven, CT.*

Background: The pathophysiology of sodium retention in heart failure with preserved ejection fraction (HFpEF) remains largely unknown. A potential mechanism is attenuated renal response to natriuretic peptides (NPs). Urinary cyclic guanosine monophosphate (ucGMP) is an intracellular messenger of NPs, and an attenuated ucGMP/B-type NP (BNP) ratio suggests decreased renal response to BNP. We hypothesized that patients with HFpEF have attenuated response to NPs.

Methods: We studied ucGMP/plasma BNP ratios in 9 HFpEF patients and 5 controls (no history of renal or heart disease). All participants were placed on a low (2-3 g/d) sodium diet for a week prior to the study. Urinary results were normalized using urine creatinine. Cases and controls were compared using Wilcoxon rank-sum tests.

Results: Mean age and body mass index for the HFpEF participants were 62+/-12 years and 36.3+/-8.5 Kg/m^2, and for control participants were 47+/-18 years and 24.6+/-3.7 Kg/m^2 respectively. Plasma BNP tended to be higher (median 54.0 (29.0, 118.0) versus 5.0 (5.0, 34.0) pg/ml; p = 0.15), while ucGMP/plasma BNP ratio was lower (median 0.7 (0.4, 0.8) versus 7.3 (1.7, 8.5) (pmol/mg)/(pg/ml); p = 0.014) in cases as compared to controls.

Conclusions: Our pilot study shows that ucGMP/plasma BNP ratio, which reflects renal response to BNP, was attenuated in patients with HFpEF. These data suggest that impaired renal response to NPs may be implicated in the pathogenesis of fluid retention in HFpEF.



PO1113

Association of Urinary Potassium Excretion with Progression of CKD

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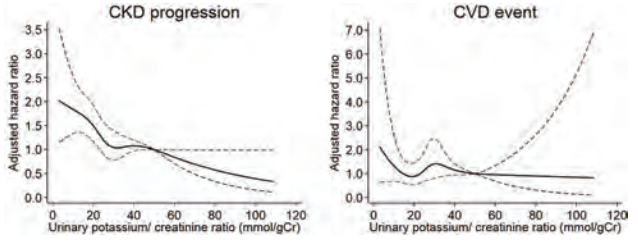
Background: Out of range serum potassium levels are associated with worsening renal function and increased occurrence of cardiovascular disease (CVD) events in

chronic kidney disease (CKD). However, conflicting results have been reported regarding the predictive value for adverse health outcomes of urinary potassium excretion. Therefore, we conducted a cohort study to determine whether urinary potassium excretion is an independent risk factor for renal function deterioration or increased CVD events.

Methods: We identified 650 patients with pre-dialysis CKD who were hospitalized for CKD educational program between 2010 and 2018. Study outcomes analyzed were CKD progression and incidence of CVD events. Baseline urinary potassium to creatinine ratio (UK/Cr, expressed as mmol/gCr) was ranked into quartiles as follows: Q1, <19.8; Q2, 19.9–27.7; Q3, 27.8–37.9; and Q4, >38.0.

Results: During follow-up (median 35 months), 509 CKD progression and 129 CVD events were identified. Further, 62 patients died during follow-up. Multivariate Cox models showed that an increased risk of CKD progression was observed in patients with low UK/Cr compared to those with high UK/Cr, after adjustment for demographic factors and laboratory data. In a fully adjusted model, adjusted hazard ratios (HRs) with the fourth (highest) quartile as reference category were 2.02 (95% CI, 1.50–2.71), 1.34 (95% CI, 1.02–1.77), and 1.14 (95% CI, 0.87–1.50), for Q1–3 respectively (trend: $P < 0.001$). Similarly, an inverse probability weighting analysis showed an increased risk of CKD progression in Q1 and Q2 comparing with Q4. We did not observe any significant modification in subgroup analyses. Furthermore, consistent association was confirmed between low fractional excretion of potassium and worsening renal function. However, UK/Cr had no association with the incidence of CVD events.

Conclusions: A low UK/Cr is independently associated with worsening renal function but not with an increased risk of a CVD event in patients with pre-dialysis CKD.



PO1114

Licorice-Induced Syndrome of Mineralocorticoid Excess

Nisarg Gandhi, Hassan N. Ibrahim. *Houston Methodist Hospital, Houston, TX.*

Introduction: Edema and volume overload are common complaints. Here, we present a case of a chronic licorice consumption resulting in edema and generalized weakness.

Case Description: A 34 y/o Caucasian women with history significant for hypothyroidism and recurrent episodes of bronchitis presented for evaluation of recurrent facial, arm, and lower extremity swelling over the past year. She has been evaluated extensively with no etiologies found in the past. She takes Bumex 0.5 mg at least once weekly when she has swelling. She does not have any evidence of kidney dysfunction, heart failure, liver failure, or evidence of proteinuria on laboratory findings. She has been evaluated by rheumatology and was only found to have a weakly positive ANA with no other associated findings (hematuria, arthralgias, or muscle pain). She denies any shortness of breath or orthopnea. Her vitals were within normal limits (BP: 115/70, Pulse: 55). She is very active and exercises daily. Despite limiting her sodium intake, she continues to have recurrent swelling. On further questioning, she mentioned drinking a tea high in licorice. Her basic metabolic panel shows Na^+ at 140, K^+ at 4.3, Cl^- at 100, and CO_2 at 26. Her urinalysis was bland with her urine $Na^+ < 20$. Measured plasma renin and aldosterone activity, shown in the table, were found to be low at baseline. Afternoon free cortisol level was measured to be 0.199. After discontinuation of licorice, they increased back to normal limits with complete resolution of symptoms.

Discussion: Chronic ingestion of licorice is a rare but a known cause of syndrome of mineralocorticoid excess (AME). Licorice contains a steroid, glycyrrhetinic acid, which inhibits the function of the enzyme 11-beta-HSD2. This same enzyme is deficient in AME. This can occur at even low amounts of licorice (50g per day). Typically, these cases present with hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity, and low plasma aldosterone levels. The only treatment necessary is cessation of licorice and symptoms typically resolve in about 1 week. This case illustrates the importance of obtaining a complete medication history including supplement use.

	At Presentation	3 Months after Discontinuation
Aldosterone (ng/dL)	2.3	32.4
Renin (ng/mL/hr)	1.111	2.235

PO1115

Not Just Licorice: Abiraterone and Apparent Mineralocorticoid Excess

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Introduction: Abiraterone is a CYP17A1 inhibitor which blocks androgen synthesis and is used to treat castration-resistant prostate cancer. This drug also decreases cortisol synthesis, causing a compensatory increase in adrenocorticotropic hormone (ACTH) and accumulation of mineralocorticoids. The result is the syndrome of apparent mineralocorticoid excess (AME) which manifests clinically as hypokalemia, metabolic alkalosis and hypertension. Abiraterone is approved for use only with concurrent glucocorticoid replacement to prevent these effects. We present a case of refractory hypokalemia resulting from abiraterone use.

Case Description: A 74-year-old man with metastatic prostate cancer and head and neck cancer presented with urinary retention and acute kidney injury (AKI) as well as hypokalemia and metabolic alkalosis which were present a week prior. Home medications included abiraterone, cisplatin (given two weeks prior), prednisone 5 mg daily (recently decreased from 5 mg twice daily) and spironolactone. A urinary catheter was placed, the AKI improved rapidly and the patient remained with refractory hypokalemia. A urine potassium-to-creatinine ratio was high. Post-obstructive polyuria was considered as a reason for kaliuresis; however, hypokalemia and metabolic acidosis preceding this event made it unlikely to be the sole cause. Given abiraterone use, serum cortisol was checked and was low with no increase after giving cosyntropin. Serum aldosterone, renin and their ratio were normal. The patient was diagnosed with abiraterone-induced AME. Prednisone was increased to 5 mg twice daily and eplerenone was started in place of spironolactone. Two months later, the serum potassium was normal without supplementation.

Discussion: Abiraterone-induced AME is characterized by low serum cortisol but unlike adrenal insufficiency, presents with hypokalemia, metabolic alkalosis and hypertension. In this case, AME results from inhibition of the 17α-hydroxylase activity of the CYP17A1 enzyme, leading to decreased cortisol, increased ACTH, and accumulation of the potent mineralocorticoid dexoycorticosterone. Glucocorticoid supplementation (prednisone 5 mg twice daily recommended) is needed to suppress ACTH and prevent these effects. Eplerenone is an adjunct and is preferred over spironolactone in patients with castrate-resistant prostate cancer as spironolactone interacts with the androgen receptor.

PO1116

Jägermeister-Induced Pseudohyperaldosteronism

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Introduction: Hypertension and hypokalemia is known to be caused by hyperaldosteronism. We report a case of hypertension, hypokalemia, and supressed renin and aldosteronen levels. Dietary work-up revealed copius ingestion of Jagermeister liquor which contains licorice, a known cause of pseudohyperaldosteronism.

Case Description: A 54-year-old man with a history of HIV on Genvoya and CAD, HTN on metoprolol and isosorbide monoitrate was referred to nephrology for evaluation of hypokalemia and accelerated hypertension. Prior to nephrology referral, he was started on oral potassium for 6 weeks and the repeat potassium was 3.5 mmol/L. On review of systems, he had no specific complaints except occasional diarrhea. On exam, his BP was 190/110, 1+ lower extremity edema; his exam was otherwise unremarkable. Initial workup revealed serum sodium 143 mmol/L, bicarb 24 mmol/L, potassium 3.5 mmol/L, creatinine 1.1 mg/dL, magnesium 1.5 mg/dL, urine K 78 mmol/L, FeK 13.6%, TSH 2.95 uIU/mL, plasma renin activity 1.191 ng/mL/hr, and aldosterone <3.0 ng/dL, and plasma metanephrines <10 pg/mL. Repeat K was 3.1, bicarb 30, plasma renin activity 0.195 ng/mL/hr, and aldosterone <3.0 ng/dL; urine K 34, FeK 11%; renal dopplers without evidence of RAS. Given hypokalemia, metabolic alkalosis with evidence of potassium wasting, and suppressed renin and aldosterone levels, a thorough dietary review was conducted which revealed chronic Jagermeister ingestion of up to 500mL per day. He stopped drinking Jagermeister and on subsequent follow-up, his BP was controlled on amlodipine, carvedilol, and isosorbide mononitrate, and he no longer required potassium supplementation.

Discussion: Licorice contains glycyrrhizic acid which inhibits 11 beta-hydroxysteroid dehydrogenase, preventing inactivation of cortisol to cortisone, and resulting in excess mineralocorticoid activity manifested by suppressed renin and aldosterone levels, sodium retention, hypervolemia, hypokalemia, hypertension, and edema. According to the manufacturer, Jagermiester liquor contains under 10 mg/L of licorice, however, the amount that can cause toxicity is not certain and literature suggests that the glycyrrhizic acid content of licorice is widely variable. Physicians ought to consider dietary, non-medication causes for electrolyte abnormalities in patients with initial negative workups.

PO1117

Posaconazole-Related Mineralocorticoid Excess in a Patient with Acute Myeloid Leukemia

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Introduction: Posaconazole is an antifungal used for treatment and prophylaxis of invasive fungal infections in cancer patients. We report a case of posaconazole related mineralocorticoid excess in a patient with acute myeloid leukemia (AML).

Case Description: Patient is a 40-year-old male with past medical history of relapsed AML status post stem cell transplant, was admitted on 08/16/2020 to UTMDACC for pain, nausea, vomiting, diarrhea, and fatigue. He developed multiple complications streptococcus viridans bacteremia, candidemia, Graft Versus Host Disease, disseminated adenovirus, fungal pneumonia on posaconazole, tracheostomy due to severe mucositis with HSV-1 on Foscarnet. Nephrology was consulted for hypernatremia, hypokalemia and alkalosis. No nausea, vomiting, diarrhea was reported. Due to a combination of hypertension, metabolic alkalosis, hypokalemia and being on Posaconazole, we suspected

Pseudo-hyperaldosteronism. Renin, aldosterone levels were checked which are low. CT scan of abdomen/pelvis did not show any adrenal tumors. Fractional excretion of potassium was high suggestive of renal loss. High 24-hour urine cortisol/cortisone ratio suggestive of mineralocorticoid excess. Posaconazole was changed to Voriconazole on 10/28/20. Due to persistent hypertension, spironolactone was increased and due to hypokalemia, amiloride was added. Twelve days after stopping Posaconazole all electrolyte and acid base abnormalities are resolved.

Discussion: Combination of hypokalemia, hypertension and metabolic alkalosis need to suspect mineralocorticoid excess. Posaconazole inhibits 11 beta-hydroxysteroid dehydrogenase2 which prevents conversion of cortisol to cortisone. High cortisol than aldosterone leads to amplification of mineralocorticoid receptor action causing increase in activity, number of epithelial sodium channels (ENaC), Na-K-ATPase channels. Excess uptake of sodium leads to hypertension and creates increased negativity causing K^+ and H^+ losses leading to hypokalemia and alkalosis. Patients with mineralocorticoid excess can be treated with aldosterone receptor antagonist or ENaC blockers or by stopping or decreasing the dose of Posaconazole. Patients on posaconazole need to be monitored for hypokalemia, hypertension and alkalosis. However, not every patient will develop these which may be likely due to genetic predisposition.

PO1118

Prednisolone-Related Mineralocorticoid Excess: Case of Hypokalemia and Metabolic Alkalosis

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Introduction: We report a case of the mineralocorticoid effect of prednisolone resulting in hypokalemia, metabolic alkalosis and hypertension in a patient treated with checkpoint inhibitor in the setting of oropharyngeal cancer.

Case Description: A 78 year-old male with past medical history of oropharyngeal squamous cell carcinoma presented with fatigue. One week prior, he was treated with pembrolizumab. Admission vital signs were significant for fever to 39.1°C and normotensive blood pressure 130/58. Laboratory results revealed serum potassium (K) 4.1 mmol/L, bicarbonate (HCO_3) 26 mmol/L and newly elevated liver enzymes. He was diagnosed with immune checkpoint inhibitor hepatitis and treated with prednisolone 70 mg via nasogastric tube (NGT). Two days later, blood pressure increased to 170/80 and laboratory studies revealed hypokalemia and metabolic alkalosis with serum K 3.0 mmol/L and HCO_3 30 mmol/L. Potassium was repleted with a total of potassium chloride (KCl) 80 mEq via NGT. The next morning, blood pressure 164/78, serum K 2.7 mmol/L and HCO_3 33 mmol/L. Nephrology was consulted for persistent hypokalemia and metabolic alkalosis. The triad of hypokalemia, metabolic alkalosis and hypertension lead us to suspect a hyper mineralocorticoid state. Workup revealed spot urine K of >100 mmol/L, serum aldosterone <3.0 ng/dL and serum renin <0.1 ng/dL. Findings were consistent with an exogenous source of mineralocorticoid activation. Prednisolone was thought to be the cause. He required a total of KCl 180 meq (40 mEq intravenous, 140 mEq NGT) to raise serum K to 3.4 mmol/L in 24 hours. As such, we recommended discontinuing prednisolone in favor of dexamethasone which has no mineralocorticoid effect. Two days after discontinuation of prednisolone, serum K was 5.1 mmol/L on KCl 40 mEq via NGT twice a day and serum HCO_3 was 28 mmol/L. Supplemental KCl was discontinued. One week later, serum K remained in normal range at 4.1 mmol/L.

Discussion: We demonstrated clinically significant mineralocorticoid effect of prednisolone resulting in hypokalemia and metabolic alkalosis. Physicians should be aware of electrolyte disorders associated with steroid use. With increased used of checkpoint inhibitors, this scenario may be encountered more often. Treatment may require stopping prednisolone and using alternative steroids with no mineralocorticoid activity.

PO1119

From Hypokalemia to Sjögren Syndrome: What a Twist!

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Introduction: Potassium disorders are one of the many serious conditions that could attempt against a patient's life. Understanding the clinical presentation, diagnosis, management, and treatment of hypokalemia is fundamental for the development of successful clinical physician. In addition, being aware of the associations between electrolyte disturbances and rheumatologic conditions increases the benefits of correctly treating and educating patients.

Case Description: This is the case of a 24 y/o female patient, G1P2A0, with a past medical history of hypoglycemia and hypokalemia since pregnancy with twins. Patient presented to emergency department with shortness of breath, general malaise, muscle weakness, and unable to ambulate. Physical examination was remarkable for proximal muscle weakness, diminished reflexes with intact sensation. Laboratory bloodwork reported positive mycoplasma pneumonia infection, normal anion gap metabolic acidosis with severe bicarbonate and potassium deficiency with EKG changes as ST depression with flattening of T wave and U-wave. Urinalysis had a basic pH with positive urine anion gap. Findings were suggestive of renal tubular acidosis (RTA). In addition, patient reported several episodes of nephrolithiasis during childhood, supporting distal RTA. Hypokalemia history and renal findings trigger were unknown. However, due to association of RTA type 1 and autoimmune disease, workup was performed. Rheumatoid factor, ANA screen, aldolase and SS-A/Ro antibody were positive consistent with Sjogren syndrome diagnosis. There are only a few documented cases. After discussing results with patient, she reported the daily use of artificial tears due to xerophthalmia. She did not report it sooner because, she considered the fact irrelevant to her clinical presentation.

Discussion: Sjogren syndrome is a chronic autoimmune inflammatory disease that could negatively affect the patient's quality of life. Triggers have not been completely identified due to multifactorial involvement and diversity of clinical manifestation. In Puerto Rico, there is a small population currently diagnosed with the syndrome. However, research studies of epidemiological characteristics or clinical profile in Puerto Rico are still ongoing.

PO1120

Idiopathic Bartter Syndrome-Like Phenotype Diagnosed in a Diabetic Patient with COVID-19 Infection

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Introduction: Bartter's syndrome (BS) is a rare genetic tubulopathy affecting the loop of Henle leading to salt wasting. Acquired BS is very rare and is associated with underlying medical conditions or certain drugs. We report a unique case of idiopathic BS-like phenotype that was diagnosed in the setting of COVID infection.

Case Description: 71-year-old man with coronary artery disease, hypertension and diabetes presented after a mechanical fall. On admission, he was found to be hypotensive to 107/88 mmHg. Physical exam was within normal limits. Initial blood work was significant for Potassium 2.6 mEq/L, Bicarbonate 34 mEq/L, Calcium 8.0 mg/dL and Magnesium 1.7 mg/dL. Patient also tested positive for COVID-19. Upon further questioning, patient reported a remote history of hypokalemia but never needed any oral supplementation. He denied diuretic use or surreptitious vomiting. Hypokalemia work up revealed increased urinary potassium of 85.4 mEq/L, Renin 15.72 ng/mL/hour and Aldosterone 8 ng/dL. Patient was then started on aggressive intravenous and oral potassium repletion. He continued to require multiple doses of intravenous potassium to maintain potassium levels of 3 mEq/L. He was subsequently started on Eplerenone on Day 3 of admission with excellent response. He remained otherwise asymptomatic from COVID and as his infection improved, hypokalemia stabilized and he was ultimately discharged with a Potassium level of 3.6 mEq/L.

Discussion: The primary defect in BS is in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle resulting in hypokalemia, metabolic alkalosis and secondary hyperaldosteronism. Rare cases of acquired BS are reported in association with tuberculosis, sarcoidosis, sjogrens, and certain drugs. All of these were ruled out in our patient and hence a diagnosis of idiopathic BS like phenotype was made. In our patient, we attribute the BS like phenotype to underlying COVID infection. As his infection improved, his hypokalemia also resolved. Hyperkalemia is a more common finding in COVID infection. However, in our patient, hypokalemia secondary to BS like phenotype was a unique presentation which was challenging to treat. In the absence of usual causes of acquired BS, unexplained hypokalemia in a patient with COVID infection should prompt suspicion for BS-like phenotype. Early and aggressive correction of electrolyte abnormalities is crucial.

PO1121

Late-Onset Bartter Syndrome

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Introduction: Bartter syndrome (BS) is an autosomal recessive disorder that results from mutations in sodium chloride reabsorption in the thick ascending loop of Henle. The age of onset is usually late childhood or early adulthood and it is rare to have the disease onset in adulthood. We are presenting a rare case of late-onset Bartter syndrome.

Case Description: A 55-year-old female with PMH of supraventricular tachycardia was admitted to the hospital with chest pain and palpitations. She had a history of multiple hospital admissions in the past with hypotension and electrolyte abnormalities. She denied any history of diarrhea or recent use of diuretics or laxatives. Initial Blood pressure was 100/60 mmHg and HR was 100 bpm. **The lab results are summarized in Table A**. CT scan of the pelvis showed bilateral nephrocalcinosis. She received IV fluid resuscitation, magnesium and potassium supplementation and spironolactone with subsequent improvement of her symptoms.

Discussion: BS is classified into five types based on the genetic characters of the disease. Type 3 is associated with classic BS. The chromosomal mutations are associated with a variable degree of disease severity. The mutation types have been identified as large deletions, missense and nonsense mutations. This patient likely has type 3 BS but her mutation type could be a missense mutation so that only one or few amino acids are altered leading to late-onset of her syndrome. The standard treatment is electrolyte repletion. Specific treatment therapy continues to be an ongoing source of research. ACE inhibitors and spironolactone can play a role in blocking the RAAS system. NSAIDs can be used to suppress the high level of PGE2 associated with the disease.

Urine study		Blood Work	
POTASSIUM	30 meq	SODIUM	135 med
CACLIUM	15 mg/dl	POTASSIUM	2.9 meq
Calcium creatinine ratio	0.2	PHOSPHORUS	1 meq
TTKG	14	MAGNSIUM	1.4 meq
Urine cortisone	27 ug/l	CACLIUM	8.2 mg/dl
Urine cortisol	1.8 ug/l	CL	84 mmol/ l
Cortisone cortisol ratio	50	HCO3	40 mmol/ l
		Renin	7 ng/ml/hr
		Aldosterone	8 ng/dl
		Aldosterone renin ratio	50

Table A: Lab results

PO1122

Colonic Pseudo-Obstruction and Hypokalemia

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Introduction: Ogilvie's syndrome, or colonic pseudo-obstruction, is the pathologic dilation of the colon without underlying mechanical obstruction. It is caused by increased sympathetic activity or reduced parasympathetic activity. The common manifestation is constipation, but sometimes it may be associated with diarrhea when potassium secretion is greatly increased by stretch-activated maxi-K channel, also known as BK channel, resulting from dilatation of the colon. While exact mechanism is unclear, diagnosis is based on clinical and radiologic grounds.

Case Description: A 69 year old African American female with history of diabetes mellitus, hypertension, hyperlipidemia, and HIV infection presented with worsening lower back pain. Initial labs showed leukocytosis, anemia, mild renal impairment, and paraprotein gap. MRI of the spine showed extensive compression deformities and epidural extension, with lytic lesions on skeletal survey. Bone biopsy showed >80% blast cells with marked increase in circulating plasma cells, confirming plasma cell leukemia. Abdominal CT showed dilated ascending colon suggestive of obstruction, but she was having normal bowel movements. She successfully underwent induction therapy and was discharged. When she was readmitted for second cycle of chemotherapy, serum potassium of 1.8 mmol/L with U wave on ECG noted. She also complained of abdominal distension, diarrhea, and bilateral lower extremity edema. Despite aggressive potassium supplementation, her potassium level persistently remained below 3.5 mmol/L. Initial urine potassium was 23 mmol/L, which peaked at 45.8 mmol/L before becoming anuric. First stool potassium was >100 mmol/L with stool volume of 900 mL. Repeat stool study after a week showed stool potassium 95.9 mmol/L with stool sodium 42 mmol/L. Abdominal x-ray on admission showed colon distension measuring up to 11.4 cm at the cecum. Serial imaging of the bowel showed worsening diffused colonic dilation. Remarkably, our patient required large doses of potassium supplement while she remained anuric.

Discussion: Colonic pseudo-obstruction may result, in some patients, in dramatic upregulation of the maxi-K channel. When potassium secretion is greatly increased, diarrhea rather than constipation becomes predominant manifestation. Diarrhea is the result of high potassium content of the stool, unlike most other secretory diarrhea which contains sodium as the main cation.

PO1123

Prevalence and Recurrence of Hyperkalemia (HK) in Medicare Patients Admitted to Long-Term Care or Post-Acute Care (LTC/PAC) Settings

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Background: HK is a common electrolyte imbalance among elderly populations with comorbidities such as chronic kidney disease (CKD) and congestive heart failure (CHF). This study describes the prevalence and recurrence of HK in patients in the LTC/PAC setting.

Methods: This retrospective study used 100% Medicare Fee-For-Service data for patients age ≥65 with ≥1 LTC/PAC stay from 01/01/2017 to 11/30/2019; index date was admission date of first LTC/PAC stay. HK-related stay was defined as ≥1 HK diagnosis (ICD-10: E87.5) or evidence of potassium binder use during LTC/PAC stay or within 14 days pre-index. Baseline characteristics and prevalence of HK during 1 year of follow up among HK index stays were compared to non-HK index stays. HK index stays were stratified into 3 cohorts: CHF, CKD or end-stage renal disease (ESRD), and CHF+CKD/ESRD.

Results: Of 4,562,231 patients with ≥1 LTC/PAC stay, prevalence of HK during pre-index, index, or follow up periods was 14.7%. The final sample (4,081,103) excluded patients with an HK event only during follow up. Of the final cohort, 290,567 (7.1%) of index stays were HK-related. All-cause (HK-related) index stays consisted of 54.0% (46.8%) home health agencies, 27.8% (41.4%) skilled nursing facilities, 6.7% (8.8%) inpatient rehabilitation facilities, and 0.9% (3.1%) long term acute hospital settings. HK vs non-HK patients were more often male (43.0% vs 35.4%), Black (13.5% vs 8.0%), and dual eligible for Medicaid (34.2% vs 25%), with higher mean Charlson Comorbidity Index scores (6.19 vs 3.93) (all p<0.0001). Mean annual HK events during follow up were highest in patients with CHF+CKD/ESRD (all patients=1.47; HK=6.98), followed by CKD (0.66; 5.53), and CHF (0.18; 3.00), with similar patterns across settings. In the HK cohort, 34.5% had HK recurrence during follow up; 2.7% filled a potassium binder prescription during index LTC/PAC stay, and 4.3% did so within 1 year.

Conclusions: HK patients were more often non-White and low income, indicating possible disparities in care. Prevalence and recurrence of HK was high among patients with LTC/PAC stays, but few patients filled a potassium binder prescription, suggesting potential gaps in treatment during or after an LTC/PAC stay.

Funding: Commercial Support - AstraZeneca

PO1124

Impact of Hyperkalemia and the Disruption of Emergency and Surgical Care

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Background: Due to the increasing prevalence of kidney disease, hyperkalemia (HK) may be diagnosed with greater frequency in Surgical and Emergency Departments (ED). Despite this, specific guidelines do not exist and patients with elevated potassium (K+) are typically managed on a case by case basis.

Methods: An anonymous structured survey was emailed to (n=11,287) clinicians in the Advocate Aurora Health system regarding HK knowledge and treatment paradigms (n=237 responded). Survey was conducted from Feb to March 2021.

Results: Nearly half (47%) of respondents treat > 10 HK patients annually, with most primary diagnosis of HK occurring in the ED (34%) and surgical (33%) setting. HK was considered a significant concern by 47% of respondents at a serum K+ level of 5.6-5.9 mEq/L and by 39% at K+ >6 mEq/L. Only 50% of respondents recognized RAASi medications as a potential risk factor for HK. IV fluids and kayexalate were the two most common treatments for HK. Limitations to pharmacological management included the need to monitor potassium, patient compliance, and time of onset. In the surgery survey, 66% felt that K+ more than 5.5. mEq/L on day of surgery will lead to cancelations and 52% believed pharmacologic agents having a shorter onset of action may reduce surgery cancellations and delays. Vascular (34%) and general (30%) surgeries were reported to be most impacted by HK. 82% stated urgent dialysis is difficult to arrange and admission is inevitable for dialysis.

Conclusions: The presences of HK creates challenges to ED or surgical clinical teams to manage and avoid cancellations. Standard treatment options for lowering serum K+ are limited due to time of onset and compliance considerations. Dialysis is difficult to arrange on short notice and almost always requires patient admission. In cases of emergent HK, newer K+ binding agents having a more rapid onset of action to lower serum K+, may reduce avoidable admission, surgical cancellation, and delay of surgery. More evidence-based care is needed in surgical settings to characterize patients at high risk for HK to prevent unnecessary surgical cancellation and limit health care costs.

Funding: Commercial Support - AstraZeneca

PO1125

Transient Hyperkalemia Following Treatment of Chronic Hypokalemia: A Case Report and Review of Distal Tubule Physiology

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Introduction: Hypokalemia is a frequently encountered electrolyte disorder usually resulting from decreased dietary intake, gastrointestinal, and/or renal wasting. In distal tubule cells, with no lysine (WNK) kinases bind with Ste20-related proline-alanine-rich kinase (SPAK) and oxidative stress-responsive kinase-1 (OSR1) to form WNK bodies. WNK bodies are thought to increase the activity of the sodium-chloride cotransporter (NCC) leading to decreased sodium delivery to the epithelial sodium channel (ENaC) found in principal cells. This process is critical in hypokalemic states as it results in decreased urinary potassium wasting through the renal outer medullary potassium channel (ROMK). Here we report a case of a young man with alcohol use disorder and chronic hypokalemia who was hospitalized for muscle weakness, abdominal pain, and intractable emesis. During treatment of his hypokalemia, he unexpectedly developed transient hyperkalemia.

Case Description: The clinical intrigue of this case was the unexpected finding of acute transient hyperkalemia during treatment for hypokalemia. His potassium was 2.5 mEq/L on the day of admission. Four days later, with a creatinine at baseline (0.9 mg/dL), potassium abruptly increased to 6.7 mEq/L. Repeat measurement one hour later was 6.4 mEq/L. Over the course of his hospitalization prior to the critical hyperkalemia lab result, he had received approximately 340 mEq of potassium supplementation. 24 hour urine potassium was 35 mEq/L. Aldosterone was 5.8 ng/dL and renin was 0.3 ng/mL/hr (ratio 19). Potassium levels returned to normal following administration of furosemide and sodium polystyrene sulfonate.

Discussion: We propose that the adaptive mechanisms of the distal tubule during hypokalemia require time to revert back to a nonactive state. Transient hyperkalemia may be observed during these "refractory" periods. The time required for disassembly of WNK bodies following resolution of hypokalemia is unknown. Our postulation could explain a

similar observation of transient hyperkalemia seen in a case published in 1953 of a young woman treated for chronic hypokalemia (Schwartz, 1953). Critical hyperkalemia is an important consideration when treating patients with chronic hypokalemia.

PO1126

Pseudohyperkalemia with Concurrent Hyperkalemia

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Introduction: In sickle cell patients, acute hemolytic crisis and sickle cell nephropathy are relatively common. Risk of hyperkalemia increases with hemolysis and tubular dysfunction. Sepsis can also worsen the complication of hemolytic crisis with significant thrombocytopenia, a well-known cause of pseudohyperkalema. We report a case of concurrent true hyperkalemia and pseudohyperkalemia in the setting of thrombocytosis due to acute sickle cell crisis.

Case Description: A 36 year old African American male with history of sickle cell disease, asthma and DVT presented with bilateral shoulder, knee, and back pain. In ED, he was hypotensive, and tachycardic. Labs were notable for leukocytosis, anemia, reticulocytosis, renal failure, and elevated lactate dehydrogenase. Chest x-ray showed left base atelectasis. He was admitted for acute sickle cell crisis and fluctuant right thigh abscess, which was surgically drained and managed with antibiotics. Platelet level was 585 K/uL; serum potassium was 4.7 mmol/L; and creatinine was 1.78 mg/dL with normal urine output. Potassium level steadily rose and peaked at 6.5 mmol/L with sinus bradycardia but no other ECG changes. At the same time, platelet level peaked to 1105 K/uL.

Discussion: In our patient with significant thrombocytosis, pseudohyperkalemia was suspected. Degranulation of platelets during clotting releases about 50% of potassium inside platelets. For platelet count of 1000 K/uL with normal MPV, serum potassium level is expected to be higher than plasma potassium level by about 0.7 mmol/L. Serum-plasma potassium differences in our patient were within the expected range. In our patient, as shown below, mild concurrent true hyperkalemia is also noted likely due to sickle cell nephropathy, a known cause of hyperkalemia due to hyporeninemic hypoaldosteronism. Due to potassium release from platelets during clotting, serum potassium is always higher than plasma potassium in all normal persons by 0.2 to 0.3 mmol/L. With thrombocytosis, the difference becomes larger, and serum potassium is likely to reach hyperkalemic level if the baseline potassium is already higher than usual due to concomitant impairment of renal potassium excretion.

Platelet (K/uL)	Plasma Potassium (mmol/L)	Serum Potassium (mmol/L)
1105	5.3	6.1
942	4.9	5.8
464	4.3	4.9

PO1127

Missing the Obvious? A Story of Salt, Water, and Unexplained Hyperkalemia

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Introduction: Most clinicians are familiar with the differential diagnosis of hyperkalemia, from pseudohyperkalemia to rare tubulopathies. Herein, we describe three patients with years-long histories of unexplained hyperkalemia despite extensive investigations (details in Table 1). While all achieved normokalemia with various prescription regimens, the underlying etiology remained elusive. We suggest that all cases were likely due to chronic, mild hypovolemia in the context of self-imposed dietary salt restriction.

Case Description: Patient A: A 6-week-old girl with persistent hyperkalemia and very low urine Na^+. Normokalemia was achieved with hydrochlorothiazide and dietary K^+ restriction but maintained with optimized fluid and Na^+ intake alone. **Patient B**: An 11-year-old boy with spastic cerebral palsy with persistent hyperkalemia after a mild AKI attributed to rhabdomyolysis. Serum K^+ improved with sodium polystyrene (SPS) and dietary K^+ restriction; it normalized after IV saline infusion, while NPO. **Patient C**: A 5-month-old boy with Stüve-Wiedemann Syndrome and feeding difficulties with persistent hyperkalemia that normalized on SPS. After G-tube insertion at 2 years, K^+ remained normal despite stopping the SPS due to improved fluid and Na^+ intake.

Discussion: It has long been established that adequate Na^+ and fluid delivery to distal nephrons is necessary for optimal K^+ handling. It is therefore surprising to find almost no mention of Na^+-responsive hyperkalemia in the literature for children beyond the neonatal period. Our patients all had hyperkalemia in the context of normonatremia, but very low fractional excretion of Na^+ (FeNa) and low trans-tubular K^+ gradient (TTKG). They all remained normokalemic when salt and water intake was optimized, despite stopping their hyperkalemic prescriptions. Careful, early consideration of low distal Na^+ and water delivery as a cause for unexplained hyperkalemia could prevent extensive workups and unnecessary prescriptions.

Relevant investigations

Patients	Time points	Serum values (mmol/L)				Serum creat (μmol/L)	Urine values (mmol/L)			TTKG	FeNa (%)
		K^+	Na^+	Osm	Total CO_2		K^+	Na^+	Osm		
A	6 wk	7.0 ↑ (a)	140	298	21	35	28	<20	178	6.7	N/A
	10 y	5.1 ↑ (b)	143	305 ↑ (d)	23	46	76	192	1088	4.2	0.4
B	Pre-tube	5.5 ↑ (b)	144 ↑ (c)	301 ↑ (d)	29	42	42	54	876	2.6	0.07
	Post-tube	3.6 ↓ (b)	151 ↑ (c)	308 ↑ (d)	N/A	34	38	330	975	3.3	0.6
C	5 mo	5.9 ↑ (a)	137	284	22	13	14	<20	125	5.4	N/A
	2 y	4.7	136	280	26	23	134	189	877	9.1	0.7

Normal ranges: a: 3.5-5.6 mmol/L (mEq/L), b: 3.7-5.0 mmol/L (mEq/L), c: 135-143 mmol/L (mEq/L), d: 282-300 mmol/L (mOsm/kg H2O)

PO1128

Machine Learning Models to Predict Cardiovascular and Renal Outcomes and Mortality in Hyperkalemic Patients

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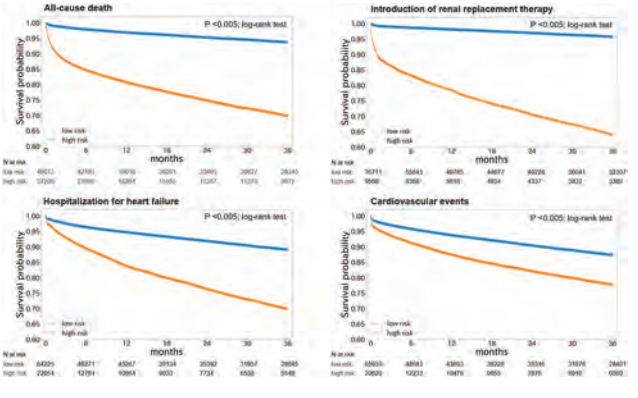
Background: Hyperkalemia is associated with increased risks of mortality and adverse clinical outcomes. To date, limited evidence is available for personalized risk evaluation in this heterogeneous and multifactorial pathophysiological conditions.

Methods: We developed prediction models using extreme gradient boosting (XGB), logistic regression (LR), and neural network. Models were derived and cross-validated in a retrospective cohort of hyperkalemic patients with either heart failure or stage ≥3a chronic kidney disease and aged ≥18 years from a Japanese administrative hospital database (April 1, 2008–September 30, 2018). The outcomes of interest included all-cause death, introduction of renal replacement therapy (RRT), hospitalization for heart failure (HHF), and cardiovascular events within 3 years after first hyperkalemic episode. The best performing model was further validated using a separate hospital-based database.

Results: 24,949 adult patients with hyperkalemia were selected for the model derivation and internal validation. The mean age was 75 years and 54% were male. Among machine learning algorithms tested, XGB outperformed other models, showing AUROC of XGB vs. LR for all-cause death, RRT, HHF, and cardiovascular events as 0.823 vs. 0.809, 0.957 vs. 0.947, 0.863 vs. 0.838, and 0.809 vs. 0.798, respectively. In the external validation set including 86,279 patients, AUROC of XGB for all-cause death, RRT, HHF, and cardiovascular events were 0.747, 0.888, 0.673, and 0.585, respectively. The Kaplan-Meier curves of high-risk predicted group showed a significant differentiation from that of low-risk predicted group for all outcomes (Figure).

Conclusions: These findings suggest the possible use of machine learning models for real-world risk assessment as a guide for treatment decision making that may lead to the improvement of cardiovascular and renal outcomes, and mortality in hyperkalemic patients.

Funding: Commercial Support - AstraZeneca K.K.



PO1129

Severe Hyperkalemia Secondary to Hypermagnesemia in a Patient with Preeclampsia

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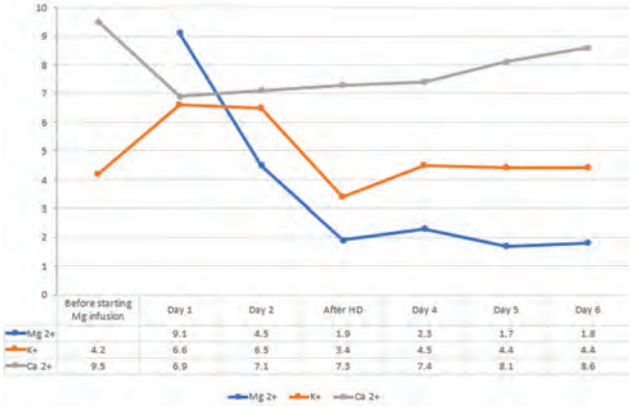
Introduction: Mg infusion remains the first-line treatment of preventing and controlling eclamptic seizures. While hypocalcemia is a well-known side effect, hyperkalemia is not. We present a case of severe hyperkalemia secondary to magnesium infusion requiring hemodialysis.

Case Description: 36-year-old healthy female with no HTN or liver disease, pregnant at 25 weeks with twins, admitted for close monitoring given concern for intra-uterine growth restriction. Initial vitals on admission: BP 149/88 mm Hg, HR 89,

RR 20, and T 36.4. Physical exam: Grossly unremarkable except for gravid uterus. Lab workup showed elevated liver function tests (>2x UNL) and LDH, low haptoglobin, and normal renal function. BP remained >140s with medical treatment. Patient also started complaining of new-onset severe headache. Given concern for pre-eclampsia with severe features, Mg infusion was started (6 grams followed by 2 g/hr as a continuous infusion) and was scheduled for emergent c-section. Post-delivery course was complicated by severe hyperkalemia at 6.6 meq/l in a setting of supratherapeutic Mg levels at 9.1 mg/dl (figure 1). Creatinine was normal at 0.7. Mg infusion was stopped. Other etiologies for hyperkalemia were ruled out including rhabdomyolysis or worsening hemolysis. Patient required one session of emergent hemodialysis which led to improvement in all electrolyte abnormalities.

Discussion: While the relationship between hypomagnesemia and hypokalemia is well understood, the relationship between hyperkalemia in the presence of hypermagnesemia remains not clear. Some of the mechanisms suggested (1) direct effect of magnesium on suppressing renin and aldosterone leading to impaired renal handling of K homeostasis (hyporeninemic hypoaldosteronism). (2) direct inhibition of the ROMK channel by Mg. Our case highlights a rare cause of hyperkalemia in a pre-eclampsia patient. Monitoring electrolytes closely while on Mg infusion is advised.



	Before starting Mg infusion	Day 1	Day 2	After HD	Day 4	Day 5	Day 6
Mg 2+		9.1	4.5	1.9	2.3	1.7	1.8
K+	4.2	6.6	6.5	3.4	4.5	4.4	4.4
Ca 2+	9.5	6.9	7.1	7.3	7.4	8.1	8.6

Changes in potassium and calcium concentrations in relation to hypermagnesemia (figure 1)

PO1130

Severe Hypermagnesemia: A Potential Cause of Acute Hyperkalemia

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Introduction: Hypermagnesemia is not a well-established cause of hyperkalemia. In this case report we explore the association of acute hypermagnesemia and hyperkalemia.

Case Description: 30 year old female G1P0 with chronic HTN since age 26, CACUT was admitted for preeclampsia with severe features (new proteinuria 5.5 g/24h, AKI (cr peaked at 1.33 from baseline 0.65), HTN, LE edema). Patient delivered via C-section at 27 weeks 6 days. Extensive AKI work-up was negative. At admission had normal K 4.4, Na 143, Ca 8.6 (albumin 3.4), bicarb 21, cr 0.96, LDH 213, glucose 111, Hb 10, Plt 177, renin 1.39, aldosterone 13.6. At admission, she was started on Mg sulfate infusion for seizure prophylaxis. After patient's serum Mg acutely increased (peak 8), she simultaneously developed acute hyperkalemia (peak K 6.1, bicarb 19, cr 1.1, normal EKG). Hyperkalemia improved to 5.3 with IV Lasix, bicarbonate, and NS but persisted until Mg infusion was discontinued and Mg levels normalized to 2.5 leading to normalization of K (4.3). Only two previous case studies have described a potential association between hypermagnesemia and hyperkalemia. We described a case when acute hypermagnesemia led to acute hyperkalemia, which persisted until Mg levels normalized. There were no other etiologies of hyperkalemia in this case (AKI was not severe to lead to hyperkalemia; patient was on beta-blocker but this was a chronic medication; no other medications known to cause hyperkalemia; normal aldosterone, no significant change in bicarb).

Discussion: Magnesium plays an important role in potassium homeostasis in kidney and intestines. One possible mechanism is that cytoplasmic magnesium concentration has a profound effect on ROMK potassium channels (expressed in the thick ascending and cortical collecting tubules); a high intracellular Mg concentration blocks channel activity. Additionally, ROMK is an important pathway for potassium secretion in the distal nephron. Therefore, potassium levels should be closely monitored in patients who receive high dose magnesium infusions and are at high risk of hypermagnesemia and subsequent hyperkalemia.

PO1131

When Sipping K Is Not OK

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Introduction: Hyperkalemia is one of the most common and potentially lethal electrolyte abnormalities that occurs in approximately 1% to 10% of hospitalized patients. It is associated with an increased risk of arrhythmias, poor cardiovascular outcomes, and increased morbidity and mortality. We highlight an unusual etiology of severe hyperkalemia in a patient with underlying CKD.

Case Description: A 74-year-old Black male with known arterial hypertension, coronary artery disease, CKD 3 [baseline serum creatinine (Cr) 1.7 mg/dl] presented with syncope secondary to severe bradycardia (heart rate 30/min) consequent to severe hyperkalemia, which necessitated a pacemaker placement, and non-oliguric AKI on CKD. Pertinent serum labs on presentation include Cr 2.8 mg/dl, potassium (K) 7.6 mmol/L, and bicarbonate 19 mmol/L. Serum osmolarity, glucose, and creatinine kinase levels were within normal limits. Urine pH was 5. Renal imaging was unremarkable. He was not on any medication(s) commonly attributed with a propensity to elevate serum K, including renin angiotensin inhibitors, non-selective β blockers, or non-steroidal anti-inflammatory agents. Given that the hyperkalemia was out of proportion to his kidney injury, upon further questioning he attributed consuming a diet rich in K along with drinking multiple cups of Essiac tea daily for the last 2 months. Hyperkalemia was managed medically, including initial temporizing measures, bicarbonate supplementation, K binders, and intravenous crystalloids to enhance distal nephron K excretion. Emphasis was placed on consuming a K restricted diet along with discontinuing Essiac tea use. Serum K normalized in 3 days; however Cr was 3 mg/dl on discharge.

Discussion: Essiac tea contains red clover, sheep sorrel, burdock root, and rhubarb which has extremely high potassium content. It is hepatotoxic and nephrotoxic when consumed in large amounts. We highlight the importance of obtaining a thorough dietary history, especially when the degree of hyperkalemia cannot be solely attributed to the extent of kidney injury. Dietary counselling is paramount in such cases.

PO1132

Metabolic Acidosis That Exists with Hyperkalemia (HK) Among Patients That Initialize Binder Therapy: The MAXIMIZE Study

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Background: Approximately 25% of chronic kidney disease (CKD) patients with serum potassium (sK^+)>5.0 mEq/L may also have metabolic acidosis (MA). However, successful management of comorbid HK and MA in CKD patients is unclear. This real-world evidence study examines the association between patient characteristics and binder treatment among CKD patients with HK and MA.

Methods: This was a retrospective study of stage 3-5 CKD patients with HK (sK^+>5.0 mmol/L) and MA (serum bicarbonate ($sHCO3^-$) between 16-20 mmol/L) in a US EMR network of 64 million patients. The index event was the first qualifying sK^+ result between 07/01/19 and 12/31/20. Baseline demographic and clinical characteristics were assessed among SZC, SPS, and NKB treated cohorts including age, sex, race, HK severity, $sHCO3^-$ level, visit type, and comorbidities. Logistic regression produced adjusted odds ratios (ORs) and 95% confidence intervals describing the association between baseline characteristics and treatment: sodium zirconium cyclosilicate (SZC) vs sodium polystyrene sulfonate (SPS) and SZC vs no potassium binder (NKB).

Results: Of the 32,113 patients who met study criteria 11.6% were treated with SZC (n=939) or SPS (n=2,774), 88.4% with NKB (n=28,400), and 11.1% with sodium $HCO3^-$ (n=3,572). Age and sex were similar among SZC, SPS, and NKB cohorts and 81%, 77%, and 70% had moderate-to-severe acidosis ($sHCO3^-$ <20mmol/L), respectively. Baseline characteristics associated with increased odds of SZC vs SPS and SZC vs NKB treatment included $sHCO3^-$<20mmol/L [OR=1.29 (1.03-1.61); OR=1.24(1.04-1.47)] and liver disease [OR=1.61(1.16-2.23); OR=1.47(1.14-1.89)], respectively. Treatment with SZC vs NKB treatment was more likely in inpatient settings [OR=3.73(3.06-4.55)] and in patients with comorbid congestive heart failure [OR=1.43 (1.12-1.84)].

Conclusions: Clinicians were more likely to treat HK with SZC than SPS or NKB in CKD patients with moderate-to-severe acidosis in a recent large, US, real-world sample. Secondary findings from prior clinical trials suggest that SZC may improve MA as well normalize sK^+. Future clinical trials are needed to assess the impact of SZC on $sHCO3^-$ concentrations.

Funding: Commercial Support - Research funded by AstraZeneca

PO1133

Real-World RAAS Inhibitor Use and Its Predictors Among Patients Initiating Sodium Zirconium Cyclosilicate

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Background: Renin-angiotensin-aldosterone system inhibitors (RAASi) are associated with reduced risk of death and slower disease progression in patients with heart failure (HF) and chronic kidney disease (CKD). However, RAASi use increases the risk of hyperkalemia (HK), which may disrupt RAASi use and mitigate its benefits. There is limited real-world evidence characterizing RAASi use after sodium zirconium cyclosilicate (SZC) treatment.

Methods: Adult patients initiating SZC (index date) while on a RAASi in outpatient care were included from a large US claims database (January 2018-June 2020). Analyses were conducted among all patients, patients with CKD and patients with CKD + diabetes (DM). The percent of patients with a RAASi prescription after index was summarized. Characteristics among patients with and without a new RAASi fill were compared using descriptive statistics. A multivariable logistic regression model assessed predictors of a new RAASi fill.

Results: A total of 589 patients initiating SZC while on a RAASi were included (mean age 61 years, 65.2% male). Overall, 82.7% of patients had a new RAASi fill after index. The median time to discontinuation was not reached among patients with a new RAASi fill, of whom 88.1% at day 180 and 74.0% at 1 year remained on RAASi therapy. Median time on RAASi was 29 days (95% CI [27-43 days]) for those with no new RAASi fill. Compared to patients without a new RAASi fill, patients with a new fill had a higher burden of CKD (69.4% vs 58.8%) but a similar prevalence of DM (70.6% vs 67.6%) and HF (24.6% vs 28.4%). Results were similar in the CKD cohort (N=398; 84.9% had a new RAASi fill) and CKD and DM cohort (N=311; 85.2% had a new fill). Predictors of having a new RAASi fill included fewer prior hospitalizations (0.77 [0.60-0.98]; p<0.05) and emergency department (ED) visits (0.78 [0.63-0.97]; p<0.05).

Conclusions: In a real-world setting, 83% of patients had a new RAASi fill within 90 days after ending their index RAASi. Results are consistent with clinical trial finding and similar among patients with CKD and patients with CKD + DM. Patients with hospital and ED visits will require follow up care to encourage RAASi continuation.

Funding: Commercial Support - AstraZeneca

PO1134

Compatibility Study of Patiromer with Juices/Liquids and Soft Foods

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Background: Patiromer is a novel, once-daily, sodium-free K+-binder approved for treatment of hyperkalemia. The drug–a tasteless, odorless powder–is administered orally suspended in water. Recently, the FDA approved apple or cranberry juice as suspension vehicles. As patients may prefer to take patiromer with alternative liquids/foods, the ability to mix patiromer with small amounts (per allowed dietary intake recommendations) of various liquids and foods may improve palatability and medication adherence. This *in vitro* study assessed the compatibility of patiromer with six different juices/nectars and six soft foods or other liquids (**Table**).

Methods: For all mixtures, compatibility was assessed at two ratio levels: low (8.4 g patiromer in 40 mL of vehicle, ~1/6 cup); high (12.7 g patiromer in 20 mL of vehicle, ~1/12 cup), equivalent to patiromer doses of 8.4 g and 25.2 g per 80 mL (1/3 cup), respectively. Mixtures with soft foods were spoon stirred for 30 s; juices were stirred for 5 min on a magnetic stirrer. After a 45-min rest period, suspensions were diluted with 50 mL (juices) or 100 mL of water (soft foods) and centrifuged at 1000 rpm for 30 s. Residues were washed, vacuum filtered, and dried. Total potassium binding capacity (TKEC) was tested (acceptance criterion: 8.4–10 mmol/g).

Results: Mean TKEC for patiromer mixed with juices/nectars were 8.7–8.9 mmol/g for the low ratio and 8.5–8.6 mmol/g for the high ratio (**Table**). For soft foods or other liquids, the mean TKEC at low and high ratios was 8.5–8.7 mmol/g (reference: 9.2 mmol/g); exchange capacity for tested vehicles was within the prespecified range.

Conclusions: Mixing of patiromer with small amounts of juices/nectars, soft foods, and other liquids does not adversely affect the drug's potassium-binding capacity. Use of different vehicles for mixing patiromer may improve palatability and reduce the risk of nonadherence.

Funding: Commercial Support - Vifor Pharma

Mean total potassium binding capacity (TKEC) after mixing of patiromer with juices and soft foods. RSD, relative standard deviation

Juice/nectar vehicle	Low ratio	TKEC, RSD [%]	mmol/g High ratio	RSD [%]	Soft food vehicle	Low ratio	TKEC, RSD [%]	mmol/g High ratio	RSD [%]
Pineapple juice	8.9	1.5	8.5	0.8	Yoghurt	8.7	0.4	8.6	0.4
Orange juice	8.8	2.0	8.5	0.7	Milk	8.6	0.9	8.5	1.2
Grape juice	8.8	2.0	8.6	0.8	Apple sauce	8.6	0.9	8.7	1.6
Apricot nectar	8.8	0.4	8.6	0.5	Thickener	8.6	0.4	8.6	0.6
Peach nectar	8.7	0.7	8.5	0.5	Vanilla pudding	8.5	1.2	8.6	0.6
Pear juice	8.7	1.6	8.5	0.4	Chocolate pudding	8.5	0.8	8.6	0.7

PO1135

Risk of Heart Failure in Patients Who Initiated Sodium Zirconium Cyclosilicate vs. Patiromer

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Background: Hyperkalemia is common in patients with chronic kidney disease (CKD), heart failure, and diabetes. Sodium zirconium cyclosilicate (SZC) and patiromer were recently approved for the treatment of hyperkalemia. Since SZC contains significant amounts of sodium, we assessed the risk of heart failure hospitalization (HHF) associated with the initiation of SZC versus patiromer in non-dialysis patients.

Methods: We used a U.S. commercial insurance claims database (Optum Clinformatics® Data Mart) between May 2018 (after SZC approval) and September 2020. Participants were non-dialysis adults who had ≥ 180 days of insurance enrollment and were newly prescribed SZC or patiromer. The primary outcome was a hospitalization with a discharge diagnosis of heart failure. The secondary outcome was a hospitalization or an emergency room visit with a diagnosis of any edema. Propensity score (PS) matching in a variable ratio up to 1:3 was used to adjust for more than 80 variables, including demographic characteristics, comorbidities, medication use, and health care utilization. Cox proportional hazards regression models were used to generate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Our cohort included 1,126 SZC initiators and 2,839 PS-matched patiromer initiators (total N=3,965). The mean age was 72 (±10) years, 30% had a history of heart failure and 85% had CKD stages 3-5. The risk of HHF was higher in the SZC initiators compared to patiromer initiators (HR 1.22, 95%CI 0.95-1.56), but the confidence interval included the null value (**Table**). Edema was more common in the SZC initiators (HR 1.89, 95%CI 1.05-3.39). In subgroup analyses, initiation of SZC was associated with an increased risk of HHF (HR 1.58, 95%CI 1.01-2.46) amongst patients without a history of heart failure.

Conclusions: Patients initiating SZC may need to monitor volume status and consider dietary salt restrictions and initiation or adjustment of diuretics. Larger studies are needed to more precisely evaluate the safety of SZC in routine practice.

Number of events, incidence rate (IR)*, rate difference (RD)*, and HRs before and after PS-matching

Outcome	Before PS-matching				After PS-matching			
	SZC N=1,265	Patiromer N=3,388	RD (95% CI)	HR (95% CI)	SZC N=1,126	Patiromer N=2,839	RD (95% CI)	HR (95% CI)
HHF, N (IR)	97 (35.0)	309 (26.5)	8.6 (1.0, 16.1)	1.32 (1.05, 1.66)	88 (35.8)	245 (25.1)	10.7 (2.6, 18.9)	1.22 (0.95, 1.56)
Edema, N (IR)	21 (7.3)	43 (3.5)	3.8 (5.0, 7.1)	2.08 (1.24, 3.51)	18 (7.1)	35 (3.4)	3.6 (1.7, 7.1)	1.89 (1.05, 3.39)

*In 100 person-years

PO1136

RDX013, a Novel, Oral, Small Molecule Being Developed for Treatment of Hyperkalemia, Increases Colonic Secretion and Fecal Excretion of Potassium

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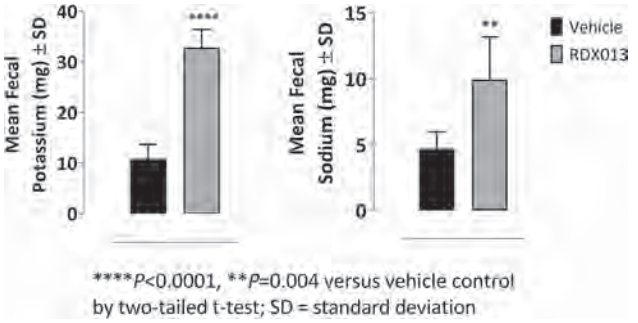
Background: Potassium (K^+) homeostasis is maintained by the balance of dietary K^+ intake, extra- and intracellular K^+ distribution, and renal and intestinal excretion. Hyperkalemia (serum K^+>5.0 mM) occurs frequently in CKD patients and can lead to cardiac arrhythmias and sudden death; controlling serum K^+ may reduce mortality in this population. Current therapeutic options for the chronic treatment of hyperkalemia are limited to K^+-binding agents. Here, we describe the discovery of RDX013, a novel, oral, small molecule K^+ secretagogue in development for treatment of hyperkalemia.

Methods: Male Sprague Dawley rats (n=6/group) were orally administered vehicle or 6 mg/kg RDX013 twice daily for 6 days. 24-hour fecal samples collected from rats housed individually in metabolic cages on the final study day were homogenized, and K^+ and sodium were analyzed by cation exchange chromatography.

Results: RDX013 significantly increased fecal K^+ excretion compared to vehicle control animals (figure). Fecal sodium was also increased by RDX013 (figure), which was expected as luminal sodium retention in the intestine is key to the pharmacodynamic response.

Conclusions: Based on its unique mechanism of action which involves pharmacologically enhancing K^+ secretion through apical K^+ channels in the colon, RDX013 is a potential first-in-class therapy which may provide a new approach to managing serum K^+ in patients versus commonly prescribed K^+ binders. A phase 2 clinical study with RDX013 (NCT04780841) is ongoing in non-dialysis CKD patients with hyperkalemia.

Funding: Commercial Support - Ardelyx, Inc.



PO1137

Artificial Intelligence-Assisted Electrocardiography for Early Diagnosis of Thyrotoxic Periodic Paralysis

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Background: Thyrotoxic periodic paralysis (TPP) characterized by acute weakness, hypokalemia and hyperthyroidism is a medical emergency with a great challenge in early diagnosis since most TPP patients do not have overt symptoms. Since both hypokalemia and hyperthyroidism in TPP significantly affect the cardiovascular system, electrocardiography (ECG) as a prompt and non-invasive bedside tool universally used in the ED may detect these electrical changes. To assess artificial intelligence (AI)-assisted electrocardiography (ECG) combined with routine laboratory data in the early diagnosis of TPP.

Methods: A deep learning model (DLM) based on ECG12Net, an 82-layer convolutional neural network, was constructed to detect hypokalemia and hyperthyroidism. The development cohort consisted of 39 ECGs from patients with TPP and 502 ECGs of hypokalemic control; the validation cohort consisted of 11 ECGs of TPP and 36 ECGs of non-TPP with weakness. The AI-ECG based TPP diagnostic process was then consecutively evaluated in 22 male patients with TTP-like features.

Results: In the validation cohort, the DLM-based ECG system detected all cases of hypokalemia in TPP patients with a mean absolute error of 0.26 mEq/L and diagnosed TPP with an area under curve (AUC) of ~80%, surpassing the best standard ECG parameter (AUC=0.7285 for the QR interval). Combining the AI predictions with the estimated glomerular filtration rate (eGFR) and serum chloride (Cl^-) boosted the diagnostic accuracy of the algorithm to AUC 0.986. In the prospective study, our AI ECG system achieved perfect performance (F-measure 100%) on the task of hypokalemia detection in them and the integrated AI with routine laboratory had a PPV of 100% and F-measure 87.5% for TPP diagnosis.

Conclusions: An AI-ECG system reliably identifies hypokalemia in patients with paralysis and its integration with routine blood chemistries provides valuable decision support for the early diagnosis of TPP to avoid life-treatening complication.

PO1138

Will the Real Sodium Stand Up!

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Introduction: Hyponatremia is a common finding as it could be precipitated by multiple factors ranging from medications to simply dehydration. Accurate approach to management depends on assessing serum osmolality in an effort to distinguish cases of true, factitious or pseudohyponatremia. We present a case of hyponatremia secondary to hyperlipidemia.

Case Description: 36 year old Asian woman with HTN, Type 2 DM, HLD presented with 1 day of epigastric pain. On exam S1, S2 were heard with vesicular breath sounds throughout, epigastric tenderness and no focal neurological deficits. Initial labs: sodium 114 potassium 3.5 chloride 85 glucose 254, BHB 3.7. Sodium corrected for glucose 116 CO2, BUN, Cr and AG were incalculable. Urinalysis: ph 6.0, ketones > 160, glucose > 1000, protein > 1000. Total cholesterol 1020, HDL 25, Triglycerides >5680, LDL incalculable, serum osmolality 314, lipase 57. Venous blood gas: 7.37/30.1/94.8/17.8, sodium on VBG 132. Abdominal ultrasound revealed a normal pancreas with hepatic steatosis. She was treated in ICU with normal saline, insulin infusion, icosapent ethyl and gemfibrozil. Abdominal pain resolved and insulin was changed to Glargine. Over three days triglycerides trended down to 1744 and sodium to 132. She was discharged on icosapent ethyl, gemfibrozil, atorvastatin, glargine, metformin and lisinopril, with a sodium of 132.

Discussion: Sodium is most commonly measured by indirect potentiometric (ISE) measurement. By this method serum specimens are diluted based on estimated typical balance of serum to solid blood components. By this method factitious low sodium results are known to occur in patients with significantly elevated lipids and protein. As in this case, direct sodium measured by VBG/ABG are most accurate. Typically markedly elevated serum triglyceride with concentrations> 1500 mg/dl are thought to be responsible for factitious hyponatremia. In our patient the value of serum sodium on admission was unexpectedly low at 114 and severe hypercholesterolemia may have contributed. Applying the following formula to correct for triglycerides = Measured Na+ (Plasma triglycerides (g/L) x 0.002); measured serum sodium would have been expected to be 125 meq. Thus in cases of extremely high lipids, one must consider lab techniques for measuring serum sodium, as well as full lipid panel in the evaluation and treatment of factitious hyponatremia.

PO1139

Admission Sodium and Related Features to Predict Falls in Machine Learning Models

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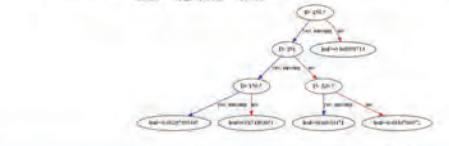
Background: Hyponatremia has been associated with an increased risk for falls, but evidence is primarily limited to outpatient events. Hyponatremia is a potential surrogate of conditions that may lead to falling including volume depletion, malignancy, pain, polypharmacy, and weakness. We hypothesized that a model could be developed to predict falls based upon accessible variables present on all hospital admissions. An accurate model could allow for measures to lower in-hospital falls.

Methods: Medical records from a single institution were collected over a period of 2011 to 2019. Subjects included admitted patients who suffered a recorded in-hospital fall and were admitted, and controls matched for admission on the same date. Variables collected include sodium, glucose, age and gender. There were 17,013 patients total of which 1,203 had unique falls. Data was split into an 60% training, 20% validation and 20% testing split. We computed an unadjusted odds ratio of falls for those with very low sodium (<126). We trained logistic regression, random forest, XGBoosted forest, and neural net classifiers. Classifier cutoff was calculated using Youden values.

Results: We did not see an increased incidence of falls in the population with a low sodium (N=377) with an unadjusted odds ratio of 0.62 (CI 0.38-1.01). Similarly, the model performances did not result in clinically useful predictions with a unanimously high false positive and false negative rates (**Figure 1**).

Conclusions: Despite reports of hyponatremia as an indicator of fall risk we did not observe this. The fall-prediction models did have the capacity for high performance on the training data, but this does not translate to validated performance. This discrepency is termed 'overfitting' and is important to evaluate as machine learning models have a much larger capacity than traditional statistical models to incorporate previously seen examples. If a model cannot make predictions on new data it cannot be clinically useful. These models may be enhanced using other basic admission features and is the subject of future work.

Figure 1: Decision Tree Example and Model Characteristics



Model	Accuracy	Positive Precision	Positive Recall	Positive F1	Negative Precision	Negative Recall	Negative F1
Logistic Regression	0.46	0.08	0.59	0.13	0.94	0.45	0.61
Random Forest	0.55	0.08	0.48	0.13	0.93	0.56	0.7
XGBoost Forest Small	0.65	0.09	0.42	0.14	0.94	0.67	0.78
XGBoost Forest Large	0.9	0.13	0.07	0.09	0.93	0.97	0.95
Neural Net Small	0.57	0.45	0.08	0.13	0.58	0.93	0.72
XGBoost Forest Train	0.95	0.59	1	0.74	1	0.95	0.97

Example of decision tree. Metrics on scale 0 to 1. All data predicted on held out data set except for final "XGBoost Forest Train" which is included to show How a model can fit to training data but not to unseen data.

PO1140

Association of Serum Sodium Levels with Bone Mineral Density, Fracture, and Mortality in Patients Undergoing Maintenance Hemodialysis

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Background: Hyponatremia is implicated in pathological bone resorption and has been identified as a risk factor for bone fracture in the general population, but limited data exist in patients undergoing dialysis.

Methods: We analyzed a historical cohort of 2,292 patients undergoing maintenance hemodialysis in Japan. We first examined the association of baseline serum sodium levels with metacarpal bone mineral density (BMD) in a subcohort of 456 patients with available data. Next, we examined the association of baseline serum sodium levels with incident fracture and mortality in the overall cohort, using Cox regression models adjusted for potential confounders (age, sex, dialysis vintage, diabetes, prior cardiovascular disease, history of fracture, body mass index, hemoglobin, albumin, and creatinine) and competing risks regression models accounting for death as a competing endpoint.

Results: Baseline mean ± SD serum sodium level in the overall cohort was 139.7 ± 2.9 mEq/L, and among patients with available data, median metacarpal BMD T-score was -2.05 (IQR, -3.35 to -0.99). Serum sodium levels were not associated with metacarpal BMD T-score in unadjusted or adjusted models. During a median follow-up of 5.4 years (IQR, 2.5-7.0 years), 712 patients died; 113 experienced clinical fractures; and 64 experienced asymptomatic vertebral fractures as estimated by height loss. In adjusted Cox regression models, serum sodium levels were associated with mortality (HR, 0.95 per 1 mEq/L higher; 95% CI, 0.92-0.98) but not incident clinical fracture (HR, 0.97 per 1 mEq/L higher; 95% CI, 0.90-1.04) or any fracture (a composite of clinical fracture and vertebral fracture). Similar results were obtained in competing risks regression models.

Conclusions: Serum sodium levels were associated with mortality but not BMD or incident fracture in maintenance hemodialysis patients.

PO1141

Hyponatremia, Inflammation, and Hospital Mortality in Hospitalized COVID-19 Patients

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Background: Systemic inflammation has been associated with severe COVID-19 disease. Hyponatremia can result from inflammation due to non-osmotic stimuli for vasopressin production. Hyponatremia is an independent risk factor for hospital mortality.

Methods: Hospitalized patients with COVID-19 were prospectively evaluated between March and November 2020 at Hospital Posadas in Buenos Aires, Argentina, in order to evaluate the association between hyponatremia and inflammation and its impact on clinical outcomes. Admission biochemistries, high-sensitivity C-reactive protein (hsCRP), ferretin, patient demographics, and outcome data were recorded. Outcomes (within 30 days after symptom) that were evaluated included admission tothe ICU during hospitalization, mechanical ventilation, dialysis-requiring AKI, and in-hospital deaths. In-hospital mortality, length of hospital stay (in days), and hospital readmission for any cause within 30 days after discharge were evaluated using comprehensive data from the EHR.

Results: Among 799 hospitalized COVID-19 patients, hyponatremia was present on admission in 366 (45.8%). Hyponatremic patients had higher hsCRP levels than normonatremic patients (median 10.3 [IR 4.8-18.4] mg/dl vs 6.6 [IR 1.6 – 14.0] mg/dl, respectively, p< 0.01), and hsCRP level was inversely correlated with plasma sodium level (Spearman's correlation coefficient = – 0.23; p = < 0.01). Hyponatremic patients had higher serum ferritin levels than normonatremic patients (median 649 [IQR 492-1168] ng/dl vs 393 [IQR 156-1440] ng/dl, respectively, p = 0.02), and serum ferritin level was inversely correlated with plasma sodium level (Spearman's correlation coefficient= – 0.26; p = < 0.01). Hyponatremic patients had increased mortality on unadjusted (odds ratio 1.87, 95%CI:1.28-2.73) and adjusted (odds ratio 1.61, 95%CI:1.05-2,49) Cox proportional hazard models. Crude 30-day survival was lower for patients with hyponatremia at admission (mean [SD] survival 22.1 [0.70] days) compared with patients who were normonatremic (mean [SD] survival 27.1 [0.40] days, p < 0.01).

Conclusions: This study demonstrates that hyponatremia on admission is common in patients with COVID-19 and is associated with inflammation and in-hospital mortality. Thus, hyponatremia could be a novel marker for identifying patients with COVID-19 at risk for hospital mortality.

PO1142

Trends of Overall Mortality by Severity of Hyponatremia: Five-Year Mortality Rates

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Background: We have previously reported increasing strengths of association between degree of hyponatremia on hospital admission and proportions of overall mortality at 1 year post-hospitalization. It is unclear if this association persists in the long term and if this association with overall mortality occurs in a linear manner. Here, we further explore this association over a longer mean follow up period. We hypothesized that a dose response relationship occurs between varying degrees of hyponatremia and overall mortality.

Methods: We obtained data from 46,783 patients, average age 62.2 years, 51.3% males, admitted from January 1, 2012 to December 31, 2016 at a tertiary referral hospital in Central Wisconsin. Of these, 7468 patients had admitting serum sodium <135 and 39315 controls with normal serum sodium (135-145). We parsed hyponatremia based on their admitting serum sodium as mild (130-134), moderate (125-129) and profound (<125) degrees of hyponatremia and compared them with controls. We obtained their vital status (alive or deceased) up to December 31, 2018 over a mean follow up period of 4.7 years. We used Cox proportional hazards model to estimate hazard ratios between varying degrees of hyponatremia compared with normonatremia group after adjusting for covariates.

Results: Hyponatremia occurred in 17.9% of total hospitalizations during the study period. Of 7468 patients with hyponatremia, there were 6,135 (82.2%), 995 (13.3%) and 338 (4.5%) with mild, moderate, and profound degrees of hyponatremia respectively. Hazard ratios for mild, moderate and severe hyponatremia when compared to controls was 1.35 (95% CI: 1.28 – 1.43), 1.81 (95% CI: 1.24 – 2.56) and 2.01 (95% CI: 1.24 – 3.27) respectively (all p<0.001) after adjusting for covariates.

Conclusions: All-cause mortality from CVD, stroke, cancer, liver cirrhosis deaths were occurring to a significant proportion even in patients with milder degrees of hyponatremia with a dose response relationship. Clinicians should incorporate hyponatremia in their assessment of critical patients as this is associated with mortality. These findings need to be explored further with research geared towards elucidating mechanisms that contribute to death in hyponatremia, and if correcting sodium levels early in hospitalizations may prevent mortality in the future.

PO1143

The Prognostic Importance of Serum Sodium for Mortality Among Critically Ill Patients Requiring Continuous Renal Replacement Therapy

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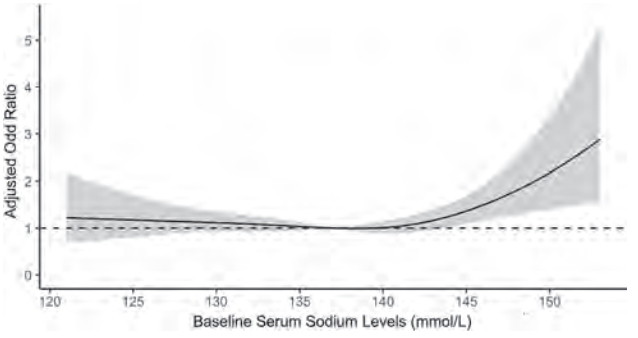
Background: Serum sodium derangement is common in critically ill patients requiring continuous renal replacement therapy (CRRT). We aimed to assess the association between serum sodium (normal range 138-142 mmol/L) before and during CRRT with mortality.

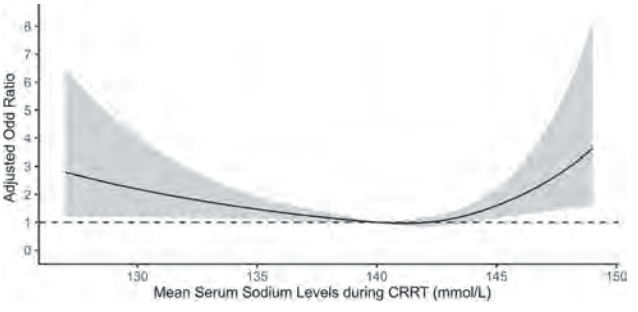
Methods: This is a historical cohort study of 1,520 critically ill patients who received CRRT for at least 24 hours from December 2006 through November 2015 in a tertiary hospital in the United States. Using logistic regression analysis, we used serum sodium before CRRT, mean serum sodium, and serum sodium changes during CRRT to predict 90-day mortality after CRRT initiation.

Results: Compared with the normal serum sodium levels, the odds ratio (OR) of 90-day mortality in patients with serum sodium before CRRT of 143-147 and ≥148 mmol/L were 1.45 (95% CI 1.03-2.05), 2.24 (95% CI 1.33-3.87), respectively. There was no significant increase in 90-day mortality in serum sodium of ≤137 mmol/L. During CRRT, the mean serum sodium levels of ≤137 (OR 1.41; 95% CI 1.01-1.98) and ≥143 mmol/L (OR 1.52; 95% CI 1.14-2.03) were associated with higher 90-day mortality. The greater serum sodium changes during CRRT were associated with higher 90-mortality (OR 1.35; 95% CI 1.21-1.51 per 5-mmol/L increase).

Conclusions: Before CRRT initiation, hypernatremia and during CRRT, hypo-, and hypernatremia were associated with increased mortality.



Restricted cubic spline of the association between serum sodium before CRRT and 90-day mortality



Restricted cubic spline of the association between mean serum sodium during CRRT and 90-day mortality

PO1144

Use of Tolvaptan to Maintain Eunatremia in Acute Brain Injury-Induced SIADH

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Introduction: Eunatremia is a predictor of in-hospital mortality in intracerebral hemorrhage. In hyponatremia from SIADH, usual therapies may not be ideal in patients with stroke. We present a case of hyponatremia from acute brain injury induced SIADH being managed with Tolvaptan.

Case Description: Our patient is a 68 year old man with a history of hypertension who was admitted for an acute hemorrhagic stroke. He had a blood pressure of 204/127 mmHg and an NIHSS of 10. His initial work up shows: glucose 199 mg/dL, creatinine 0.75 mg/dL, Na 137 mmol/L, potassium 3.8 mmol/L, HCO3 of 25 mmol/L, chloride 95 mmol/L. A head CT scan demonstrated a 10 cc right thalamic hemorrhage. He was then started on a nicardipine drip. On the next day, he was noted to have a Na of 129 mmol/L. His serum osmolality, urine osmolality, urine Na were 289 mOSM/kg, 6,783 mOSM/kg and 146 mmol/L respectively. He was given salt tablets with

improvement of Na to 131. However, he developed headaches and became hypertensive at 188/94 mmHg. Instead, he was started on a high protein diet, 1 liter fluid restriction and lasix. The next Na level was 129. He was given Tolvaptan 15 mg, which improved the Na to 132, urine osm 645, and urine Na to 12. The dose was increased to 30 mg to achieve eunatremia with these values: Na 135-138, urine Na 12, urine osm 487. His BP improved, tolvaptan was discontinued and salt tablets were resumed. The patient maintained eunatremia throughout the hospital stay.

Discussion: Hyponatremia is a predictor of mortality due to cellular edema. Eunatremia with Na levels between 135-145 mmol/L is targeted in acute brain injury. SIADH induced by brain injury may be due to an increase in ADH from the overstimulation of the neurohumoral axis. ADH promotes water reabsorption at the cortical and medullary collecting tubules, and inappropriate levels lead to hyponatremia. Tolvaptan is a V2 receptor antagonist which combats this mechanism, thus increasing free water excretion. Additional therapies for hyponatremia from SIADH include fluid restriction, a high protein diet and salt tablets. However, salt tablets increases fluid retention; which increases blood pressurre, and leads to recurrent hemorrhage and poor outcomes. The use of Tolvaptan increases free water excretion to achieve eunatremia, thereby decreasing the risk of brain edema and controls blood pressure, especially in this patient population.

PO1145

Acute Severe Symptomatic Hyponatremia in the Post-Partum Period: The Syndrome of Oxytocin-Induced Anti-Diuresis (SOIAD)

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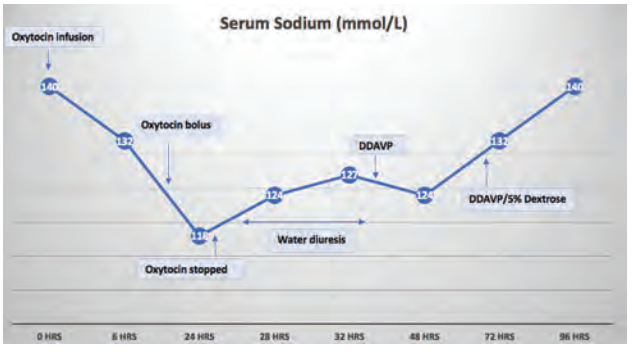
Introduction: Oxytocin (OXT) is a neuropeptide used in pregnancy to induce uterine contraction. It is structurally related to vasopressin (AVP) by a difference of only 2 amino acids. While it does not have antidiuretic activity at physiologic levels, it can when administered at pharmacologic doses (>20 mU/min). We present a case of severe symptomatic hyponatremia after receiving oxytocin in the post-partum period.

Case Description: A 31 y/o G1PO woman was admitted with premature membrane rupture at week 38. An IV oxytocin infusion (2mU/min) was started to augment labor. Her serum sNa 6 hrs later was 132 mmol/l (baseline sNa 140). Her delivery was c/b uterine atony and postpartum hemorrhage requiring a bolus of IV oxytocin (10 U over 30 min) followed by infusion at 8 mU/min. The sNa 18 hr later was 118 mmol/l. She reported nausea. Her sOsm was 252 mOsm/kg with UNa of 95 mmol/l and Uosm 880 mOsm/kg consistent with the syndrome of anti-diuresis (SIAD). OXT was suspected and was stopped. 2 hr later, a rapid water diuresis ensued (u vol 150-200 cc/hr, with uOsm 92 mOsm/kg). The sNa 4 and 8 hrs later increased to 124 and 127 respectively. Because of concern for over-correction, she was given DDAVP and D5W. This resulted in a gradual (6-8 mmol/l/24 hr) sNa increase to 140 mmol/l over the next 48 hr (Fig 1).

Discussion: Therapeutic OXT can result in anti-diuresis with water retention. OXT half-life is only 1-6 min and is further reduced during pregnancy. Women are more likely to have severe neurologic sequelae of hyponatremia so it is fortuitous that the half-life of OXT is so short, and discontinuation alone should result in a rapid water diuresis. Still, although acute hyponatremia can usually be safely corrected rapidly, concern over what could have been an increase in sNa of 28 mmol/l over several hrs necessitated a DDAVP clamp to slow correction. She had a complete recovery. SOIAD can be a severe complication of OXT. Since it can occur rapidly and severely, sNa should be followed closely when patients are on OXT infusion.



PO1146

A Rare Cause of Hyponatremia: Renal Salt Wasting Syndrome of Unclear Etiology Post Autologous Hematopoietic Stem Cell Transplant

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Introduction: Hyponatremia is common in cancer patients. We report a rare case of acute hyponatremia in a patient with multiple myeloma (MM) who developed renal salt wasting syndrome (RSWS) as a complication of autologus hematopoietic stem cell transplant (SCT)

Case Description: A 57-year-old female with history of Plasmacytoma treated with radiation therapy that subsequently relapsed as MM with POEMS syndrome and was treated with VRd regimen presented for autologous SCT. MM was in remission and patient underwent Melphalan pre-conditioning with last melphalan dose 48 hours prior to transplant. 36 hours post-transplant patient had a seizure. Labs revealed acute drop in serum sodium from 137 to 117 over 17 hours. CT head revealed mild generalized cerebral edema. Patient also had acute polyuria (> 4 L/day). Patient was treated emergently with hypertonic saline bolus and had resolution of neurological symptoms however, serum sodium continued to drop and she required around 2 L of hypertonic saline infusion over the next 24 hours to correct sodium at desired rate. Urine studies at the time of hyponatremia revealed urine osmolality of 477, sodium 161 and potassium 34. Initial working diagnosis was SIADH that was quickly revised to RSWS based on high urine sodium, hypovolemia and polyuria. The patient was able to be transitioned to salt tablets once polyuria resolved over the next 36 hours. Urine sodium remained elevated. A repeat CT head showed resolution of cerebral edema.

Discussion: RSWS post SCT is rarely reported. Among the few reported cases an underlying CNS complication or a post-transplant hyponatremia inducing medication exposure that predated acute hyponatremia was present. Moreover the reported cases appeared to be non autologous transplants. SIADH and RSWS (including CSWS) are similar in the sense that both present with similar urine studies. Volume status and urine output are the key factors to help differentiate between the two entities. Clinically differentiating between these two entities is important as fluid restriction is the key management in the one and solute plus volume replacement in the other. Based on our case we recommend that hyponatremia post SCT should be carefully evaluated and RSWS be considered in the differential even if there is no obvious underlying cause.

PO1147

An Unexpected Case of Osmotic Demyelination Syndrome (ODS)

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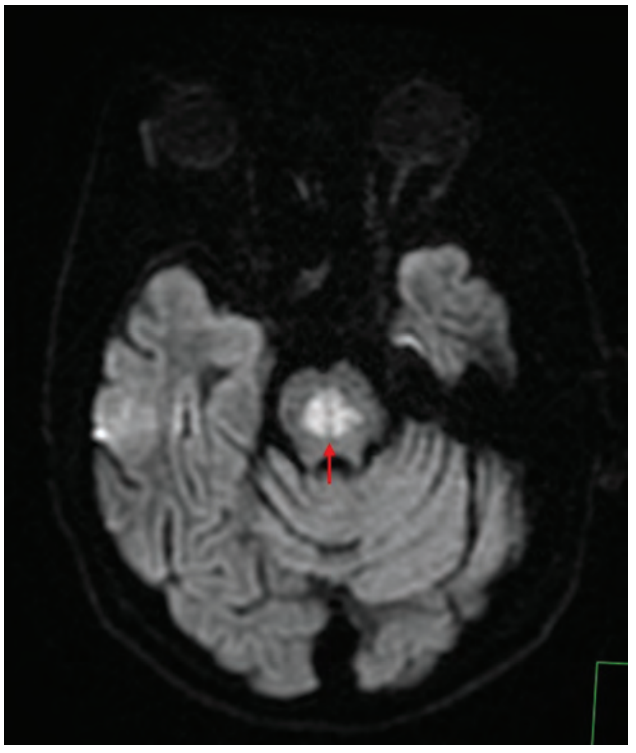
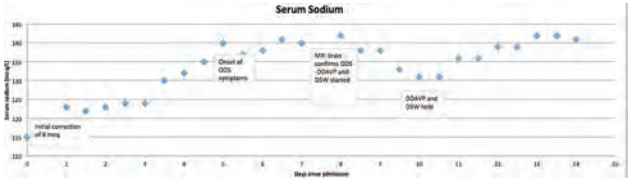
Introduction: ODS is a neurological condition characterized by altered mentation, extrapyramidal symptoms, and pseudobulbar palsy in response to a rapid increase in serum osmolality. Classically ODS was been described after rapid correction of severe, chronic hyponatremia but can occur with slower rates of correction in high-risk patients, as described herein.

Case Description: A 44-year-old man with alcoholism presented with a sodium of 115meq/L. Normal saline was administered and his sodium corrected to 123meq/L over the initial 24 hours. His sodium corrected slowly over the next 5 days to normal range, never exceeding 8 meq/L per day. On day 5, he developed nystagmus, cogwheeling rigidity, hallucinations and aspirations. Brain MRI revealed abnormalities in the central pons (fig. 1), and a diagnosis of ODS was made. D5W and desmopressin were administered, lowering the sodium from 142meq/L to 131meq/L over 2 days, where it was maintained for 24 hours. No clinical improvement resulted and neurological sx progressed. The sodium was then allowed to rise slowly to normal over 2 days, shown in fig. 2. By discharge the patient had moderate improvement in speech and swallowing.

Discussion: This case of ODS was unusual in that it occurred despite modest hyponatremia, which corrected at only 8meq / day. ODS can occur despite slow sodium correction in the context of risk factors such as alcoholism. Therapeutic relowering of sodium resulted in no improvement, possibly because relowering was not pursued until MRI confirmation, leading to a delay of 72 hours from symptom onset.



MRI brain (DWI sequence) demontrating restricted diffusion in the central pons (arrow).



PO1148

Cerebral Salt Wasting in a Renal Transplant Patient

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Introduction: Hyponatremia is a common occurrence in patients with cerebral injury and is usually thought to be secondary to SIADH. Though cerebral salt wasting is documented in literature it has been debated on if it is truly a phenomenon. Among patients with CNS disease, CSW is a much less diagnosed cause of hyponatremia and remains underdiagnosed owing to the challenge of proving its existence. Here we present a patient with a CNS injury who showed clear benefit from treatment not centered around SIADH, thus pushing us to diagnose him with CSW.

Case Description: A 63yo Male with a PMHx of DDKT presented with nausea/vomiting. A cerebellar abscess from a previous biopsy site was found and he underwent a debridement and washout. On POD#4 the patient had a drop in sodium to 131. Urine studies [urine osmolarity: 789, urine Na: 72]. With continued drop in sodium and orthostatic hypotension he was started on NS 75cc/hr. The sodium continued to drop to a low of 123. At that time the NS was increased to 125cc/hr. This resulted in an upswing in serum sodium to 130. A drop in NS rate was trialed with sodium dropping back to 127. The NS was eventually ramped up to 200cc/hr with good response. During the uptitration of fluids there was no significant drop in urine osmolality noted. The patient was eventually transitioned to a dose of salt tabs close to the equivalent to the amount of fluids he was receiving [5g Q4H]. He was also started on Fludrocortisone 0.1mg daily. This resulted in our ability to drop the Salt tabs to 4g Q6H with stability in serum sodium noted. He was discharged on this regimen and was noted to have stable serum sodium on follow up a few weeks later.

Discussion: CSW is difficult to diagnose due to the similarities in laboratory diagnostic markers with SIADH. One major difference is that in CSW patients are usually hypovolemic. Another aspect that differs from SIADH is the approach to treatment. In SIADH a combination of fluid restriction, lasix, and salt tabs are used. What makes our case unique is the successful use of NS to correct the patient's sodium. If this was SIADH, continuous administration of NS would have dropped the sodium level. We believe we met the burden of proof to diagnose this patient with CSW. Though there may still be debate about the existence of CSW, we believe that with the difference in treatment approach it should always be considered in the differential in patients with CNS injury.

PO1149

Explainable Prediction of Overcorrection in Severe Hyponatremia: A Post Hoc Analysis of the SALSA Trial

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Background: Overcorrection of hyponatremia can result in irreversible neurologic disability like osmotic demyelination syndrome. Few prospective studies have identified the individuals at high risk of overcorrection under controlled hypertonic saline treatment.

Methods: We performed a post hoc analysis of a multicenter, prospective randomized controlled study – the SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline In Patients With Moderately Severe or Severe Symptomatic Severe Hyponatremia) trial in 178 patients older than 18 years with symptomatic hyponatremia (mean age 73.1 years, mean serum sodium (sNa) concentrations 118.2 mmol/L). Overcorrection was defined as an increase in sNa by >12/18 mmol/L within 24/48 hours at any time.

Results: Thirty-seven of 178 patients experienced overcorrection (20.7%). Overcorrection was independently associated with initial sNa level (≤ 110 mmol/L: 7 points; 110-115 mmol/L: 4 points; 115-120 mmol/L: 2 points; 120-125 mmol/L: 0 point). chronic alcoholism (7 points), severe symptoms of hyponatremia (3 points), and initial potassium level (< 3.0 mmol/L: 3 points). The NASK score was derived from these four risk factors for overcorrection (hypoNatremia, Alcoholism, Severe symptoms, and hypoKalemia) and was significantly associated with overcorrection (odds ratio 1.41, 95% CI 1.24 to 1.61; P <.001) with good discrimination (area under the receiver operating characteristic curve 0.76, 95% CI 0.66 to 0.85; P <.001). The AUROC value of the NASK score was statistically better comparing to those of each risk factor.

Conclusions: In treating patients with symptomatic hyponatremia, individuals at high risk of overcorrection were predictable using a novel risk score summarizing baseline information.

Figure 1A. Marginal plot of the NASK score against overcorrection

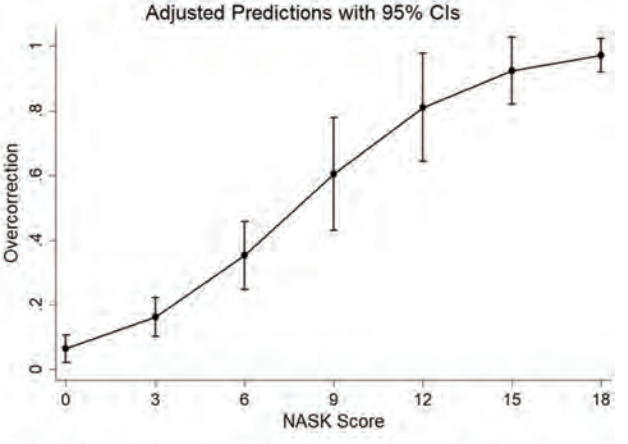
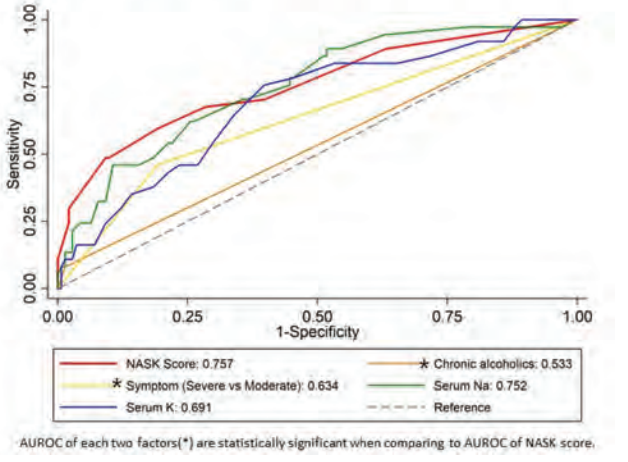


Figure 1B. The area under the receiver operating characteristics curve for the NASK score and each risk factor for overcorrection



AUROC of each two factors(*) are statistically significant when comparing to AUROC of NASK score.

PO1150

On the Correction of Plasma [Na] in Hyperglycemia

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Background: The effect of hypertonic states on metabolism was first considered by Seldin *et al* in 1949. An empirical equation to correct the plasma [Na] for hyperglycemia was put forth by Katz (*NEJM, 1973*). About 25 years later, Hillier *et al* (*AJM, 1999*) presented another equation based on normal volunteers with experimentally induced hyperglycemia. Both equations are linear with correction factors (in mM [Na]/100 mg/dL [glucose]) of -1.6 (Katz) and -2.4 (Hillier). Non-linearity, however, is apparent in the original data of Hillier, which are better fit by a second-order equation (corrected plasma [Na] = $\{-3.49 * 10^{-5} * (plasma\ [glucose])^2 - (3.91 * 10^{-5} * plasma\ [glucose]) + 140\}$). Previous equations also presume normonatremia prior to hyperglycemia and a constant volume of distribution for glucose.

Methods: Here, a new model is proposed that also provides a reasonable fit to the patient data of Seldin *et al* from 70 years ago (*JCI, 1951*) and Hillier *et al*. Unlike previous equations that are based solely on current plasma [glucose], this program takes weight, sex, the presence of edema, and the apparent volume of distribution (aVd) of glucose into consideration. The latter is especially important because the aVd of glucose may change in hyperglycemia.

Results: For example, consider a patient from the 1951 *JCI* study by Seldin *et al*: a 59.1-kg edematous patient with cirrhosis who initially had a plasma [Na] of 130 mM when the plasma [glucose] was 126 mg/dL. The program starts by calculating the number of effective osmoles in the ICF and ECF based on the initial labs, and then incorporates the change in ECF volume measured by the investigators, which in this case was +1.9 L. Following infusion of hypertonic glucose, the plasma [Na] fell to 110 mM at the peak plasma [glucose] of 666 mg/dL. The corrected plasma [Na] predicted are (in mM): 130.9 (Katz), 126.4 (Hillier), and 124.5 (quadratic fit of Hillier's data); all of which do not compare well with 110 mM. Although the program predicts 121.3 mM, after correction for the change in the aVd of glucose, it predicts 112 mM, in good agreement with the measured value of 110 mM.

Conclusions: Now that making numerous calculations can be done easily and efficiently with apps most physicians have on their phones, it is proposed that equations with linear correction factors be replaced by this new program when clinicians would like to predict or correct the measured serum [Na] in the presence of hyperglycemia.

PO1151

Extreme Hyponatremia with Serum Sodium Less Than 100 mEq/L: A Case Report and Review of the Literature

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Introduction: Hyponatremia is the most common electrolyte abnormality in hospitalized patients and is associated with increased mortality, hospital length of stay and cost. Rapid overcorrection of hyponatremia can increase the risk of osmotic demyelination syndrome (ODS) which can have debilitating and often fatal consequences. Extreme hyponatremia with serum sodium concentration less than 100 mEq/L is rare, but is associated with high a rate of morbidity and mortality.

Case Description: A 52-year-old woman presented with a one-week history of weakness and fatigue. She was cachectic and had signs of severe hypovolemia and malnutrition. Her serum sodium concentration was less than 100 mEq/L on three separate samples. She did not have any focal neurological deficits or any witnessed seizures. Additionally, she was found to have oliguric acute kidney injury and critical hyperkalemia. She was treated with aggressive volume expansion with subsequent increase in serum sodium concentration and resolution of AKI and hyperkalemia. Desmopressin and 5% dextrose infusion were used to prevent rapid overcorrection of hyponatremia and minimize the risk for ODS. Her sodium level was corrected at the recommended rate of 6 mEq/L per day. She was discharged with serum sodium concentration of 136 mEq/L on hospital day 16 and did not have any long-term neurological sequelae.

Discussion: Extreme hyponatremia with serum sodium concentration less than 100 mEq/L is a rare but critical situation. Review of the previously published cases found that the main risk factors are female gender, age greater than 40 years, malnutrition, alcohol use, thiazide use or SIADH due to antidepressant use. Serum osmolality should be used to estimate serum sodium concentration and guide the rate of correction if the precise sodium value below 100 mEq/L cannot be determined. Careful management is required due to the high risk of ODS in these patients and proactive administration of desmopressin is recommended to avoid overcorrection. Continuous venovenous hemofiltration with hypotonic replacement fluid is an effective strategy for patients with extreme hyponatremia who also require renal replacement therapy for AKI and/or critical hyperkalemia.

PO1152

SIADH and Postoperative Urinary Retention

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Introduction: Hyponatremia is a common electrolyte abnormality in hospitalized patients with increased prevalence noted in geriatric populations. The increased susceptibility is multifactorial from age-related GFR reduction in addition to medication effects (diuretics, antidepressants), decreased solute intake and endocrinopathies (SiADH). Herein we present a case of severe hyponatremia induced by urinary retention, an infrequently described and often overlooked etiology of hyponatremia in elderly patients.

Case Description: A 58-year-old male with past medical history of hypertension on amlodipine and losartan presented with nausea, emesis and abdominal pain. The patient was recently discharged 2 weeks earlier s/p uncomplicated distal pancreatectomy with splenectomy for pancreatic adenocarcinoma. Post-operative course was stable with no complications and patient was discharged home on oxycodone/acetaminophen for pain. At home, the patient noticed constipation with worsening abdominal distension with bilateral lower extremity swelling. He had been oliguric for the past week, performing manual suprapubic compression to void. On readmission patient was noted to be severely dehydrated with a large, distended abdomen. Vital signs were BP 102/53, HR 87, SpO2 97%. Notable labs include (mEq/L): Na 111, BUN 132, Cr 4.4, HCO3 18. Urine studies noted (mEq/L): Na 8, Cl <10, K 25, serum osmolality 366 mOsm/kg. Abdominal CT noted a large LUQ fluid collection, distal colonic distension with fecal retention and mild bilateral hydronephrosis. Subsequent foley insertion immediately drained 2.5L. Repeat labs 12 hours later were (mEq/L): Na 118, BUN 118, Cr 2.89. Hypotonic fluids were started to prevent Na overcorrection. Over the next several days the patient's Serum Na (135) and renal function improved (BUN 21, Cr 0.9) back to baseline.

Discussion: During the post-operative period urinary retention is commonly noted due to anesthesia, analgesics, pain and constipation. This can be exacerbated in elderly male patients due to the ubiquity of BPH. Therefore physicians must be aware of common post-operative complications of urinary retention like hyponatremia, especially given the higher prevalence and predisposition of geriatric populations to develop hyponatremia. The proposed mechanism of urinary retention induced hyponatremia involves bladder distension and/or pain-mediated ADH release.

PO1153

La Belle Indifférence: Unusual Adaptation to an Antidiuretic Hormone Deficit

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Introduction: Langerhans cell histiocytosis (LCH) also known as Histiocytosis X is a rare granulomatous disease characterized by abnormal proliferation of Langerhans cells. LCH may be systemic or localized and its clinical manifestations are variable. Diabetes Insipidus (DI) is the most commonly found endocrine anomaly, with a prevalence varying between 5 and 50%.

Case Description: 48-year-old Hispanic male previous smoker with a history LHC was admitted c/o rectal pain. Three years prior to admission he had developed recurrent bilateral pneumothoraxes requiring multiple video assisted thoracoscopic surgeries with lysis of adhesions. A lung biopsy at that time demonstrated LHC. He had not had follow-up care since that time due to economic issues. He said he was drinking 4 liters of water a day to be proactive with his health. He denied thirst. On admission he was noted to have a large anterior anal ulcer, which was positive for Langerhan cell. While waiting in the emergency department without access to water his sodium increased from 137 mEq/L to 147 mEq/L in 6 hours. On evaluation his urine osmolality (osm) was 93 mosm/kg with a serum osm of 305 mosm/kg, and a serum sodium of 146. A repeat sample demonstrated a serum osm of 311 mosm/kg and Copeptin level of 4.0 pmol/L confirming central diabetes insipidus. Brain MRI shown in Figure 1 demonstrated abnormal thickening and nodularity of the distal pituitary stalk. Patient was started on nasal desmopressin.

Discussion: Although this patient denied thirst or polyuria, with incidental water restriction while in the ED, DI became apparent. The pathological diagnosis of an infiltrative disease such as LHC should provoke a high degree of suspicion for the evaluation of DI.

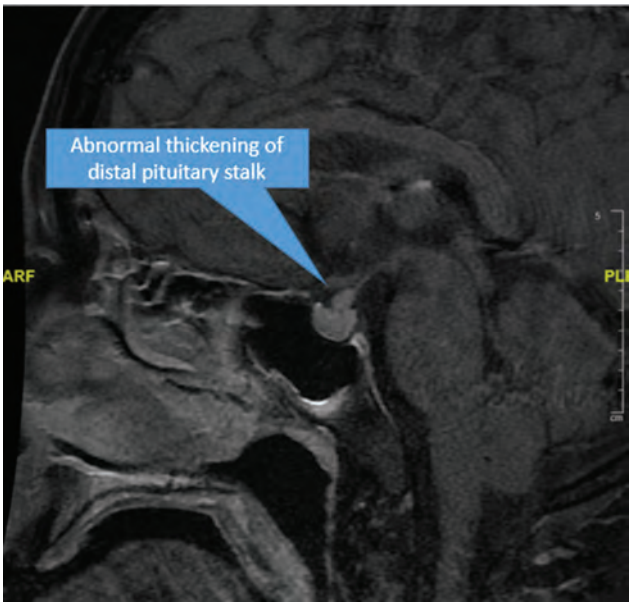


Figure 1

PO1154

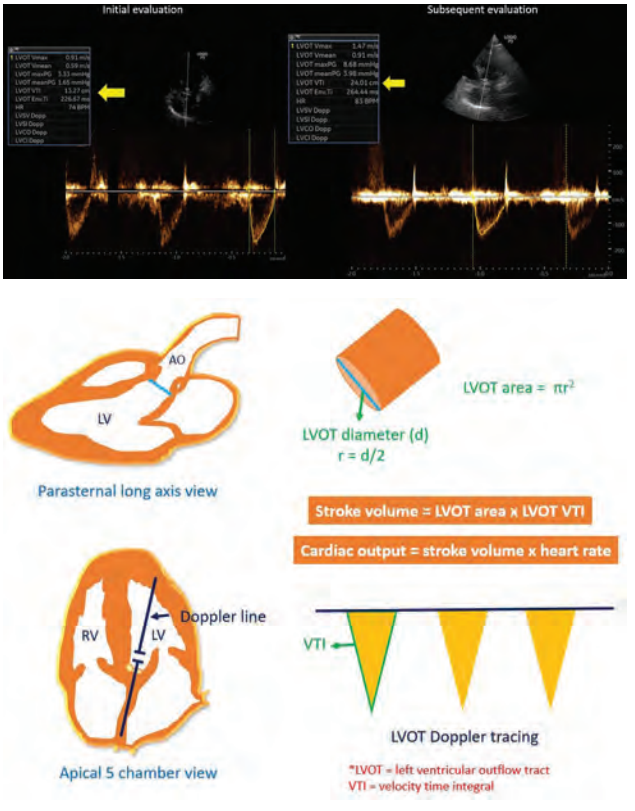
Point-of-Care Ultrasound-Assisted Management of Hyponatremia

Totini S. Chatterjee, Abhilash Koratala. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Point of care ultrasound (POCUS) is emerging as a valuable adjunct to conventional physical examination in patients with complex fluid and electrolyte disorders. Herein, we present a case of hyponatremia where nephrologist-performed focused cardiac ultrasound (FoCUS) aided in accurate diagnosis.

Case Description: A 73-year-old woman was admitted for the treatment of fractures after sustaining a fall. Nephrology was consulted for decrease in serum sodium level (to 123 mmol/L; baseline 130s). Laboratory data was significant for a urine sodium level of 46 mmol/L, urine osmolality 257 mOsm/kg, serum creatinine 0.5 mg/dL and BUN 9 mg/dL. As the patient had exertional dyspnea and crackles at lung bases, IV diuretic was administered by the rounding physician prior to urine studies. No active pain or thiazide use. X-ray showed a huge hiatal hernia with bowel contents in the chest, which was possibly mimicking crackles on auscultation and causing dyspnea. Systolic BP was in 140s. Urine sodium, though suggestive of euvolemic state, was confounded by diuretic. We performed a FoCUS exam. Left ventricular outflow tract velocity time integral (LVOT-VTI), which is a surrogate for stroke volume was lower than expected (~13 cm [normal 18-22]) suggestive of hypovolemia. Flow changes precede drop in BP. We recommended to administer normal saline and the serum sodium improved to 130 mmol/L in 2 days; VTI normalized to ~22 cm [Fig. 1]. Fig.2 illustrates stroke volume estimation using LVOT diameter and VTI. As the diameter is constant for a given person, VTI alone can be used to monitor response to therapy.

Discussion: POCUS is a valuable bedside diagnostic tool in day-to-day nephrology practice.



PO1155

Polyethylene Glycol-Induced Pseudohyponatremia

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Introduction: Pseudohyponatremia due to Polyethylene glycol (PEG) is poorly described and goes unrecognized. We describe a case of hyperosmolar hyponatremia due to PEG absorption into the systemic circulation.

Case Description: An 84-year-old lady with hypertension and CKD stage 4 was admitted with an asymptomatic serum sodium of 121. Initially thought be due to SIADH. She was started on 1-liter fluid restriction, sodium chloride tablet and torsemide. Nephrology was consulted on day 3 as her serum creatinine was 2.9 (baseline 2.3 mg/dl) and sodium improved to only 124. Patient complained of increased thirst and had dry mucus membrane on examination. Labs on admission revealed a serum sodium of 121 mEq/L, a serum osmolality of 286 mOsm/kg, urine osmolality of 230 mOsm/kg and urine sodium of 40. Serum creatinine was 2.3 mg/dL, BUN 50 mg/dL, glucose of 100mg/dl, uric acid 8.1 mg/dL. Thyroid function tests and cortisol were within normal range. An osmolar gap of 22 was noted. In the absence of hyperglycemia and other potential causes of an osmotic gap, such as mannitol or alcohols, a careful review of medication showed that she was on 3 weeks of PEG for constipation. PEG was held, fluid restriction and torsemide discontinued. Resolution of osmolar gap was confirmed in two weeks with return in sodium to 134 and creatinine to 2.3.

Discussion: The prevalence of hyponatremia is reported at 7% in bowel prep patients. Etiology in these cases was due to increased free water intake. Hyperosmolar hyponatremia is caused by the addition of an 'effective solute' (e.g. glucose, mannitol or sucrose) to the serum. Commonly used as an osmotic laxative, PEG is described as 'a nonabsorbable, nonmetabolized polymers' that when administered orally acts as a 'pure osmotic agent' in the gastrointestinal tract. Systemic absorption can occur in rare cases. When PEG absorption occurs, most of its clearance occurs via renal filtration, this process is likely impaired in a patient with CKD such as seen in our patient. When a patient presents with hyponatremia, the expectation of a low-serum osmolality needs to be confirmed with the actual measurement of serum osmolality. This case highlights the importance of detecting the etiology of hyponatremia without which treatment of the same can be impossible and expands the understanding of normal to high serum osmolality can go beyond the commonly known mannitol, paraproteinemia and lipidemia.

PO1156

Identifying Hypernatremia Subgroups with Differing Survival by Machine Learning Among Hospitalized Patients

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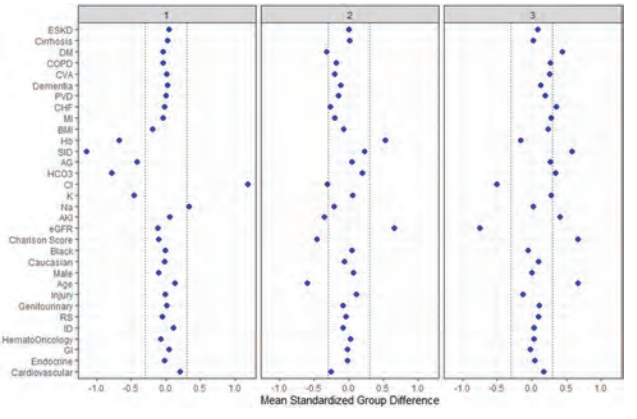
Background: The objective of this study was to characterize patients with hypernatremia on hospital admission into clusters using an unsupervised machine learning approach and to evaluate the mortality risk among these distinct clusters.

Methods: We performed consensus cluster analysis based on demographic information, principal diagnoses, comorbidities, and laboratory data among 6,297 hospitalized adult patients with hypernatremia present at admission. We calculated the standardized difference of each variable to identify each cluster's key features. We assessed the association with each hypernatremia cluster with in-hospital and one-year mortality.

Results: There were three distinct clusters of hypernatremia: 1,570 patients (25%) in cluster 1; 2,648 (42%) in cluster 2; and 2,079 (33%) in cluster 3. Figure 1 is a plot of standardized mean differences to visualize key features for each cluster. Compared to cluster 2, the odds ratios for in-hospital mortality were 6.99 (95% CI 4.03-12.13) for cluster 1 and 5.73 (95% CI 3.31-9.90) for cluster 3, whereas hazard ratios for one-year mortality were 3.38 (95% CI 2.69-4.25) for cluster 1 and 4.71 (95% CI 3.82-5.80) for cluster 3.

Conclusions: The characteristics and outcomes of hospitalized patients admitted with hypernatremia were heterogenous. Our cluster analysis identified three clinically distinct phenotypes with differing mortality risks. Identification of heterogeneity in hypernatremic patients using this approach may provide guidance for the management of hospitalized patients with hypernatremia at the time of hospital admission.



The standardized differences across three clusters for each of the baseline parameters. The x axis is the standardized differences value, and the y axis shows baseline parameters. The dashed vertical lines represent the standardized differences cutoffs of <-0.3 or > 0.3.

PO1157

A Rare Case of Acute Myeloid Leukemia Presenting as Central Diabetes Insipidus

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Introduction: Central Diabetes Insipidus (CDI) is an uncommon condition, with an overall incidence of approximately 1:25,000 and is usually associated with neurosurgery, trauma, autoimmune and vascular disease, infiltrative disorders, hypoxic brain injury, and brain metastasis. Patients with acute myeloid leukemia (AML) mostly present with symptoms of pancytopenia, noted to have hematologic abnormalities and are subsequently diagnosed with AML after bone marrow biopsy. Here we describe a unique case of a patient who presented with symptoms of CDI and incidentally diagnosed with AML.

Case Description: A 64-year-old male with a history of coronary artery disease presented to his primary physician complaining of polyuria and polydipsia which affected his work as a truck driver. Labs were notable for mild anemia (Hgb 11 g/dL) with macrocytosis, thrombocytosis (platelet 667 K/uL), serum sodium was 146 mmol/L, Hgb A1c 5%, prostate-specific-antigen 1.4 ng/dL, normal lipid panel, and normal thyroid function. No definitive diagnosis was made and he underwent evaluation by hematology. Peripheral smear showed increased (44%) blasts/promyelocytes, consistent with acute leukemia. Cytogenetic analysis showed an abnormal clone of cells with an inverted chromosome 3 and monosomy for chromosome 7. He was admitted for induction therapy and presenting symptoms worsened (~10 L urine output per day) along with hypernatremia which peaked at 160 mmol/L, serum osmolality 319 mOsmo/kg and urine osmolality of 174 mOsmo/kg despite large oral and peripheral free water supplementation. MRI brain was negative for intracranial findings or abnormal enhancement. Given the degree of hypernatremia, and history concerning for CDI, empiric treatment with intra-nasal vasopressin (DDAVP) was given with significant improvement of symptoms, serum sodium, serum osmolality and urine osmolality.

Discussion: The presentation of AML with concurrent CDI is associated with chromosome 3 or 7 abnormities, not brain lesions, as in this case; the management of CDI involves continued DDAVP administration. Unfortunately this translocation has been associated with poor clinical outcome. With this case, we suggest screening patients for CDI who have an unclear reason of developing of polydipsia and polyuria and if hematologic abnormalities are noted, should undergo prompt evaluation for AML.

PO1158

A Case of Ketamine-Induced Diabetes Insipidus

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Introduction: To our knowledge there have been six previously published case reports describing central diabetes insipidus (DI) related to ketamine. We present a unique case of central DI associated with ketamine infusion in a critically ill patient with acute respiratory failure.

Case Description: A 52-year-old African American man with medical history of bipolar disorder, polysubstance abuse, chronic obstructive pulmonary disease, hypertension, and deep vein thrombosis was admitted to the medical intensive care unit with hemoptysis and acute respiratory failure. Due to agitation and refractory hypoxemia he required multiple sedating agents. Within hours of starting a ketamine infusion his urine output increased from a mean of 71 mL/hr to 305 mL/hr. Over 48 hours serum sodium (SNa) rose from 142 to 159 mmol/L. Urine osmolality (Uosm) was 132 mOsm/kg. 4 mcg intravenous (IV) desmopressin was administered. 90 minutes later Uosm had increased to 646 mOsm/kg. Urine output fell to 49 mL/hr. About 28 hours after the initial dose of desmopressin polyuria recurred and Uosm fell to 272 mOsm/kg. IV desmopressin was re-administered at 2 mcg with a similar response to the first dose. SNa normalized with free water replacement. Ketamine was stopped. Urine output, Uosm, and SNa remained stable without further intervention. Alternative etiologies for central DI such as hypoxic brain injury were considered but felt to be less likely due to the strong temporal relationship with ketamine. The Naranjo adverse drug reaction (ADR) likelihood score was 5 indicating a probable ADR.

Discussion: This case reinforces the association between ketamine and central DI which has been described in prior case reports. A hypothesized mechanism is ketamine's antagonism of N-methyl-D-aspartate receptors in the posterior pituitary thus inhibiting arginine vasopressin production. Ketamine is being used with greater frequency in critical care. It's important to recognize this rare but potentially serious complication. Monitoring of SNa, Uosm, and urine output should be considered. When central DI related to ketamine is identified, withdrawal of the drug appears to be corrective.

PO1159

Multi-Electrolyte Storm Associated with Non-Exocrine Manifestations of Sjögren Syndrome

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Introduction: Kidneys are one of the more commonly affected non-exocrine glands by Sjögren's syndrome. Renal involvement includes glomerulonephritis, interstitial nephritis, or both. Chronic TIN is the most common renal manifestation in Sjögren's syndrome. Clinical manifestations of TIN present as abnormalities of tubular function such as Fanconi syndrome, Distal RTA and Nephrogenic DI.

Case Description: 26 y/o Hispanic female with no known past medical history present with nausea and vomiting at 21 weeks gestation of her second pregnancy. Workup was significant for elevated creatinine with proteinuria and pyuria, normal anion gap metabolic acidosis, hypokalemia, and hyphosphatemia. Urine studies revealed an inappropriately alkaline urine with impaired renal reclamation of potassium and phosphorous. Serological workup was significant for positive ANA, SSA, and SSB antibodies. Kidney biopsy revealed acute tubulointerstitial nephritis. The patient was started on an IV steroid course with oral taper and hydroxychloroquine with improvement in Cr from 2.2 to 1.2 mg/dL. with a potassium, phosphate and sodium bicarbonate supplementation regimen.

Discussion: Sjögren's syndrome is typically associated with lymphocytic infiltration of exocrine glands. However, this can also affect the kidneys causing tubulointerstitial nephritis and defects in tubular function initiating a cascade of electrolyte abnormalities. Understanding the renal physiology behind the observed electrolyte abnormalities is important to optimize our treatment regimen. While the management of a distal RTA that has been well described in Sjögrens syndrome typically involves judicious potassium and alkali supplementation, this case highlights the worsening potassium wasting and phosphorous wasting which also needs to be addressed with a concomitant proximal tubulopathy. We propose that this set of features can best be explained by dysfunctional carbonic anhydrase, a cause of the extremely rare type III RTA. We use this case presentation to highlight the spectrum of renal manifestations of Sjogren's syndrome and their treatment principles.

PO1160

Estimating 24-Hour Urinary Excretion Using Spot Urine Measurements in Kidney Stone Formers

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Background: One limitation of the use of the 24-h collection, a key element in the management of kidney stone (KS) disease, is impracticality. To overcome this limitation, we analyzed the performance of spot urine measurements to estimate 24-h excretion in patients with KS.

Methods: 74 adult KS patients from two centres were instructed to perform a 24-h urine collection. A sample of the last micturition (fasting, upon awakening) was sent for spot urine analysis. Twenty patients were asked to collect two additional spot urine samples, one before dinner (pre-prandial) and the other after dinner (post-prandial). Urinary concentrations of creatinine, calcium, oxalate, uric acid, citrate and magnesium were measured in the 24-h and each of the spot urine samples. Three approaches were used to estimate 24-h urinary excretion, multiplying the ratio of the spot urinary analyte to creatinine concentration by 1) measured 24-h urinary creatinine excretion ["Prediction #1"], 2) estimated 24-h urinary creatinine excretion ["Prediction #2"], or 3) assumed 1 gram 24-h urinary creatinine excretion ["Prediction #3"]. For each parameter we computed Lin's concordance correlation coefficients (CCCs), Bland-Altman plots, and 95% limits of agreement.

Results: The performance of estimates obtained with Prediction #1 and Prediction #2 was similar for all parameters, except for citrate and uric acid for which Prediction #2 performed significantly worse. Both estimation approaches performed moderately well: citrate CCC 0.82 (95% CI 0.75, 0.90), oxalate 0.66 (0.55, 0.78), magnesium 0.66 (0.54, 0.77), calcium 0.63 (0.50, 0.75), uric acid 0.52 (0.36, 0.68). The performance of Prediction #3 was consistently worse. Post-prandial samples tended to perform numerically worse compared with fasting morning and pre-prandial samples except for uric acid.

Conclusions: Utilizing measured or estimated 24-h creatinine substantially increases the utility of spot urine samples in estimating 24-h excretion of urinary analytes in KS formers.

PO1161

Evidence for Abnormal Linkage Between Urine Oxalate and Citrate Excretion in Human Kidney Stone Formers

Megan Prochaska,[1] Orson W. Moe,[2] John R. Asplin,[3] Fredric L. Coe,[1] Elaine M. Worcester.[1] *[1]University of Chicago Division of the Biological Sciences, Chicago, IL; [2]The University of Texas Southwestern Medical Center, Dallas, TX; [3]LithoLink Corp, Chicago, IL.*

Background: Animal models have demonstrated an interactive relationship between the epithelial anion exchanger SLC26A6 and transporter NaDC-1 that regulates citrate and oxalate homeostasis. This relationship is a potential mechanism to protect against kidney stones as higher urine oxalate is accompanied by higher urine citrate but it has not been explored in humans.

Methods: We examined 24-hour urine data on 13,155 kidney stone forming patients (SF) from separate datasets at the University of Chicago and Litholink, a national laboratory, and 143 non-kidney stone forming participants (NSF) to examine this relationship in humans. We used multivariate linear regression models to examine the association between oxalate and citrate in all study participants and separately in SF and NSF.

Results: Higher urinary oxalate was associated with higher urinary citrate in both SF and NSF. In NSF, the multivariate adjusted urine citrate excretion was 3.0 (1.5 to 4.6) (mmol)/creatinine (mmol) per oxalate (mmol)/creatinine (mmol). In SF, the multivariate adjusted urine citrate excretion was 0.3 (0.2 to 0.4) (mmol)/creatinine (mmol) per oxalate (mmol)/creatinine (mmol).

Conclusions: Higher urinary oxalate excretion was associated with higher urinary citrate excretion and this effect was larger in non-kidney stone forming participants compared with those who form kidney stones.

Funding: Other NIH Support - KL2

PO1162

Higher Risk of Incident Kidney Stones in Patients with Metabolic Acidosis and CKD

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Background: Epidemiological studies have shown an association between kidney stones and risk for CKD and its progression. Some types of stones are less likely to form at higher urine pH. Metabolic acidosis is a risk factor for CKD progression, but the association of serum bicarbonate with risk of incident kidney stones is not well understood.

Methods: Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried to identify patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate values of 12 to <22 mEq/L (metabolic acidosis) or 22 to <30 mEq/L (normal serum bicarbonate) with data ≥3 years pre-index. The first qualifying serum bicarbonate test established the index date. Primary exposure variables were baseline serum bicarbonate and change in serum bicarbonate over time. Adjusted time-dependent Cox Proportional Hazards models were performed to evaluate time to first occurrence of kidney stones (by ICD-9 or ICD-10 diagnosis codes) during an average 3.6 year follow-up period. Other covariates included age, sex, race-ethnicity, education and income status, history of kidney stones, pre-index comorbidities associated with kidney stones, bariatric surgery, obesity, smoking history, baseline eGFR.

Results: 142,904 patients qualified for the study cohort. Patients with metabolic acidosis at index experienced kidney stones at greater frequency than those with normal serum bicarbonate at index (12% vs 9%, p<0.0001). Other significant factors associated with incident kidney stones included male sex, history of kidney stones, hyperoxaluria, gout and osteoporosis. Both higher serum bicarbonate at baseline (HR 0.956, 95% CI: 0.948-0.964) and higher serum bicarbonate over time (HR 0.968, 95% CI: 0.961-0.974) were associated with reduced risk of kidney stone development. The observed associations were unchanged in analyses examining death as a competing risk.

Conclusions: In patients with CKD, metabolic acidosis (vs. normal serum bicarbonate) was associated with a higher incidence of kidney stones and shorter time to incident stone formation. Future investigations should evaluate these associations by stone type.

Funding: Commercial Support - Tricida, Inc.

PO1163

The Association of Body Mass Index with the Development of Metabolic Acidosis in Patients with CKD

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Background: Bone is the largest body buffer and body mass index (BMI) is directly related to bone mass. We explored the relationship between BMI and incident metabolic acidosis in patients with CKD.

Methods: Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried to identify patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate values in the normal range (22 to <30 mEq/L), 28–365 days apart, with data ≥12 months pre-index during which covariates were assessed. The first qualifying serum bicarbonate test established the index date. The primary exposure variable was BMI category (World Health Organization classification). Other exposures included hypertension diagnosis, triglycerides ≥1.7 mmol/L, HDL cholesterol ≤1 mmol/L in women or ≤0.9 mmol/L in men. Adjusted Cox Proportional Hazards models were performed to evaluate the time to development of new-onset metabolic acidosis (serum bicarbonate 12 to <22 mEq/L) over a follow-up period of ≤11.5 years. Other covariates included age, sex, race, education and income status, diabetes or heart failure, eGFR, log albumin-to-creatinine ratio, angiotensin converting enzyme inhibitors or angiotensin receptor blockers prescription, and diuretic prescription.

Results: 97,294 patients qualified for this study. There was an inverse association between BMI category and the risk of developing metabolic acidosis. Compared to BMI category of 18.5-25, each incremental category of higher BMI was associated with a decreasing risk of developing metabolic acidosis: BMI 25 to <30, HR 0.866, 95% CI: 0.824-0.911; BMI 30 to <35, HR 0.770, 95% CI: 0.729-0.813; BMI 35 to <40, HR 0.664, 95% CI: 0.622-0.709; BMI 40+, HR 0.612, 95% CI: 0.571-0.655. Additionally, hypertension decreased and low HDL cholesterol and elevated triglycerides increased the risk of new-onset metabolic acidosis.

Conclusions: In this large cohort of patients with CKD, an incremental increase in BMI was inversely associated with the development metabolic acidosis. The mechanism of this association merits further study.

Funding: Commercial Support - Tricida, Inc.

PO1164

Effects of Pseudohyponatremia on the Diagnosis of Severe Metabolic Acidosis

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Introduction: Pseudohyponatremia is defined as falsely low sodium levels in plasma caused by severe hyperlipidemia or hyperproteinemia. We discuss a case of pseudohyponatremia due to hypertriglyceridemia in a patient admitted with severe metabolic acidosis and acetaminophen induced liver toxicity.

Case Description: 43-year-old male with hyperlipidemia, diabetes mellitus, and obesity presented with 4 day-history of abdominal pain, nausea, vomiting, and polydipsia. He had decreased intake and was not taking his insulin for 4 days. Medications include glargine insulin, dulaglutide, empagliflozin, glimepiride, rosuvastatin, fenofibrate and losartan. BP:141/59 mmHg, HR:125 bpm, respirations 28/min, Temperature: 98.7, SpO2. 95% on room air. He appeared clinically volume depleted. Laboratory testing revealed severely lipemic serum, elevated acetaminophen level 44.1 ug/ml, severely elevated transaminases, arterial pH: 7.03, pCO2 11 mmHg, HCO3 <5 mEq/l. Plasma sodium:109 mEq/L and chloride 81 mEq/l using indirect potentiometry and 131 and 111 mEq/l using direct potentiometry. Serum triglycerides 2951 mg/dl, blood glucose 204 mg/dl, plasma lactate 7.5 mmol/l, and creatinine 0.6 mg/dl. Plasma anion gap was 11 mEq/l using direct potentiometry and could not be calculated using indirect potentiometry, as bicarbonate concentration could not be determined due to lipemia. Based on severe metabolic acidosis, elevated lactate, and positive urinary ketones, a diagnosis of lactic acidosis and suspected euglycemic DKA was made. Patient was treated with DKA-protocol with insulin and fluid resuscitation, and N- acetylcysteine for acetaminophen induced liver toxicity. Metabolic acidosis markedly improved over the next 72 hours. Hypertriglyceridemia, transaminase elevations, and metabolic acidosis fully resolved during 6 week follow up visit.

Discussion: Severe hyperlipidemia reduces water content of plasma such that autoanalyzers utilizing indirect potentiometry requiring sample dilution, result in pseudohyponatremia. Direct potentiometry does not require sample dilution and measures true sodium concentration, however, plasma anion gap is reduced due to higher measured chloride concentrations with direct potentiometry. Therefore, physicians must be familiar with the laboratory methods to correctly interpret the plasma anion gap in mangagement of metabolic acidosis when using direct potentiomery measurements.

PO1165

Anion Gap Metabolic Acidosis on Continuous Renal Replacement Therapy: Are You Missing Something?

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Introduction: Anion gap metabolic acidosis is a common metabolic abnormality seen in the clinical practice. Causes includes Lactic acidosis, Ketoacidosis, Renal failure, volatile acid toxicity and salicylate poisoing. Ketoacidosis is due to decreased glucose and insulin availability leading to starvation ketosis and diabetic ketoacidosis respectively. Ketoacidosis is uncommonly seen in patients on prolonged continuous renal replacement therapy. We present 2 cases at Grady Hospital admitted with Acute hypoxic Respiratory Failure due to COVID 19 pneumonia, developed euglycemic ketoacidosis on Continuous Renal Replacement Therapy

Case Description: case 1: 73 male with the history of HTN, DM, CKD III admitted for acute hypoxic respiratory failure due to COVID 19 pneumonia. He was intubated on admission day 9. Course got complicated by hypotension during intubation leading to Acute Renal Failure on day 11. Patient was started on Renal Replacement Therapy on day 12 due to volume overload and acidosis. Day 19, Anion gap worsened and betahydroxybutyrate was elevated. Patient was started on insulin drip with resolution of acidosis on day 20. Case 2: 48 yo male with the history of HTN, DM II, CKD stage III admitted for Altered mental status, hypertensive emergency and cough. He was diagnosed with COVID 19 Pneumonia. Patient had non oliguric acute kidney injury on admission. Hospital day 11, patient was oliguric, volume overloaded and hyperkalemia prompted Renal replacement therapy initiation. Day 14, Anion gap worsened and betahydroxybutyrate was elevated. Tube feed were initiated and Dialysate prescription was reduced leading to resolution of anion gap on day 12.

Discussion: Diabetic ketoacidosis is a medical emergency commonly in patients with Type I DM but also in Type II DM patients as well. It occurs due to decrease insulin concentration or increase insulin resistance with or without decreased glucose availability leading to release of counterregulatory hormone and fatty acid metabolism producing ketoacids. Diagnostic criteria include pH <7.3, Serum HCO3 <18, Serum glucose >250 mg/dl and positive serum +/- Urine ketones. Euglycemic DKA is a subtype of DKA with serum glucose of <200 mg/dl. Incidence of Euglycemic DKA varies from 2.6-3.2%. Continuous renal replacement therapy is an under-recognized cause of Euglycemic DKA in patients with Diabetes Mellitus.

PO1166

A Wide-Awake Patient with Severe Hypoglycemia and Lactic Acidosis

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Introduction: Severe hypoglycemia is associated with altered mental status or loss of consciousness. We report an intriguing patient who had advanced liver disease and presented with severe hypoglycemia and lactic acidosis without any alteration in mental status.

Case Description: 57-year-old female with severe decompensated alcoholic liver cirrhosis, ascites and recurrent hepatic hydrothorax presented to the Emergency Room with worsening shortness of breath. She had poor oral intake except for actively consuming ethanol. Chest X ray revealed worsening right hydrothorax. Routine blood tests revealed severe hypoglycemia (serum glucose 28mg/dL, severe anion gap metabolic acidosis (arterial pH 7.11, serum bicarbonate 6mmol/L, anion gap 40 mmol/L) and acute kidney injury with elevation of serum creatinine to 2.2 mg/dl. Subsequent laboratory investigation revealed serum lactic acid level of 23mmol/L. Serum ethylene glycol, methanol, salicylate and acetaminophen levels were undetectable. She had no seizures, malignancy or hypoxia. The patient was alert and oriented. She was hemodynamically stable. There was no evidence of sepsis, tissue hypoperfusion or bowel ischemia. She was not taking any medications which may have led to hypoglycemia or lactic acidosis. The patient was administered intravenous glucose with rapid improvement of her serum glucose and lactate level.

Discussion: This patient had no alteration in mental status despite severe hypoglycemia. Under normal circumstances, the brain primarily depends on glucose as the primary fuel. Studies have shown that under conditions of hypoglycemia and elevated serum lactic acid levels, lactate may serve as an alternative source of energy for the brain. We hypothesize that hyperlactatemia, by providing an alternate energy source, prevented mental status changes in this patient with severe hypoglycemia. Correction of hypoglycemia led to rapid correction of hyperlactatemia suggesting that perhaps lack of glucose may have contributed to hyperlactatemia. We did not identify any obvious cause of hypoglycemia or hyperlactatemia except for her end stage liver disease, continued ethanol use and perhaps also her oliguric acute kidney injury. This patient illustrates that hyperlactatemia may be neuroprotective in severely hypoglycemic patients.

PO1167

Sleeping Beauty: Hypersomnolence and Hyperammonemia in a Patient with Multiple Myeloma

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Introduction: Metabolic encephalopathy in a patient with multiple myeloma is commonly reported in association with prevalent biochemical syndromes such as uremia, hypercalcemia, and or hyperviscosity due to immunoglobulin, but very rarely hyperammonemia has been described as another cause of encephalopathy.

Case Description: The patient is a 45 year old woman with a prior diagnosis of multiple myeloma in July 2020. A bone marrow biopsy confirmed plasma cell neoplasm with 90% plasma cells, and SPEP was positive for monoclonal IgA kappa. The patient was brought to the hospital again in August 2020, with the chief complaint of worsening confusion and hypersomnolence over two weeks. Labs included hemoglobin 7.3 g/dL, serum calcium 13.8 mg/dL, chloride 108 mEq/L, bicarbonate 16 mEq/L with anion gap of 19, lactate 1.4 mmol/L, albumin 3.2 g/dL, and a CT of the head showed numerous lytic skull lesions, including a 3.8 cm posterior skull lesion with extraosseous intracranial extension. ABG showed pH 7.56, pCO2 24.5 mmHg, pO2 63.3. Hypercalcemia was treated with medical therapies and improved. The nephrology service was called due to metabolic acidosis. Given the respiratory alkalosis, a plasma ammonia level was checked and noted to be elevated at 89 umol/L. Imaging of the liver was not compatible with cirrhosis. The patient was given oral lactulose for several days without improvement. To address the hyperammonemia, the patient was transferred to the ICU to begin CRRT and she also required intubation due to unsustainable respirations. The plasma ammonia level improved while on CRRT but the patient had a grim prognosis, was not a candidate for chemotherapy, and the family elected to pursue palliative care.

Discussion: Hyperammonemia is a rare complication of multiple myeloma and is associated with high inpatient mortality. CRRT can treat hyperammonemia that is refractory to medical therapy (Gupta et al, CJASN 2016). However, hyperammonemia is a poor prognosticator in patients with multiple myeloma. Hyperammonemia should be included in the differential diagnosis of metabolic encephalopathy in patients with multiple myeloma.

PO1168

Renal Outcomes and Safety Profile of Direct Peritoneal Resuscitation (DPR)

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Background: DPR is a novel technique used after damage control surgery where peritoneal dialysis fluid is continuously irrigated and drained from the peritoneal cavity in a open abdomen. This has been shown to improve intestinal perfusion, leading to faster abdominal closure. We analyzed the safety profile in terms of changes in the electrolyte profile.

Methods: This is a retrospective study of 17 patients who underwent DPR. All were treated using Dianeal 2.5% Ca 2.5 PD fluid for 2-16 days. The renal outcomes were analyzed. Patients who did not develop AKI were studied further. We evaluated changes in the serum sodium, potassium, phosphorus, calcium, and magnesium levels. The trend of creatinine was also evaluated.

Results: Our study showed that the AKI occurred in 11/17 patients (64.7%) of which 5 (45%) required renal replacement. Of the 6 patients without AKI, 3 had a rising trend of sodium which needed correction. Potassium trended downward slightly. All patients had low calcium even prior to initiation of DPR possible releated to the underlying clinical diagnoses, and the creatinine trended downward with levels remaining in the normal range.

Conclusions: Frequent AKI in these critically ill patients was not unexpected. It is plausible, though not demonstrated, that DPR by its mechanism of visceral vasodilation may have reduced this incidence somewhat. The trend toward higher sodium could be due to increased ultrafiltration effects. The downward trend of creatinine could have resulted from increased clearance by DPR. All the patients had decreased ionized calcium. Though present at the outset, the lower calcium bath may have contributed to its persistence. Magnesium, phosphorus and potassium remained stable. Due the convective and diffusive effects of the PD fluid used, safe use requires close monitoring of electrolytes and ultrafiltration to prevent volume shift and dysnatremia. Hypocalcemia can be mitigated by using a high calcium PD solution such as Dianeal 3.5% Ca.

	sodium			potassium			Magnesium		
	Day 0	Day2	Day4	Day 0	Day2	Day4	Day 0	Day2	Day4
patient 1	138	139	136	4.5	3.8	4.2	1.9	2.1	1.8
patient 2	138	138	135	4	4.5	3.9	1.8	1.7	2.1
patient 3	138	147	156	4.9	3.8	4.1	1.9	2.2	2.1
patient 4	135	137	143	4.5	3.7	3.6	2	1.9	2
patient 5	139	145	150	3.4	4.1	3.4	2	2.2	2.3
patient 6	140	139	142	3.9	4.3	3.4	1.8	2	1.9

	phosphorus			Calcium			creatinine		
	Day 0	Day2	Day4	Day 0	Day2	Day4	Day 0	Day2	Day4
patient 1	4.8	3.3	3.7	7.1	7.1	7.7	0.9	0.65	0.63
patient 2	3.3	2.8	3.2	7.4	7.8	7.8	0.97	0.85	0.72
patient 3	3.2	3.6	3.3	7.1	7.1	7.2	0.83	0.77	0.73
patient 4	3.9	3.6	2.9	7.2	7.7	7.5	0.7	0.68	0.6
patient 5	1.7	3.3	2.7	7.1	7.3	7.3	0.67	0.48	0.49
patient 6	4.1	3.5	3.4	7.2	7.2	7.1	0.54	0.54	0.48

PO1169

Pyroglutamic Acidosis: Gaps in the Gaps

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Introduction: Prolonged use of acetaminophen can lead to an acquired form of pyroglutamic acidosis, a form of anion gap metabolic acidosis (AGMA) from increased production of 5- Oxoproline (pyroglutamic acid). 5- Oxyproline accumulates in the body due to the failure its breakdown by 5- Oxoprolinase and is excreted in urine causing positive urine anion gap (AG).

Case Description: Case 1: First patient is a 59 y/o man with normal prior renal function with baseline creatinine (Cr) of 0.7mg/dl, admitted with severe pancreatitis. At the time of presentation his serum calcium level 15mg/dL (8.5-10.5) and his serum Cr level was 2.21 mg/dl. His hospital course was complicated by sepsis due to multiple intra-abdominal infections and required iv pressor and ventilator support. He was later started on continuous veno-venous hemofiltration (CVVH) temporarily with recovery of renal function. Acetaminophen 1 gram three times daily was administered for pain control. On the 65th day of hospitalization, his bicarb was 15 with an AG of 14, but when corrected for low albumin of 1.8, it increased to 20. HE had a positive urine AG and his urine 5-Oxyroline was 1583 mmol/mol Cr (range < 62). Case 2: Second patient is a 74-year-old man with a history of stage 4 CKD admitted with sepsis due to perforated viscus. He had long hospital course due to ischemic gut with continued bleeding and sepsis due to perforation. He was on Acetaminophen 1 gram four times daily for pain control. His serum bicarbonate started trending down to a nadir of 11 mmol/L on the 43rd day of admission. He had an anion gap of 12, but corrected anion gap was 18 and had a positive urine AG. His urine 5- oxyproline was 6361 mmol/mol creatinine (range <62).

Discussion: Both patients in our case series had critical illness, were malnourished, and was recovering from prolonged infection and sepsis which are risk factors for pyroglutamic acidosis and low serum albumin levels. Their AG might appear to be within normal range if not corrected for albumin. Urine anion gap is an indirect method of measuring urine ammonia excretion and is elevated in renal tubular acidosis and from excretion of organic anions like 5-Oxyproline and ketone bodies. Correction for AG is proposed as measured AG + 2.5× (“normal” albumin ~4.2 – measured albumin [g/dl]). This uncorrected “normal AGMA” with a positive urine AG due to pyroglutamic acidosis can mimic renal tubular acidosis and can be easily missed.

PO1170

Diffuse Large B Cell Lymphoma and Synchronous Colon Adenocarcinoma Presenting with Type B Lactic Acidosis Secondary to the Warburg Effect in a Hispanic Man

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Introduction: Lactic acidosis is a major metabolic dysregulation characterized by hyperlactatemia and acidemia that is commonly associated with tissue hypoperfusion. In very rare circumstances, hematological malignancies have been associated with a paraneoplastic syndrome characterized by the modification of the metabolism of cancerous cells from aerobic to anaerobic glycolysis.

Case Description: A 61-year-old male presented to the hospital due to generalized body weakness. He was recently admitted to the hospital due to left knee pain; at that time incision, drainage, and tissue sample were done. The patient was discharged to home with wound care and antibiotics. On presentation, patient was found to be tachypneic, hypotensive with Kussmaul breathing. A warm erythematous lesion was seen on left lower extremity. Laboratory results showed WBC 20200/mm3, Hemoglobin 10 g/dL, Platelets 340 /mm3, creatinine 7.9 mg/dL, Bicarbonate 5 mmol/L, Lactate 6.21 mg/dL, and Ferritin 326 ng/dL, blood cultures positive for Enterobacter. Broad-spectrum antibiotics were administered. Nephrology consulted and dialysis started emergently. The pathology report showed Diffuse Large B-Cell Lymphoma. During the hospital stay, patient acidosis was persistent despite adequate renal replacement therapy and resolution of the septic process. ABG was done showing serum pH of 7.2, Bicarbonate 9 mmol/L, Lactic acid 17.5 mg/dL. Bowel ischemia was ruled out with CT angiogram however imaging showed neoplastic infiltration of peritoneal abdominal structures associated with multiple small nodules. Colonoscopy demonstrated synchronous colon adenocarcinoma. The decision was made to treat the patient with chemotherapy. One week after chemotherapy lactic acid trended down to 1.1 mg/dL. The metabolic acidosis and renal function improved and RRT was stopped.

Discussion: Usually, lactic acidosis is a sign of hypoperfusion and septic shock. In this case, the source of lactic acidosis was not hypoperfusion but rather a rare paraneoplastic syndrome that leads to anaerobic metabolism of malignant cells, known as the Warburg effect. This condition can be fatal. Prompt initiation of chemotherapy is recommended

PO1171

Distal Renal Tubular Acidosis in Patients with Autoimmune Diseases

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Background: Distal renal tubular acidosis (DRTA) is reported in association with autoimmune diseases. DRTA can evolve without symptoms and systemic acidosis, this form being defined as incomplete DRTA. The incomplete form necessitates the use of a urinary acidification test like the Furosemide and Fludrocortisone test for establishing the diagnosis.

Methods: We conducted a prospective observational study in a selected cohort of 48 patients diagnosed with autoimmune diseases (SLE, Sjögren syndrome, ANCA vasculitis, cryoglobulinemic vasculitis), who presented in our clinic from December, 2020 until May, 2021. The patients were submitted to Furosemide and Fludrocortisone test.

Results: The study included 48 patients (36 females, mean age 41.92 ± 15.7 years), diagnosed with SLE (33 patients), pANCA vasculitis (7 patients), cANCA vasculitis (1 patient), Sjögren syndrome (3 patients) and cryoglobulinemic vasculitis (4 patients). There was a significant difference regarding age ($p<0.001$) and eGFR ($p<0.001$) between the groups with vasculitis (mean age 60.7523roups with vasculitis ± 7.47 years, eGFR 41.66 ± 16.71 ml/min/1.73 m^2), SLE (mean age 35.18 ± 11.74 years, eGFR 73.24 ± 25.18 ml/min/1.73 m^2) and Sjögren syndrome (mean age 40.65 ± 20.03 years, eGFR 35.56 ± 17.24 ml/min/1.73 m^2). The test was positive for 11 patients out of 48. There was not a significant change in kalemia during the test ($p=0.860$). There was a significant increase in the level of serum bicarbonate (26.23 ± 3.5 mmol/l before the test vs 28.21 ± .13 mmol/l after the test, $p<0.001$) and also in the level of serum pH (7.36 ± 0.44 before the test vs 7.38 ± 0.43 after the test, $p=0.001$). None of the patients reported digestive or allergic side effects. There was not a significant difference regarding eGFR ($p=0.665$), proteinuria ($p=0.372$) and CRP ($p=0.246$) between the patients with or without a positive test. Regarding immunological activity, patients with a positive test had a higher ANA value at the moment of the test (4.71 ± 3.04 U/ml vs 2.50 ± 2.55 U/ml, $p=0.05$) and a lower C4 value (12.66 ± 9.39 mg/dl vs 23.4 ± 11.54 mg/dl, $p=0.016$).

Conclusions: Incomplete DRTA was found in 11 out of 48 patients with autoimmune diseases. None of the patients developed severe hypokalemia or metabolic alkalosis or any other side effect after Furosemide and Fludrocortisone test.

PO1172

Effect of Continuous Dialysis on Blood pH in Acidaemic Hypercapnic Animals with Severe AKI: A Randomized Experimental Study Comparing High vs. Low Bicarbonate Affluent

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Background: Controlling blood pH during acute ventilatory failure and hypercapnia in individuals suffering from severe acute kidney injury (AKI) and undergoing continuous renal replacement therapy (CRRT) is of paramount importance in critical care settings. In this situation, the concentration of sodium bicarbonate in dialysate is still an unsolved question in critical care since high concentrations may worsen carbon dioxide levels and low concentrations may not be as effective in controlling pH.

Methods: We performed a randomized, non-blinded, experimental study. AKI was induced in twelve female pigs via renal hilum ligation and hypoventilation by reducing the tidal volume during mechanical ventilation with the goal of achieving a pH between 7.10 - 7.15. After achieving the target pH, animals were randomized to undergo isovolemic haemodialysis with one of two concentrations of bicarbonate dialysate (40 mEq/L [*group 40*] vs. 20 mEq/L [*group 20*]).

Results: The haemodynamic, respiratory, and laboratory data were collected. The median pH value at CRRT initiation was 7.14 [7.12, 7.15] in *group 20* and 7.13 [7.09, 7.14] in *group 40* (P=ns). The median baseline $PaCO_2$ was 74 [72, 81] mmHg in *group 20* vs. 79 [63, 85] mmHg in *group 40* (P=ns). During the last hour of CRRT, the pH value was 7.05 [6.95, 7.09] in *group 20* and 7.12 [7.1, 7.14] in *group 40* ($P<0.05$), with corresponding values of $PaCO_2$ of 85 [79, 88] mmHg vs. 81 [63, 100] mmHg (P=ns). The difference in pH after three hours was due to a metabolic component [standard base excess: -10.4 [-12.5, -9.5] mEq/L in *group 20* vs. -7.6 [-9.2, -5.1] mEq/L in *group 40*) ($P<0.05$)]. Despite the increased infusion of bicarbonate in *group 40*, the blood CO_2 content did not change during the experiment. The 12-hour survival rate was higher in *group 40* (67% vs. 0, p=0.032).

Conclusions: A higher bicarbonate concentration in the dialysate of animals undergoing hypercapnic respiratory failure was associated with improved blood pH control increasing the $PaCO_2$ levels.

PO1173

CRRT-Associated Ketoacidosis: A Series of 5 Cases

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Introduction: Continuous renal replacement therapy (CRRT) is a dialysis modality used in critically ill patients with acute kidney injury (AKI). Although most dialysate and replacement fluids are dextrose-containing, CRRT-associated hypophosphatemia sometimes warrants the use of phosphorus containing solutions which are dextrose-free. As glucose is a small molecule which is readily cleared with dialysis, use of these solutions can result in increased dialysate caloric loss, net glucose deficit, and shifting of the metabolic pathway towards gluconeogenesis and ketogenesis. Starvation ketoacidosis can result, which at times can be severe.

Case Description: We describe five patients who developed worsening metabolic acidosis despite adequate clearance from CRRT, and were diagnosed with CRRT associated ketoacidosis (Figure 1 describes the clinical details, lab values and follow up of these patients) Administration of dextrose containing fluids or tube feeds promptly resulted in resolution of ketonemia and acidosis.

Discussion: These cases present an interplay of three processes ultimately culminating in a state of net glucose deficit: (1) decreased glucose supplementation in the critically ill patient, (2) increased clearance of glucose via CRRT with dextrose-free solutions and (3) AKI leading to deranged kidney gluconeogenesis. New HAGMA in patients on CRRT in the ICU can frequently be attributed to inadequate CRRT dose. The reflex increase in dialysate or replacement fluid flow rate is associated with a slew of problems including electrolyte abnormalities, decreased effectiveness of antibiotics due to increased clearance all of which can be detrimental to the patient. A new consideration that must be made when utilizing dextrose free CRRT fluids is CRRT associated ketoacidosis. Early identification of this diagnosis is important and easily reversible.

	Case 1	Case 2	Case 3	Case 4	Case 5
Bicarbonate & Anion Gap prior to initiating CRRT	12;26	14; 25	16; 20	21;15	19;17
Bicarbonate & AG on day 1 of CRRT	15; 26	20; 26	19; 18	23;11	23;14
Bicarbonate & AG on day of [illegible]	17; 17	13; 24	17; 16	15; 20	19; 19
Lowest Bicarbonate and Associated Anion Gap	14;25	10;25	16;20	15;20	18;19
Glucose prior to initiating CRRT	127	137	190	113	93
Lowest Glucose after initiation of CRRT	92	84	88	85	94
Lactate	1.3 (day 3 of CRRT)	1.2 (day 3 of CRRT)	1.3 (Day 3 of CRRT)	1.2 (Day 1 of CRRT)	0.8 (Day 3 of CRRT)
Beta Hydroxybutyrate	4.8 (Day 3)	5.4 (Day 10)	3.7 (Day 2) 0.5 (Dav 6)	3.7 (Day 4 of dextrose-free solution)	1.5 (Day 3)
CRRT Fluid	Prismasate 0 K/3.5 Ca/0	Phoxillum BK 4 / 2.5	Prismasol 4K /2.5 Ca	Phoxillum BK 4 / 2.5 Ca	Phoxillum BK 4 / 2.5 Ca
Effluent dose	31 (Day 0) 44 (Dav 3)	29 (Day 0) 41 (Day 7-	28	26	31
Treatment	dextrose 5% + sodium chloride	N/A	dextrose 10% at	Discontinuation of dextrose-free solution	dextrose 5% at 50cc/hr and discontinuation of
Bicarbonate & Anion Gap after initiation of	19; 15	N/A	20; 10	23;9 (1 day after discontinuation of	22;12

PO1174

A Patient with Combined Metformin-Induced Lactic Acidosis and Euglycemic Diabetic Ketoacidosis

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Introduction: Metformin is a small, non-protein-bound molecule that can cause lactic acidosis in 6 out of 100,000 patients with a mortality rate of 30-50%. Concurrent euglycemic diabetic ketoacidosis (DKA) from sodium-glucose co-transporter-2 (SGLT2) inhibitor has been reported in one case. We report a unique case of a patient with acute kidney injury (AKI) in the setting of metformin-induced lactic acidosis and osmotic diuresis due to euglycemic DKA complicated by celecoxib use.

Case Description: A 66-year-old female with a past medical history of type 2 diabetes mellitus for 21 years on metformin 1000 mg twice daily and empagliflozin 25 mg daily with baseline eGFR 51 mL/min/1.73m^2 5 months prior, who was also on celecoxib 200 mg daily for 40 days presented for elective cervical discectomy which was canceled due to AKI. On exam, blood pressure was 119/59 mmHg, pulse was 92 beats/min, and the temperature was 36.1°C. She was tachypneic at 24 breath/min. Labs showed sodium 136 mg/dL, potassium 8.4 mg/dL, bicarbonate 9 mg/dL, BUN 83 mg/dl, creatinine 8.78 mg/dL, and glucose 117 g/dL. Lactic acid was 13.5 mmol/L, beta-hydroxybutyrate 5.9 mmol/L, serum osmolality 336 mOsmol/kg with no osmolar gap. She underwent conventional hemodialysis (HD) for 3 hours followed by 18 hours of continuous kidney replacement therapy (CKRT). She required an insulin drip with 5% dextrose in normal saline for 24 hours. Lactic acid was 3.8 mmol/L after 24 hours. Creatinine improved to 2.46 mg/dL on day 4 without further intervention. She was discharged home off metformin, empagliflozin, and celecoxib.

Discussion: Metformin is readily dialyzable but has a large volume of distribution. There is no specific antidote available to reverse the toxic effects of metformin or consensus on the modality of renal replacement therapy. Previously demonstrated biphasic elimination pattern of metformin intoxication suggests that a brief HD session is not sufficient to eliminate metformin due to a rebound phenomenon, but it is essential to correct severe acidosis and electrolyte derangements. Hyperkalemia required the use of HD which needed to be followed by CKRT as a more physiological way to maximize metformin removal and prevent ongoing lactic acid production. We suggest prudence in the combination of metformin with SGLT2 inhibitor use, specifically in patients exposed to nephrotoxic drugs or procedures.

PO1175

Mind the Gap: An Anion Gap of 52 Fully Explained

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Introduction: The Anion Gap (AG) remains the main clinical tool to elucidate acid-base disturbances in patients with metabolic acidosis. We present a case with an extremely elevated AG of 52 mmol/L, and describe our search for its biochemical explanation.

Case Description: A 66-year-old female was admitted with loss of consciousness, shock, and severe acute kidney injury. She had type 2 diabetes mellitus, treated with metformin. At presentation, she had an AG of 52 mmol/L and osmolal gap of 34 mOsm/kg. Her arterial blood gas showed: pH <7, HCO3 7.5 mmol/L, pCO2 16 mm/Hg. Phosphorus level was unusually high, 21.3 mg/dL, with unknown etiology. There was no history of enema or laxative use. A significant contributor of AG was lactate at 14.5, given her history of metformin use. Urine drug screen was positive for amphetamines. The volatile alcohol panel was positive for acetone; methanol, ethanol, ethylene glycol and isopropyl alcohol were not detected. Continuous venovenous hemofiltration (CVVH) was initiated. After 3 days, renal function started recovering, lactate and phosphorus levels normalized and AG closed. The patient did not need CVVH thereafter. Two months later, the patient was discharged to a nursing facility in a stable condition.

Discussion: Extremely elevated AG of 52 in this patient can be explained by a rise in concentrations of organic acid anions, lactate, ketoacids, hyperphosphatemia, and retention anions.

AG 52 **Albumin cAG 55**	Lab values **Sodium 135 mmol/L, Chloride 76 mmol/L, Bicarb 7 mmol/L, Phosphorus 21.3 mg/dL, Albumin 3.2 g/dL, Lactate 14.5 mmol/L, β-hydroxybutyrate 8.17 mM**
Contributions to Anion Gap, mmol/L	Explanation
P/ 12.36	([Lab phosphorus, mg/dL*10] / 31 (molecular weight of phosphorus)) * 1.8 (average valency depending on pH) [(21.3 *10)/31] * 1.8 = 12.36 mM/L
Lactate 14.5	Lactate is univalent and not influenced by pH Measured lactate = contribution to AG=14.5 mM/L
βHB 8.17	β-hydroxybutyrate is univalent and not influenced by pH Measured βHB = contribution to AG = 8.17 mM/L
Normal AG 12	Unmeasured anions Various inorganic and organic anions
Remaining AG 7.97	Accumulated anions due to severe Acute Kidney Injury (creatinine 12.4 at presentation) (sulphate and hippurate)

Explanation of the high AG: The Figure describes the calculation of AG. In this patient, phosphate was a major contributor to the AG.

PO1176

Is an Increase in Anion Gap a Predictor of Hemodialysis Initiation in Patients with Advanced CKD?

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Background: Because uremic symptoms and manifestations vary among patients with advanced chronic kidney disease, it is sometimes difficult to decide on the timing of dialysis initiation only from them. Thus, we attempted to investigate whether anion gap (AG) that may reflect the accumulation of total organic acids in uremia can be a marker of uremia and may predict the timing of dialysis initiation.

Methods: This study included pre-dialysis patients who attended to our hospital for more than six months prior to the beginning of hemodialysis (HD), and retrospectively analyzed the relationship between their serological data, AG, and various uremic symptoms. The AG was calculated as the corrected AG (cAG) = Na-Cl-HCO_3 [nmol/L]+2.5 x (4-serum albumin concentration [g/L]). The statistical analysis was performed by logistic regression analysis, correlation analysis, and factor analysis using SPSS®.

Results: A total of 283 patients [diabetes mellitus: 136 (48.1%), nephrosclerosis: 66 (23.3%), glomerulonephritis: 36 (12.7%)] were included in this study. The most common clinical symptom before dialysis initiation was fluid overload, which was seen in 134 patients (47.3%), followed by anorexia 104 patients (36.7%) and general malaise 96 patients (33.9%). The cAG began to increase 3 months before the initiation of HD (14.2 mmo/L), which showed a rapid increase just before the initiation, and was correlated with anorexia and fatigue, better than fluid retention. Of note is that cAG was most significantly associated with dialysis initiation among various factors. The ROC of cAG for dialysis initiation showed the highest value of AUC 0.797 (95% CI=0.72 to 0.85, p=0.05), with a cutoff value of adjusted cAG 15.975 (sensitivity 0.689, specificity 0.786).

Conclusions: Uremic symptoms and some serological markers including azotemia, metabolic acidosis, and hyperphosphatemia have been usually used to predict the magnitude of uremia and the timing of dialysis initiation. In our study, it is suggested that a rapid increase in cAG over 16 mEq/L may also be a good predictor of dialysis initiation within the subsequent 3 months.

PO1177

Mysterious Case of Recurrent Life-Threatening Lactic Acidosis

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Introduction: Patients living with diabetes are prone to type-B lactic acidosis, often presenting with profound acid-base derangements. The reason for lactate production is not obvious hence management can be challenging. We present a case of life-threatening recurrent lactic acidosis in a diabetic patient.

Case Description: A 67-year-old man with type 2 diabetes, hypertension, presented to the hospital with malaise for 2 days. He had been on metformin in the past but had recently switched to insulin. There was no history of alcohol ingestion nor use of herbal supplements. The lactic acid level was 24.2 mmol/L with Ph of 6.82, PCO2 of 27 mmHg, serum bicarb of 7 mEq/L, anion gap of 28, and serum Cr of 1.4 mg/dL with baseline of 1 mg/dL. No evidence of infection or ischemia found. Toxicology screen was negative and serum metformin level was undetectable. Lactic acidosis resolved with continuous renal replacement (CRRT) for 24 hours. A month later he returned with similar complaints

and his lactate level was 14.8 mmol/L. This was treated with supportive care alone. Six months later he returned again with lactate of 13.5 mmol/L, worsening to 18.6 mmol/L. He improved after treatment with CRRT and supportive care. Alcohol levels, liver function tests, pyruvate, glutamate, metformin levels were all negative or normal. The thiamine level was not checked during his first admission. During the second visit, the value was normal but this was drawn after thiamine had been given. During the third visit, the thiamine level was noted to be less than 6 nmol/L. The patient was started on thiamine and has not had further episodes of lactic acidosis.

Discussion: Patients with diabetes are prone to excess lactic acid generation due to the derangement in mitochondrial oxidative phosphorylation with relative hypoxia at the microvascular level. In addition, it has been noted that many diabetics are thiamine deficient. In the absence of thiamine, pyruvate cannot enter the Krebs cycle and is converted to lactic acid predisposing diabetics to type-B lactic acidosis. Thiamine is filtered in the glomerulus and is reabsorbed in the proximal tubule through the thiamine/H+ antiporter. Long term use of diuretics has been associated with thiamine deficiency. However our patient was not taking any nor did he have chronic kidney disease or any evidence of malnutrition.

PO1178

Serum Bicarbonate and Gait Abnormalities in Older Adults

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Background: Low serum bicarbonate levels are associated with slow gait speed in older adults. However, the association between serum bicarbonate and other quantitative gait markers is unknown.

Methods: Quantitative gait assessments were performed on 330 community-dwelling, nondisabled adults ≥65 years old. Serum bicarbonate was categorized into tertiles (≤24, 25-27, ≥28 mEq/L). The relationship between bicarbonate and gait markers was investigated with multivariable linear regression adjusting for demographics, comorbidities including COPD, medication use, smoking status, BUN, and eGFR (CKD-EPI). Factor analysis on eight gait markers was performed to synthesize individual gait characteristics into unifying domains. CKD was defined as eGFR<60 mL/min/1.73 m^2.

Results: There were 116 (35%), 146 (44%), and 68 (21%) participants in the low (mean bicarbonate 22 mEq/L), middle (26 mEq/L), and high (29 mEq/L) bicarbonate tertiles, respectively. After multivariable adjustment, compared with participants in the middle tertile, those in the low tertile had significantly slower speed (8.4 cm/s [95% CI 3.1-13.8]), shorter stride length (7.7 cm [95% CI 3.4-12.1]), and longer time in the double support phase of the gait cycle (0.03 s [95% CI 0.002-0.05]). Within the lowest tertile, there was a graded association of lower bicarbonate with greater severity of gait deficits (Figure 1). Associations were similar when limited to participants with CKD. Associations remained significant after additional adjustment for muscle strength, cognitive function, sensory nerve function, and balance. No significant associations were found for the high tertile or for other gait markers (e.g., cadence). Factor analysis produced 3 independent gait domains: pace, rhythm, and variability. Compared with the middle tertile, the low tertile had significantly poorer performance in the pace domain (0.3 standard deviation [95% CI 0.1-0.6]).

Conclusions: Low serum bicarbonate is associated with gait abnormalities in older adults.

Funding: Other NIH Support - NIA

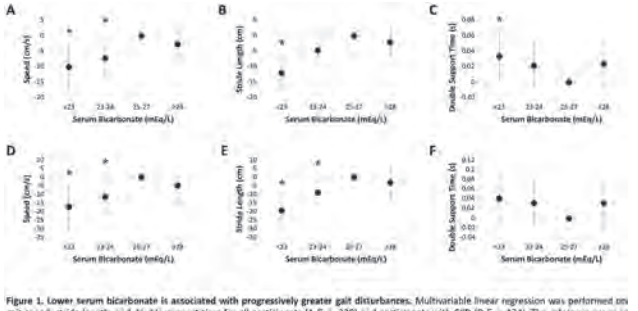

Figure 1. Lower serum bicarbonate is associated with progressively greater gait disturbances. Multivariable linear regression was performed on gait speed, stride length, and double support time for all participants (A-C, n=330) and participants with CKD (D-F, n=134). The reference group is serum bicarbonate 25-27 mEq/L (middle tertile). Models were adjusted for age, sex, race, education, smoking status, BMI, number of comorbidities, number of medications, diuretic use, diagnosis of neuropathy, cardiovascular disease, hypertension, diabetes, COPD, BUN, and eGFR (CKD-EPI). Error bars denote 95% confidence intervals. Asterisks denote $P < 0.05$.

PO1179

Bicarbonate Target in Treating Renal Acidosis: Is Higher Better?

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Background: Metabolic acidosis is commonly seen in patients with CKD from a decrease in ammonium excretion which gets buffered by the extracellular bicarbonate, hence, low plasma carbon dioxide is a surrogate of acidosis. treatment of acidosis (usually sodium bicarbonate to decrease the progression of, maintain bone health, nutrition status, In clinical practice, we aim for plasma bicarbonate of ≥ 22 mmol/L, the upper limit target is unclear.

Methods: This was a single-center retrospective chart review of CKD patients with acidosis from 2010-2017. Inclusion criteria were adult patients receiving NaHco3 for CKD-associated acidosis with baseline estimated glomerular filtration rate (eGFR) ≥25 and < 60 ml/min/1.73 m^2 when starting NaHco3. Patients with glomerulonephritis, kidney transplant, acute kidney injury (not back to at least 75% of (eGFR) baseline) were excluded. Four groups were identified for comparison based on mean serum Co2 (in mmol/L), from outpatient measures during 3 years follow-up, group A (< 22), group B (22 - < 24), group C (24 - <25), and Group D (≥ 25). Albumin, urine protein-creatinine ratio (UPCR), PTH, and eGFR were compared, p-values are calculated by a one-way ANOVA model.

Results: There were 383 patients with CKD-associated acidosis receiving NaHco3, 93 patients qualified for the study. Group A (n=21), group B (n=41), group C (n=13), and Group D (n=18). Racial demographics: 35=black (38%), 57=white (61%), 1=Other. Females 49 (53%). Median age 69 years. Follow-up 3 years. At baseline mean eGFR, UPCR, and albumin, and diuretics use and osteoporosis diagnosis in the four groups were similar (p = 0.46, 0.32, 0.15, 0.09, 0.36 respectively). Mean hemoglobin A1C in each group did not exceed 8.2. At 3 years of follow-up, changes in eGFR, UPCR, and osteoporosis status between the four groups were similar (p ≥ 0.14, ≥ 0.27, ≥ 0.19 respectively). Change of albumin was significantly worse in group A comparing to groups B, and C (p = 0.007, 0.049 respectively), and average PTH was significantly worse in group A comparing to group C (p = 0.045).

Conclusions: In our cohort, all groups of treated CKD-associated acidosis (B, C, and D) showed no statistical difference in CKD progression, the severity of parathyroidism, developing osteoporosis, or nutrition status assessed after 3years follow-up. Hence, higher Co2 targets don't carry worse outcomes.

PO1180

Acute Metabolic Alkalosis due to Citrate-Containing Oral Rehydration Solution

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Introduction: Patients with ileostomies have high obligatory gastrointestinal (GI) losses, predisposing to volume depletion and electrolyte derangements. Over-the-counter oral rehydration solutions (ORS) are advertised for dehydration. We present a case of acute metabolic alkalosis associated with an ORS containing citrate.

Case Description: 66 year old man with Crohn's disease, status post small bowel excision, sigmoid colectomy with Hartman's pouch, and ileostomy presented with weight loss and hypotension. He had high output ileostomy loss of > 3 L per day. Initial lab work showed acute kidney injury (AKI), hyponatremia, hypokalemia, and metabolic alkalosis. Nephrology obtained history that for several months he consumed about 8-10 ORS packets daily (Figure). The patient was treated with IV 0.9% sodium chloride, potassium repletion, and cessation of ORS, which resulted in complete resolution of his metabolic disturbances.

Discussion: We present a novel case of acquired acute metabolic alkalosis due to consumption of citrate containing ORS. In the body, 1 citrate is converted by liver, kidney, and muscles to 3 bicarbonate equivalents. Our patient's volume contraction and pre-renal AKI due to high GI output resulted in elevation of aldosterone leading to increased urine potassium excretion, and alkalosis secondary to augmented ammonia excretion. This was compounded by the high citrate load and low GFR. The ORS distributor would not disclose the full amount of citrate per packet despite several contact attempts. Each standard size ORS contains 330 mg of sodium. Presuming similarity to prescription sodium citrate-citric acid solutions, which are 1:1 equimolar sodium and bicarbonate equivalent, we estimate a minimum bicarbonate equivalent of 14.3 mmol per ORS packet, or 143 mmol daily for our patient. This is before accounting for contributions of potassium and magnesium citrate components, thus potentially higher. We recommend cautious use of citrate-containing ORS, particularly in patients with risk for severe volume depletion and AKI.

	Admission Value
Blood	
Sodium (mmol/L)	130
Potassium (mmol/L)	2.3
Chloride (mmol/L)	66
Total CO2 (mmol/L)	43
BUN (mg/dl)	47
Creatinine (mg/dl)	2.27 (baseline 1.03)
Urine	
pH	7
Sodium (mmol/L)	< 10
Potassium (mmol/L)	57
Chloride (mmol/L)	< 15

PO1181

Pseudo-Hypobicarbonatemia with Severe Hypertriglyceridemia Corrected by Insulin Infusion

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Introduction: Anion gap metabolic acidosis (AGMA) is a condition characterized by low serum bicarbonate and unaccounted anions in the blood. Lactate or ketones are the most common anions causing AGMA. Severe hypertriglyceridemia and paraproteinemia can result in Pseudo-hypobicarbonatemia due to interference by these components when the commonly used enzymatic assay is utilized for serum bicarbonate measurement. The calculated bicarbonate derived from blood gas machines show accurate bicarbonate level. It is very important to recognize Pseudo- hypobicarbonatermia to avoid expensive work-up.

Case Description: A 42-year-old-male patient with a past medical history significant for diabetes mellitus type 2, obesity, and hyperlipidemia. The patient presented with nausea, vomiting and epigastric pain. Physical examination was significant for tenderness in the epigastrium and xanthelasma. The basic metabolic profile (BMP) was significant for Na^+ 127meq/L, Cl^- 94mEq/L, $HCO3^-$ 9mEq/L, glucose 408mg/dL, BUN 10mg/dL, creatinine 0.87mg/dL and AGAP 24. A lipid panel showed a cholesterol 461mg/dL and triglycerides 4061mg/dL. Lipase and amylase were 1183U/L and 202U/L respectively. Urinalysis revealed trace ketones. CT abdomen revealed peripancreatic stranding. The patient was diagnosed with AGMA due to diabetic ketoacidosis and pancreatitis secondary to hypertriglyceridemia. An arterial blood gas analysis (ABG) subsequently revealed a pH 7.39, paCO2 40, PaO2 73 and a HCO3- 24. A significant dissociation between the calculated and measured bicarbonate was noted. Following aggressive lowering of the triglycerides, with Insulin infusion there was an immediate resolution of the pseudo-hypobicarbonatemia and anion gap metabolic acidosis.

Discussion: This measurement error is due to the mechanism by which the analyzer interprets the bicarbonate level in the serum. Most analyzers utilize either anion-selective electrode (ISE) or function via an enzymatic/photometric method. High amounts of lipid particles may cause light scattering altering the photometric analysis. This likely caused the discrepancy between the enzymatic/photometric measured serum bicarbonate and the calculated bicarbonate of the aqueous phase ISE analyzer used by the ABG. Clinicians should be able to recognize that its essential to obtain a blood gas sample for determination of the acid-base status to avoid expensive work up.

PO1182

Pseudohypobicarbonatemia in a Patient with Paraproteinemia

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Introduction: The first step in acid-base disorders' diagnosis is obtaining measurement of blood bicarbonate (HCO3-), pH and partial pressure of carbon dioxide (pCO2) levels. Blood HCO3- levels are estimated via two methods: direct measurement of serum total carbon dioxide (TCO2), or via Henderson-Hasselbalch equation using arterial blood and directly measuring pH and pCO2 levels. With the enzymatic method, there have been reported cases of falsely low serum HCO3- due to interference by elevated triglyceride levels, but only two cases have been reported of spuriously low serum HCO3- due to interference by paraproteins.

Case Description: A 74-year-old male with a history of bladder carcinoma in situ and hypertension presented with complaints of malaise after a recent bladder irrigation. Basic metabolic panel (BMP) was unremarkable except for a HCO3- of 8 mmol/L measured using a Siemens Vista (SV) enzymatic chemistry analyzer. He was hospitalized for high anion gap metabolic acidosis with anion gap of 22. He was started on intravenous NaHCO3 (150 mEq/L) after nephrology was consulted. Repeat serum HCO3- was 11 mmol/L the next day with transition to oral NaHCO3 650 mg therapy thrice daily. On outpatient follow-up, he had low serum HCO3- ranging from 8-11 mmol/L (using SV analyzer) despite his reported compliance with NaHCO3. He was evaluated by another nephrologist with repeat BMP and an arterial blood gas (ABG). The results revealed a serum HCO3- of 8 mmol/L in contrast with ABG pH of 7.41 and HCO3- of 25 mmol/L. Due to the discrepancy, his serum HCO3- was analyzed at a different facility using a Beckman Coulter analyzer which revealed a normal serum HCO3- level of 21 mmol/L. Further work up was pursued with SPEP and SIFE revealing an M-spike and presence of IgM and IgA kappa monoclonal proteins respectively, which led to a diagnosis of monoclonal gammopathy.

Discussion: Paraproteins have been reported to cause interference with multiple laboratory test results. Paraproteins in our case may have resulted in artifactual error of serum HCO3- by direct interaction with assay reagents, binding of paraproteins to an assay reagent, or turbidity caused by precipitation of the monoclonal proteins. Our case highlights the importance of being aware of this phenomenon of pseudohypobicarbonatemia that can occur with certain chemical analyzers.

PO1183

Proton Pump Inhibitor (PPI) for the Treatment of Metabolic Alkalosis due to Gastric Losses

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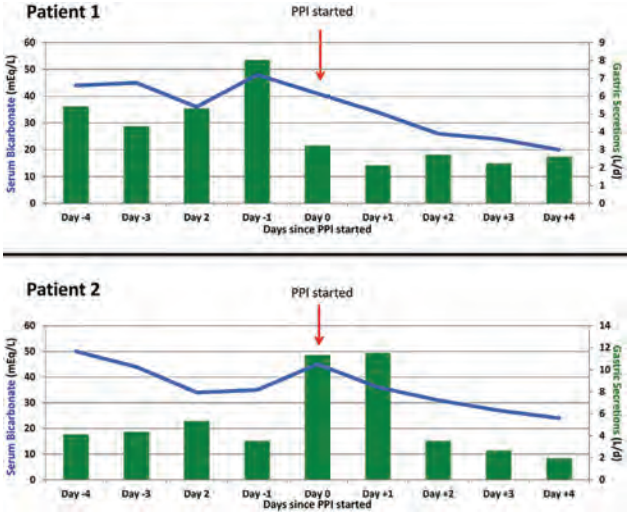
Introduction: Gastric losses of hydrochloric acid can result in severe metabolic alkalosis (met alk). We describe two cases where patients with significant losses of gastric secretions presented with severe met alk and AKI. In both cases, PPI therapy was used to reduce the volume of the gastric secretions with excellent effect.

Case Description: Patient 1: A 44 year-old woman with Gardner Syndrome with near-total enterectomy and colectomy on total parenteral nutrition with a venting gastric tube (G-tube), presented with met alk (HCO_3 50 meq/L) and AKI (Scr 4 mg/dL from baseline 1.3 mg/dL). Met alk persisted despite normal saline (NS) administration and gastric tube losses ranged from 4-8 liters per day. Twice daily intravenous PPI was started with immediate decrease of gastric losses and normalization in HCO_3. This patient was admitted one year later (off PPI therapy) with a similar derangements and resuming PPI therapy caused similar improvement. Patient 2: A 59 year-old man with gastric outlet obstruction and venting G-tube presented with met alk (HCO_3 47 meq/L) and acute kidney injury (SCr 4.5 mg/dL from 1.3 mg/dL). Met alk persisted despite NS administration and his gastric tube losses ranged from 4-11 liters per day. Daily intravenous PPI was started with decrease of gastric losses and normalization of HCO_3. This patient presented again to the hospital one month later with normal HCO_3, on PPI therapy. Both patients' bicarbonate and gastric fluid output trend relative to PPI therapy is detailed in figure 1.

Discussion: There are few reported cases of PPI therapy for metabolic alkalosis due to gastric losses. Generally, met alk that occurs due to gastric losses is readily rectified by increased renal bicarbonate excretion, but this compensatory mechanism is limited in the setting of AKI. We report two cases in which PPI therapy successfully decreased the quantity of gastric fluid losses and rapidly improved metabolic alkalosis.



PO1184

A Case of Extreme Metabolic Alkalosis

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Introduction: Metabolic alkalosis results from an increase in serum bicarbonate concentration due to loss of hydrogen ions and/or gain in bicarbonate ions. We present a case of extreme metabolic alkalosis due to multiple etiologies rarely co-existing.

Case Description: A 30-year-old male with Duchenne muscular dystrophy, chronic respiratory failure on mechanical ventilation via tracheostomy, gastrojejunostomy (G-J) tube dependent and genetic cardiomyopathy presented with drowsiness and lethargy for last 2 days per mother. His tube feed regimen was Nutren 1 can with 120 cc free water 4 times/day. He was recently started on Lasix 20 mg daily. Initial labs showed blood PH of 7.81, bicarb 66 and PCo2 53. He had AKI with Creatinine (Cr) of 2.66, BUN 266 and Cystatin C 11. His baseline Cr was 0.9-1.1. UA showed 3+ protein and no sediment. Urine (Ur) sodium 87, Ur chloride <15, Ur Cr <10 and Ur PH was 9. Chest Xray showed cardiomegaly with mild venous congestion and kidney ultrasound showed bilateral small echogenic kidneys. He was treated with normal saline (NS) IV @100 cc/hr, acetazolamide IV, potassium IV, proton pump inhibitor to decrease gastric acid and minute ventilation was decreased to allow for compensatory hypercapnia. AKI improved with adequate diuresis and PH normalized (Image 1) by day 5. He had hypernatremia after 24 hours of IV NS and fluid were changed to hypotonic + free water via G-J tube. High daily output of ~700cc was recorded from the G-J tube. He was discharged home without diuretics and tube feeds were changed to Suplena + increase free water but was re admitted in 1 week with hyponatremia and severe metabolic alkalosis. He underwent G-J tube exchange during 2nd admission followed by persistent normalization of blood PH.

Discussion: This is a unique case of extreme metabolic alkalosis primarily due to the loss of gastric acid in the G-J tube, but volume depletion, hypokalemia, AKI, high protein tube feeds, lack of respiratory compensation due to ventilator dependence and loop diuretics contributed to the development and maintenance of metabolic alkalosis.

We corrected his metabolic alkalosis and AKI with cautious use of IV fluids and Acetazolamide without needing dialysis, although metabolic alkalosis relapsed until the G-J tube was changed.

	PH	Bicarbonate	Creatinine	BUN	Sodium	Potassium
Day 1	7.81	64	2.47	266	147	2.7
Day 2	7.65	56	2.47	191	162	3.3
Day 3	7.50	36	1.25	97	149	4.1
Day 5	7.37	28	0.75	51	145	3.1

Daily PH and Cr

PO1185

Hypercalcemia and Metabolic Alkalosis Induced by the Novel Potassium Binder Patiromer: Report of Rare Event

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Introduction: Patiromer is a calcium (Ca)-potassium (K) exchange resin approved for the treatment of hyperkalemia. Disorders of Ca or acid base balance were not reported in pre-approval clinical trials. Post-marketing, only 2 case reports of hypercalcemia associated with the use of patiromer have been recently published. We present a case of a patient with chronic kidney disease (CKD) with an unusual picture of hypercalcemia, metabolic alkalosis and hypokalemia upon intensification of patiromer dosing.

Case Description: A 56-year-old white man with CKD stage 4 (baseline creatinine 2.8 mg/dL) due to type 1 diabetes mellitus, proteinuria (1.5 g/g) and persistently high serum potassium (sK, 5.5 – 5.9 mEq/L) attributed to type 4 renal tubular acidosis was evaluated in clinic. Due to high risk of CKD progression, patiromer 8.4 g qd was prescribed to enable RAS blockade. Five months later, sK remained elevated at 5.0 mEq/L. Patiromer dosage was thus increased to 16.8 g qd. Three months later, sK fell to 4.1 mEq/L. Hence, patiromer was maintained at 16.8 g qd and irbesartan initiated. At that time, corrected serum calcium (sCa) was 9.3 mg/dL and serum bicarbonate ($sHCO_3$) 26 mEq/L. Five months later, routine laboratory tests revealed a sK 2.5 mEq/L, sCa 12.6 mg/dL and $sHCO_3$ 34 mEq/L. The patient denied recreational or over-the-counter drugs, diuretics or calcium supplements. Patiromer was discontinued. Thorough investigation (PTH, PTH-related peptide, 1,25-OH-vitamin D, 25-OH-vitamin D, TSH, serum protein electrophoresis, free light chains, cortisol and ACTH) was negative for other causes of hypercalcemia. Five days later, sK was 4.1 mEq/L, sCa 7.7 mg/dL and $sHCO_3$ 32 mmol/L.

Discussion: Patiromer promotes gastrointestinal elimination of potassium by binding of the molecule to potassium in exchange for calcium. Increased in intestinal absorption of calcium results in hypercalciuria but not sustained hypercalcemia. The clinical course of our patient suggests that the increased dose of patiromer led to a profound exchange of calcium and potassium ions leading to hypercalcemia, iatrogenic hypokalemia and resulting metabolic alkalosis. The role of secondary hyperparathyroidism in this case remains unclear. We recommend cautious vigilance of patients receiving patiromer and undergoing dose escalation

PO1186

Beads of Calcium

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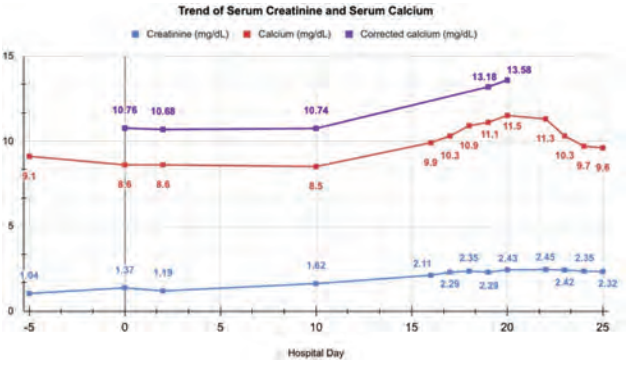
Introduction: Hypercalcemia is a common disorder that can cause acute kidney injury (AKI) and result in significant morbidity and mortality.

Case Description: A 50-year-old male with diabetes and hypertension presented with left knee septic arthritis. He had an AKI from volume depletion and vancomycin toxicity (trough level 35.1). Incision and drainage (I&D) was done on day 13 for refractory knee infection. Postoperatively, serum creatinine (Cr) and Calcium (Ca) rose to peak Cr of 2.45mg/dL (baseline 1.04mg/dL) and a corrected Ca of 13.58mg/dL. Workup showed PTH-rP 14pg/mL, PTH 8pg/mL, 1,25-Dihydroxy Vitamin D 13pg/mL, 25-Hydroxy Vitamin D 29pg/mL and normal SPEP. Kappa/Lambda ratio was 1.55. SIFE showed IgG Kappa Monoclonal gammopathy and lambda free light chain proteinemia. Given normal SFLC and an unquantifiable M-Spike, it was ascribed to monoclonal gammopathy of undetermined significance. Recent studies including, MRI cervical, thoracic, lumbar spine, CT chest, abdomen, pelvis, and left lower extremity, did not show lytic lesions. Urine sediment showed calcium oxalate crystals. These results ruled out primary hyperparathyroidism, hypervitaminosis D, paraneoplastic syndrome, and granulomatous disease. Serum Ca improved with intravenous fluids and furosemide. It was found that in I&D, 20cc of stimulan spacer was placed, which can cause hypercalcemia. Hypercalcemia coincided with spacer placement.

Discussion: Hypercalcemia has been reported with antibiotic-eluting calcium sulfate beads (CSBs) such as stimulan in several case reports and a large cohort assessing antibiotic spacers. CSBs are used for periprosthetic joint infections for new bone formation or local antibiotic delivery. Agitation of the beads during washout is hypothesized to cause postoperative hypercalcemia. Thus, it is necessary to monitor serum Ca and Cr levels with CSBs placement. Patients with intrinsic calcium or parathyroid disorders, prolonged immobility, existing renal impairment, or critical illness are at elevated risk of developing hypercalcemia and should be observed closely.



PO1187

Prediction of Ionized Hypocalcemia and Hypercalcemia: External Validation of a Novel Model

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Background: The popular adjustment of serum total calcium (tCa) for albumin (Alb) yields a corrected value (cCa) that doesn't detect abnormal ionized calcium (iCa) well in critical care patients (pts), possibly because it ignores the fraction of tCa complexed by small anions. To account for such anions, we derived a model that estimates iCa (iCa_{EST}) by adjusting tCa for Alb and the anion gap's 3 components, Na, Cl, and tCO_2. It was far better than cCa in detecting low iCa (↓iCa) on internal validation (Yap, JALM 2020). In this study, we externally validated iCa_{EST} in a large, publicly available critical care database.

Methods: From the MIMIC III v1.4 database, we paired chemistry panel tCa (mg/dL), Alb (g/dL), Na, Cl, and tCO_2 values with gas panel iCa values (ref range: 1.12-1.32 mM) measured up to 20 min. apart. Limiting each pt. to the most closely-timed pair left 4105 pairs (median:10 min apart). We calculated cCa (tCa +0.8×[4-Alb]) and iCa_{EST} (0.219 +0.091×tCa -0.034×Alb -0.0042×Na +0.0073×Cl +0.0047×tCO_2) and compared their ROC curves (area±SE) for detecting ↓iCa (iCa<1.10; rate=33.1%), and high iCa (↑iCa) (iCa>1.32; rate=3.8%).

Results: ICa_{EST} was better than cCa by ROC analysis for both ↓iCa (0.834±0.007 vs 0.752±0.008, $p<10^{-300}$) and ↑iCa (0.975±0.004 vs 0.963±0.006, p<.0006). The table compares the sensitivity and specificity (SENS/SPEC) and positive and negative predictive values (PPV/NPV) of iCa_{EST} and cCa at similar cutoffs. ICa_{EST} overestimated iCa by 0.04 mM (1.17±0.002 vs 1.13±0.002, $p<10^{-166}$), a bias that was fairly consistent across the full prediction range.

Conclusions: The iCa_{EST} model is superior to cCa in ranking critically ill pts for both ↓iCa and ↑iCa. It can help clinicians decide when to directly measure iCa. ICa_{EST} overestimated iCa but applying a local correction of -0.04 would make its absolute predictions accurate, on average, in the MIMIC setting.

Diagnosis	Cutoff	N	SENS / SPEC	PPV / NPV
↓iCa	iCaEST <1.15	1572	74.1% / 79.4%	63.9% / 86.1%
	cCa < 9.0	1561	64.0% / 74.8%	55.6% / 80.8%
↑iCa	iCaEST > 1.30	247	80.5% / 96.9%	50.2% / 99.2%
	cCa > 10.76	247	72.7% / 96.6%	45.3% / 98.9%

PO1188

A Case Report of Hypercalcemia Secondary to Calcium Sulfate Antibiotic Beads

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Introduction: Periprosthetic joint infections are rare complications in arthroplasties of the hip or knee, happening in ~0.7% of these procedures. Placement of antibiotic eluting beads, sometimes referred to as calcium sulfate beads (CSB), which are bio-compatible hydrophilic crystals used to deliver antibiotics locally, are one solution to prevent such complications. Hypercalcemia post-CSB placement is a rare complication that has only been presented in the literature a handful of times. We report on a such a patient, illustrating the importance of surgical history in investigating the cause of hypercalcemia.

Case Description: 63 yo F with PMH of HTN, HLD, Crohn's, T2DM, CKD3 who had a recent hospital admission 2 weeks prior for new arthritis secondary to pseudogout crystals, s/p bilateral synovectomy and CSB placement by orthopedics. She re-presented to hospital for AMS and worsening knee pain. Labs showed evidence of AKI with creatinine 1.9, severe hypercalcemia at 17.5 mg/dl with concomitant hypophosphatemia at 1.1 mg/dl. PTHrP WNL & PTH low at 7pg/ml and histo antigen neg, suggesting this was not related to PTH. Malignancy ruled out based on past imaging that was done in 2 months prior. MM ruled out since normal SPEP, UPEP, and kappa:lambda. Unlikely that this was milk alkali as patient did not have alkalosis. Vitamin 1,25 low at 10pg/ml ruling out sarcoidosis. Vitamin 25 WNL. Urine Ca 24hr WNL suggesting no FHH. Hypercalcemia improved after pamidronate, IV fluids and calcitonin. Chart review suggested that CSB implanted in her knees as the likely cause of her hypercalcemia.

Discussion: One of the rare and underappreciated causes of severe hypercalcemia is CSB placement. Vigilant monitoring of calcium levels pre and post CSB placement is indicated, particularly in patients with a history of CKD. It has been hypothesized that there is a dose-dependent relationship between CSB volume and hypercalcemia, and limiting CSB to less than 40ml per operation may be beneficial. A 10ml pack of CSB contains 5.73 grams of elemental calcium which is released over a 30–60-day interval. There is limited information on the mechanism of hypercalcemia in CSB use, so further studies need to be implemented. It is crucial for physicians to have a high suspicion for CSB induced hypercalcemia post-arthroplasty as CSB use expands.

PO1189

Hypercalcemia in a Patient with Visceral Leishmaniasis (VL) and Immune Reconstitution Inflammatory Syndrome (IRIS)

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Introduction: Hypercalcemia is a relatively common clinical problem with a wide range of etiologies. We report an unusual case of hypercalcemia due to visceral leishmaniasis triggering immune reconstitution inflammatory syndrome in a patient with AIDS.

Case Description: A 45-year-old male with history of previously treated VL complicated by a relapse now on suppressive amphotericin presented with 2 weeks of poor appetite, weight loss, and malaise. Recent history was notable for AIDS restarted on Triumeq in the preceding 2 months with slow recovery of CD4 count to 18 but robust reduction in HIV viral load. He denied other infectious symptoms. Labs were notable for AKI, calcium of 13.1, and pancytopenia. Work up revealed low PTH, low calcidiol, elevated ACE levels and high-normal calcitriol levels with bone marrow biopsy revealing non-necrotizing granulomas. Remainder of infectious work up including mycobacterium, histoplasma, and fungal cultures all remained negative. Of note, CD4 count rebounded to 354 during his month-long stay. He was ultimately diagnosed with IRIS secondary to VL leading to granulomatous hypercalcemia. Initial therapy consisted of fluids which resolved AKI and improved calcium. However, he proved to be fluid dependent as attempts at weaning would result in rise in calcium and creatinine. Definitive therapy consisted of steroids which resolved his hypercalcemia allowing him to come off fluids. Appetite improved and fatigue resolved over course of his stay with stabilization of calcium levels and creatinine returning to baseline. He was continued on suppressive Amphotericin B for VL.

Discussion: Granuloma formation is a known effect of leishmania infection to combat the invading parasites. Presumably, such inflammation could lead to hypercalcemia via increased conversion of calcidiol to calcitriol. To our knowledge, this is the first case of hypercalcemia caused by VL in humans. It was likely triggered by the reconstitution of his immune system given recent re-initiation of anti-retroviral therapy and rebound of CD4 cell count. Initial management consists of fluids and bisphosphonates with definitive management consisting of steroids and amphotericin. We report this novel case of hypercalcemia in hopes of expanding the literature on the various potential manifestations of VL, particularly in the setting of IRIS and AIDS.

PO1190

Systemic Sarcoidosis Presenting with Hypercalcemia

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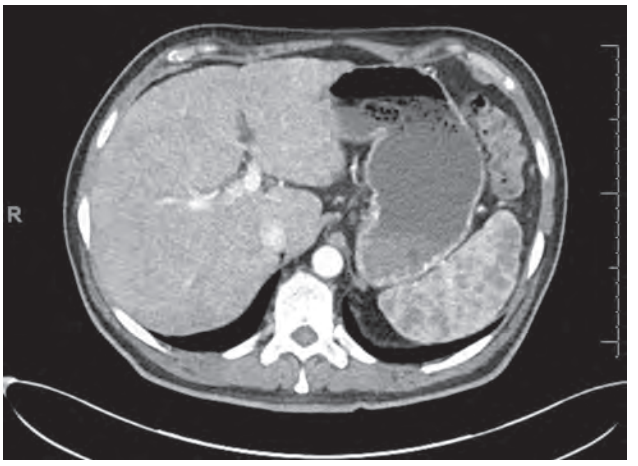
Introduction: Sarcoidosis is an idiopathic autoimmune illness that typically presents with pulmonary involvement but can affect virtually any organ. This often makes it challenging to diagnose as its manifestations can be quite varied. We report an interesting case of systemic sarcoidosis presenting with hypercalcemia of unclear mechanism.

Case Description: A 53-year-old Caucasian male presented to the clinic with polyuria, forgetfulness and weight loss. Medical history included hypercalciuria with recurrent nephrolithiasis, diabetes and positive ANA (titer 1:160) without any prior history of constitutional, respiratory or joint symptoms. Serum calcium returned 13 mg/dl. The patient also had an AKI and an elevated ALP. Further workup revealed a suppressed PTH, normal 25-OH and 1,25-OH vitamin D, but a borderline elevated PTHrP (2.5 pmol/L [0-2.3 pmol/L]). This prompted a CT CAP with contrast to rule out malignancy that instead showed mediastinal lymphadenopathy, heterogeneous liver enhancement suggestive of cirrhosis and an enlarged, nodular spleen. Transbronchial lymph node biopsies were normal and an extensive infectious and malignancy workup remained negative. The patient was given fluids followed by zoledronate with resolution of hypercalcemia and AKI. A liver biopsy was ultimately pursued which showed non-caseating granulomas. The patient was prescribed steroids with improvement in symptoms and normalization of ALP.

Discussion: In patients with sarcoidosis, the development of hypercalcemia is thought to be mediated via aberrant activation of vitamin D leading to calcitriol excess. Our patient's calcitriol level was normal and hypercalcemia may also occur in the absence of elevated levels. Possible described mechanisms include "inadequate normal" calcitriol concentration without elevation in systemic levels, elevated PTHrP and direct action of pro-inflammatory cytokines causing osteolysis.



CT with contrast showing heterogenous liver enhacement and a nodular spleen.

PO1191

Disseminated Histoplasmosis Presenting as Severe Hypercalcemia

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Introduction: Hypercalcemia (HC) is a significant complication of Disseminated Histoplasmosis (DH). While there are case reports on DH causing HC in immunosuppressed patients including HIV and chemotherapy, there are very rare case reports on DH causing HC in Non-immunosuppressed hosts. The diagnosis of DH in HC may be delayed due to other differential diagnoses such a Sarcoidosis leading to prolonged and worsening hypercalcemia and subsequent renal failure. We report a case of HC in a patient who presented with generalized skin ulcers and bilateral adrenal masses. The initial manifestation of DH with HC, painful skin ulcers, bilateral large lobulated adrenal masses, prompted an initial concern for sarcoidosis. After presenting to our institution 5 months later, a diagnosis of DH was made as the cause of his Hypercalcemia.

Case Description: A 58-year-old male with new onset generalized skin rash was diagnosed with HC, empirically treated with prednisone for sarcoidosis due to elevated 1,25 di hydroxy Vitamin D, 5 months ago at an outside hospital. After starting prednisone, his skin lesions progressed to disseminated painful ulcers and was referred to our institution after developing AKI with a serum creatinine of 4.6mg/dl (Cr 1.6mg/dl, 5 months ago) calcium 14mg/dl, PTH 2pg/ml. CT abdomen revealed large lobulated bilateral adrenal masses. Bone marrow biopsy revealed non-necrotizing granulomas with yeast form fungal organisms on GMS stain. A Shave skin biopsy of an abdominal ulcer revealed Fungal yeast forms consistent with histoplasmosis, associated with ulcers on GMS stain. Urine Histoplasma antigen positive. Adrenal mass biopsy revealed necrotic material and fibroconnective tissue. DH was initially treated with IV liposomal amphotericin and transitioned to oral Itraconazole. At the time of discharge, calcium was 9.8 mg/dl and serum creatinine was 2.9mg/dl.

Discussion: Hypercalcemia, in the setting of elevated 1,25 di hydroxy Vitamin D levels, prompts concern for granulomatous disease. Sarcoidosis is a common etiology, however, other causes must be entertained. The cluster of findings of adrenal non caseating granulomas coupled with diffuse skin ulcers with hypercalcemia should prompt the provider to consider infectious etiologies such as disseminated histoplasmosis as early diagnosis and prompt treatment can result in improved outcomes

PO1192

Electrolyte Disturbances Among Those with Malignancy on Anti-Neoplastic Agents

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Background: The clinical characteristics of electrolyte disturbances among patients with malignancy in contemporary cohorts are lacking.

Methods: This is a retrospective cohort study on 2644 patients with malignancy on anti-neoplastic agents from 2019 to 2020. Antineoplastic agents associated with electrolyte disturbances were examined by multi-level mixed-effects logistic regression analyses. The data were adjusted for age, sex, serum albumin, eGFR, kinds of malignancy, and other medications which potentially affect electrolytes.

Results: Mean age was 64.8 (15.8) years, 55.5% were male, and median eGFR was 72.9 (58.1-88.1) mL/min/1.73m^2. The prevalences of hyponatremia (Na ≤130 mEq/L), hypomagnesemia (Mg ≤1.5 mg/dL), hypophosphatemia (P ≤2.0 mg/dL), and hypokalemia (K≤3.0 mEq/L) were 2.1 (1.8-2.2), 2.0 (1.7-2.3), 1.7 (1.6-1.9), and 1.2 (1.1-1.4) events/100 patient-measurements, respectively. The use of bortezomib was associated with hyponatremia (OR: 3.04 [1.96-4.71]) and three immnue checkpoint inhibitors were significantly associated with hyponatremia. The use of cetuximab and gemccitabine were strongly associated with hypomagnesemia (OR 11.79 [7.56-18.38] and 5.95 [3.36-10.55],

respectively). Other agents associated with electrolyte disturbances were shown in Table. Other than anti-neoplastic agents, lower albumin levels were consistently associated with development of electrolyte disturbances.

Conclusions: Electrolyte disturbances were common and associated with the use of novel anti-neoplastic agents among those with malignancy. Identifying the agents and patient population at high risk of developing electrolyte disturbances is important in taking appropriate preventive measures and monitoring for those undergoing treatments with anti-neoplastic agents.

Anti-neoplastic agents associated with hyponatremia

	OR (95% CI)
Bortezomib	3.04 (1.96-4.71)
Ipilimumab	2.30 (1.00-5.29)
Docetaxel	1.69 (1.27-2.27)
Cetuximab	1.66 (1.04-2.65)
Irinotecan	1.65 (1.09-2.50)
Cyclophosphamide	1.62 (1.10-2.37)
Cisplatin	1.52 (1.18-1.96)
Pembrolizumab	1.42 (1.02-1.97)
Nivolumab	1.37 (1.00-2.37)

Anti-neoplastic agents associated with hypokalemia

	OR (95% CI)
Cyclophosphamide	1.79 (1.31-2.45)
Gemcitabine	1.57 (1.10-2.25)

Anti-neoplastic agents associated with hypomagnesemia

	OR (95% CI)
Cetuximab	11.79 (7.56-18.38)
Gemcitabine	5.95 (3.36-10.55)
Methotrexate	2.26 (1.61-3.19)
Cisplatin	2.01 (1.34-3.00)
Oxaliplatin	2.00 (1.17-3.40)
Irinotecan	1.74 (1.07-2.83)

Anti-neoplastic agents associated with hypophosphatemia

	OR (95% CI)
5-FU	2.25 (1.19-4.25)
Cyclophosphamide	2.06 (1.45-2.92)

PO1193

Resistant Hypophosphatemia with Vitamin D Deficiency

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Introduction: The renal regulation of phosphate homeostasis is mediated mainly by reabsorption of P by NaPi-IIc in the proximal tubule, whereas intestinal absorption is mediated by NaPi-IIb. Normally, about 2/3 of dietary intake (1500 mg/day) is absorbed, but when given by mouth as Na or K phosphate, absorption is nearly 100% in a normal person. We report here a patient with severe hypophosphatemia due to phosphate malabsorption caused by prior gastric bypass surgery along with vitamin D deficiency.

Case Description: A 34 year old African American female with past medical history of benign carcinoid syndrome, pernicious anemia, Hashimoto thyroiditis, and gastric sleeve surgery for morbid obesity 3.5 years ago, was admitted for acute dizziness and lightheadedness at rest without vertigo. Initial labs were: BUN 4 mg/dL; creatinine 0.6 mg/dL; Ca 9.2 mg/dL; Mg 2.17 mg/dL; P 1.3 mg/dL; 25-OH vitamin D 10.88 ng/mL; 1,25(OH)2 vitamin D 15.3 pg/mL; PTH 77.7 pg/mL; urine P 77 mg/dL; urine creatinine 342.51 mg/dL. She has been getting vitamin B12 injections for her pernicious anemia. She was treated with oral Na and K phosphate solution containing 560 mg of P, 320 mg of Na, and 500 mg of K in each dose for every 4 hours, and once daily dose of IV K phosphate containing 465 mg of phosphate for 14 days. She was also treated with 800 units of vitamin D2 daily. Serum phosphate remained persistently low around 1.8 mg/dL despite the above treatment.

Discussion: Hypophosphatemia in our patient was caused by impaired intestinal absorption of phosphate, and inappropriately increased urinary excretion due to secondary hyperparathyroidism due to vitamin D deficiency. The total daily amount of phosphate the patient received while in the hospital was 3825 mg per day. A 24 hour urine excretion of P estimated from urine creatinine concentration (342 mg/dL), assuming normal GFR (180 L/day), is very low (245 mg/day). Although P administered as Na or K salt is well absorbed in a normal person, she was unable to absorb P likely due to the gastric sleeve surgery causing rapid emptying of the gastric content, simulating the dumping syndrome, resulting in diarrhea by unabsorbed Na and K phosphate. Further impairment in intestinal P absorption may have been caused by vitamin D deficiency due to the inadequate dosing (800 units daily) and the inappropriate vitamin D type (Vitamin D2 instead of D3).

PO1194

Severe Hypophosphatemia Induced by Oncogenic Osteomalacia

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Introduction: Oncogenic Osteomalacia (OncOM) is an uncommon paraneoplastic syndrome characterized by FGF-23 overexpression from benign mesenchymal tumors causing severe hypophosphatemia. Very few cases of OncOM with concomitant paraneoplastic syndromes have been described. Herein we present a rare case of carboplatin-associated hyponatremia in the setting of SiADH-induced chronic hyponatremia unmasking an even rarer secondary paraneoplastic syndrome; oncogenic osteomalacia.

Case Description: A 52 year old male with past medical history of chronic hyponatremia on salt tablets secondary to recently diagnosed metastatic small cell lung cancer was admitted for initiation of chemotherapy with carboplatin/etopside. Two days after competing cycle 1 the patient developed acute hyponatremia; serum Na decreased from 141 to 129 mEq/L. Serum electrolytes were (mEq/L): K 3.9, Cl 94, HCO3 28, BUN 20, Cr 0.47. Cortisol (17.8 ug/dl) and TSH (2.28 uIU/ml) were within normal limits. Urine studies noted (mEq/L): Na 75, Cl 69, K 43.5, elevated osmolality 860 mOsm/kg. Etiology of acute hyponatremia was attributed to platinum chemotherapy in the setting of SCC-associated SiADH and patient was treated with tolvaptan after several days of non-response to fluid restriction and urea. Patient's hyponatremia subsequently corrected but was incidentally noted to have severe hypophosphatemia (<1 mEq/L) refractory to aggressive IV and PO phosphate repletion. ALP was elevated 279 U/L, corrected Ca 10 mEq/L, low 25(OH)-vitamin D 23.8 ng/mL, normal PTH 45.6 pg/mL and PTHrP <0.4 pmol/L. Urinary fractional excretion of phosphorus was increased at 24%. An FGF-23 level obtained 12 days after completing cycle 1 of carboplatin-etopside was considerably elevated at 219 pg/mL. Thus, the patient was diagnosed with oncogenic osteomalacia.

Discussion: This case highlights a unique and diagnostically challenging patient presentation of severe hypophosphatemia in the setting of dual paraneoplastic syndromes. OncOM should be considered in the differential for severe refractory hypophosphatemia. This occurs via FGF-23 mediated downregulation of PCT Na-Pi transporters and 1a-hydroxylase causing renal phosphate wasting and reduced 1,25-hydroxyvitamin D levels. Over time chronic hypophosphatemia impairs bone mineralization causing osteomalacia. Measurement of the fractional excretion of phosphorus is critical and FGF-23 levels should be obtained to confirm diagnosis.

PO1195

Phenotypes of Patients with Abnormal Phosphate on Admission by Consensus Clustering and Associated Mortality Risks

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Background: Hospitalized patients with abnormal phosphate are heterogeneous and cluster approaches may identify specific homogenous groups. This study aimed to cluster patients with abnormal phosphate on admission using unsupervised machine learning approach and to evaluate the mortality risk among these distinct clusters.

Methods: Consensus cluster analysis was performed on hospitalized adult patients with abnormal phosphate on admission, based on clinical and laboratory data. We determined each cluster's key features using the standardized mean difference. We assessed the association of the clusters with hospital and one-year mortality.

Results: Cluster 2 patients with hypophosphatemia had older age, higher comorbidity burden, hypertension, diabetes, coronary artery disease, lower eGFR, and more acute kidney injury (AKI) (Fig 1a). Cluster 2 patients with hyperphosphatemia had older age, more admission for kidney disease, hypertension, end-stage kidney disease, AKI, and higher admission K^+, Mg^{2+}, or PO_4 levels (Fig 1b). Both cohorts in cluster 2 had higher one-year mortality while hyperphosphatemic cluster 2 patients had higher hospital mortality (Fig 2).

Conclusions: The cluster analysis identified clinically distinct phenotypes with differing mortality risk in hospitalized patients with abnormal phosphate on admission. The age, comorbidities, and kidney function were key features.

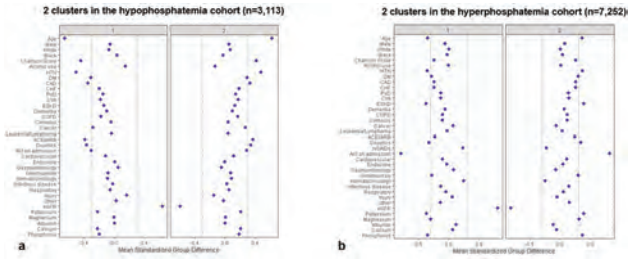

Fig 1. The Manhattan plot of standardized differences in the hypophosphatemia (a) and hyperphosphatemia cohort (b).

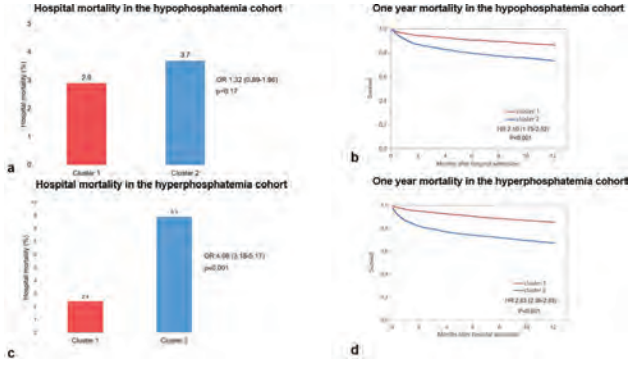

Fig 2. The hospital mortality (a) and one-year mortality (b) in the hypophosphatemia cohort, and the hospital mortality (c) and one-year mortality (d) in the hyperphosphatemia cohort.

PO1196

Annatto Leaf Tea Intoxication: An Unusual Cause of Green Urine

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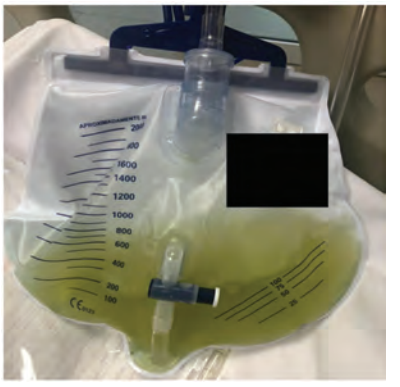
Introduction: The roots and leaves of the annatto ("urucu") tree (*Bixa Orellana*) are used by the lay population in the treatment of many diseases. We describe a case of AKI with severe fluid and electrolyte (F+E) imbalance due to annatto leaf tea use.

Case Description: A 59-year-old male without known comorbidities presented with a 2-week history of severe diarrhea. Three days prior to admission, he was diagnosed with renal dysfunction, received 500 mL of saline and was discharged. Subsequently, he presented with muscle weakness, uremic encephalopathy, severe AKI, F+E imbalance and greenish urine (Figure). He received fluid resuscitation and underwent two sessions of hemodialysis. He reported having ingested annatto leaf tea to treat his diarrhea. Blood and urine cultures were negative and there was no history of drug use. He was discharged on day 14 with no remaining F+E imbalance or renal dysfunction.

Discussion: The diuretic effect of annatto leaf extracts has been shown in experimental models. To our knowledge, this is the first report of severe AKI and F+E imbalance due to annatto leaf tea use. In our patient, AKI was aggravated by the diarrhea and the diuretic effect of the tea.

Table 1.

	Admission	Discharge	Reference range
Hemoglobin (mg/dL)	17.3	11.6	13.5 - 17.5 g/dL
Serum creatinine (mg/dL)	8.09	0.79	0.7 - 1.2 mg/dL
Urea (mg/dL)	502	23	10 - 50 mg/dL
Sodium (mEq/L)	111	136	135 - 145 mEq/L
Potassium (mEq/L)	4.8	4.6	3.5 - 5 mEq/L
Chloride (mEq/L)	55	99	98 - 107 mEq/L
Magnesium (mg/dL)	2.99	1.7	1.58 - 2.55 mg/dL
Phosporus (mg/dL)	20.5	2.5	2.7 - 4.5 mg/dL
Ionizide calcium (mg/dL)	3.15	4.92	4.49 - 5.29 mg/dl
Uric acid (mg/dL)	25.5	2.9	3.4 - 7 mg/dl
pH	7.27	7.46	7.35 - 7.45
Bicarbonate (mmol/L)	12	22.5	23 - 27 mmol/L



PO1197

Foam Sclerotherapy for Directed Treatment of Symptomatic Cysts in Autosomal Dominant Polycystic Kidney and Liver Disease

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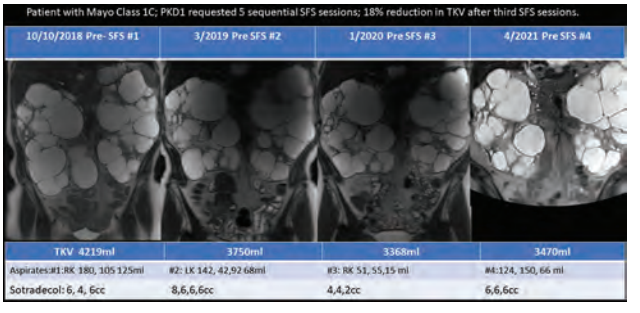
Background: Patients frequently describe mass symptoms & reduced quality of life (QoL) that correlate with large (≥5cm diameter) organ cysts in ADPKD/ADPLD. Since 1/18/2017, we have studied the safety & impact of cyst drainage followed by sotradecol foam sclerotherapy (SFS) to treat symptomatic, large cysts.

Methods: In this single-center, single-arm, prospective observational study, ADPKD and ADPLD patients with compressive symptoms due to liver or kidney cysts are referred for SFS. Small volumes (20cc max) of 3% sotradecol sclerosant admixed with air are injected (fluoroscopy-guided under local anesthesia) to ablate the epithelial cyst lining. QoL measures using polycystic liver disease QoL tool (PLD-Q) & organ volumes (planimetry using CT/MR) are recorded at baseline & 12+ months post-SFS. Changes over time were tested using Wilcoxon tests and confirmed using repeated measures mixed models. Improvements >0.5 SD were considered clinically meaningful.

Results: We performed 148 SFS procedures among 68 cases (mean age 55yr 77% Female, mean 2.2 procedures per pt): 53 (77.9%) with ADPKD/ADPLD, 5 (7.4%) with ADPLD, & 10 (14.7%) with cystic disease NOS. PLD-Q scores improved by 7.7 (IQR 0.1, 24.8) (p=0.012) at mo 12. A subgroup (13 patients) (mean age 54.7yr, 69% F) have undergone multiple sequential SFS procedures: 10 (77%) with ADPKD/ADPLD, 2 (15%) ADPLD, & 1 (8%) cystic disease NOS. Among 5 with multiple kidney procedures, median kidney volume decreased by 135mL/yr. Among 5 with multiple liver procedures, median liver volume decreased by 114mL/yr. SFS was well tolerated with low complication rates.

Conclusions: SFS directed at large, symptomatic liver and kidney cysts was well tolerated, improved QoL at 12 months, & decreased early satiety, SOB, pain & fullness. Furthermore, multiple sequential SFS procedures are feasible, efficacious, and have an acceptable safety profile.

Funding: NIDDK Support, Private Foundation Support



ADPKD Case Who Underwent 5 sequential SFS Procedures

PO1198

Development of AL01211, a Novel Glucosylceramide Synthase Inhibitor, to Treat Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a common genetic disease affecting ~1:1000 individuals and is characterized by progressive renal cysts growth, kidney enlargement and renal dysfunction. Glycosphingolipids (GSL) are elevated in the kidneys of ADPKD animal models and ADPKD patients where they promote renal epithelial cell growth and kidney inflammation. Glucosylceramide synthase inhibitors (GCSi) reduce GSL production, slow cyst growth, and preserve kidney function in multiple animal models. Clinical development of other GCSi have shown that this enzyme can be safely targeted therapeutically. We are developing AL01211, a potent and selective GCSi with excellent drug-like properties, for the treatment of ADPKD.

Methods: The IC50 of AL01211 against GCS was determined in cells and cell-free activity assays. PK, PD, tissue distribution and clearance studies were conducted in mice, rats and dogs. AL01211's pharmacological profile was characterized *in vitro* including off-target selectivity panels, plasma protein binding, transporter assays, cyp inhibition and induction, and other assays. Disease model efficacy studies were conducted in several murine models including *pkd1* cKO and *jck* models.

Results: AL01211 binds the active site of GCS and has an IC_{50} toward GCS of ~7 nM with limited off-target activity. PK studies support once daily, oral administration. AL01211 has low renal clearance in rats. AL01211 readily distributes to peripheral tissues (such as kidney) but does not cross blood-brain-barrier. Thus, it efficiently reduces GSL production in mouse, rat and dog kidney (reduced by >85% of control levels) with minimal effects in brain GSL. Importantly, AL01211 reduces cyst growth and kidney weight and preserves kidney functions in murine models.

Conclusions: Relative to other GCSi in development, AL01211 is more potent with single digit nanomolar potency, has greater reduction of GSL (>85%), is not subject to kidney clearance, and does not enter the brain. Phase I clinical trials, consisting of Phase IA (single ascending dose study in healthy volunteers), Phase 1B (14-day multiple ascending dose study in healthy volunteers, and Phase IC (28-day biomarker study in ADPKD patients), are underway.

Funding: Commercial Support - AceLink Therapeutics

PO1199

The Tyrosine Kinase Inhibitor Nintedanib Ameliorates Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and is characterized by progressive growth of fluid-filled cysts in the kidneys. Growth factor binding to receptor tyrosine kinases (RTKs) are known to stimulate cell proliferation and cyst growth in PKD. In the current study we tested the effect of Nintedanib, an RTK inhibitor and FDA approved drug for non-small cell lung carcinoma and idiopathic lung fibrosis, in mouse models of ADPKD. Nintedanib is a triple RTK inhibitor which targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR).

Methods: The effect of Nintedanib on renal cyst growth and fibrosis was tested in two orthologous models of ADPKD, the *Pkd1$^{f/f}$Pkhd1^{Cre}* mouse, and *Pkd1$^{RC/RC}$* mouse. Nintedanib treatment (20 mg/Kg on alternate days by intraperitoneal injections) was from postnatal day P10 to P18 in *Pkd1$^{f/f}$Pkhd1^{Cre}* mice and in for 8 weeks starting at the age of 3 months in *Pkd1$^{RC/RC}$* mice. *In vitro* studies were performed using primary culture human ADPKD renal cystic epithelial cells and renal myofibroblasts.

Results: Nintedanib treatment significantly reduced kidney-to-body weight ratio, renal cystic index, cystic epithelial cell proliferation and blood urea nitrogen levels compared to vehicle treated *Pkd1$^{f/f}$Pkhd1^{Cre}* and *Pkd1$^{RC/RC}$* mice. Western blot data indicates reduction in the phosphorylation of ERK1/2, AKT, STAT3 and mTOR activation and pro-proliferative factors, including Yes associated protein (YAP), c-Myc and Cyclin D1 protein levels. Moreover, nintedanib treatment significantly reduced renal fibrosis in *Pkd1$^{RC/RC}$* mice, however, fibrosis in *Pkd1$^{f/f}$Pkhd1^{Cre}* mice remained unaffected. *In vitro* data suggests that nintedanib significantly reduced proliferation and cyst size of human ADPKD cystic epithelial cells as well as cell viability and migration of human ADPKD renal myofibroblasts.

Conclusions: The results suggest that Nintedanib is effective in reducing cyst growth and may be repurposed to treat ADPKD.

Funding: NIDDK Support

PO1200

KidneyNetwork Uses Kidney-Derived Gene Expression Data to Predict and Prioritize Novel Genes Involved in Kidney Disease

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Background: Genetic testing in patients with suspected hereditary kidney disease does not always reveal the genetic cause for the patient's disorder. Pathogenic variants can reside in genes that are not yet known to be involved in kidney disease. To help identify candidate genes for kidney disease we have developed KidneyNetwork, in which tissue-specific expression is utilized to predict kidney-specific gene functions.

Methods: KidneyNetwork is a co-expression network built upon 878 kidney RNA-sequencing samples and a multi-tissue dataset of 31,499 samples. It uses expression patterns to predict which genes have kidney-related functions and which phenotypes might result from variants in these genes. As proof of principle, we applied KidneyNetwork to prioritize rare variants in exome-sequencing data from 13 kidney disease patients.

Results: We assessed the prediction performance of KidneyNetwork by comparing it to GeneNetwork, our previously developed multi-tissue co-expression network. In KidneyNetwork, we observe significantly improved prediction accuracy of kidney-related HPO-terms and an increase in the total number of significantly predicted kidney-related HPO-terms (figure 1). Applying KidneyNetwork to exome-sequencing data allowed us to identify *ALG6* as candidate gene for kidney and liver cysts.

Conclusions: KidneyNetwork is a kidney-specific co-expression network that predicts which genes have kidney-specific functions that can result in kidney disease. Gene-phenotype associations of genes unknown for kidney-related phenotypes can be predicted. We show its added value by applying it to kidney disease patients without a molecular diagnosis. KidneyNetwork can be applied to clinically unsolved cases, but it can also be used by researchers to better understand kidney physiology and pathophysiology.

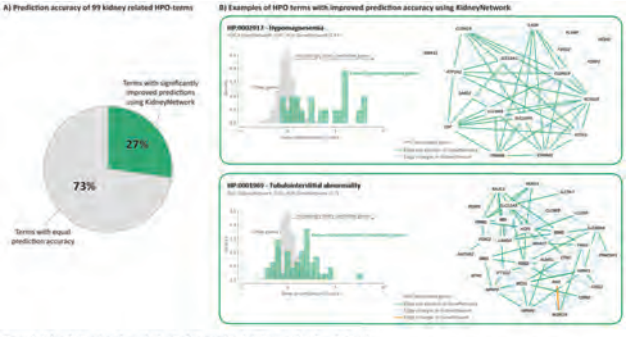

Figure 1. KidneyNetwork performs better for kidney-related HPO terms than GeneNetwork
A) 27% of kidney-related phenotypes are predicted significantly better using KidneyNetwork, as compared to GeneNetwork (a multi-tissue co-expression network we previously developed). B) Density plots of gene prediction scores within two of the most improved phenotypes, hypomagnesemia and tubulointerstitial fibrosis, show higher prediction values for genes annotated for the phenotype, while also predicting potential unknown candidate genes. The networks predicted using KidneyNetwork shows more and stronger correlations between the annotated genes than the networks predicted using GeneNetwork.

PO1201

Modeling Gene-Targeted Strategies for Therapeutic Correction of PKD1 Loss-of-Function Mice

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Background: Autosomal dominant polycystic kidney disease (ADPKD) causes cyst progression leading to renal failure, mainly by PKD1 mutations. Since microscopic cysts in ADPKD kidneys are likely formed *in utero*, we targeted at fetal stage wild type *Pkd1/Pc1* protein in *Pkd1$^{-/-}$* mouse from 3 series of transgenic (Tg) lines, to assess for long-term cure of severe cystogenesis and neonatal death.

Methods: Pc1 re-expression in *Pkd1$^{-/-}$* mouse was targeted by 3 genetic matings: a) a systemic *Pkd1$_{TAG}$* mouse b) 2 renal-specific *SBPkd1$_{TAG}$* mice mild and high expressor (1&10 Tg copies) c) a novel Tg line targeting Pkd1 cDNA with renal-specific elements, *SBP* (16 Tg copies). Longitudinal renal molecular (Q-PCR, IB), histologic (tubular origin IF, RNAScope) and survival analyses were performed.

Results: Mice *Pkd1$_{TAG}$;Pkd1$^{-/-}$* expressing 7-fold over endogenous Pkd1 gene and intense signal over all tubular segments are totally rescued. Mice *SBPkd1$_{TAG}$;Pkd1$^{-/-}$* with mild (~0.64) Pc1 expression are not only rescued from neonatal death but renal cysts are delayed to P5 affecting mainly collecting tubules, causing death at P15, generating a 4-fold increased life expectancy. Mice *SBPkd1$_{TAG}$;Pkd1$^{-/-}$* with high (7-fold) Pc1 expression, initiate distal renal cysts at P15 and survive till ~4 mo with 25-fold increased life expectancy. Mice *SBP;Pkd1$^{-/-}$*, with ~16 SBP copies expressed 0.87-fold the Pkd1 endogenous level, exhibit few renal cysts at P0 whereas at P5 are mainly of distal and

collecting tubular origin and survived until P12-15. While *SBP* reached Pkd1 therapeutic levels similar to the mild *SBPkd1*$_{TAG}$, the additional Tg copies suggest the presence of regulatory region within Pkd1 gene-body. Renal cysts in *SBPkd1*$_{TAG}$*;Pkd1*$^{-/-}$ and *SBP;Pkd1*$^{-/-}$ co-detected by RNAScope and IF, arise likely from insufficient and chimeric Pkd1 re-expression. These analyses also shed light on Pkd1 spatio-temporal expression pattern with highest expression in collecting tubules during renal maturation that shifts to distal tubules following maturation.

Conclusions: Pkd1 is regulated by elements both upstream for spatio-temporal pattern and intragenic sequences for expression levels. The renal-specific SB minimal regulatory region is sufficient for therapeutic correction in one copy Tg. Our study demonstrates that Pc1 re-expression can substantially delay cystogenesis and markedly extend lifespan.

Funding: Government Support - Non-U.S.

PO1202

Wheat-Gluten Diet Attenuates Ccl2-Mediated Immune Response and Slows Polycystic Kidney Disease

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Background: Disease severity of autosomal-dominant polycystic kidney disease (ADPKD) is highly variable, even among families with the same gene mutation. A high protein diet is a well-recognized ADPKD progression-accelerating factor. Dietary protein composition is important, as pre-clinical studies have shown a soy protein-based diet slows kidney cyst formation in rodent PKD models. Recruitment of macrophages in the kidney are known to promote cystogenesis in PKD. We hypothesize that type of protein in the diet may serve as a potential environmental stimulant to immune response and cyst growth.

Methods: Using tamoxifen-inducible *Pkd1*-global knockout mice, we fed the mice with either a high casein-protein (animal-based protein: 60%), a low casein-protein (6%) or a high wheat-gluten (plant-based protein: 60%) for a total of 1 week or 6 weeks. Some mice fed a high casein protein diet were treated with liposomal clodronate or saline for a total of 5 weeks. Mice were euthanized and kidney cyst area, number of macrophages and chemokine/cytokine levels were measured.

Results: *Pkd1*-knockout mice fed a high casein diet increased the number of kidney macrophages, expression of macrophage-recruiting chemokine *Ccl2* (but not chemokines *Csf1 or Ccl5*), pro-inflammatory cytokine (*Il6*, *Tnf-a*) and accelerated cyst growth compared to counterparts fed an iso-caloric high wheat-gluten (WG) diet or a low casein protein diet. We found that in very early stages during dietary casein load (1 week after diet modification), cyst expansion precedes macrophage recruitment in the kidney, indicating that diet *per se* triggers early cyst growth rather than as a consequence of macrophage recruitment and inflammation. High casein protein diet fed *Pkd1*-knockout mice treated with liposomal clodronate, resulted in decreased number of macrophages, cytokine and fewer cysts.

Conclusions: Wheat-gluten diet fed *Pkd1*-knockout mice resulted in decreased the number of macrophages, suppressed levels of kidney *Ccl2*, but not *Csf1* or *Ccl5*, and slowed cyst growth compared to counterparts fed an isocaloric casein based diet. Dietary protein modification may suppress immune response and cyst growth in PKD.

Funding: NIDDK Support

PO1203

High Prevalence of Kidney Cysts in Hereditary Hypophosphatemic Rickets with Hypercalciuria

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Background: Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) is a rare monogenic disorder caused by *SLC34A3* pathogenic variants, characterized by renal phosphate wasting, hypophosphatemia, hypercalciuria (HC), elevated 1,25-dihydroxyvitamin D, nephrocalcinosis (NC), and urinary stone disease (USD). Previously we reported a high prevalence of kidney cysts in CYP24A1 deficiency. Thus, in the current study, we characterized cyst presence in HHRH, another monogenic cause of HC, NC, and USD.

Methods: Medical records from Mayo Clinic and Rare Kidney Stone Consortium research results were queried for all patients with genetically confirmed HHRH diagnosis. Clinical characteristics and imaging data are summarized in **table 1**.

Results: Among 12 patients with *SLC34A3* pathogenic variants (7 monoallelic, 5 biallelic), 42% (5/12) were males. Median age at clinical presentation was 17 yrs (range 8-46) and at genetic confirmation 42 yrs (range 9-66). None had a family history of cystic kidney disease. Kidney cysts (**Figure 1**) were present in 75% (9/12), among whom median age at first kidney imaging and first cyst detection was 41 yrs (range 9-64). Median number of cysts per patient was 3 (range 1-23). The number of cysts ≥ 5 mm in size was above the 97.5th percentile of an age- and sex-matched control population in 6/9 (67%). At least 2 cysts ≥ 5 mm in size were found in 100% of children.

Conclusions: We found a strong association between HHRH and kidney cysts. Similarities in the biochemical profiles of HHRH and CYP24A1 deficiency suggest elevated active vitamin D, and/or HC may be potential factors in cyst formation. Further studies are needed to evaluate the role of the *SLC34A3* gene in cyst formation.

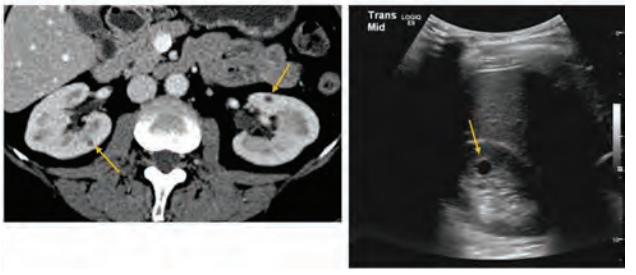
Funding: Other NIH Support - This work was funded by the Rare Kidney Stone Consortium (RKSC; U54DK83908), which is part of Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS) and R21TR003174. The RKSC was funded through collaboration between NCATS, and the National Institute of Diabetes and Digestive and Kidney Diseases.

Table 1 | Kidney cyst characteristics in the HHRH cohort

Case number	Age at first kidney cyst detection (yr)	Age at imaging for study data collection (yr)*	Imaging modality	Total number of cysts, location	Smallest cyst size, mm	Largest cyst size, mm	No. of cysts ≥5 mm
1	9	10	US	3, M	5	9	3
2	13	13	US	2, CMJ	5	9	2
3	13	13	US	2, U	13	20	2
4	n/a	23	NCCT	0, n/a	n/a	n/a	n/a
5	n/a	18	NCCT	0, n/a	n/a	n/a	n/a
6	18	18	CECT	4, CMJ	6	31	4
7	50	50	US	1, C	n/a	76	1
8	n/a	55	NCCT	0, n/a	n/a	n/a	n/a
9	41	46	US	1, M	n/a	8	1
10	52	57	CECT	5, C/CMJ	3	18	4
11	62	63	NCCT	3, C	6	29	3
12	64	64	CECT	23, C/CMJ	3	55	13

US, ultrasound; NCCT, noncontrast computed tomography; CECT, contrast-enhanced computed tomography.
M, renal medulla; CMJ, renal corticomedullary junction; C, renal cortex; U, unknown; n/a, not applicable.
* Preference was given to last CECT or US available, then to NCCT if it was the only available imaging modality.

Figure 1: CECT (left) and US (right) with renal cysts (arrows)



PO1204

Dysregulated Tryptophan Metabolism Promotes Polycystic Kidney Disease Progression

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Background: Metabolic reprogramming is a feature and modifier of autosomal dominant polycystic kidney disease (ADPKD) progression. Moreover, immune cells regulate cyst growth. In cancer, a disease with parallels to PKD, the metabolic landscape created by tumors significantly impacts immune cell function and tumor growth. Yet, this link is unexplored in PKD. Here, we study tryptophan metabolism, a known immunosuppressive pathway, in cyst growth.

Methods: Metabolites were profiled in ADPKD patient plasma and kidneys of an orthologous ADPKD model (C57Bl/6J *Pkd1*$^{RC/RC}$). We also crossed the ADPKD model to *Ido1*$^{-/-}$ mice, the enzyme metabolizing tryptophan to kynurenines, and inhibited IDO1 using the tryptophan analog 1-MT (400mg/kg, twice daily, orally). From these mice, kidney immune cells were profiled via flow cytometry.

Results: Tryptophan metabolites were significantly increased in *Pkd1*$^{RC/RC}$ mice at 3-, 6-, and 9-months compared to wildtype and correlated with disease progression. Plasma levels of kynurenines significantly associated with HtTKV at baseline, and positively correlated with annual percent change of HtTKV in adult ADPKD patients. IDO1 levels were significantly increased in kidneys of PKD mice and patient cell lines. At 6-months of age, *Pkd1*$^{RC/RC}$; *Ido1*$^{-/-}$ mice had significantly milder PKD compared to *Pkd1*$^{RC/RC}$ mice as measured by % KW/BW and cystic/fibrotic index. Similarly, treatment of 1-month-old *Pkd1*$^{RC/RC}$ mice with 1-MT for 3 weeks slowed cyst growth; overall providing functional evidence of the pathway's relevance to PKD. Kidney immune profiling of *Pkd1*$^{RC/RC}$; *Ido1*$^{-/-}$ and 1-MT-treated mice revealed a significant reduction of resident macrophages, regulatory T cells, and immune checkpoint protein expression (PD-1/PD-L1), while the percentage of CD8^{+} T cells/total T cells increased.

Conclusions: Our data highlight tryptophan metabolism as a novel dysregulated pathway in murine and human ADPKD and suggest that tryptophan metabolites are biomarkers of disease progression. Further, inhibition of the pathway presents a new treatment approach. IDO1 inhibitors are FDA approved for various cancers. Our data suggest a link between metabolic reprogramming, immune cell function, and disease progression, as IDO1 loss/inhibition impacted immune cell populations/pathways shown to regulate cyst growth.

Funding: NIDDK Support, Private Foundation Support

PO1205

Creatine Kinase Elevation in Patients with Autosomal Dominant Polycystic Kidney Disease on Tolvaptan Treatment

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease worldwide. Studies such as the TEMPO 3:4 and 4:4 have demonstrated tolvaptan's (vasopressin V2 receptor antagonist) effectiveness in slowing the progression of this disease. The best described adverse effect seen with this treatment is drug-induced liver injury, however, creatine kinase (CK) elevation has also been described anecdotally in a couple of case reports.

Methods: This is a prospective observational study of adult patients with rapidly progressive ADPKD on tolvaptan treatment under follow-up at Hospital Clínic de Barcelona from October 2018 to March 2021. Quantitative variables are described as mean and standard deviation, while qualitative ones are reported as absolute and relative frequencies.

Results: A total of 37 patients started treatment with tolvaptan during this period. In 34 of them, serum CK levels were measured as part of the monthly biochemical follow-up. A total of 29.11% (10 of 34) of the patients elevated this parameter with a mean of 1368.2 ± 2807.28 U/L. Seven patients had a transient elevation with a mean of 446.43 ± 359.22 U/L, which reversed upon dose decrease or treatment pause. However, treatment had to be interrupted in the remaining three patients (mean 3519 ± 5016.36). In one of them due to concomitant drug-induced liver injury and in the other two due to persistent CK elevation despite dose reduction or temporary treatment interruption. CK elevation was not related to exercise (although one patient did report a weekly intense cycling exercise with increased myalgia afterward) and was not significantly correlated with LDH levels, liver enzymes, calcium, potassium, urinary or plasma osmolarity.

Conclusions: By performing a general screening, we found that CK elevation is more frequent than previously described in the literature, reaching significantly increased levels or producing symptomatology requiring definitive treatment interruption. Based on these results, although the studied sample is small, we suggest adding this parameter as a part of tolvaptan treatment's follow-up, at the beginning of treatment and when increasing its dose, to promptly detect undesirable adverse effects and gain a better understanding of this phenomenon.

PO1206

Protein Kinase A Downregulation Delays the Development and Progression of Polycystic Kidney Disease

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Background: Upregulation of cAMP-dependent as well as -independent PKA signaling is thought to promote cystogenesis in polycystic kidney disease (PKD). We have shown that the PKA-I regulatory subunit RIα is increased in kidneys of orthologous mouse models and that kidney specific knockout of RIα upregulates PKA activity, induces cystic disease in wild-type mice, and aggravates it in *Pkd1*$^{RC/RC}$ mice.

Methods: This study was designed to ascertain (1) the effect of PKA-I activation or inhibition compared to EPAC or PKA-II inhibition on *ex vivo* cystogenesis using *Pkd1*$^{RC/RC}$ metanephric organ cultures, (2) whether PKA (preferentially PKA-I) downregulation by kidney specific expression of a dominant negative RIαB allele (obtained by crossing *Prkar1α*$^{R1αB/WT}$, *Pkd1*$^{RC/RC}$, and *Pkhd1*-Cre mice) is protective *in vivo* in *Pkd1*$^{RC/RC}$ mice on the C57BL/6 background, (3) whether a novel, small molecule, selective PRKACA inhibitor (BLU0588) blocks *in vitro* mIMCD3 and *ex vivo* cystogenesis (40-200 nM) and is protective *in vivo* in *Pkd1*$^{RC/RC}$ mice on the C57BL/6 x 129S6/Sv F1 background (30 mg/kg b.w. by oral gavage starting at 4 weeks of age). Mice were sacrificed at 16 weeks of age.

Results: PKA-I activation promoted, and inhibition prevented, *ex vivo* cystogenesis, whereas EPAC activation or PKA-II activation or inhibition had no or only minor effects. BLU0588 inhibited *in vitro* mIMCD3 cystogenesis and *ex vivo* cystogenesis. Genetic and pharmacological downregulation of PKA activity were both protective *in vivo* (Table). BLU0588 had no detectable on- or off-target adverse effects.

Conclusions: PKA-I is the main effector of cAMP in cystogenesis. Direct downregulation of PKA activity is demonstrated as a novel strategy to treat PKD. By acting directly on PKA, PKA inhibitors may be more effective alone or substantially augment the efficacy of treatments that only affect the cAMP-dependent PKA activity by lowering cAMP.

Group (sex)	Body Wt (g)	Kidney/Body Wt x 100 (g)	Cyst index (%)	P. creatinine (mg/dl)	PKA activity (pmol ATP/min/mg protein)	
					Basal	Total
Control (F=28, M=43)	26.2±4.1	2.06±0.45	13.7±6.7	0.32±0.10	459±176	2868±741
RIαB-ON (F=9, M=15)	26.8±4.5	1.63±0.40	9.25±3.52	0.24±0.09	427±176	1877±517
P-value	0.61	<0.001	<0.001	0.001	0.44	<0.001
Control (F=10, M=9)	25.5±3.1	3.13±0.60	28.6±5.7	0.39±0.04	455±92	2387±603
BLU0588 (F=9,M=9)	25.3±2.4	2.61±0.52	22.4±6.4	0.38±0.06	141±34	379±138
P-value	0.86	0.008	0.003	0.55	<0.001	<0.001

PO1207

Protein 4.1O Links Polycystin 1 to the Actin Cytoskeleton and Modulates Hippo Signaling

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Background: The majority of ADPKD patients have a PKD1 gene mutation. PKD1 codes for Polycystin-1 (PC-1). Cyst formation is caused by altered renal tubular cell proliferation. Protein 4.1 family members are actin adaptors, which link plasma membrane receptors to the actin cytoskeleton. Protein 4.1O (FRMD3) is a candidate gene for diabetic nephropathy. Furthermore, protein 4.1O has properties of a tumor suppressor. This study investigates the molecular and cellular properties of protein 4.1O as a potential ADPKD modifier and therapeutic target.

Methods: PC-1 full-length and truncation mutants were transiently expressed. PC-1 interaction with protein 4.1O and its truncation mutants were investigated. Truncation mutants cover the N- and C-terminal domains of protein 4.1O (Band 4.1, FERM, actin-binding domain and coiled coil domain). Coimmunoprecipitations of protein 4.1O with PC-1 in IMCD cell lysates were done. Pulldown experiments with bacterial recombinant protein 4.1O and F-actin were performed. The modulation of the PC-1 signaling properties by protein 4.1O were investigated in luciferase assays for c-myc and TEAD. FRMD3 core promotor regions were cloned into luciferase reporter.

Results: Coimmunoprecipitations show an interaction of protein 4.1O to PC-1 full-length. The C-terminus of PC-1 interacts with four isoforms of protein 4.1O (201, 202, 204, 207). The truncation mapping and isoform alignment identfies a potential leucine zipper domain in protein 4.1O as the C-terminal binding domain to PC-1. The N-terminal protein 4.1O FERM domain is also sufficient to mediate PC-1 interaction. Protein 4.1O C-terminus binds to F-actin and links the PC-1 C-terminus to the cytoskeleton. Protein 4.1O silences the PC-1 mediated transactivation of c-myc and hippo signaling (TEAD). Furthermore, F-actin destabilization influences the PC-1 induced hippo signaling. PC-1 activates the protein 4.1O promotor.

Conclusions: Both, the FERM domain and leucine zipper containing coiled coil domain of protein 4.1O interact with the PC-1 C-terminus. The interaction of protein 4.1O links PC-1 to the actin cytoskeleton. The protein 4.1O interaction inhibits the PC-1 mediated activation of c-myc and hippo signaling. Furthermore, protein 4.1O provides a F-actin based sensitivity to the PC-1 mediated hippo signaling. In summary, protein 4.1O shows features of an anti-cystogenic protein.

PO1208

Polycystin 2 Mediates Endoplasmic Reticulum K+-Ca2+ Exchange to Protect Against Polycystic Kidney Disease

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Background: Prevailing view is that PKD is a ciliopathy. Yet, PC2 is most abundantly expressed in ER. Early studies showed that PC2 is involved in agonist-induced ER Ca2+ release. Decrease in ER Ca2+ release in PC2-deficient cells is believed to contribute to cAMP overproduction and cystogenesis. Recent patch-clamp recordings reveal that PC2 channel is ~40X more selective to K+ than Ca2+, raising the question regarding how PC2 mediates ER Ca2+ release and role of ER-localized PC2 in PKD pathogenesis. To avoid potential polarization impeding ion fluxes, Ca2+ release from ER lumen to cytosol requires coupled counter cation exchange and/or parallel anion movement.

Methods: ER Ca2+ release is assayed by fura2 fluorimetry stimulated by ATP. PC2-deficient morphant zebrafish and doxycycline-inducible adult-onset PC2-deficient mice are used for in vivo PKD model.

Results: ATP-stimulated ER Ca2+ release is blunted in PC2-null epithelial cells in which re-expression of WT, but not LOF, PC2 restores ER Ca2+ release. TricB (trimeric intracellular cation-B) is an ER resident K+ channel mediates K+-Ca2+ exchange for IP3R-mediated Ca2+ release. Expressing WT, but not LOF mutant, TricB rescues ER Ca2+ release in PC2-null cells. Vice versa, TricB-null cells have defective ER Ca2+ release, which is rescued by expression of recombinant WT PC2. Zebrafish injected with PC2 antisense morpholino develops dorsal curvature. Co-injecting WT, but not LOF mutant, PC2 RNA rescues phenotypes in PC2-deficient morphant fish. Co-injecting WT, but not LOF, TricB RNA rescues defects in PC2-morphant fish. ER targeting of ROMK K+ channel normally expresses on the cell surface rescues Ca2+ release defect and PC2-morphant phenotypes. PC2L1, a PC2 related channel normally expresses on cell membrane and cilia, does not rescue PC2-deficient morphant fish. Transgenic expression of TricB in adult-onset kidney-specific Pkd2-inactivated mice ameliorates cystogenesis. Double deletion of TricB and Pkd2 in mice reveal synergistic genetic interactions.

Conclusions: Our results provide compelling support for the notion that ER resident PC2 plays an important role in anti-cystogenesis of PKD. The mechanism of action is likely through mediating cytosol-to-ER lumen K+ flux to facilitate Ca2+ release via IP3R.

Funding: NIDDK Support

PO1209

Interactions Between TULP3 and ARL13B in Lipidated Protein Transport to Cilia and Regulation of Renal Cystogenesis

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Background: Signaling outputs from cilia maintain renal tubular homeostasis preventing cystogenesis; however, the ciliary proteins in this process are not well understood. The tubby family protein–TULP3 coordinates with the intraflagellar transport

complex-A (IFT-A) in trafficking transmembrane proteins to cilia. Lack of Tulp3 in mouse promotes renal cystogenesis during embryogenesis but suppresses adult-onset polycystic kidney disease. Discovering cargoes of TULP3 and deciphering mechanisms underlying ciliary compartmentalization will help understand how signaling at and by cilia contributes to cystogenesis.

Methods: We used direct *in vitro* binding, proximity biotinylation and mass spectrometry to map TULP3-cargo interactions. We generated knockouts of *Tulp3* and cargoes in kidney epithelial cells stably co-expressing different variants of *TULP3* or cargoes, respectively. We generated conditional knockout of *Tulp3* in mouse kidney nephrons using *Cre*-drivers and performed immunofluorescence for lipidated proteins with respect to kidney cystogenesis.

Results: The transmembrane cargoes have short motifs that are necessary and sufficient for TULP3-mediated trafficking. We now show that TULP3 is required for transport of the atypical GTPase ARL13B into cilia, and for ciliary enrichment of ARL13B-dependent farnesylated and myristoylated proteins. ARL13B transport requires TULP3 binding to IFT-A core but not to phosphoinositides, unlike transmembrane cargo transport that requires binding to both by TULP3. A conserved lysine in TULP3′s tubby domain mediates direct ARL13B binding and trafficking of lipidated and transmembrane cargoes. An N-terminal amphipathic helix in ARL13B flanking the palmitoylation site mediates binding to TULP3 and directs trafficking to cilia. Tulp3 trafficked lipidated proteins are depleted with distinctive temporal kinetics from kidney epithelial cilia during *Tulp3* deletion-induced cystogenesis.

Conclusions: We conclude that TULP3 transports transmembrane proteins and ARL13B into cilia by capture of short sequences through a shared tubby domain site. Drugging this interaction domain could provide therapeutics in polycystic kidney disease. The depletion of lipidated cargoes with distinct kinetics from kidney epithelial cilia following *Tulp3* deletion suggests their differential roles in cilia in regulating renal cystogenesis.

Funding: Other NIH Support - NIGMS, Private Foundation Support

PO1210

Augmented Renal TRPV4 Activity Attenuates Cystogenesis in ARPKD Rats

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Background: PKD is characterized by development of cysts in the kidney. Abundant evidence suggested that the impaired mechanosensitivity and disturbed $[Ca^{2+}]_i$ homeostasis are the major determinants of the rate of cystogenesis. The rapidly progressing ARPKD is caused by missense mutations in fibrocystin. ARPKD is characterized by the development of cysts almost exclusively in the collecting duct. We have previously demonstrated that mechanosensitive Ca^{2+}-permeable TRPV4 channel is preferentially expressed in the collecting duct where its activity is imperative for setting resting $[Ca^{2+}]_i$ levels and mediating flow-dependent $[Ca^{2+}]_i$ elevations. TRPV4 activity and expression is markedly augmented by high K^+ intake, known to increase flow in the collecting duct. Thus, we hypothesized that dietary K^+ supplementation would be beneficial in counteracting cystogenesis during ARPKD by stimulating TRPV4-dependent Ca^{2+} influx.

Methods: We used dietary and pharmacological inputs to establish a correlation between the rate of cystogenesis and TRPV4 function in freshly isolated cyst monolayers in a homologous ARPKD rodent model, PCK453 rats.

Results: We report that treatment of PCK453 rats with high KCl (10%) diet for 1 and 2 months significantly reduced kidney-to-body weight ratio, cystic index, and interstitial fibrosis. We also found a greatly increased total renal TRPV4 expression, channel activity and higher basal $[Ca^{2+}]_i$ levels in native cyst cells compared with respective controls. Importantly, the beneficial effects of high KCl diet were abrogated when PCK453 rats were also treated with the selective TRPV4 inhibitor, GSK2193874. GSK2193874 treatment also exacerbated cystogenesis in control PCK453 rats by modestly increasing kidney-to-body weight ratio. Surprisingly, high K^+ alkali diet (10% $KHCO_3$/Citrate) also aggravated the disease progression despite augmented renal TRPV4 expression. However, TRPV4-dependent Ca^{2+} fluxes were dramatically suppressed in freshly isolated cyst cell monolayers from high K^+ alkali fed rats, which is consistent with impaired TRPV4 activity.

Conclusions: Our experiments establish the direct link between TRPV4 function and diminished cystogenesis during ARPKD. We propose that stimulation of TRPV4 by pharmacological or dietary cues could be of clinical relevance to counteract PKD progression.

Funding: NIDDK Support

PO1211

The Transcription Factor Tfap2a Maintains the Epithelial Integrity of Renal Collecting Ducts

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Background: The transcriptional regulator Tfap2a is a member of the AP-2 family of transcription factors. In humans, heterozygous mutations of Tfap2a result in branchio-oculo-facial syndrome (BOFS), which is associated with renal anomalies, including dysplastic, absent and multicystic kidneys. In this project, we aimed to elucidate the molecular functions of Tfap2a in the renal collecting duct.

Methods: We generated mice carrying a collecting duct-specific knockout of Tfap2a ($Tfap2a^{CD-/-}$) by crossing Hoxb7;Cre and $Tfap2a^{flox/flox}$ mice. Newborn and adult mice were analyzed using histology, in situ hybridization, bulk RNA sequencing and single nucleus RNA sequencing.

Results: Tfap2a was expressed in the ureteric bud and distal region of the S-shaped body in kidneys of newborn wildtype mice and expression was maintained in mature distal tubules and collecting ducts. $Tfap2a^{CD-/-}$ mice displayed moderately reduced kidney weights (20 % reduction compared to controls) and a progressive dilation of outer medullary collecting ducts throughout six months of life. Bulk and single nuclei RNA sequencing of kidneys of three months old $Tfap2a^{CD-/-}$ mice and littermate controls indicated deregulated expression of genes associated with cellular adhesion and epithelial integrity, such as Cldn8 and Npnt. In addition, Wnt9b, a factor previously described as a regulator of planar cell polarity and tubule diameter, was downregulated in collecting ducts of $Tfap2a^{CD-/-}$ mice.

Conclusions: Our data indicate that the transcription factor Tfap2a regulates kidney size and contributes to the continued integrity of the collecting duct epithelium. Our data provide insights into potential molecular mechanisms underlying renal defects observed in BOFS.

PO1212

Comparative Multiple-Species Analysis of Renal Disease Mutations in HNF1B

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Background: Hepatocyte nuclear factor 1-beta (HNF1B) is a transcription factor involved in various stages of nephrogenesis and maintenance of renal tubular functions. Mutations in *HNF1B* are the most common monogenic causes for developmental renal disease, yet the underlying pathways affected are not fully understood. By comparative analysis in *Xenopus* and directly reprogrammed mammalian cells (iRECs) we investigated a patient-specific mutation (R295C) associated with cystic-dysplastic kidneys.

Methods: We used HNF1B to form renal-like organoids from *Xenopus* explants. In parallel, we analyzed how HNF1B R295C affects nephrogenesis in iRECs. Transcriptional changes were comparatively analyzed in two different species. We confirmed HNF1B target candidates *in vivo* using CRISPR/Cas9 editing of *Xenopus* embryos.

Results: We show that HNF1B is not only an essential component in direct reprogramming but can also induce ectopic pronephric tissue in *Xenopus* ectodermal explants. Changes in the transcriptomic profile demonstrated alterations in specific transcriptional modules and identified novel direct and indirect targets of the transcription factor HNF1B, which are linked to signaling pathways associated with renal morphogenesis, cilia and organic anion transport.

Conclusions: In conclusion, the combined use of directly reprogrammed mammalian cells and *Xenopus* renal organoid experiments allow us to gain a unique perspective into evolutionary conserved mechanisms of renal development and HNF1B associated kidney disease.

PO1213

Mosaic Inactivation of Pkd1 in Resistance Arteries Leads to Endothelial Dysfunction in Mice

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Background: Cardiovascular problems are the leading cause of mortality in autosomal dominant polycystic kidney disease (ADPKD) and hypertension is observed in 50-70% of patients before significant reduction in renal function. The pathogenesis of ADPKD-associated vasculopathy, however, remains largely unclear.

Methods: Mesenteric resistance arteries (MRA) of male normotensive non-cystic $Pkd1^{+/-}$ mice (HT) and their $Pkd1^{+/+}$ controls (WT) as well as in hypertensive cystic $Pkd1^{flox/flox}$:$Nestin^{cre}$ mice (CY) and their non-cystic $Pkd1^{flox/flox}$ controls (NC) were studied. HT and WT animals were analyzed at the ages of 8-12 and 55-60 weeks and had systolic blood pressure (SBP) recorded by tail plethysmography from 15 to 55 weeks of life, while CY and NC mice were analyzed at 8-12 weeks of life. The endothelium-dependent [acetylcholine (ACh) 10^{-9}-10^{-5} M] and -independent relaxation [sodium nitroprusside (SNP) 10^{-11}-10^{-5} M]; norepinephrine (NE, 10^{-9}-10^{-4} M)- and KCl (120 mM)-mediated contraction were assessed in MRA rings by wire myograph. Structural and mechanical parameters (SMP) were evaluated at 55-60 weeks in HT and WT rings using pressure myograph.

Results: At 8-12 weeks, no significant difference in ACh-induced relaxation was observed in MRA between HT and WT mice. CY mice, on the other hand, displayed lower ACh-induced relaxation compared to NC animals (Maximal response: 44.5±7.7 *vs* 19.9±6.7%; $P<0.05$), although this parameter was impaired in NC compared to WT ($P<0.0001$). SNP-induced relaxation was similar among groups. The contraction induced by NE or KCl did not differ between HT and WT or between CY and NC mice. At 55-60 weeks, vascular reactivity and SMP did not differ in MRA between HT and WT mice. Interestingly, no difference in SBP was identified between these groups.

Conclusions: Mosaic inactivation of both copies of *Pkd1* led to endothelial dysfunction in MRA, a phenotype not induced by *Pkd1* haploinsufficiency. Aging did not lead to development of hypertension or vascular dysfunction and remodeling in *Pkd1*-haploinsufficient mice. While our data suggest that the endothelial abnormality observed in these cystic mice may be a primary dysfunction, current investigation is assessing a potential contribution of chronic hypertension.

Funding: Government Support - Non-U.S.

PO1214

Autophagy Inhibition Ameliorates Polycystic Kidney Disease

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Background: We published that there is a decrease in autophagy proteins in Pkd1$^{RC/RC}$ mouse kidneys. Our study aimed to determine the mechanistic role of suppressed autophagy in causing cyst growth using pharmacological and genetic autophagy inhibition.

Methods: Male *Pkd1*$^{RC/RC}$ (RC) mice were treated with 2-Deoxyglucose (2DG) or Chloroquine (CHLQ) from 50-120d of age. Kidney specific *Pkd1, Atg7* double knockout mice were generated by Ksp1.3 Cre-lox recombination. Relative densitometry units (RDU) were determined on immunoblot. Autophagic flux was measured by the change in LC3-II (autophagosomes) -/+ Bafilomycin (Baf).

Results: Autophagic flux was present in wild type (WT) and 120 d old RC but suppressed in 150 d old RC kidneys. LC3-II (RDU) -/+ Baf was 0.1 vs 0.7 in WT ($p<0.01$), 0.6 vs 1.0 in 120 d old ($p<0.05$) and 2.4 vs 2.1 (NS) in 150 d old RC. 2DG resulted in a decrease in ATG12-5 complex and suppressed autophagic flux in RC kidneys. LC3-II (RDU) -/+ Baf was 0.5 vs 0.8 in VEH ($p<0.05$), 0.7 vs 0.7 in 2DG (NS). 2DG significantly reduced cyst growth and improved kidney function. Cystic index (%), count -/+ 2DG: 7.7 vs 3.7 ($p<0.01$), 211 vs 161 ($p<0.05$). BUN (mg/dL) -/+ 2DG: 35 vs 27 ($p<0.01$). Next, RC mice were treated with CHLQ, a specific autophagy inhibitor. CHLQ resulted in suppressed autophagic flux, less PKD and improved kidney function in RC mice. LC3-II (RDU) -/+ Baf was 1.2 vs 1.2 (NS) in CHLQ treated kidneys. Cyst index (%), Cyst no -/+ CHLQ in RC mice was 15.5 vs 7 ($p<0.07$), 231 vs 105 ($p<0.05$). BUN and creatinine (by HPLC) (mg/dL) -/+ CHLQ: 41 vs 26 ($p<0.05$), 2.9 vs 2.3 mg/dL ($p<0.05$). Next, autophagy was inhibited in PKD kidneys by generating double Pkd1 Atg7 KO mice. The 2 kidney/BW (%) was improved in Pkd1 Atg7 KO vs. single Pkd1 KO mice (32 vs 39 $p<0.05$). Atg7 KO kidneys had a massive increase in p62 indicating a build-up of autophagic cargo. p62 in WT vs Atg7 KO (RDU) 0.1 vs 1.8 $p<0.001$. Interestingly Atg7 KO kidneys were filled with tertiary lymphoid organs (TLO): large condensed infiltrates of T and B cells. pAMPK^{T172} was increased in Atg7 KO kidneys. AMPK activation is known to reduce PKD.

Conclusions: Both 2DG and CHLQ suppressed autophagic flux in RC kidneys and resulted in less PKD and improved kidney function. Double Pkd1 Atg7 KO mice had significantly lower kidney weight than single Pkd1 KO mice. Both pharmacological and genetic autophagy inhibition resulted in less PKD.

Funding: Veterans Affairs Support, Other U.S. Government Support

PO1215

ARL13B Negatively Regulates Kidney Cysts from Within Cilia

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Background: Polycystic kidney disease (PKD) is intricately linked to the primary cilium. Polycystin proteins localize to cilia and loss of cilia leads to renal cysts. PKD mouse models often disrupt ciliary genes, removing both ciliary and cellular pools of these gene products; however, the molecular pathway(s) that drive cyst formation is unknown. ARL13B is a regulatory GTPase highly enriched in cilia due to a VxPx motif near its C terminus. ARL13B is also localized to extraciliary sites within the cell. In most tissues, complete deletion of *Arl13b* leads to short cilia but in kidney *Arl13b* deletion leads to a loss of cilia and kidney cysts. As cilia loss leads to renal cysts, it was impossible to determine whether these cysts were due to the loss of cilia or the loss of ARL13B-dependent signaling in cilia. In order to determine the specific function of ARL13B within cilia, we needed a genetic tool that would allow us to isolate the ciliary function of ARL13B.

Methods: We engineered mice in which we mutated the valine to alanine within ARL13B's VxPx cilia-localization motif so the mice express cilia-excluded ARL13B^{V358A} from the endogenous locus. ARL13B^{V358A} protein retains all known ARL13B biochemical functions, is stably expressed and is undetectable in cilia. We measured renal cysts and cilia phenotypes to functionally characterize the cystic phenotype of cilia-excluded *Arl13b*$^{V358A/V358A}$ mice.

Results: *Arl13b*$^{V358A/V358A}$ mice are viable and fertile with slowly progressing renal cysts. *Arl13b*$^{V358A/+}$ mice exhibit no cystic phenotypes and *Arl13b*$^{V358A/null}$ mice develop cysts at a more rapid rate than *Arl13b*$^{V358A/V358A}$ mice. We detect cysts in all nephron segments of *Arl13b*$^{V358A/V358A}$ mice. Renal epithelia of *Arl13b*$^{V358A/V358A}$ mice retain cilia in normal nephrons as well as cystic regions.

Conclusions: Our findings indicate that ARL13B plays a critical role within the cilium in regulating kidney cystogenesis. These results suggest that ARL13B functions as a negative regulator of renal cysts, specifically from within the cilium. Further studies are ongoing to dissect the mechanism(s) by which ciliary ARL13B regulates kidney cystogenesis.

Funding: NIDDK Support, Other NIH Support - NIGMS

PO1216

Tsc Gene Locus Disruption and Differences in Renal Epithelial Extracellular Vesicles

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Background: In tuberous sclerosis complex (TSC), *Tsc2* mutations are associated with more severe disease manifestations than *Tsc1* mutations and the role of extracellular vesicles (EVs) in this context is not yet studied. We report a comparative analysis of EVs derived from isogenic renal cells except for *Tsc1* or *Tsc2* gene status and hypothesized that in spite of having similar physical characteristics, EVs modulate signaling pathways differently, thus leading to TSC heterogenicity.

Methods: We used mouse inner medullary collecting duct (mIMCD3) cells with the *Tsc1* (T1G cells) or *Tsc2* (T2J cells) gene disrupted by CRISPR/CAS9 methodology. EVs were isolated from the cell culture media by size-exclusion column chromatography followed by detailed physical and chemical characterization. Physical characterization of EVs was accessed by tunable resistive pulse sensing and dynamic light scattering, electron microscopy, and western blot analyses.

Results: Physical characterization of EVs revealing similar average sizes and zeta potentials (at pH 7.4) for EVs from mIMCD3 (123.5 ± 5.7 nm and –16.3 ± 2.1 mV), T1G cells (131.5 ± 8.3 nm and –19.8 ± 2.7 mV), and T2J cells (127.3 ± 4.9 nm and –20.2 ± 2.1 mV). EVs derived from parental mIMCD3 cells and both mutated cell lines were heterogeneous (>90% of EVs < 150 nm) in nature. Immunoblotting detected cilial Hedgehog signaling protein Arl13b; intercellular proteins TSG101 and Alix; and transmembrane proteins CD63, CD9, and CD81. Compared to *Tsc2* deletion, *Tsc1* deletion cells had reduced EV production and release rates. EVs from *Tsc1* mutant cells altered mTORC1, autophagy, and β-catenin pathways differently than EVs from *Tsc2*-mutated cells. Quantitative PCR analysis revealed the down regulation of miR-212a-3p and miR-99a-5p in EVs from *Tsc2*-mutated cells compared to EVs from *Tsc1*-mutant cells.

Conclusions: EV-derived miR-212-3p and mIR-99a-5p axes may represent therapeutic targets or biomarkers for TSC disease.

Funding: Other U.S. Government Support

PO1217

ADPKD Mutations in the Stalk/Tethered Agonist of Polycystin-1 CTF Affect Signaling and GPS Cleavage

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Background: Like Adhesion G protein-coupled receptors (aGPCRs), the N-terminal ectodomain of polycystin-1 (PC1) contains a membrane-proximal GAIN domain that catalyzes self-cleavage at its embedded GPCR proteolysis site (GPS), dividing these proteins into extracellular N-terminal (NTF) and membrane-embedded C-terminal (CTF) fragments. PC1 GPS cleavage is required for JAK/STAT signaling, PC1 maturation/trafficking and for prevention of renal cystogenesis in mice. ADPKD mutations that map within the GAIN domain inhibit GPS cleavage. We previously reported that the PC1 CTF utilizes an aGPCR-like tethered agonist mechanism to activate G-protein signaling to an NFAT reporter, which involves the short, N-terminal, extracellular stalk of the CTF serving as the tethered agonist. Deletion of the stalk dramatically inhibited signaling, while synthetic stalk-derived peptides could rescue signaling by the stalkless CTF and inhibit cystogenesis in metanephric organ cultures of hypomorphic *Pkd1*$^{RC/RC}$ kidneys. Here we assess the effect of stalk-localized ADPKD missense mutations on signaling by the dissociated CTF subunit and on GPS cleavage of full-length (FL) PC1 to gain additional insight for this regulatory mechanism.

Methods: Wild type (WT) or mutant, FL or CTF forms of PC1 were expressed in HEK293T cells and compared for activation of an NFAT promoter-luciferase reporter, levels of total and cell surface expression and GPS cleavage. Homology modeling of the PC1 GAIN domain was also performed.

Results: Of 11 substitutions throughout the stalk, 6 significantly reduced, 2 increased, and 3 had no effect on signaling by PC1 CTF. Total and surface expression levels of the CTF mutants ranged from 62-125% of WT CTF. Most mutations had no effect on GPS cleavage of FL-PC1. Mutations that inhibited signaling or GPS cleavage mapped to the N-terminal portion of the stalk, while the 2 mutations that increased signaling were in the latter half.

Conclusions: PC1 stalk has more than one region important in regulation of CTF signaling- perhaps as part of the agonistic sequence or for its proper orientation. This study underscores the importance of PC1 GPS cleavage and suggests disruption of a tethered agonist mechanism may also contribute to renal cystogenesis. Better understanding of the tethered agonist mechanism is necessary for development of *PKD1* mutation-specific therapies.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

PO1218

Metabolomic Analysis of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Associations with Disease Progression and Treatment

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Background: ADPKD is characterized by epithelial proliferation and cyst growth. Metabolic abnormalities have been identified in murine models, but little is known about alterations in metabolic pathways in human ADPKD. We evaluated plasma metabolomic profiles in ADPKD subjects prior to and after exposure to tolvaptan (T) as compared to healthy controls to better understand metabolic alterations in ADPKD and potential associations with disease progression and treatment response.

Methods: Plasma samples were collected and analyzed at baseline and month 12 in 100 ADPKD subjects (50 in T and 50 in placebo [P] arms) enrolled in TEMPO 3:4 (NCT00428948). The protein fraction was removed, and the remaining extract split into equal parts for analysis on liquid chromatography tandem mass spectrometry and gas chromatography mass spectrometry platforms. Proprietary software (Metabolon, Inc., Durham, NC) matched ions to an in-house library of standards for metabolite identification and quantitation. Forty age- and sex-matched healthy subjects were analyzed as a control group. Linear mixed effect modeling identified associations of metabolites with ADPKD vs control, height-adjusted total kidney volume (htTKV), Mayo Imaging Classification (MIC), and T vs P.

Results: Baseline metabolic profiles differed between ADPKD and controls, with significant differences in lipid metabolism, TCA cycle, and amino acid metabolism. Baseline MIC 1C, 1D, 1E (vs 1B) were associated with accumulation of the uremic toxin pseudouridine, elevated fatty acid synthesis, and altered tryptophan metabolism, with similar findings when baseline htTKV was analyzed. Thyroxine, urea, and dimethylsulfone were decreased in T vs P at month 12, as well as other metabolites involved in lipid and amino acid metabolism.

Conclusions: We identified novel associations of amino acid and lipid metabolic pathways with ADPKD vs control and with measures of disease severity (MIC and htTKV). Metabolite intensity was differentially affected in T vs P at 12 months of treatment, supporting a role for discovery metabolomics in evaluating response to therapy.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

PO1219

Short-Term Ketogenic Interventions Are Feasible and Effective in Triggering Ketosis in Autosomal Dominant Polycystic Kidney Disease (ADPKD): Results from the RESET-PKD Study

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Background: Short-term ketogenic dietary interventions slow disease progression in animal models of ADPKD. The RESET-PKD study translates these promising results to a pilot study in humans.

Methods: 10 ADPKD patients with rapid disease progression were enrolled (baseline V1) and initially followed their usual carbohydrate-rich diet for up to 4 weeks. At visit 2 (V2) patients chose to either perform a 3-day water fast (WF) or a 14-day ketogenic diet (KD) until V3 and returned to their normal nutrition until V4. MRI kidney volumetry was performed at all visits. Ketone bodies were evaluated at all visits and in between. Feasibility was examined using questionnaires.

Results: All participants (KD: n=5, WF: n=5; age 39.8±11.6 years; eGFR 82±23.5 ml/min; TKV 2224±1156 ml) were classified as Mayo Class 1C to 1E. The dietary interventions did not alter serum creatinine (V2: 1.17±0.33 mg/dl vs. V3: 1.20±0.35 mg/dl, p = 0.826) but serum glucose levels decreased significantly (V2: 84±3 mg/dl, V3: 70±13 mg/dl, p = 0.004). Acetone levels in breath as well as BHB blood levels increased in both study arms (average acetone before dietary intervention (V1 to V2): 2.6±1.18 ppm, on diet (V3): 22.8±11.9 ppm, p< 0.0001; BHB before dietary intervention: 0.22±0.08 mmol/l, on diet: 1.89±0.92 mmol/l, p<0.0001). 9 out of 10 patients reached a ketogenic state during the intervention and 90 % evaluated ketogenic interventions as feasible. No significant TKV changes were observed (ΔTKV V1 to V2: +0.75±0.54%, ΔTKV V2 to V3: -1.06±1.16%).

Conclusions: RESET-PKD shows that ADPKD patients adhere to short-term ketogenic interventions, reliably reach ketosis without ADPKD-specific adverse effects, and judge this diet as feasible in every-day life. Short-term ketogenic interventions did not lead to a significant reduction in TKV or serum creatinine. Larger clinical trials examining longer-term dietary interventions will be crucial to further evaluate long-term feasibility and the therapeutic potential of ketogenic diets in ADPKD.

PO1220

Analysis of MicroRNAs as Regulators of Expression of Transcripts Associated with Stem Cell Pluripotency in Pkd1-Deficient Mouse Models

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by cysts formation deriving from collecting ducts. Pluripotent stem cells associated with the formation of renal structures have been used in *in vitro* studies of nephrogenesis or cystogenesis related to ADPKD. However, the association between transcripts integrating pathways involved in stem cells pluripotency and cystogenesis deserves further investigation. The microRNAs (miRNAs) that participate in the regulation of these transcripts in kidney tissues of mouse models orthologous to ADPKD have not yet been validated. To identify regulatory miRNAs and differently expressed transcripts associated with stem cell pluripotency in kidney tissues of *Pkd1*-deficient mouse models.

Methods: A transcriptomic computational identification and validation of the expression level of regulatory miRNAs and genes by RT-qPCR, normalized by their respective housekeepings, *miR-26a* and *Ppia* was performed. The analyses were performed on kidneys from 10- to 12-week-old cystic mice ($Pkd1^{flox/flox}$:$Nestin^{cre}$ or $Pkd1^{flox/-}$:$Nestin^{cre}$, CY, n = 10) and their non-cystic controls ($Pkd1^{flox/flox}$ or $Pkd1^{flox/-}$, NC, n = 10); mice haploinsufficient for *Pkd1* ($Pkd1^{+/-}$, HT, n = 6) and their wild controls ($Pkd1^{+/+}$, WT, n = 6); and 15-day-old severely cystic mice ($Pkd1^{V/V}$, SC, n = 7) and their controls (CO, n = 5).

Results: The validation of the computational analyses performed in our three animal models with reports from the literature in other *Pkd1*-deficient models, identified 10 differently expressed genes associated with the regulation of stem cells pluripotency. Increased expression of *Stat3* and *Map3k1* genes and decreased regulatory miRNA *Let-7a* were observed in SC versus CO kidneys. On the other hand, *Mapk14* gene showed decreased expression while its potential regulator, *miR-21*, revealed increased expression in SC versus CO kidneys. *Fgf10* expression was decreased in SC versus CO kidneys whereas a trend of increased expression in the CY versus NC group has been observed.

Conclusions: Present results suggest a potential regulatory effect of *miR-21* on *Mapk14* expression and of *miR-Let-7a* on the expression of *Stat3*, *Map3k1* and *Fgf10*, namely transcripts involved in stem cells pluripotency and cystogenesis in kidney tissues of *Pkd1*-deficient mouse models.

Funding: Government Support - Non-U.S.

PO1221

Investigation of Lad1 as a Candidate Modifier of Polycystic Kidney Disease in Pkd1 Mouse Models

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Background: Polycystic Kidney Disease (PKD) is a monogenic disease caused by mutations in either *PKD1* or *PKD2*, which encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. One proposed function for PC1 is to regulate cell migration and cell-cell interaction, possibly through modulation of the cytoskeleton. In prior transcriptomic studies of *Pkd1* mutant kidneys, we had identified *Lad1* as one of the few genes whose expression was dysregulated early in the course of the disease. The limited available literature suggests *Lad1* may encode a cytoskeleton protein that acts as an anchoring filament to the basement membrane of epithelial cells. The goal of this study is to investigate the role of Lad1 in mediating/modifying PKD phenotypes.

Methods: We quantified *Lad1* gene and protein expression in the tissues of *Pkd1* conditional mutant mice, kidney epithelial cell lines derived from *Pkd1* conditional mice and human keratinocyte HaCat cells by quantitative polymerase chain reaction (qPCR) and western blot analyses. We used CRISPR technology to generate two *Lad1* mutant mouse lines that have large deletions spanning most of the coding region of *Lad1* and characterized the phenotype of homozygous mutants. *Lad1* mutants were crossed with $Pkd1^{cond/cond}$ mice with Ksp-Cre and tamoxifen-Cre to test for genetic interaction in early and late onset PKD models.

Results: We confirmed that *Pkd1* mutant kidneys and epithelial cells have lower *Lad1* expression levels compared to wild type samples. Mice with homozygous deletion of *Lad1* exons 3 to 8 were born at normal mendelian ratios and lacked obvious abnormalities up to 1 year of age. Histopathologic analyses of the kidney and organs with the highest expression of *Lad1* also were normal. *Pkd1/Lad1* double mutants were born at expected rates and lacked distinctive phenotypic features. However, early data suggest that $Pkd1^{cond/cond}$; Ksp-Cre+/ *Lad1* homozygous mutants have increased kidney-body weight ratios with worse cystic disease. Further analysis, including *Lad1* CRISPR knock-out animals crossed with late-stage conditional *Pkd1* knock-out animals, is ongoing.

Conclusions: *Lad1* expression is reduced in *Pkd1* mutant kidneys. CRISPR knock-out of *Lad1* alone shows no obvious phenotype. Loss of *Lad1* may worsen disease in the early onset *Pkd1*-cystic model.

Funding: NIDDK Support

PO1222

Sildenafil Inhibits ADPKD-Derived Cyst Growth in 3D Culture and Induces Apoptosis in the Han/SPRD Cy+/Cy+ Rat Model of Renal Cystic Disease

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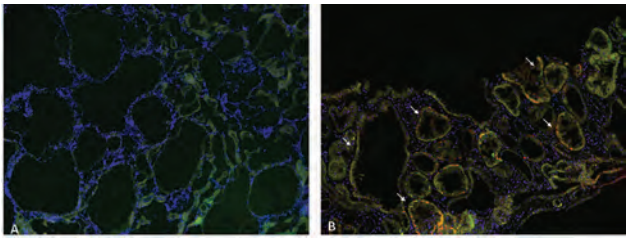
Background: In prior studies we found that human renal cyst cells express high levels of cGMP phosphodiesterase 5, 6 and 9 as compared to normal human kidney cells. In breast cancer, inhibition of cGMP phosphodiesterases induces apoptosis. We tested the hypothesis that sildenifil blocks cell proliferation and/or induces apoptosis in cyst epithelia.

Methods: PKD Q4004X cells were grown in Matrigel and treated with vehicle or sildenifil for 7 days. Cyst size was assayed by light microscopy. Differences in cyst area were analyzed by two-way ANOVA. In separate experiments, male cy+/cy+ rats were given either vehicle or sildenifil in their water supply for 7 or 28 days. Kidneys were harvested and apoptosis was assayed by staining with anti-M30, a monoclonal antibody that binds to apoptosis mediated cleavage of cytokeratin 18 in epithelial cells.

Results: In 3D cultures of PKD Q4004X cells, cultures treated with sildenafil (1, 2 and 4 ug/ml) are significantly smaller than vehicle-treated cultures ($p<0.05$ for all doses). Further analysis showed that cysts larger than 150 um^2 were not observed in any sildenafil treated cultures. Figure 1 shows M30 staining in sildenafil (20 ug/kg/day x 7 to treated rats (panel B, red channel merged with the green autofluorescence channel) versus vehicle treated animals. M30 positive cells are found predominantly around cyst lumens. Apoptotic changes in cyst epithelia were also observed in rats treated with sildenafil for 40 days.

Conclusions: Sildenafil inhibits human kidney cyst cyst growth in 3D culture. In male $cy^{+/+}$ rats, sildenafil at a dose of 20 mg/kg/day for 7 or 40 days results in apoptosis of cyst epithelia.

Funding: Private Foundation Support



Seven days of sildenafil treatment induces apoptosis in cystic kidneys. Sections stained with anti-cytokeratin 8/18 (red channel). Nuclei are labeled with Hoechst 33342. Green channel is autofluorescence. A: Vehicle treated male rats. Note the absence of cytokeratin 8/18. B: Vehicle + 20 mg/kg sildenafil treated for 7 days. Arrows point to cytokeratin 8/18 positive (red cytosolic stain) in cyst epithelia.

PO1223

Polycystin 1 Ciliary Localization Is Regulated by Its aGPCR Activity

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by loss of function mutations in the PKD1 and PKD2 genes, which encode PC1 and PC2, respectively. PC1 is a 460kD multi-spanning membrane protein that undergoes multiple proteolytic cleavages, one of which occurs at a G Protein Coupled Receptor (GPCR) Proteolytic site near the junction between the large extracellular N terminus (NTF) and the first transmembrane domain. PC1 and 2 both localize to the primary cilium where they may participate in mechano-sensation and other sensory processes. Recent studies demonstrate that PC1 can function as an atypical GPCR and that it binds to Wnt ligands. We have shown that removal of the PC1 NTF exposes a tethered agonist (TA) peptide that activates the PC1 GPCR function. Activation of GPCRs in the cilia induces their trafficking out of the cilium in association with their ligand-induced desensitization.

Methods: Confocal IF, Mechanical stimulation, PC1 mutagenesis.

Results: We find that the localization of PC1 to cilia is similarly regulated by its GPCR activity. A constitutively active PC1 construct that lacks the NTF ($PC1^{\Delta NTF}$) is absent from the primary cilia when expressed in LLC-PK_1 cells, whereas a constitutively inactive PC1 construct that lacks the NTF and the TA ($PC1^{\Delta NTF\Delta TA}$) resides in the primary cilia. Addition of a soluble form of the TA peptide to cells expressing $PC1^{\Delta NTF\Delta TA}$ results in redistribution of the $PC1^{\Delta NTF\Delta TA}$ protein out of the cilium. Blocking β-arrestin-mediated receptor desensitization with barbadin prevents the removal of $PC1^{\Delta NTF}$ and of TA peptide-treated $PC1^{\Delta NTF\Delta TA}$ from the cilium. When full length PC1 is co-expressed with PC1 in LLC-PK_1 cells both proteins localize to the cilium. Extended exposure to the Wnt9b ligand or to mechanical stimuli both lead to reduced quantities of PC1 in the cilium and at the apical cell surface, and this redistribution is blocked by β-arrestin inhibitor barbadin.

Conclusions: Our data demonstrate that PC1 ciliary localization is regulated by physiological stimuli including ligand binding and mechanical stress and, like GPCR regulation, is subject to receptor desensitization processes. Our findings indicate that the GPCR activation state of PC1 can be observed by examining the distribution of PC1, suggesting new approaches through which PC1 activity can be assessed in vivo and in the context of drug discovery.

Funding: NIDDK Support

PO1224

Mutation Position and Genetic Background Modulate Disease Expression in Pkhd1 Mouse Models

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Background: Multiple *Pkhd1* mutant mouse models have been generated by gene-targeting methods (*del3-4*, *del67*) or resulted from spontaneous mutations (*cyli*). When these mutations are homozygous on inbred backgrounds (DBA/2J (D2); C57BL/6 (B6)), there is either no renal cystic disease or very mild dilatation of the PCTs rather than CCDs. A recent ARegPKD report showed that the position of human *PKHD1* mutations correlates with ARPKD kidney and liver disease severity (*Burgmaier, KI 2021*). In the current study, we examined the impact of age, mutation position, and mixed genetic background on kidney, liver, and pancreatic disease in *Pkhd1* mutants.

Methods: D2-$Pkhd1^{cyli/+}$; B6-$Pkhd1^{del3\text{-}4/+}$ and B6-$Pkhd1^{del67/+}$ mouse lines. Intercross strategy to generate a suite of F2 mutants on mixed genetic backgrounds (D2.B6). Histopathological analysis of the kidney, liver, and pancreas from 18-month-old, nulliparous mutant females.

Results: D2.B6-$Pkhd1^{cyli/cyli}$ mutants expressed both marked dilatation of the CCDs and liver ductal plate malformation (DPM); no pancreatic cysts were observed. Similarly, D2.B6-$Pkhd1^{del3\text{-}4/del3\text{-}4}$ mutants expressed corticomedullary cysts, involving DCTs and CCDs and DPM lesion but no pancreatic cysts. In contrast, D2.B6-$Pkhd1^{cyli/del3\text{-}4}$ compound heterozygotes had occasional dilated DCTs, a marked DPM lesion, and diffuse cyst formation in the pancreatic ducts. The D2.B6-$Pkhd1^{cyli/del67}$ and D2.B6-$Pkhd1^{del67/del67}$ mutants had occasional dilated DCTs, no DPM or pancreatic cysts.

Conclusions: Age, genetic background, and mutation position modulate organ-specific disease expression in *Pkhd1* mutants. On the mixed D2.B6 background both *cyli* and *del3-4* aged F2 mutants develop CCD cysts, similar to human *PKHD1 renal* disease. Surprisingly, D2.B6-$Pkhd1^{cyli/del3\text{-}4}$ mice had minimal kidney pathology but marked pancreatic duct cysts, suggesting that genetic background differentially modulates kidney and pancreatic cystic phenotypes. Mice heterozygous or homozygous for the *del67* mutation expressed minimal kidney, liver, or pancreatic cystic changes. Thus, defects at the 3′ end of *Pkhd1* appear to have minimal pathobiological impact, that is not influenced by age or the mixed D2.B6 genetic background. These findings will inform our experimental strategies to identify organ-specific *Pkhd1* genetic modifiers.

Funding: NIDDK Support, Private Foundation Support

PO1225

Abstract Withdrawn

PO1226

Rab GTPase Regulation in Ciliogenesis and Polycystic Kidney Disease

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Background: Primary cilia are sensory organelles with widespread roles in development and epithelial function. Mutations resulting in dysmorphic cilia and ciliary dysfunction are associated with renal ciliopathies such as polycystic kidney disease (PKD), yet primary cilia remain enigmatic in terms of their molecular and functional characterisation. Rab GTPases are master regulators of vesicular trafficking that have been shown to regulate ciliogenesis and cilium composition, with downstream effects on ciliary function and signalling. Rabs are therefore poised to vary or modify primary ciliary function, by working in conjunction with key cilia proteins, including those mutated in PKD and other ciliopathies. Hence, we are examining novel roles for Rab GTPases in cilia formation and function and Rab13 has been the focus of recent studies.

Methods: Expression of fluorescently tagged, recombinant Rab13 and knockout of endogenous Rab13 were used to assess the roles of Rab13 GTPase in ciliogenesis and cilia function in mouse renal epithelial cell lines grown as monolayers and spheroids. Ciliary morphogenesis, cell polarity and growth were assessed by confocal imaging in live and fixed cells, while biochemical approaches were used to test cilia-dependent signalling and associated molecular pathways, along-with Rab13 expression, activation and effector functions.

Results: Our data show that Rab13 localises to the primary cilia of mouse kidney cells and Rab13 loss of function affects ciliogenesis in a variety of *in vitro* and *in vivo* models including zebrafish embryos. Characterisation of Rab13 knockout epithelial cells reveal altered cilia, the perturbation of ciliopathy-associated protein localisation, and the formation of dysmorphic renal spheroids. Rab13 knockout zebrafish embryos display a range of cilia-associated developmental defects and Rab13 expression is diminished in mouse PKD cells.

Conclusions: Here we reveal a novel cilia-associated role for Rab13 GTPase. Investigating the genes and molecules that contribute to the cilial landscape is important to improve knowledge, for potential translation and discovery of new therapeutic approaches for renal ciliopathies including PKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1227

Efficacy and Adverse Effects of a Novel Mesoscale Nanoparticle-Guided Sirolimus Delivery Strategy in a Pkhd1PCK Rat Model

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Background: Pre-clinical studies have shown that mTOR inhibition attenuated renal cystic disease progression but it did not improve outcomes in patients with autosomal dominant polycystic kidney disease (ADPKD). This was attributed to the dose limitations in humans due to mTOR inhibitor toxicity. To increase the mTOR inhibition efficacy and reduce its toxicity in renal cystic diseases, we studied mesoscale nanoparticle (MNP)-guided delivery of an mTOR inhibitor, sirolimus (MNP-sirolimus), in *Pkhd1*$^{PCK/PCK}$ rats. We used our recently developed MNPs that selectively and with high affinity target the renal tubular epithelium.

Methods: We synthesized Empty-MNPs or MNP-sirolimus and used them in an experiment that resembles seminal pre-clinical studies of tolvaptan, the only FDA-approved ADPKD therapeutic. Newly outbred *Pkhd1*$^{PCK/PCK}$ rat males were divided into 3 groups (each N= 8-9) and treated for 8 weeks (p22 to p77) with: Empty-MNP (50 mg/kg IV q96 hours), Free-sirolimus (0.15 mg/kg IV q48 hours) and MNP-sirolimus (50 mg/kg IV equivalent to 0.3 mg/kg sirolimus q96 hours). Pre- and post-treatment cyst volumes were assessed by MRI at p21 and p78.

Results: The MNP-sirolimus or Free-sirolimus both inhibited renal mTOR activity in *Pkhd1*$^{PCK/PCK}$ rats. The mean pS6/total S6 ratios were: 7.9 for MNP-Sirolimus vs 19.1 for Free-Rapa and 105.1 for Empty-MNP ($p<0.001$) while total S6 levels did not differ ($p=0.806$). Similarly, an 8-week mTOR inhibition reduced mean renal cyst volumes: 39.9 mm^3 for MNP-sirolimus vs 59.3 mm^3 for Free-sirolimus vs 148.4 mm^3 for Empty-MNP (overall $p=0.011$). However, in pairwise comparison with Empty-MNP treatment, this difference was significant only for MNP-sirolimus ($p=0.017$) while for Free-sirolimus, the significance was marginal ($p=0.052$). The pre-treatment renal cyst volumes at 3 weeks were not significantly different ($p=0.772$). Among side effects, mTOR inhibition reduced body and heart weights ($p<0.001$ and $p=0.004$); in both cases, their averages were less severely reduced in MNP-Sirolimus as compared to Free-sirolimus treated rats.

Conclusions: Together, our studies support the concept that a novel MNP-guided sirolimus delivery increases renal mTOR inhibition and therapeutic efficacy in renal cystic diseases, while reducing systemic toxicity.

Funding: NIDDK Support, Other U.S. Government Support

PO1228

Biomarkers Reflecting Extracellular Matrix Turnover Are Prognostic for Kidney Function Decline in Patients with ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited disorders in humans and is caused by mutations in the PKD1 and PKD2 genes. The disease is characterized by development and growth of cysts leading to loss of kidney function. Fibrosis is a driving force in progression to end-stage kidney disease in ADPKD and is characterized by an imbalanced turnover of extracellular matrix (ECM). Here, we investigated the association of ECM biomarkers with rate of kidney function decline in patients with ADPKD.

Methods: We measured four markers of ECM turnover in serum and urine from 305 patients with ADPKD from the DIPAK-1 study (NCT01616927): three markers of interstitial collagen turnover (C3M, PRO-C3 and PRO-C6) and one laminin degradation marker reflecting basement membrane turnover (LG1M). The association of the biomarkers with kidney function decline was investigated with a linear mixed model (change in eGFR/year) and logistic regression (decline in eGFR of >30%). Data was log-transformed if appropriate.

Results: All four markers of kidney fibrosis in serum were associated with eGFR at baseline when adjusting for sex, age, height adjusted total kidney volume (htTKV) and PKD mutation in serum (C3M, $P<0.05$; PRO-C3, $P<0.001$; PRO-C6, $P<0.001$; LG1M, $P<0.001$). In urine, only C3M and PRO-C6 (C3M, $P<0.001$; PRO-C6, $P<0.01$) and not PRO-C3 and LG1M (PRO-C3, $P=0.07$; LG1M, $P=0.31$) were independently associated with eGFR. Serum C3M ($P=0.005$) as well as urinary PRO-C3 ($P=0.001$) and PRO-C6 ($P<0.001$) were associated with the rate of eGFR decline per year when adjusting for age, sex, baseline eGFR, htTKV and PKD mutation. A total of 60 patients had a decline in eGFR of >30% and when adjusting for sex, age, baseline eGFR htTKV and PKD mutation, only serum C3M (OR=1.48, $P=0.02$) was independently associated with a decline in eGFR of more than 30%.

Conclusions: Serum C3M as well as urinary PRO-C3 and PRO-C6 were associated with the rate of kidney function decline when adjusting for known determinants of disease severity. Also, serum C3M could identify fast progressors (decline in eGFR of >30%). These markers hold promise that components from the ECM may be used as prognostic markers in ADPKD, but should be validated first in an independent ADPKD cohort.

PO1229

Magnetic Resonance Fingerprinting (MRF) Identifies Potential Imaging Biomarkers for Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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Background: Autosomal Recessive Polycystic Kidney Disease (ARPKD) is an important cause of morbidity and mortality in children with chronic kidney disease (CKD). Novel therapies have shown efficacy in ARPKD animal models, but clinical trials in ARPKD patients have not been possible due to the lack of sensitive measures of kidney disease progression. Non-invasive Magnetic Resonance Imaging (MRI) techniques, including novel MR Fingerprinting (MRF), show promise in addressing this unmet need. We previously identified MRF-based T1 and T2 mapping as potential biomarkers of ARPKD kidney disease in animal models and initial human studies. In the current study, we evaluated the relationship between these imaging parameters and renal function in ARPKD subjects with mild CKD.

Methods: ARPKD subjects (age 6-25 yrs) with estimated glomerular filtration rate (eGFR) >60ml/min/1.73m^2 (bedside Schwartz <18 yo; CKD-EPI ≥18 yo) were scanned on a Siemens 3T MRI scanner utilizing novel MRF technology to simultaneously generate mean kidney T1 and T2 maps in 15 secs/imaging slice with no sedation or injectable contrast agent. The relationship between eGFR (U25 eGFR formula) and imaging parameters was assessed by Pearson correlations with significance set at <0.05.

Results: 7 subjects (2M/5F, age=12±5 years) were imaged. eGFR was 87±21, range=52-109 ml/min/1.73m^2; 5 had hypertension. Mean kidney T2 (94±10 msec) showed a significant negative correlation with eGFR ($R=-0.86$, $p=0.013$). Mean kidney T1 (2162±376 msec) also showed a strong negative correlation ($R=-0.69$) but did not yet reach significance ($p=0.086$). Mean T1 and T2 values for the right and left kidneys also demonstrated a significant correlation (T1: $R=0.99$, T2: $R=0.79$).

Conclusions: This is the first study to establish a relationship between MRI-derived imaging biomarkers (T1 and T2) and kidney function (eGFR) in ARPKD subjects. Despite the small cohort, data clearly demonstrate that mean T1 and T2 both increase with declining eGFR. These important findings suggest that MRF-based T1 and T2 mapping may provide a safe, non-invasive, quantitative, and reproducible measure of kidney disease severity to support future clinical trials to identify subjects at high risk for disease progression and monitor response to treatment.

Funding: NIDDK Support, Commercial Support - Siemens

PO1230

Interaction/Modulation of PKD2 by TACAN

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Background: TACAN (also named TMEM120A), recently reported as a mechano- and pain-sensing ion channel, is distributed in diverse non-neuronal tissues such as heart, intestine and kidney, which indicates its potential role besides pain sensation. Previous proteomic screenings suggested the presence of an interaction between PKD2 and TACAN. In this study, we investigated the physical and functional interaction between the two proteins.

Methods: We employed mutagenesis, molecular cloning, co-immunoprecipitation, immunofluorescence, biotinylation, two-electrode voltage clamp in *Xenopus* oocytes to measure whole-cell currents and patch-clamp in Chinese hamster ovary (CHO) cells to measure single-channel currents.

Results: We found that TACAN is co-localized and in complex with PKD2 in primary cilia of different kidney cell lines and oocytes. Using oocyte expression, we found that TACAN inhibits the channel activity of PKD2 gain-of-function mutant F604P. Using CHO cell expression, we found that TACAN inhibits both wild-type PKD2 and mutant F604P through reducing their single-channel conductance and open probability. Co-expression of TACAN significantly enhanced the sensitivity of PKD2 to stretch. Further, our data showed that while the first and last transmembrane domains (TM1 and TM6) of TACAN are involved in interaction with transmembrane domains of PKD2 only the TACAN TM6 is functionally relevant.

Conclusions: Our study revealed inhibition of PKD2 channel activity through physical TACAN-PKD2 complexing and that TACAN, but not PKD2, mediates mechanosensitivity of the channel complex. Whether and how TACAN participates in the pore formation remains to be determined.

Funding: Government Support - Non-U.S.

PO1231

Suppressed Autophagy Drives Increased Cellular Metabolic Activity in Human ADPKD Cells

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Background: We published that the autophagy phenotype in *Pkd1*$^{RC/RC}$ mouse kidneys is characterized by decreases in crucial autophagy proteins (Cell Signal 2020). We attempt to determine the mechanistic role of suppressed autophagy as it relates to cell metabolic activity (viability and proliferation) in ADPKD cells.

Methods: Human primary immortalized cultured cells were used: normal renal cortical tubular epithelium (RCTE, PKD1+/+) and ADPKD cyst-lining epithelium (9-12, PKD1-/-). To measure autophagic flux, cells were treated with lysosomal inhibitor chloroquin (C) and LC3-II (immunoblot), a marker of autophagosomes or mCherry LC3 (fluorescence) was analyzed. MTT assay was used to measure cellular metabolic activity (cell viability and proliferation). Relative densitometry units (RDU) were measured on immunoblots.

Results: There was an increase in MTT and a decrease in AnnV in 9-12 vs RCTE cells. MTT OD was 0.36 in RCTE vs 0.44 in 9-12 ($p<0.01$). AnnexinV (AnnV) (% gated), marker of apoptosis, was 67 in RCTE vs 18 in 9-12 ($p<0.0001$). The increase in LC3-II with C in RCTE was not seen in 9-12 indicating suppressed autophagic flux. LC3-II (RDU) -/+ C was 0.6 vs 1.4 in RCTE ($P<0.01$) and 0.9 vs 1.1 (NS) in 9-12. mCherry (% gated) -/+ C was 6 vs 16 ($p<0.05$) in RCTE and 6 vs 13 (NS) in 9-12 cells. p62, marker of autophagic cargo, was increased in 9-12 vs RCTE. p62 (RDU) was 0.7 in RCTE and 1.2 in 9-12 ($p<0.05$). Cells were treated with an ATG7 shRNA (SH) to inhibit a crucial autophagy protein. There was a 50% decrease in LC3-II and ATG7 protein in SH-treated 9-12 cells. SH resulted in an increase in MTT and a decrease in AnnV indicating that suppressed autophagy drives MTT and inhibits apoptosis. MTT OD was 0.7 with scrambled shRNA (SCR) and 0.9 with SH ($p<0.05$). AnnV was 26 with SCR vs 16 with SH ($p<0.05$). Tat-Beclin peptide (TAT), a specific autophagy inducer, resulted in a decrease in MTT in 9-12 suggesting that autophagy decreases MTT. MTT OD was 0.5 with Veh vs. 0.2 with TAT ($p<0.001$). TAT did not affect AnnV.

Conclusions: In ADPKD cyst lining epithelial cells there is increased MTT, suppressed autophagic flux, and decreased apoptosis. Autophagy inhibition increased MTT and autophagy induction decreased MTT. Suppressed autophagy drives increased cellular metabolic activity in ADPKD cells. The effect of autophagy inhibition/induction on cyst growth in vivo merits further study.

Funding: Veterans Affairs Support, Other U.S. Government Support

PO1232

Tsc2 Mutation Induces Renal Tubular Cell Nonautonomous Disease

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Background: TSC renal cystic disease is poorly understood and has no approved treatment. In a new principal cell-targeted murine model of Tsc cystic disease, the renal cystic epithelium is mostly composed of type A intercalated cells with an intact *Tsc2* gene confirmed by sequencing, although these cells exhibit a Tsc mutant disease phenotype.

Methods: We used a newly derived targeted murine model in lineage tracing and extracellular vesicle (EV) characterization experiments and a cell culture model in EV characterization and cellular induction experiments to understand TSC cystogenesis. For the lineager tracing experiments we used Aquaporin-2 Cre, Floxed Tsc2, and Confetti mice in breeding experiments. To characterize the EVs, we used tunable resistive pulse sensing, dynamic light scattering, electron microscopy, and western blot analyses.

Results: Using lineage tracing experiments, we found principal cells undergo clonal expansion but can contribute very few cells to the cyst. We determined that cystic kidneys contain more interstitial EVs than noncystic kidneys, excrete fewer EVs in urine, and contain EVs in cyst fluid. Moreover, the loss of the *Tsc2* gene in EV-producing cells greatly changes the effect of EVs on renal tubular epithelium, such that the epithelium develops increased secretory and proliferative pathway activity. We demonstate that the mTORC1 pathway activity is independent form the EV production, and that the EV effects for a single cell line can vary significantly. mTORC1 inhibition reduces EV production.

Conclusions: TSC cystogenesis involves significant contribution from genetically intact cells conscripted to the mutant phenotype by mutant cell derived EVs.

Funding: Other U.S. Government Support

PO1233

Exploring the Heterogeneity of Kidney Resident Macrophages Using Single-Cell RNA Sequencing

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Background: Tissue resident macrophages are highly diverse, even when located within the same tissue. This diversity is thought to be driven by localization, ontological origin, time in tissue, and niche specific cues. Importantly, these underlying factors likely influence resident macrophage phenotype and function during disease initiation and progression.

Methods: To understand the diversity of kidney resident macrophages (KRM), we performed single cell RNA sequencing, parabiosis, and fate mapping on kidneys isolated from wild type and transgenic knock-in reporter mice.

Results: Using single cell RNA sequencing, we identified three subpopulations of KRM including one with enriched expression of *Ccr2*. Using *Ccr2*-RFP knock-in mice and Ms4a3^{cre} Rosa Stop$^{f/f}$ TdT mice, we confirm that these resident macrophages were derived from monocyte precursors and preferentially localize to the renal cortex. Based on our single cell RNA sequencing data, we propose that monocytes undergo a series of differentiation steps upon entering the kidney in order to become *Ccr2*+ KRM. Analysis of single cell data using RNA Velocity and Monocle suggest that monocytes require *Cx3cr1* in order to differentiate into *Ccr2*+ KRM. Loss of *Cx3cr1* prevented the accumulation of *Ccr2*+ KRM and resulted in a skewed macrophage profile that prevented cilia mutant mice from developing severe cystic disease.

Conclusions: Collectively, our data indicate that monocytes undergo a series of differentiation steps upon entering the kidney and require *Cx3cr1* for differentiation into pathogenic *Ccr2*+ KRM.

Funding: NIDDK Support, Other NIH Support - 2T32AI007051-38, 1P20GM134973

PO1234

Species-Specific Differences in FPC-CTD Trafficking: Implications for Differential Activation of Intracellular Signaling Pathways

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Background: ARPKD (MIM 263200) is caused by mutations in *PKHD1,* which encodes FPC. But, orthologous mouse *Pkhd1* models either have no renal cystic disease or very mild PCT dilatation. We previously showed that *MYC/Myc* is overexpressed in human ARPKD and mouse *Cys1*$^{cpk/cpk}$ (*cpk*) kidneys, but not in several *Pkhd1* mutants. We also showed that expression of the intracellular carboxy-terminus of mouse FPC (mFPC-CTD), but not human (hFPC-CTD), activates the *Myc/MYC* P1 promoter (ASN 2020). The current study focused on: 1) the intracellular trafficking of mFPC-CTD and hFPC-CTD, and 2) activation of the Src/STAT3 signaling pathway, linked to hFPC-CTD (*Strubl 2020*), in a mouse *Pkhd1* mutant lacking FPC-CTD and in the *cpk* mouse model of ARPKD, with and without *Cys1* rescue.

Methods: Comparative informatic analysis. Immortalized mouse CCD (mCCD) and human (hCCD) cell lines stably expressing mFPC-CTD and hFPC-CTD, respectively. Kidneys from *cpk, Cys1*-rescued *cpk,* and *Pkhd1*$^{del6/del67}$ (*del67*) mutant mice; western blot and immunofluorescence.

Results: FPC-CTD is the least conserved domain, with 55% identity between human-mouse CTDs, compared with 73% identity across the full-length FPC. The CTD is unique, with an AA-sequence not found in other terrestrial vertebrate proteins. In stable cell lines, mFPC-CTD localized to both nuclei and cilia, whereas hFPC-CTD primarily localized to the apical membrane. In non-cystic *del67* kidneys (lacking FPC-CTD), pSTAT3^{Y705} and c-Myc levels were similar to wild-type controls. In *cpk* kidneys, pSTAT3^{Y705} and c-Myc were upregulated, but their levels in *Cys1*-rescued *cpk* kidneys (*Yang 2021*) were comparable to wild-type.

Conclusions: Differences in intracellular trafficking of mFPC-CTD and hFPC-CTD may explain the species-specific differences in *Myc/MYC* P1 promoter activation. Distinct subcellular localizations may reflect divergence in the functional evolution of human and mouse FPC-CTD, with mFPC-CTD evolving to function as a nuclear regulatory factor, whereas hFPC-CTD functions as a membrane-associated signaling regulator of Src-STAT3. Activation of Src-STAT3 signaling and *Myc* upregulation are signatures of cystic epithelia, suggesting that renoprotective mechanisms in FPC-deficient mouse kidneys may modulate these pathways.

Funding: NIDDK Support, Private Foundation Support

PO1235

Reduction of Klotho Promotes Cyst Growth and Epigenetic Age Acceleration in ADPKD

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Background: Symptoms of ADPKD vary in severity and age of onset and tend to accelerate quickly in older patients, eventually resulting in kidney failure. αKlotho has been identified as an anti-aging protein, and the kidney is the organ expressing the highest levels of αKlotho protein and the main origin for systemic αKlotho. The soluble serum form of αKlotho (extracellular domain of αKlotho) was found to be decreased in ADPKD patients, however, the role of αKlotho in ADPKD remains unknown.

Methods: To investigate the role and mechanism of αKlotho in ADPKD, we introduced an αKlotho transgene into *Pkd1* conditional knockout mice and performed single cell RNA sequencing (scRNA-seq) in kidneys collected at postnatal days 7, 14 and 21 to determine the differentially expressed genes (DEGs) and signaling pathways mediated by αKlotho in different renal cell types. The expression of key DEGs identified with scRNA-seq was confirmed with qRT-PCR analysis.

Results: We found that full length αKlotho was decreased in collecting duct cells, macrophages, fibroblasts and T/NK immune cells in *Pkd1* homozygous kidneys. Transgenic αKlotho delayed cyst growth in *Pkd1* conditional knockout mice by normalizing the expression of genes associated with a number of diverse functions, including the genes associated with the transitions between collecting duct cell subtypes and genes involved in epigenetic mechanisms. In addition, we found that the genes associated with the epigenetic clock (DNA methylation age) were dysregulated in those cells in cystic kidneys, and that they could be normalized by transgenic αKlotho, suggesting that transgenic αKlotho might slow down the process of epigenetic age acceleration in cystic kidneys. The dysregulation of the epigenetic age-acceleration genes, *Apoe, Cldn4, Mgp* and *Slc38a2,* might contribute to PKD pathogenesis and might serve as potential biomarkers for ADPKD. Finally, transgenic αKlotho affected a large number of genes associated with metabolic and oxidative signaling, suggesting that αKlotho might act by slowing down metabolic processes to extend the life span of mice.

Conclusions: Reduction of aKlotho regulates cyst growth through diverse signaling pathways. *Pkd1* mutation accelerates epigenetic age in ADPKD. Transgenic aKlotho not only delayed cyst growth but also slowed down epigenetic age acceleration.

Funding: NIDDK Support

PO1236

Mechanistic Interaction Between Cystin and Fibrocystin/Polyductin in Model Cell Lines and cpk/cpk Kidneys

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Background: *Cys1$^{cpk/cpk}$ (cpk)* mice exhibit ARPKD-like renal phenotype due to a mutation in the *Cys1* gene and loss of cystin. ARPKD (MIM 263200) is caused by mutations in *PKHD1,* encoding FPC. Both cystin and FPC are present in the primary cilium, but no physical interaction has been reported. Using mouse CCD cell lines, we have shown that FPC levels were reduced in *cpk* cells by 75% relative to wt. Cystin deficiency is specifically linked to FPC reduction and did not affect cilia development, but altered ciliary architecture (ASN 2020). The current study focuses on cellular mechanisms driving FPC reduction in cystin-deficient cells, and the consequences of FPC loss. We note that FPC is necessary for proper E3 ubiquitin ligase function and consequently cellular proteome management (Kaimori 2017).

Methods: Immortalized wt and *cpk* mouse CCD cells. Wt and cpk mouse kidneys. siRNA silencing of *Cys1;* qRT-PCR, western blot, confocal microscopy, morphometry, patch clamp.

Results: Silencing *Cys1* in wt cells results in a siRNA dose-dependent reduction of both cystin and FPC. Correlative studies showed marked reduction of FPC in *cpk* kidneys. Similar *Pkhd1* mRNA levels in wt and *cpk* cells, and kidneys implicate FPC regulation at the protein level. Proteasome or lysosome inhibition did not recover FPC, but activation of autophagy further reduced FPC levels, suggesting a role for selective autophagy in FPC removal. Diminished FPC levels lead to E3 ubiquitin ligase defects and reduced polyubiquitination of proteins, necessary for proteome management. In *cpk* cells, we observed membrane retention of the epithelial sodium channel and increased sodium transport.

Conclusions: Our studies provide the first functional link between cystin and FPC in renal epithelial cells. We propose cystin as a gatekeeper for FPC at the base of the cilium and in the E3 ligase complex. In cystin-deficient cells, FPC is continuously degraded leading to dysregulated ubiquitination and altered proteome homeostasis. These data show a mechanistic connection between the renal phenotypes observed in human ARPKD and *cpk* mice. The recent identification of human *CYS1*-related ARPKD (*Sci Report, in press*) highlights the potential significance of the cystin-FPC mechanistic interaction in the complex pathobiology of ARPKD.

Funding: NIDDK Support, Private Foundation Support

PO1237

Tubular Flow Disruption During Cyst Development in Polycystic Kidney Disease

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Background: Polycystic kidney disease is an inherited disorder in which clusters of cysts develop within the kidneys, causing the kidneys to enlarge and lose function. Cyst development can be due to functional changes caused by mutations in ciliary localized proteins Pkd1 and Pkd2 or changes in cilia formation/structure (e.g. ift88 mutants). It is currently unknown how cysts impact tubule flow and cilia, or whether flow alterations occur prior to or after cyst formation is initiated.

Methods: We used inducible Cre conditional mutant mouse models with an optical imaging chamber along with injection of fluorescent dextran to analyze tubule flow at multiple timepoints during cystogenesis in live kidneys. Additionally, we evaluated dextran absorption into proximal tubules as an indicator of tubule flow in mutant and control mice during cyst development. We determined the number of dextran+ proximal tubule cells by FACS to quantify changes in the percentage of tubules with flow in cystic versus non cystic kidneys. We performed H&E staining to quantify cyst severity and analyzed sections by immunofluorescent microscopy to assess changes in flow.

Results: Our results suggest that during the cyst formation, there is a marked decrease in flow through the tubules and that this reduction in flow occurs early during cyst formation. This corresponds to a 56.8% of cells that are both dextran+ and LTA+ (proximal tubule) by flow cytometry and similar results were obtained by IF analysis. We also find an increase in resident and infiltrating macrophages around the forming cysts.

Conclusions: The use of intravital imaging approaches allows us to evaluate changes in tubule flow as cysts progress. With the addition of cilia markers, we will examine the responses of the cilium to the changes in flow. Preliminary data suggests that that alterations in tubule flow occur at early time points during cyst initiation with larger cysts seldom containing epithelium that are dextran+. These data indicate that loss of tubule flow may be an early event associated with cystogenesis. Our data also suggests that disruption of tubule flow is progressive with fewer tubules with flow at later time points (4-6 months post induction). We are currently assessing whether there is an association between the disruption of flow in a tubule and localized immune responses.

Funding: NIDDK Support

PO1238

FoxM1 Promotes Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is driven by mutations in *PKD1* and *PKD2* genes and is characterized by renal cyst formation, inflammation and fibrosis. Forkhead box protein M1 (FoxM1) is a transcription factor of the Forkhead box (Fox) protein super family which is defined by a conserved winged helix DNA-binding domain 1. FoxM1 has been reported to promote tumor formation, inflammation and fibrosis in many organs. However, the role and mechanism of FoxM1 in regulation of ADPKD progression is still poorly understood.

Methods: To evaluate the role and mechanisms of FoxM1 in cyst growth *in vivo,* we treated early stage and long lasting *Pkd1* mutant mice with the FoxM1 specific inhibitor, FDI-6. To identify novel FoxM1 target genes involved in cystogenesis, we performed ChIP-sequencing analysis.

Results: We found that FoxM1 was upregulated in cyst-lining epithelial cells in polycystin-1-deficient murine kidneys and human ADPKD kidneys. Inhibition of FoxM1 with FDI-6 delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, cyst lining epithelial cell proliferation, and increased cyst lining epithelial cell apoptosis in *Pkd1* mutant mice (all $p < 0.01$). Targeting FoxM1 also decreased renal fibrosis in long last Pkd1 mutant kidneys. Upregulation of FoxM1 promotes cyst growth through: 1) upregulation of the expression of Akt and Stat3 and activation of ERK and Rb signaling to increase cystic renal epithelial cell proliferation, 2) inhibition of p65-dependent cystic renal epithelial cell death, 3) facilitation of the recruitment and retention of renal macrophages, and 4) upregulation and activation of fibrotic markers to promote renal fibrosis. In addition, FoxM1-dependent macrophage recruitment was associated with upregulation of monocyte chemotactic protein 1 (MCP-1) and inflammatory cytokine TNF-α. Further, we identified novel FoxM1 target genes by ChIP-seq analysis, which may connect FoxM1 signaling to the ciliopathy hypothesis in PKD.

Conclusions: FoxM1 promotes renal cyst growth and fibrosis in ADPKD through Akt, ERK, Rb and STAT3 signaling as well as NF-kB and ciliopathy associated signaling. Targeting FoxM1 in cystic renal epithelial cells may be a viable new therapy for ADPKD.

Funding: NIDDK Support

PO1239

Allosteric Mechanism of PC1 Tethered Agonist-Mediated Signaling

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Background: Polycystin-1 (PC1) is the 11-transmembrane protein product of the human autosomal dominant polycystic kidney disease (ADPKD) gene PKD1. PC1 functions as an atypical GPCR and shares multiple features with the Adhesion GPCRs, including a GPCR autoproteolysis-inducing (GAIN) domain that catalyzes cis-cleavage of the receptors into extracellular N-terminal (NTF) and membrane-embedded C-terminal (CTF) fragments. We previously reported that CTF-mediated signaling to an NFAT promoter-luciferase reporter is dependent on the presence of the stalk, is reduced by ADPKD-associated missense mutations within the stalk, and can be rescued by synthetic, stalk-derived peptides, supporting a tethered ligand mechanism of PC1-G protein signaling (JASN 2018;29:671, JASN 2019;30:882).

Methods: We have combined highly complementary experiments and computer simulations to investigate mechanism of the tethered agonist-mediated signaling of PC1 CTF. A computer model of the human PC1 CTF was generated using the cryo-EM structure of the PC1-PC2 complex with important missing regions added through I-TASSER homology modeling. All-atom enhanced simulations (1000 ns) using a robust Gaussian accelerated molecular dynamics (GaMD) technique were performed, followed by calculations of residue correlation matrices and free energy profiles. GaMD simulation-predicted residue interactions important for WT stalk-mediated activation of PC1 CTF were further investigated by mutagenesis and cellular assay experiments.

Results: GaMD simulations were consistent with experimental signaling data obtained with PC1 CTF expression constructs encoding wild type and stalk variants of the PC1 CTF. Correlation matrices revealed regions of highly correlated residue motions involving the stalk, TOP and putative pore loop domains. Key residue interactions predicted from the GaMD simulations were validated with newly designed mutation experiments.

Conclusions: Complementary experiments and simulations studies support the function of the PC1 CTF stalk region as a tethered agonist and suggest a mechanism whereby it can induce TOP-pore loop interactions which can be further translated to the C-tail for G protein activation. This in-depth knowledge is expected to facilitate future drug design efforts targeting this function of PC1 for more effective treatments of ADPKD.

Funding: NIDDK Support, Other NIH Support - NIGMS, Other U.S. Government Support, Private Foundation Support

PO1240

Abstract Withdrawn

PO1241

Analysis of Calcium Signaling in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is an inheritable kidney disease characterized by the development of fluid-filled renal cysts, mainly caused by mutations in the *PKD1* and *PKD2* genes, leading to loss of renal function. Molecular mechanisms underlying cystogenesis are poorly characterized but it is postulated that disturbed calcium homeostasis is a primary event in cystogenesis. The precise molecular players that cause this disturbance are still a poorly explored area, especially in relevant human cell types. We therefore aim to characterize the profile of calcium-coupled G-protein coupled receptors (GPCRs) in a human renal epithelial cell models, to identify which receptors are present, whether their function is affected in ADPKD and whether they can be used to modulate cyst formation and growth.

Methods: Urine-derived conditionally immortalized proximal tubule epithelial cells (ciPTECs) of ADPKD patients and healthy controls were screened for calcium-coupled GPCRs, using an agonist library on Fura-2 loaded cell populations seeded in 96-well format. Validation of specific hits was done using single-cell measurements with a fluorescence microscope and built-in perfusion system in the ciPTECs as well as in tissue-derived conditionally immortalized cystic cells (ciCCs). Matrigel-based 3D cell culture was used to grow ciCCs to assess their ability to form cystic structures. Structures were stained with nuclear and cytosolic stains and imaged via confocal microscopy.

Results: From a library of 418 GPCR agonists a selective amount of calcium-coupled GPCRs was found functionally active in ciPTECs. ciPTECs from both healthy controls and ADPKD patients were found to functionally express purinergic -, histamine -, serotonin and dopamine receptors. In single-cell experiments, we did not find any significant differences in functionality between healthy controls and ADPKD patients, but observed that response characteristics are mainly donor-specific, suggesting patient-specific disease mechanisms. ciCCs grown in in 3D cell culture were found to form hollow, cell-lined cyst-like structures.

Conclusions: We describe the first thorough characterization of calcium-coupled GPCRs in a human proximal tubule epithelial cell model. We established a 3D cyst growth assay using tissue-derived cystic cells to explore the possibility to use the identified GPCRs to modulate cyst formation and growth.

Funding: Government Support - Non-U.S.

PO1242

Loss of Polycystin Function in Lymphatic Cells Impair CTP1a Expression and Fatty Acid Uptake

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Background: Homozygous *Pkd1* or *Pkd2* null mutant mice die at mid-gestation due to vascular abnormalities including edema and hemorrhage. We have previously shown that edema in *Pkd1* and *Pkd2* knock out mice is due to abnormal lymphatic morphogenesis, with grossly dilated, blood filled dermal lymphatic vessels. Because proper lymphatic development is supported by fatty acid β-oxidation (FAO), we probed fatty acid transport in PC1/PC2 lymphatic endothelial cells (LECs).

Methods: *Pkd1* and *Pkd2* mutant LECs were isolated from mouse E14.5 embryos or generated using lentiviral shRNAs against *PKD1* or *PKD2* in human dermal LECs (HDLECs). Protein levels of PC1, PC2 and CPT1a were determined by western blotting and CPT1a/CPT2 mRNA levels were analyzed by qRT-PCR. Fatty acid uptake was assessed by BODIPY® 558/568 C_{12} staining of control and *Pkd* mutant LECs pre-incubated with or without 50 μM palmitate, and counterstained with mitotracker. Cells were imaged by confocal microscopy and the relative abundance of lipid droplets were quantified using ImageJ software. Each experiment was repeated 3 times and pairs of means (mutant versus control) were compared using Student's T-test.

Results: Embryonic *Pkd1*$^{-/-}$ and *Pkd2*$^{-/-}$ murine LECs exhibit a robust decrease of CPT1a protein levels. In addition, CPT1a protein levels were significantly reduced in *PKD1* and *PKD2* depleted HDLEC, suggesting a conserved role of Pkd1/2 in CPT1a regulation. PC1 and PC2 depletion in HDLECs results in an accumulation of cytoplasmic lipid droplets which often colocalized with mitochondria, indicative of impaired fatty acid utilization. The ability of *PKD* mutant cells to metabolize fatty acids is further challenged by pre-treatement with 50μM palmitate, which exacerbates the accumulation of lipid droplets.

Conclusions: Our results highly suggest that polycystin function is required to maintain normal levels of CPT1a expression and fatty acid transport to mitochondria in LECs. We thus speculate that a defect in FAO with consequent dysregulation of gene expression is the basis of impaired lymphangiogenesis in Pkd1/2 mutant embryos.

Funding: NIDDK Support

PO1243

Pharmacological Activation of Long-Form PDE4 Enzymes Suppresses Disease Progression in Pkd1RC/RC and Pkd1 Knockout (iKspCrePkd-1lox,lox) Mouse Models of ADPKD

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Background: Upregulation of cAMP signaling is thought to promote cystogenesis in ADPKD. Phosphodiesterase 4 (PDE4) enzymes degrade cAMP and contribute to its compartmentalized signaling. We have previously described novel small molecules that allosterically activate long isoforms of PDE4 and lower intracellular cAMP. Here we demonstrate significant efficacy with MR-L22, an advanced PDE4 activator compound, on suppressing cystic burden and preserving kidney health in orthologous models of ADPKD.

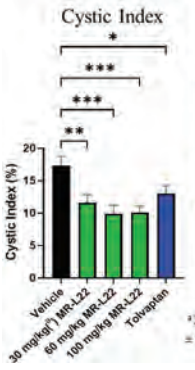
Methods: The effects of the long isoform PDE4 activator MR-L22 (administered by oral gavage) were assessed in rapidly (iKspCre*Pkd1*^{lox,lox} induced at P10, treated from P14 to P27) and slowly progressive (*Pkd1*$^{RC/RC}$, treated from 4 to 16 weeks of age) mouse models of ADPKD. Test groups were compared to control groups receiving vehicle alone or V_2 receptor antagonist.

Results: Compared to vehicle treated controls, MR-L22 treated *Pkd1*$^{RC/RC}$ mice exhibited reduced kidney cAMP levels, cystic indices, kidney weight/body weight ratios (Kw/Bw) and MRI measured total kidney volumes (TKV) (Table and Figure). Long isoform PDE4 activation significantly protected kidney function and, when compared to tolvaptan, animals receiving MR-L22 produced significantly less urine volume. MR-L22 also suppressed the aggressive cystic disease exhibited by tamoxifen induced (P10) iKspCre*Pkd1*^{lox,lox} mice, where Kw/Bw and cystic indices were reduced in comparison to vehicle control (results not shown).

Conclusions: Small-molecule activators of long isoforms of PDE4 suppress cystic disease progression in key translational models of ADPKD and may be better tolerated and more effective than vasopressin V_2 receptor antagonists.

Funding: Commercial Support - Mironid Limited

Long isoform PDE4 activation suppresses cystogenesis in the *Pkd1*$^{RC/RC}$ mouse model of ADPKD



Group (sex)	cAMP (pmol/mg)	Kw/Bw (%)	TKV (µL)
Vehicle control (F=10, M=10)	13.08 ±0.96	2.20 ±0.1	857 ±54
MR-L22 30 mg/kg[a] (F=10, M=10)	9.95* ±56.88	1.92 ±0.1	748 ±56.88
MR-L22 60 mg/kg (F=10, M=10)	10.12* ±0.80	1.85* ±0.08	682*** ±51
MR-L22 100 mg/kg (F=9, M=10)	9.70* ±0.90	1.72*** ±0.07	606*** ±30
Tolvaptan 75 mg/kg[b] (F=10, M=10)	9.58* ±0.76	1.79** ±0.07	654*** ±40

[a]MR-L22 also added to the food (0.05%), [b]tolvaptan also added to the food (0.1%)
± S.E.M. *P<0.05 **P<0.01 ***P<0.001 compared to control

PO1244

RGLS4326 Increases Urinary PC1 and PC2 Levels in Individuals with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is caused by mutations of either *PKD1* or *PKD2* genes, leading to reduced function of their respective protein products PC1 and PC2. Both proteins are secreted in exosomes, and their urinary levels inversely correlate with ADPKD severity. RGLS4326, a novel oligonucleotide inhibitor of miR-17, preferentially delivers to kidney tubules and cysts, derepresses miR-17 targets *Pkd1* and *Pkd2*, increases PC1 and PC2, and attenuates cyst growth in multiple PKD mouse models. Whether RGLS4326 treatment would increase PC1 and PC2 in individuals with ADPKD was unknown.

Methods: An open-label, adaptive design, dose-ranging, Phase 1b clinical study is ongoing to evaluate RGLS4326 safety, pharmacodynamics and pharmacokinetics in individuals with ADPKD. The study will enroll ~27 patients (9 per cohort) treated subcutaneously with one of three RGLS4326 doses (1, 0.3, and 0.1 or 0.5 mg/kg Q2W x 4 doses) and will be followed for 28 days after the last dose (Day 71). The major inclusion criteria are Mayo Imaging Classification of 1C, 1D, or 1E, and GFR between 30-90 mL/min/1.73 m^2. The urinary biomarkers include PC1 and PC2 on exosomes, kidney injury marker 1 (KIM1), and neutrophil gelatinase-associated lipocalin (NGAL).

Results: Nine patients (mean GFR 49 mL/min/1.73m^2, mean age 50 yr) were enrolled in the first cohort; each patient received four doses of 1mg/kg of RGLS4326 Q2W. RGLS4326 was well tolerated with no serious adverse events. PK profiles were similar to healthy volunteers, with a plasma half-life of 9 hours and plasma AUC levels after the first and fourth dose ~2x higher in patients. Changes in both PC1 and PC2 at the end of study from baseline were statistically significant (p=0.0004 and p=0.026, respectively), with mean % increase in PC1 and PC2 of 58% and 38%, respectively.

Conclusions: These data provide clinical proof that RGLS4326 delivers to cystic kidneys of individuals with ADPKD, where it inhibits miR-17 and thereby derepresses PC1 and PC2. The results also imply ongoing miR-17-mediated repression of *Pkd1* and *Pkd2* in humans, further validating miR-17 as a therapeutic target for ADPKD treatment.

Funding: Commercial Support - Regulus Therapeutics

PO1245

Mutations to ALG5 Cause Autosomal Dominant Fibrocystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by variants in *PKD1* or *PKD2* encoding polycystin (PC)1 and PC2, or in genes involved in PC1 biogenesis. Seven to 10% of the pedigrees remain genetically unresolved (GUR). We hypothesized that other genes involved may cause ADPKD.

Methods: Whole exome sequencing (WES) was performed in a large GUR ADPKD-like pedigree from the Genkyst cohort, and targeted next-generation sequencing (TNGS) was performed in ~250 additional ADPKD/ADTKD GUR pedigrees.

Results: WES identified a heterozygous *ALG5* frameshift variant (c.703_704delCA) in 3 sisters who developed end-stage renal disease (ESRD) at ages 62, 69, and 68 respectively and presented atrophic kidneys with small renal cysts and few to no liver cysts. Four affected relatives from three generations were subsequently identified. *ALG5* encodes an endoplasmic reticulum (ER) resident enzyme, the dolichyl-phosphate beta-glucosyltransferase that catalyzes the transfer of glucose residues to the growing N-glycan precursor in the ER lumen. TNGS led to the identification of *ALG5* likely pathogenic variants (p.Trp258*, p.Arg212His) in 2 additional families. Two other unrelated individuals harboring likely pathogenic variants of *ALG5* were identified in the Genomics England 100,000 genomes project. The clinical phenotype was consistent in the 16 affected members, with non-enlarged cystic kidneys that often evolved to kidney atrophy and few or no liver cysts; 7 subjects reached ESRD from 62 to 91y. Characterization of *ALG5*$^{-/-}$ RCTE cells showed that *ALG5* is required for maturation and surface localization of PC1. PC1 surface localization in *ALG5*$^{-/-}$ cells was rescued by wild-type (WT), but not mutant, *ALG5*. Unfolded protein response (UPR) effector analysis revealed marked upregulation in *ALG5*$^{-/-}$ and *ALG5*$^{+/-}$ as compared to WT RCTE cells.

Conclusions: *ALG5* is a novel disease gene in the genetically heterogeneous ADPKD spectrum. Mutations to *ALG5* impair PC1 maturation and localization, and are likely associated with a dysregulation of the UPR, causing renal cystogenesis and fibrosis.

Funding: Government Support - Non-U.S.

PO1246

Heterozygous Variants in NEK8 Kinase Domain Cause an Autosomal-Dominant Ciliopathy

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Background: *NEK8* encodes a protein that localizes to the primary cilium. Biallelic *NEK8* variants are known to cause multiorgan developmental defects including renal cystic dysplasia, with heterozygous carrier parents being asymptomatic. This autosomal recessive inheritance is most common for ciliopathies. Complementary to this, we now propose a dominant-negative effect for certain heterozygous *NEK8* missense variants in the kinase domain.

Methods: We performed genetic testing in patients from several medical centers. To explore the consequences of the identified *NEK8* variants we are performing cilia staining assays in patients' skin fibroblast and kidney cells, as well as in mIMCD3 cells overexpressing the identified variants.

Results: We identified three distinct heterozygous *NEK8* variants in eight families (table 1), all leading to missense alterations in the kinase domain. The large symptomatic family and the de novo occurrences are also in favor of a dominant mode of inheritance. All patients have a kidney phenotype, varying in severity, age of onset and presence of kidney failure. Interestingly the p.Arg45Trp variant is a recurrent variant found in six unrelated families. Our preliminary results from functional studies show normal localization of the NEK8 protein to the Golgi region, but abnormal primary cilia formation, in serum starved patient derived cells – a finding consistent with pathogenicity.

Conclusions: We present the first evidence for a pathogenic effect of heterozygous *NEK8* variants. Remarkably our patients present with a renal limited phenotype as compared to the multiorgan defects found in patients with biallelic variants. This reveals a new mode of inheritance for *NEK8* variants and expands genotype-phenotype correlations for this gene.

Table 1. Clinical features of individuals with heterozygous *NEK8* variants

Family	1	2	3	4	5[a]	6	7	8
Inheritance	de novo	de novo	de novo	de novo	de novo	recessive	inherited	inherited	de novo							
NEK8 Variant	Arg451Trp	Arg451Trp	Arg451Trp	Arg451Trp	Arg451Trp	Arg451Trp	Arg451Trp	Arg451Trp	1-nt ESS[b]							
Age at PKD diagnosis (years)	11	fetal	30	fetal	neonatal	unknown	15	15	fetal	>70	43	40	40	19	15
Suspected clinical diagnosis	NPHP vs. ADPKD	ARPKD	ADPKD/ ARPKD	ARPKD	ADPKD/ ADPKD NPH	ADPKD	ADPKD	ARPKD	ARPKD	ADPKD	ADPKD	ADPKD	ADPKD	FSGS vs. ADKD/D	FSGS
Age KFRT (years)	11	4	33	5	11	20	14	14	N/A	70s	N/A	N/A	N/A	N/A	N/A
Enlarged kidneys	+	+	+	+	+	unknown	+	+	+						
Liver cysts (age in years)						unknown					+ (51)				+ (43)
Hypertension	+	+	+	+	+	unknown	+	+	+	+		+			
Extra-renal features	short stature	short stature, alopecia	NR	NA	left ventricular hypertrophy	unknown	short stature	short stature	feeding difficulties	retinal dystrophy*	retinal dystrophy*	retinal dystrophy*	NA	autism	retinal

ADKCKD = autosomal dominant medullary cystic kidney disease; ADPKD = autosomal dominant polycystic kidney disease; ARPKD = autosomal recessive polycystic kidney disease; FSGS = focal segmental glomerulosclerosis; KFRT = kidney failure with replacement therapy; N/A = not applicable; NPH = nephronophthisis. [a]Unrelated case described in Obeidova et al. JCI(1).
*consistent with *RDS* variant

PO1247

Beneficial Effects of Bempedoic Acid Treatment in ADPKD Mice

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Background: ADPKD has limited therapeutic options. Bempedoic acid (BA), an inhibitor of ATP citrate-lyase (ACLY) FDA-approved for hyperlipidemia, catalyzes a key step in cholesterol synthesis that is important for cell growth and proliferation. BA also activates AMPK in mice. We hypothesized that BA could be a novel ADPKD therapy by inhibiting cyst growth and proliferation and promoting oxidative metabolism via ACLY inhibition and AMPK activation.

Methods: Murine *Pkd1*-null kidney cell lines derived from either proximal tubule (PT) or collecting duct (IMCD) were grown in Matrigel cultures and treated ± BA before cyst analysis by microscopy. In vivo, male and female *Pkd1$^{fl/fl}$; Pax8-rtTA; Tet-O-Cre* transgenic C57BL/6 mice were induced with IP doxycycline injection on P10&11. Mice were then treated ± BA (30 mg/kg/d) ± tolvaptan (30-100 mg/kg/d) by oral gavage from P12-21. As measures of disease severity, total kidney weight to body weight (TKW/BW) and blood BUN levels at euthanasia (P22) were measured. Kidney homogenates were immunoblotted for expression of key disease biomarkers and other relevant cell signaling markers.

Results: BA dramatically inhibited cystic growth in 3D cultures in PT and IMCD *Pkd1*-null kidney cells. In ADPKD mice, BA reduced TKW/BW vs. vehicle at euthanasia (6.9 vs. 11.9%; $P<0.01$). Similarly, tolvaptan (100 mg/kg/d) reduced TKW/BW to 7.8% vs. vehicle ($P<0.05$). Addition of BA to tolvaptan caused a further reduction in TKW/BW (4.9%; $P<0.05$) vs. tolvaptan alone. BA reduced BUN vs. vehicle (59 vs. 107 mg/dL; $P<0.05$). Tolvaptan also decreased BUN vs. vehicle at 30 mg/kg/d (68; $P<0.05$). Again, addition of BA to tolvaptan at 30 mg/kg/d caused a further significant reduction in BUN (38; $P<0.05$). BA reduced ACLY and stimulated AMPK activity in kidneys vs. controls. BA also inhibited mTOR and ERK signaling, which are upregulated in ADPKD. BA also sharply reduced kidney injury markers KIM-1 and, to a lesser extent, NGAL. These BA effects occurred alone and in concert with tolvaptan.

Conclusions: BA inhibited cyst growth in vitro and ADPKD severity in vivo. Combined BA and tolvaptan treatment further improved ADPKD outcomes in vivo. BA significantly reduced kidney injury markers and mTOR and ERK signaling. BA may be a promising new ADPKD therapy, having beneficial effects on disease severity when used alone and with tolvaptan in mice.

Funding: Commercial Support - Esperion Therapeutics, Inc., Private Foundation Support

PO1248

Unraveling Fundamental Mechanisms of UMOD Quality Control and Their Role in UMOD-Associated CKD

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Background: UMOD is a GPI-anchored protein expressed in the Thick Ascending Limb of the Loop of Henle. When properly folded, it transits from the ER to the membrane via the Golgi. Little is known about UMOD's specific trafficking partners and its quality control mechanisms in the early secretory pathway. Mutations in UMOD disrupt protein folding and promote ER retention, triggering ER-stress pathways and cell death that causes UMOD-related autosomal-dominant tubulointerstitial kidney disease. It was recently shown that mutant misfolded MUC1-fs is trapped in TMED9-containing vesicles and that treatment with compound BRD4780, releases it to the lysosome. We hypothesize that a similar pathogenic quality control mechanism is active in ADTKD-UMOD.

Methods: Co-immunoprecipitation (co-IP) of UMOD and TMED cargo-receptors was assessed in HEK293 cells transfected with wild type (wt) or mutant (C126R) human UMOD. Next, we performed untargeted Affinity Purification Mass Spectrometry followed by tandem MS to generate a list of UMOD interactors. We also conducted *in vivo* studies in UMOD$^{+/C125R}$ mice.

Results: We identified distinct wt and mutant UMOD interactomes using an unbiased AP-MS proteomics approach. Several interactors, including members of the TMED family, were significantly enriched in the mutant UMOD interactome. Targeted co-IP in lysates of HEK293 cells transfected with UMOD and interacting protein candidates confirmed the results from proteomics studies. Interestingly, when pulling down TMEDs, we found abundant immature non-glycosylated UMOD, suggesting entrapment in early secretory compartments. *In vivo*, treatment with BRD4780 was suggestive of disrupted interactions between mutant UMOD and interacting partners responsible for toxic entrapment in the ER, as assessed by immunoblots of kidney lysates and immunofluorescence microscopy of tissue from UMOD$^{+/C125R}$ mice.

Conclusions: Our results suggest that UMOD interacts with TMED cargo-receptors and other proteins that may mediate the pathogenic quality control mechanisms responsible for toxic ER-retention and accumulation. Shedding light on these new molecular mechanisms may unmask new therapeutic strategies for the treatment of ADTKD-UMOD.

Funding: Private Foundation Support

PO1249

Restricted Feeding Diet Overrides the Cyst Promoting Effect of Cisplatin-Induced Renal Injury in Both Ift88 and Pkd2 Mutant Mouse Models

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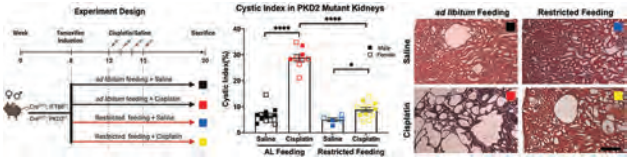
Background: Multiple renal cystic diseases, including PKD, are caused by dysfunction of the primary cilium. Links between cilia dysfunction, cyst formation, and renal injuries have been reported with evidence showing that injury exacerbated the rate of cyst formation in kidney. In addition, dietary restriction has been reported to ameliorate cyst growth in several PKD animal models. Here we evaluate the effects of both renal injury and dietary restriction on cyst formation in two different cilia-mutant mouse models.

Methods: To test the effect of renal injury on cyst formation, we established an alternative approach to induce chronic renal injury by utilizing a low-dose repeated cisplatin treatment (5.0mg/kg; IP; once a week for 4 wks). To evaluate the impact of dietary restriction and renal injury on cyst formation, adult induced conditional Ift88 and Pkd2 mutant mice were utilized. The study design including cisplatin treatment along with 85 % dietary intakes are shown in Figure 1. Mice were euthanized at 5 wks post last cisplatin injection for analysis. Multiple features including renal injury, proliferation, fibrosis, macrophage accumulation, and cystic index were analyzed.

Results: Low-dose repeated cisplatin treatment resulted in increased Kim1 expression in both Ift88 and Pkd2 mutant mice compared to controls. Analysis of the cystic phenotype showed that there was a significant increase in cyst formation in mutant mice after cisplatin comparing to saline-treated group and the location of cysts corresponded to the injured regions. Interestingly, the rapid cyst formation in cisplatin-treated kidneys was ameliorated when the mice were on the restricted diet (Figure 1). More importantly, kidneys from mice with restricted feeding displayed decreased levels of proliferation, fibrosis and macrophage accumulation around the cystic area.

Conclusions: These data show that low-dose repeated cisplatin treatment could be used as an alternative approach to IRI to accelerate cyst formation in in both ift88 and pkd2 mutant models. More importantly, it suggests that cyst progression associated with injury in cystic kidney disorders could be ameliorated through dietary interventions.

Funding: NIDDK Support



PO1250

Peroxisomes Are Dispensable for Normal Renal Function

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Background: Peroxisomes are single membrane-bound cellular organelles identified in the kidney in 1954. Peroxisomes are ubiquitously present in eucaryotic cells with highest abundance in renal proximal tubule cells and hepatocytes. The variety of metabolic and antioxidant functions in which peroxisomes are involved is highlighted by human mutations in *PEX* genes encoding peroxins proteins required for proper peroxisome biogenesis. Hence, the complete loss of peroxisomes causes Zellweger's spectrum disorders (ZSD), devastating multiorgan failure which include renal impairment. However, the (patho)physiological role of peroxisomes in the kidney remains unknown.

Methods: Here we addressed the role of peroxisomes in renal function in male and female adult or infant mice with conditional ablation of Pex5-driven peroxisomal biogenesis in the renal tubule (cKO mice).

Results: Functional and histological analyses of both infant and adult cKO mice did not reveal any overt kidney phenotype. However, male cKO mice exhibited substantial reduction in kidney weight to body weight ratio. Stereological analysis of electronic microscopy results showed a complete absence of peroxisomes accompanied by increase in the number and in the volume of mitochondria in proximal tubule cells of cKO mice. Integrated deep transcriptome-sequencing and metabolome analyses revealed profound reprogramming of a great number of metabolic pathways, including biosynthesis of different classes of lipids such as plasmalogens and sphingomyelins (two major classes of membrane lipids) and the metabolism of glutathione. Although this analysis suggested compensated oxidative stress, four weeks of high fat feeding challenging the ability of proximal tubule cells to metabolize lipids did not induce significant renal impairments in cKO mice.

Conclusions: We demonstrate that renal tubular peroxisomes are dispensable for normal renal function. This indicates a large flexibility of proximal tubule cells both in terms of lipid membrane composition and metabolic/antioxidant functions. Our data also suggest that renal impairments in ZSD patients are of extrarenal origin.

Funding: Government Support - Non-U.S.

PO1251

Weight Loss to Slow Cyst Growth in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Recent studies in animal models of ADPKD support that food restriction can profoundly slow cyst growth and maintain renal function. We have also reported that overweight and obesity are strong independent predictors of ADPKD progression. Thus, it is plausible that weight loss, caloric restriction, and/or periods of fasting may slow ADPKD progression in humans; however, the feasibility of these dietary interventions, and whether the driver of therapeutic efficacy is periods of fasting or reduction in body weight, is unknown.

Methods: We conducted a one-year study evaluating feasibility of delivery of a behavioral weight loss intervention based on either daily caloric restriction (DCR) or intermittent fasting (IMF) in adults with overweight/obesity, ADPKD, and eGFR ≥30 m/min/1.73m^2 (targeted weekly energy deficit of ~34% in both groups). We also evaluated the safety, acceptability, and tolerability of each intervention, and obtained exploratory insight into changes height-corrected total kidney volume (htTKV).

Results: 28 participants (16F/12M; 46±9 yrs, body mass index 34.7±5.0 kg/m^2, eGFR of 69±22 m/min/1.73m^2) were randomized to either DCR (n=15) or IMF (n=13). Clinically significant (>5%) weight loss was achieved in both groups at month 3 (DCR: -7.1±4.2%; IMF: -5.5±3.3%). At 12 months DCR lost additional weight while weight loss in IMF plateaued (DCR: -9.1±6.0%; IMF: 4.9±5.6%; p<0.05 DCR vs. IMF). Overall, DCR had a more favorable safety, tolerability, and adherence profile than IMF. Annual htTKV %Δ was qualitatively low in both groups in comparison to historical data, despite comparable clinical characteristics (DCR: 1.5±3.4%, IMF: 1.7±6.1%). Annual htTKV %Δ was highly correlated with %Δ in weight (r = 0.68, p=0.001). Abdominal saturated adipose tissue (SAT), visceral adipose tissue (VAT) and total adipose tissue (TAT) quantified by MRI were all reduced at one year (p<0.05). Change in VAT (r = 0.49, p<0.05) and TAT (r = 0.46, p<0.05) also correlated with annual htTKV %Δ.

Conclusions: IMF, and particularly DCR, were feasible interventions over a one-year period in adults with ADPKD and overweight/obesity and showed favorable effects on kidney growth as compared to historical controls, supporting conduction of a phase II randomized controlled trial.

Funding: NIDDK Support, Private Foundation Support

PO1252

Social Determinants of Health (SDOH) and Healthcare Resource Utilization (HRU) in Autosomal Dominant Polycystic Kidney Disease (ADPKD) by CKD Stage

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Background: SDOH contribute to health disparities in CKD. This study describes SDOH and HRU in ADPKD patients with commercial (COM) insurance compared to a lower income managed Medicaid (MM) population.

Methods: The study included 8,766 COM and 5,416 MM patients from a national claims database. Patients had ≥2 ADPKD diagnoses between 7/1/2016- 12/31/2018 and were continuously enrolled for minimum 12 months. Patients were linked to SDOH by 9-digit ZIP address providing a precise assignment compared to Census data. HRU included inpatient days and emergency room (ER) visits per 1000 patients per month (PPPM) over 1-year follow-up.

Results: MM patients were more likely to be female (60% vs 54% COM) and on average 8 years younger. MM patients had 1.3x higher Charlson Comorbidity Index (CCI) scores, 40% lower income, were 2x more likely to live below federal poverty level, 1.3x less likely to complete high school, 2.7x more likely to speak English not well or at all, 2.6x less likely to own a vehicle, 53% more likely to be unemployed, and lived in a primary/mental health care shortage area 6.8%/6.4% more often. The differences between payers were consistent across CKD stages, except CCI scores increased with higher CKD stage for both groups. Disparities in income, unemployment rates and provider shortages tended to increase with CKD stage. Mean bed days ranged from 34.6 (Stage 1) to 402 (ESRD) PPPM for COM patients and were 3-4x higher overall in MM, ranging from 112 to 874 across CKD stages. Similarly, ER visits PPPM ranged from 38 to 114 for COM and 154 to 376 for MM. Hospital readmissions and use of post-acute care were high in both groups, with 15% of COM and 20% of MM readmitted within 30-days of inpatient stay and 2.8%-15.2% COM and 3.5%-25.8% MM having at least one PAC stay during follow-up. HRU increased with CKD stage.

Conclusions: ADPKD patients have large variation in SDOH by type of insurance. Lower social status of MM patients may be associated with higher HRU, and these disparities appear to increase as CKD stage progresses. In the clinical care of this vulnerable population, consideration of SDOH such as language barriers, transportation insecurity, and poverty is recommended.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

PO1253

Eliosin, a Protein Encoded by a Transcript from the HmPKD1 Locus, Is a Component of Mitochondria-Endoplasmic Reticulum Contact Sites (MAMs) and Repairs Mitochondria Fragmentation in Polycystic Kidney Disease 12-7 Cells

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Background: The HmPKD1 gene locus is predicted to produce multiple transcripts whose functions are largely unknown. We studied one such alternative transcript that starts at intron 40 but has a protein start site in exon 41. This transcript has a splice from the 3′ end of exon 41 to the 5’ end of exon 43. Subsequent splices follow the same splicing pattern found in the full-length polycystin-1 mRNA. The subcellular localization and function of this alternative transcript is not known.

Methods: We made PCR primers designed to detect the unique splice features of the transcript which are not a feature of full-length HmpKD1 transcripts. RT-PCR studies were conducted to identify the alternative transcript. cDNA encoding the alternative transcript and its product (Eliosin) were expressed in COS-1, 293 and NIH 3T3 cells for immunoblot and light microscopy analysis. Co-localization studies were performed between mCherry-Eliosin fusion protein and dynamin related protein-1 (DRP-1) or mitofusion-1 (MFN-1). Anallysis of mitochondria morphology in co-transfection studies was performed in 293 and PKD 12-7 cells.

Results: RT-PCR reactions performed using RNA from human kidney, confirmed that a shortened PCR fragment from the PKD1 gene’s exons 41-43 is expressed. Immuneblot analysis revealed that the protein we named Eliosin is a 48 kDa protein and it is expressed by cDNA isolated from human testes. Flourescence microscopy studies show co-localization between Eliosin and inositol-3-phosphate receptor or MFN-1, known components of MAMs. However when Eliosin and DRP-1 are co-expressed, DRP-1 is found in the cytosol. Since DRP-1 mediates mitochondria scission we reasoned that it is the mutation in Eliosin that leads to unopposed mitochondria scission in PKD12-7 cells. We found that untransfected PKD 12-7 cells have fragmented mitochondria while Eliosin transfected PKD 12-7 have normal appearing mitochondria.

Conclusions: Eliosin is a 48 kDa protein that is expressed in human kidney. It is a component of mitochondria-ER membrane contact sites and it acts to displace dynamic related protein-1 from MAMs. Based on these findings we conclude that Eliosin plays a role in altering the balance between mitochondria fusion and scission. This finding extends the HmPKD1 locus role in mitochondria metabolic physiology.

Funding: Clinical Revenue Support

PO1254

Overweight and Obesity Predict Kidney Growth in Children and Young Adults with ADPKD

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Background: We have previously reported that overweight and obesity are independently associated with more rapid progression in adults with early-stage autosomal dominant polycystic kidney disease (ADPKD). We now evaluated whether overweight and obesity are also associated with faster kidney growth in children and young adults with ADPKD.

Methods: 54 non-diabetic children and young adults (6-25 years of age) with ADPKD and estimated glomerular filtration rate (eGFR) >80 ml/min/1.73m^2 who participated in a randomized controlled trial on curcumin supplementation were categorized based on BMI (if ≥18 years; n=27) or BMI percentile for age, sex, and height (if <18 years of age; n=27) as normal weight (n=40 [74%]) or overweight/obese (n=14 [26%]). The longitudinal (1-yr) association of overweight/obesity with change in height-corrected total kidney volume (htTKV) by magnetic resonance imaging was evaluated using multinomial logistic regression models.

Results: Mean±s.d. age was 18±5 years, annual % change in htTKV was 6.1±9.0%, and eGFR (full-age-spectrum equation) was 112±18 ml/min/1.73m^2. The annual % change htTKV was 5.5±9.1% in the normal weight participants and 7.9±8.6% in overweight/

obese participants. After adjustment for demographics, randomization group, SBP, and glucose, overweight/obesity was associated with a nearly significant increased odds of annual % change htTKV ≥7% compared to <5% (Odds ratio: 5.23 [95% confidence interval: 0.99, 27.75]). This association was attenuated slightly after further adjustment for baseline htTKV and eGFR (5.58 [0.89, 34.96]).

Conclusions: Consistent with data in adults, our results suggest that overweight and obesity are associated with faster htTKV growth in children and young adults with ADPKD, although power is limited in this small sample size. These results highlight the importance of children with ADPKD maintaining a normal body mass index.

Funding: NIDDK Support

PO1255

Metabolomic Changes over 1 Year Following Drug or Lifestyle Interventions in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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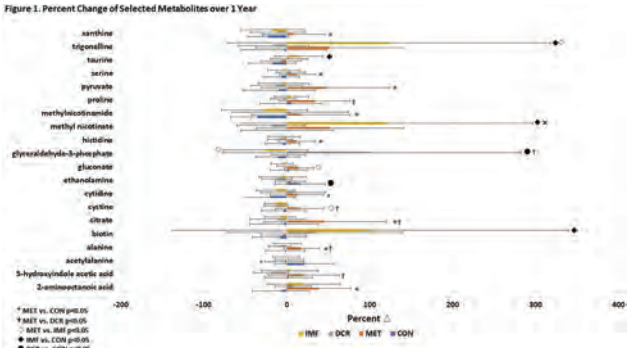
Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited progressive kidney disease. Studies have shown differences in metabolomic profiles in those with ADPKD; however few studies assess change over time.

Methods: We performed metabolomics to assess patterns of change across four groups of participants with APDKD pooled from 2 randomized clinical trials: placebo control (CON), metformin (1,000/mg/day) (MET), intermittent fasting (IMF; 3 day/wk of 80% energy restriction from baseline weight maintenance requirements), and daily caloric restriction (DCR, daily restriction of 34% per day from baseline weight maintenance requirements). Analyzed plasma samples were collected during the trials at baseline and 1-year for each group. A total of 163 metabolites were measured using liquid chromatography-mass spectrometry (LC-MS). Differences in metabolomic profiles over time and within study groups were evaluated by a one-way ANOVA and Bonferroni correction for multiple comparisons.

Results: Baseline characteristics for each trial included CON (n=22, 14 female (F), 49±7 yrs of age (mean±s.d.), estimated glomerular filtration rate [eGFR] 73±13 ml/min/1.73m^2, body mass index (BMI) 28.3±4 kg/m^2), MET (n=22, 14 F, 48±7 yrs of age, eGFR 69±14 ml/min/1.73m^2, BMI 29.7±7 kg/m^2), IMF (n=10, 5 F, 47±6 yrs of age, eGFR 77±16 ml/min/1.73m^2, BMI 34.6±5 kg/m^2), and DCR (n=9, 5 F, 46±13 yrs of age, eGFR 68±21 ml/min/1.73m^2, BMI 34.1±5 kg/m^2). Age and eGFR did not differ between groups. BMI was higher in the IMF compared to CON (p=0.031). Metabolite changes are depicted in Figure 1.

Conclusions: There are changes at one year in metabolites in adults with ADPKD between control, metformin, intermittent fasting, and daily caloric interventions. Further research is needed to identify metabolomic profile shifts involving drug and dietary interventions.

Funding: NIDDK Support, Other U.S. Government Support



Percent Δ of metabolites. Values are expressed as mean ± SD.

PO1256

Identification of CLC-5, the Electrogenic 2Cl-/H+ Exchanger, as the Dominant Apical Chloride Secreting Transporter in Kidney Cyst Epithelium in Tuberous Sclerosis

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Background: Cyst expansion in Tuberous Sclerosis Complex (TSC) or PKD requires secretion of chloride into the cyst lumen as the driving mechanism for salt accumulation. In PKD, Cl^- secretion into the cyst lumen is mediated via the cAMP/PKA-stimulation of CFTR in principal cells consequent to the V2 receptor activation by AVP. Kidney cystogenesis in TSC differs from PKD in that cyst epithelia in TSC is comprised of genotypically normal A-intercalated cells, which do not exhibit noticeable expression of either CFTR or the V2 receptor. The identity of the Cl^- secreting molecule(s) in TSC cyst epithelia remains unknown. Based on RNA Seq analysis in kidneys of *Tsc1* KO mice, we hypothesized that the chloride transporter ClC-5 is expressed on the apical membrane of A-intercalated cells in cyst epithelia of humans and animal models of TSC. CLC-5 is a $2Cl^-/H^+$ exchanger that is located in collecting duct A-intercalated cells where it is predominantly localized to endosomes and plays a critical role in dissipating H^+ secretion and membrane depolarization by H^+-ATPase. This allows parallel movement of Cl^- and H^+ into the endosomes.

Methods: Double immunofluorescent studies utilizing CLC-5 and H^+-ATPase antibodies were performed on kidney tissue from mice with principal cell inactivation of Tsc1 (*Tsc1/Aqp2* Cre), pericyte inactivation of Tsc1 (*Tsc1/Renin* Cre), principal cell inactivation of Tsc-2 (*Tsc2/Aqp2* Cre), global heterozygous Tsc2 (*Tsc2*+/-) and cysts from TSC patients.

Results: Double immunofluorescence labeling demonstrated remarkable co-localization of CLC-5 and H^+-ATPase on apical membranes of an overwhelming numbers of cyst epithelial cells in all models of TSC, including the human kidney cysts. In contrast, kidney cysts in Pkd1 mutant mice showed no apical ClC-5 expression and very few H^+-ATPase expressing cells.

Conclusions: These are the first reports on apical membrane localization of CLC-5 in A-intercalated cells in any disease state, and suggest that similar to late endosomes/lysosomes, CLC-5 and H^+-ATPase may function synergistically on cyst epithelia by secreting Cl^- and H^+ into the cyst lumen. These results strongly point to enhanced translocation of CLC-5 and H^+-ATPase from late endosomes/lysosomes to the apical membrane of cyst epithelia in TSC.

Funding: Veterans Affairs Support, Other U.S. Government Support, Private Foundation Support

PO1257

Two Years In: The Development and Basic Characteristics of a National Patient-Powered Registry in ADPKD

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Background: The therapeutic pipeline in autosomal dominant polycystic kidney disease (ADPKD) has grown, generating a need for more patient participation in clinical trials. To facilitate US ADPKD patient enrollment and to encourage the utilization of patient-reported outcomes in trial design, the PKD Foundation (PKDF) designed a national ADPKD Registry.

Methods: The ADPKD Registry is hosted on a secure, online platform (IQVIA, oc-meridian.com/pkdcure). Participants are consented through the online system and complete a series of modules. The Core Questionnaire includes diagnosis, latest kidney function tests, and comorbidities. Family history, diet and lifestyle, quality of life, and complications of liver cysts, and vascular outcomes are queried.

Results: Between 9/4/19 and 5/1/21, 1,580 ADPKD patients have registered and completed the Core Questionnaire. Participants have a median age of 49 years, 73% have not reached ESKD, and 79% reported a family history of the disease. Currently, the cohort is 71% female, 93% Caucasian, 4.8% Hispanic/Latino and 2.5% African American. Strategic efforts are in development to increase diversity in the cohort. Nearly three quarters of participants had not previously participated in research, with only 27% indicating that they had been in another PKD study or clinical trial. All participants have consented to be contacted about future studies. Many will likely qualify for ongoing trials based on completed module data. Thus far, the Registry platform has made over 2,200 participants contacts regarding six clinical studies, with some individual overlap due to similar eligibility criteria.

Conclusions: The ADPKD Registry is a longitudinal research tool intended to capture ADPKD patient-reported data and is designed to impact research in multiple ways. It will allow for a range of research questions related to the clinical management of ADPKD from early disease through dialysis and post-transplant outcomes. Additionally, modules on health care access & utilization and COVID-19 impact will help the PKDF better understand the challenges of this community.

Funding: Private Foundation Support

PO1258

Polycystic Kidney Disease and Race

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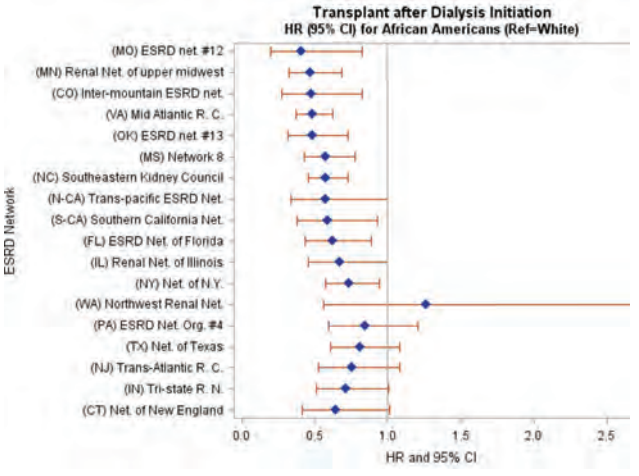
Background: Racial/ethnic differences in the development of kidney failure (ESKD) and transplant (TX) access are well-documented. ESKD is anticipated in familial autosomal dominant polycystic kidney disease (ADPKD), providing the opportunity for greater ESKD preparation. We sought to define the impact of race on ESKD/TX outcomes in ADPKD.

Methods: White (W), African-American (A), or Hispanic (H) ADPKD patients were identified in USRDS 1/2000-6/2018; demographic and laboratory data were obtained. Median income was derived from US Census. Models included: age at ESKD (linear), pre-emptive TX (logistic), and TX after dialysis initiation (Cox), adjusted for age, sex, albumin, hemoglobin, eGFR, insurance, income, ESKD Network, and employment, with W as referent.

Results: Among 41,485 patients, (77.3% W, 13.3% A, 9.4% H), characteristics/ outcomes are shown in Table 1. AA and H had lower median income and less private insurance, pre-ESKD nephrology care, and employment. For AA and H, peritoneal dialysis and TX were less common than in W. Albumin, hemoglobin, and GFR were lowest in A. ESKD occurred 2.2 ± 0.2 and 4.8 ± 0.3 years earlier in A and H, compared to W. Adjusted odds of pre-emptive TX were 0.38(0.33, 0.42) and 0.47(0.40, 0.55) for A and H. Adjusted hazards for TX after dialysis initiation were 0.60(0.55, 0.65) for A and 0.78(0.72, 0.85, for H, *P*<0.001 for all. TX rates for A vs W by network are shown in Figure 1.

Conclusions: Despite the hereditary nature of ADPKD, renal outcomes differ by race, attributed to in part, economic and geographic factors. Health inequity is a contributing factor to patient outcomes in ADPKD that needs to be addressed.

	A (n=5,517)	H (n=3,903)	W (n=32,065)	ALL (N=41,485)
Age, years mean(std)	55.3 (12.5)	52.6 (11.8)	56.9 (12.3)	56.3 (12.3)
Female sex (%)	50.0	46.2	45.5	46.2
Median Income (x $10000) Median (IQR)	41.0 (31.6, 55.1)	43.8 (32.8, 56.8)	51.2 (40.7, 67.1)	49.2 (38.6, 64.8)
Pre-ESKD nephrology (%)	83.6	80.8	91.6	89.6
Private Insurance (%)	53.8	51.8	72.5	68.0
Employed (%)				
6 months prior	38.8	42.4	46.8	45.3
At ESKD	29.1	30.5	38.7	36.6
Δ	9.7	11.9	8.1	8.7
BMI kg/m2, mean(std)	27.9 (7.2)	27.7 (6.5)	28.1 (6.8)	28.0 (6.8)
Albumin (g/dL), mean (std)	3.6 (0.6)	3.8 (0.6)	3.8 (0.6)	3.8 (0.6)
Hemoglobin (g/dL), mean (std)	9.7 (1.9)	10.1 (1.8)	10.7 (1.8)	10.5 (1.8)
eGFR mL/min/1.72 m2, mean (std)	7.0 (3.4)	7.6 (3.7)	8.8 (3.9)	8.4 (3.9)
HD first (%)	80.6	76.2	63.4	66.9
PD first (%)	14.6	15.8	17.8	17.2
Preemptive TX (%)	4.8	8.0	18.7	15.9
Ever TX (%)	31.3	41.9	51.7	48.0



PO1259

A New Ally in Evaluation of Progression of Autosomal Dominant Polycystic Kidney Disease

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Background: The available tools for evaluation of progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD) are suboptimal. The study aim is to evaluate the use of urinary glutathione S-transferase (alpha-GST) in predict progression of this disease.

Methods: Prospective, cohort study of ADPKD patients followed on Nephrology clinic. Urinary alpha-GST was normalized to urinary creatinine (U alpha-GST/U Cr), KTV adjusted to height was determined by CT and sequential measures of Scre were done on the following 3 years. The discriminatory ability of U alpha-GST to predict a decline > 30% of eGFR was determined through Sensitivity (S), Specific (SP), Positive Predictive Value (PPV) and Negative Predictive Value (NPP) using as optimal cut-off point the U alfa-GST mean and the ROC curves.

Results: 21 patients (61.9% women) were included, mean age of 45,0 (IQR 19) years. Initial Scre was 0,98 (IQR 0,64) mg/dL, KTV was 1079 (IQR 1543) mL and U alpha-GST/ U Cr was 6,88 (IQR 6,88) ug/g. U alpha-GST/ U Cr positive correlated with initial Scr (rs 0,614; p=0,002) and latest Scr (rs 0,622, p=0,003). There wasn't a significant statistical correlation between U alpha- GST/ U Cr and the percent decline of eGFR (rs 0,043, p=0,07). U alpha-GST/ U Cr demonstrated S of 71%, SP of 64%, PPV of 50% and NPV of 82% to identify patients with a decline >30% of eGFR over a 3 year period. On ROC curves, U alpha- GST/ U Cr and KVT showed a fair ability to predict a decline >30% of eGFR (AuROC 0,704 e 0,735, respectively), but when used together, the discriminatory ability significatively improve (AuROC 0,833 for the U alpha- GST/ U Cr x KVT variable).

Conclusions: Although, the small size population is limitation of the study, the ability to predict disease progression was improved through the use of KVT and urinary biomarker variable. Larger studies are need to validate its use.

PO1260

Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Clinical manifestations of autosomal dominant polycystic kidney disease (ADPKD) can begin in childhood, including evidence of vascular dysfunction, an important predictor of cardiovascular events and mortality. Curcumin is a polyphenol found in turmeric that reduces vascular dysfunction in rodent models and humans free from ADPKD. It also slows kidney cystic progression in a murine model of ADPKD.

Methods: We hypothesized that curcumin supplementation would reduce vascular dysfunction (brachial artery flow-mediated dilation [FMD_{BA}] and aortic pulse-wave velocity [aPWV]) in children and young adults with ADPKD. In a prospective, randomized, controlled, double-blind trial, n=68 participants 6-25 years of age with ADPKD and an estimated glomerular filtration rate >80 mL/min/1.73 m^2 were randomized to receive either curcumin supplementation (25 mg/kg body weight/day) or placebo administered in powder form for 12 months. We also assessed change in circulating and urine biomarkers of oxidative stress/inflammation and kidney growth (height-adjusted total kidney volume [htTKV]; exploratory endpoint) by magnetic resonance imaging. In a sub-group of participants ≥18 years, we also assessed vascular oxidative stress as the change in FMD_{BA} following an acute infusion of ascorbic acid.

Results: Fifty-seven participants completed the trial. Participants were 18±5 (mean±s.d.) years, 55% female, and 85% non-Hispanic White. The co-primary endpoint, FMD_{BA} (%Δ), did not change in the curcumin group (baseline: 9.4±4.1; 12-months: 10.6±3.9), as compared to the placebo group (baseline: 8.9±4.0; 12-months: 9.3±4.5; p=0.22), nor did the other co-primary endpoint, aPWV (cm/sec) (curcumin: 517±106; 12-months: 517±81; placebo: baseline: 518±82 cm/sec 12-months: 525±95 cm/sec; p=0.53). There was no curcumin specific reduction in vascular oxidative stress, nor any changes in mechanistic biomarkers. htTKV also did not change over the 12-month study with curcumin administration as compared to placebo.

Conclusions: Curcumin supplementation does not reduce vascular dysfunction or slow kidney growth in children/young adults with ADPKD.

Funding: NIDDK Support, Commercial Support - Verdure Sciences (study drug), Private Foundation Support

PO1261

Polycystic Kidney Disease Associates with Increased Myopia and Retinal Breaks

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Background: Ophthalmologic manifestations in Polycystic Kidney Disease (PKD) are not known.

Methods: We conducted a retrospective cohort study using EMR data extraction. All adult patients with polycystic kidney disease ("PKD") and CKD from another cause ("non-PKD/CKD"), seen at our center between 1/1/2000-4/30/2020, and Eye disorders of interest in these 2 cohorts were identified using ICD-9/10 diagnostic codes. The date of the first visit to Nephrology clinic was regarded as "Index date". The prevalence of Eye disorders at the index date was compared between "PKD" and "non-PKD CKD" cohorts.

Results: A total of 859 patients with "PKD" and 8309 patients with "non-PKD/CKD" were seen at our center over the study duration. Majority of patients in both groups were male (58% [498] and 54% [4457]) and identified as White (88% [758] and 86% [7185]). At the index date, PKD patients were younger (mean age 55 vs 60 years in non-PKD/CKD; p<0.01) and had shorter follow up time (median 901 vs 1311 days; p<0.01). PKD patients had higher eGFR (52 [31-81; N=795) vs 43 ml/min/1.73m2 [29-59; N=7342]; p<0.01) and lower prevalence of diabetes mellitus at the index date (23% [198] vs 39% [3270]; p<0.01). Hypertension prevalence was similar between the two groups (91% [778] and 90% [7444]). Myopia and all Retinal breaks (with or without detachment) were found to be higher in PKD as compared to non-PKD/CKD after multivariable adjustment for age, gender, race, diabetes and follow up time (adjusted odds ratio 1.4 [95% CI: 1.1-1.7] and 1.7 [1-2.8], respectively; p<0.01). Retinal breaks with detachments by themselves were also more frequent in PKD but did not reach statistical significance (Table). Peripheral retinal degeneration was similar between the two groups.

Conclusions: There is increased prevalence of Myopia and Retinal breaks in PKD compared to non-PKD/CKD. These ophthalmologic findings could be potential extra-renal manifestation of PKD. Comparison with general population prevalence and investigations into the mechanism are needed for confirmation.

Prevalence of Eye Disorders in PKD vs non-PKD/CKD

Disorder group	Prevalance at Index Date (% [N])			Adjusted Odds Ratio (95% CI)	P-value
	PKD (N=859)	Non-PKD/CKD (N=8309)	P-value		
Myopia	12 (103)	11.2 (928)	0.47	**1.4 (1.1-1.7)**	**<0.01**
Peripheral Retinal Degeneration	1.4 (12)	1.6 (134)	0.63	1 (0.6-1.9)	0.91
Retinal break without detachment	**1.6 (14)**	**0.8 (69)**	**0.02**	**2.4 (1.3-4.3)**	**<0.01**
Retinal break with detachment	1.3 (11)	0.95 (79)	0.35	1.6 (0.8-3)	0.17

PO1262

TSC2 Loss-of-Heterozygosity Mutations Drive Cystogenesis in Kidney Organoids Generated from Tuberous Sclerosis Complex Patient-Derived Induced Pluripotent Stem Cells

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Background: Kidney cysts are the second most common renal manifestation of TSC, accounting for 50% of kidney lesions. The genetic mechanisms driving TSC-associated cystic kidney disease remain poorly understood.

Methods: We induced nephric differentiation of a series of TSC patient-derived iPSC lines that included a line carrying a heterozygous microdeletion in the *TSC2* locus (*TSC2*$^{+/-}$), and a TALEN-engineered isogenic cell line carrying microdeletions in both *TSC2* alleles (*TSC2*$^{-/-}$).

Results: Analysis of Day-21 two-dimentsional cell cultures showed that nephrons derived from *TSC2*$^{+/-}$ and *TSC2*$^{+/+}$ hiPSCs presented normal morphology, and were sequentially segmented into distal tubules expressing cadherin 1 (CDH1), proximal tubules containing brush borders labeled by lotus tetranoglobus lectin (LTL) and glomeruli containing podocytes expressing podocalyxin 1 (PODXL). By Day-21 of differentiation *TSC2*$^{-/-}$ hiPSC-derived kidney tissues showed cavitated structures resembling cysts. Analysis of nephron segments showed positive signal for both CDH1 and LTL, indicating the cyst lining could comprise distal tubule and/or proximal tubule cells. The observed frequency of cyst formation was ~4.7 cysts/well for *TSC2*$^{-/-}$ cultures, compared with 0 and ~0.5 cysts/well for *TSC2*$^{+/+}$ and *TSC2*$^{+/+}$ cultures, respectively. Of note, 2-D cyst-like structures developed in a spontaneous manner, that is without addition of cAMP modulators. Analysis of the three-dimensional anatomy of *TSC2*$^{-/-}$ organoids also showed that while individual tubule segments were involved in cyst lining, in certain cases a combination of both proximal and distal tubule cells were detected, suggesting improper segmentation mechanisms in the absence of TSC2. While single-cell lining layers were associated with well-defined tubule segments, mixed-cell lining regions were multi-layered, resembling the columnar epithelium observed in the renal cysts of TSC patients. The distribution of LTL staining, in proximal tubules of *TSC2*$^{-/-}$ organoids indicated loss of cell polarity in contrast to the polarized cells observed in *TSC2*$^{+/-}$ tubules. Cyst formation in *TSC2*$^{-/-}$ organoids did not involve loss of polycystin 1 (PKD-1) expression.

Conclusions: Our kidney organoid models provide evidence supporting LOH events resulting in complete TSC2 inactivation in nephron tubule cells as a mechanism driving kidney cyst formation in TSC.

Funding: NIDDK Support

PO1263

Six2Cre-Mediated Deletion of Anks6 leads to Proximal Tubule Developmental Defects

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Background: Nephronophthisis-related ciliopathies (NPHP-RC) are a group of autosomal recessive kidney diseases that are characterized by renal cysts, tubulointerstitial fibrosis and basement membrane disruptions. Mutations in *ankryrin repeat and sterile alpha motif domain containing 6 (ANKS6)* gene were recently identified as causing nephronophthisis type 16 (NPHP16) in humans. Although, several mouse models with *Anks6* mutations have been reported, its function in the kidney remains incompletely understood. In order to investigate the disease mechanisms of nephronophthisis and the function of *Anks6* in kidneys we deleted *Anks6* expression in the nephron progenitor population using the Six2Cre transgenic mouse line.

Methods: *Six2Cre* transgenic mice were crossed with *Anks6fl/fl* mice to generate *Six2Cre;Anks6fl/fl* mice. Gross morphological characterization and tissue histological analysis of mutant mice was performed on E15.5, E18.5 and P1 kidneys. Kidneys were embedded in paraffin and sectioned at 5µm thickness for histological staining with hematoxylin and eosin. Immunofluorescence (IF) staining was performed to label nephron segments and glomerular components. *Anks6* expression in the kidney was examined using X-gal staining. ANKS6 role in epithelial cell polarity was investigated using a spheroid assay after *ANKS6* siRNA knockdown in IMCD3 cells.

Results: *Six2Cre;Anks6fl/fl* mice die at birth due to kidney failure. *Anks6* expression was ubiquitous in the developing kidney. Histological analysis revealed that deletion of *Anks6* in nephron progenitors leads to proximal tubule morphogenesis defects and glomerular cysts. Immunostaining of the glomeruli showed reduced recruitment of mesangial cells and decreased poodcyte numbers in mutant kidneys. Proximal tubule development was similarly arrested at an early tubular morphogenesis stage resulting in short straight tubules. Knock down of ANKS6 in cell culture resulted in polarization and lumen formation defects.

Conclusions: Our data demonstrate that Anks6 is required for proximal tubule morphogenesis and glomerular development. Deletion of Anks6 in nephron progenitors leads to severe kidney morphogenesis defects that are incompatible with life. Spheroid assay revealed that ANKS6 has an important role in epithelial polarity and lumen formation. Future work will address which morphogenic pathway(s) are regulated by Anks6 during nephrogenesis.

Funding: NIDDK Support

PO1264

The Impact of Salt Deficiency on Acid-Base Homeostasis in Autosomal Recessive Polycystic Kidney Disease

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Background: In healthy subjects, dietary salt restriction exacerbates imbalances of acid-base homeostasis. The disease progression of autosomal dominant PKD is associated with decreasing serum bicarbonate levels and metabolic acidosis, however very little is known about acid-base imbalance in autosomal recessive (AR) PKD, particularly, in response to dietary restrictions. Here we hypothesized that a salt-deficient (SD) diet leads to electrolyte and acid-base imbalance in ARPKD.

Methods: Male and female PCK/CrljCrlPkhd1pck/CRL (PCK) rats were fed a SD (0.01% NaCl, Dyets Inc) diet for 1, 3, 5, 7 and 9 weeks beginning at 4 weeks of age. Before each endpoint, urine was collected, and plasma and tissue samples were harvested. Urine and plasma creatinine, pH and electrolytes, BUN, and plasma aldosterone levels were measured. Cystic index was analyzed with ImageJ. Statistical analysis was performed with 2-way ANOVA.

Results: Two-kidney-to-body-weight, water consumption, plasma K+ and urine output decreased over the course of the SD diet in both sexes. Plasma Na+ and Cl- as well as creatinine increased; and BUN did not change. Plasma aldosterone increased from week 1 to week 5 (week 1: 2.6±1 (M) and 3.7±0.9 (F), week 5: 10.5±1.5 ng/ml (M) and 7.7±1.1 (F), $p<0.001$ (over time)), followed by a return to baseline by week 9 of the SD diet. There was a significant increase in cystogenesis in female rats from week 1 to week 9 of the SD diet (week 1: 14.2±1.9%, week 9: 36.3±2.4%). Further, we observed an increase in plasma pH (week 1: 6.98±0.08 (M) and 6.83±0.03 (F), week 9: 7.16±0.08 (M) and 7.13±0.02 (F), $p<0.001$ (over time)) and a decline in urine pH (week 1: 7.69±0.42 (M) and 8.75±0.08 (F), week 9: 5.80±0.07 (M) and 5.72±0.08 (F), $p<0.001$ (over time)) in both sexes throughout the dietary challenge.

Conclusions: PCK rats on a SD diet exhibit acidification of urine pH and an increase in plasma pH. We can speculate that acid base transporters such as NHE1, NBCe2, and pendrin are upregulated to conserve plasma sodium leading to a shift in acid-base homeostasis. Further studies aimed at elucidating the role of these transporters may add to the current knowledge regarding the pathogenesis and dietary management of ARPKD.

Funding: NIDDK Support, Other NIH Support - NHLBI R01 HL148114; NIDDK R00 DK105160; NIH T35 DK007431

PO1265

A Combination Therapy with Two Dietary Supplements Acting on Different Mechanisms Ameliorates Disease Progression in a Rat Model of Polycystic Kidney Disease

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Background: Recently, our lab reported that dietary interventions to induce ketosis ameliorate disease progression PKD animal models, and that this effect involves the natural ketone beta-hydroxybutyrate (BHB). Additionally, we have recently shown that renal microcrystals exacerbate disease progression in PKD models. We now show that a combination of citrate and BHB effectively inhibits PKD progression. These compounds act on separate mechanisms, synergistically preventing cyst formation and cyst growth in young rats. In adult rats, the combination treatment leads to a partial reversal of existing renal cystic disease.

Methods: Juvenile and adult Han:Sprague-Dawley rats were treated with BHB, citrate or in combination via drinking water for 5 or 4 weeks respectively, then sacrificed and analyzed for changes in cystic burden and markers of disease progression. Additonally, rats were placed in metabolic cages to assess changes in urine parameters.

Results: Administration of either BHB or citrate alone in the drinking water effectively ameliorates PKD progression in a rat model. Combining BHB and citrate produced a synergistic effect. Cystogenesis and cyst growth were inhibited in juvenile animals. In adult animals with pre-existing renal cystic disease, the treatment leads to partial disease regression. We also find that administration of excess sodium and potassium alone, at doses that would be provided from the salts of citrate and BHB, lead to a worsening of PKD in our rat model.

Conclusions: The beneficial effects of ketosis are mimicked by administration of BHB in the drinking water and are consistent with a number of groups findings suggesting an underlying metabolic defect in PKD. Our other recent findings suggest excessive renal crystal burden leads to accelerated disease progression in PKD models. Renal crystal formation can be prevented by administration of citrate to both chelate calcium and raise urinary pH. These results are of high clinical significance because BHB and citrate

are widely available and classified as safe dietary supplements. These results suggest that a combination of widely available and generally safe dietary supplements, when appropriately formulated, demonstrate high promise for supporting kidney health in PKD.

Funding: Other NIH Support - NIH 1 R01 DK109563-01A1, Private Foundation Support

PO1266

A Single-Center Experience of ARPKD in Adults

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is an inherited ciliopathy with 50% presenting with enlarged kidneys *in utero* or early infancy. ARPKD has an incidence of ~1:20,000 live births and arises from biallelic variants in *PKHD1* encoding for fibrocystin, with variants in *DZIP1L* accounting for <1% cases. Imaging findings include large echogenic kidneys, poor cortico-medullary differentiation, renal cysts or "salt and pepper appearance". ARPKD-congenital hepatic fibrosis (ARPKD-CHF) complex consists of renal disease with biliary dilatation portal hypertension and splenomegaly. 50% develop ESRD in childhood with limited data on renal prognosis for those that present later.

Methods: A retrospective chart review of patients > 16 yr of age with cystic kidney disease and/or congenital hepatic fibrosis to identify possible cases of ARPKD. Clinical phenotype (compatible hepato-biliary and renal involvement) and/or genetic testing were used to verify the diagnosis.

Results: We identified 29 patients with ARPKD-CHF, out of which 13 were > 16 yr (mean 32.4 yr). 38% were males, 15% identified as Hispanic and the rest as non-Hispanic whites. All had radiographic evidence of renal and/or hepato-biliary involvement and 5 of 13 patients had biallelic variants in *PKHD1*. On the most recent imaging study, 92% had renal cysts, 23% large echogenic kidneys, 23% poor renal corticomedullary differentiation, 15% medullary sponge kidney, 23% with salt and pepper pattern. Only 3 of 15 (20%) had reached ESRD or received a kidney transplant, while the remaining had a mean eGFR of 46ml/min/1.73m^2. Of these, 50% had eGFR ≥ 60ml/min/1.73m^2. Amongst those with hepato-biliary involvement, 40% had CHF, 53% portal hypertension, 40% splenomegaly, 26% liver cysts.

Conclusions: We describe a cohort of patients with ARPKD, the majority presenting as adults, with an eGFR ≥ 60ml/min/1.73m^2. A significant number of these patients had multiple large renal cysts. Absence of obvious renal phenotype in patients with congenital hepatic fibrosis can make the diagnosis challenging, requiring a high degree of clinical suspicion. We believe that we may have missed a significant number of patients without obvious combined hepatic and renal abnormalities who may have had delayed onset ARPKD. Our small series suggest that some patients with ARPKD present as adults with a more limited phenotype that can easily be mistaken for ADPKD.

PO1267

Analysis of Somatic Mosaic Mutations in Nephropathy-Associated Genes Reveal Candidate Disease-Causing Mutations in Previously Germline-Negative Cases

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Background: Somatic mosaicism variant (SMV) arises due to postzygotic mutations that results in two genetically distinct populations of cells in the same person. SMVs may be missed by standard search for germline (or inherited) mutations, and the use of dedicated analytic pipelines for SMVs can potentially explain "exome negative" cases.

Methods: We searched for SMVs in 248 patients who underwent exome sequencing for congenital kidney anomalies. Somatic mutations were identified through GATK Mutect2 software, and clinically annotated following the American College of Medical Genetics and Genomics (ACMG) guidelines We focused the analysis on 625 nephropathy-associated genes previously used for the germline analysis.

Results: Previous analyses germline variants had identified 52 diagnostic variants in this cohort (20.9% diagnostic rate). In addition, the SMV pipeline identified candidate disease-related SMVs 4 "exome-negative" patients (1.6% of cases). The SMVs were detected in *RET, ENG* and *COL4A5*, and are reported in Table 1. This improved the diagnostic rate of the cohort to 22.5%

Conclusions: Analysis of somatic mosaic variants can increase diagnostic yield in patients with congenital kidney anomalies. Application of the SMV pipeline may increase diagnostic in other forms of kidney disease

SVM identified in congenital anomalies kidney patients

variant	HGVSc	HGVSp	consequence	gene	ACMG
10-43609070-G-T	c.1826G>T	p.Cys609Phe	missense_variant	RET	P
9-130587518-G-A	c.808C>T	p.Gln270Ter	stop_gained	ENG	P
10-123247552-G-T	c.1942C>A	p.Leu648Ile	missense_variant	FGFR2	LP
X-107939580-G-A	c.5048G>A	p.Arg1683Gln	missense_variant	COL4A5	P

PO1268

Comparison of Imaging Approaches for Quantifying Total Kidney Volume (TKV) and Fibrosis in a Mouse Model of Polycystic Kidney Disease (PKD)

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Background: 3D imaging and histology are critical tools for assessing PKD in patients and animal models. Magnetic resonance (MR) imaging provides μm resolution, but is time consuming, expensive, and access to equipment and expertise is limiting. Robotic ultrasound (US) imaging is lower resolution but fast. Similarly, picrosirius red (PR) staining and standard light microscopy is used to assess fibrosis; however, alternative methods for quantifying PR staining have been shown in other tissues to allow greater sensitivity and more detailed characterization.

Methods: *Pkd1*$^{RC/RC}$ mice were compared to *Pkd1*$^{+/+}$ (WT). TKV was quantified from US and MRI (7T and 16T) at 1, 3, and 4 months old. US measurements of kidney and heart were made using the robotic Vega system from SonoVol. Inter-observer variation was assessed using Bland-Altman analysis. PR-stained kidneys were imaged using standard light microscopy, circularly (*c*) polarized light with binning into four categories of collagen thickness, and fluorescent imaging with analysis using ctFire. Renal cAMP and BUN were measured using standard approaches, and GFR was measured using a transdermal fluorescent sensor (MediBeacon).

Results: US detected increased TKV at 1 month and was similar to MR (7T or 16T). Inter-observer variability (2 observers) was greater for US than MR, but still able to detect differences between genotypes and time points. US allowed scanning in 2-5 minutes/mouse while MR required 20-30 minutes. *C*polarized light showed a greater percentage of the thickest collagen fibers in RC/RC mice, and a corresponding lower percentage of each of 3 categories of thinner collagen fibers. Preliminary data using fluorescence and ctFire showed a higher density of collagen fibers in RC/RC mice vs. WT. Analysis of collagen fiber angle, length, straightness, and width is ongoing. RC/RC had a lower GFR, higher BUN, and elevated cAMP vs WT. No differences were observed in cardiac function (ejection fraction, heart rate, or cardiac output).

Conclusions: These studies demonstrate the utility of US and alternative approaches of quantifying fibrosis using PR.

Funding: NIDDK Support

PO1269

Phenotypic Heterogeneity in Type IV Collagen-Associated Nephropathy: The Cystic Phenotype

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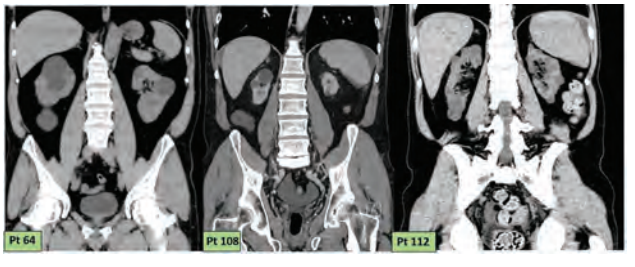
Background: Exome sequencing (ES) revealed mutations (mut) in type IV collagen (COL4) genes in patients (pt) diagnosed with other forms of chronic kidney disease (CKD), supporting the concept of *spectrum* of phenotypes for COL4-Nephropathy. Unexpectedly, some pt with CKD presenting with cystic phenotype were identified with COL4-Nephropathy by ES.

Methods: The retrospective study included 130 pt referred to outpatient clinic of genetic kidney diseases of ASST Spedali Civili of Brescia from 2002 to 2021 and diagnosed with COL4-Nephropathy. Based on the presence of multiple and bilateral renal cysts on imaging (fig1), a group of pt with cystic phenotype was selected (27/130;21%).

Results: Among cystic group (CG), diagnosis was based on genetic test (gt) and kidney biopsy in 10/27 pt, whereas it was 'biopsy-proven only' in 7 pt, gt-based in 3 pt and clinically in 7 pt. Fifteen pt underwent gt (fig2): heterozygous mut in COL4A3 and COL4A4 were detected in 9 and 3 cases, respectively; 1 patient showed mut in COL4A5 and 2 pt had a digenic pattern. At baseline, comparison between CG to non-CG showed lower eGFR (70[IQR 35;91] vs 91[IQR 74;114] mL/min/1.73m^2 p<0,001) and higher proteinuria (1.1vs0.38g/24 hrs), although the statistical significance was not reached for proteinuria (p=0.058). At last censoring, data confirmed a lower eGFR (26[IQR 7;55] vs 86[IQR 44;104]) and a tendency (p=0.0545) of greater proteinuria in CG. Prevalence of arterial hypertension, CKD (defined as eGFR < 60) and ESKD was higher in CG.

Conclusions: The study contributes to expand the emerging phenotypic heterogeneity of COL4-Nephropathy and suggests that cystic phenotype could predict progression of kidney disease.



ID	Age/ gender	Family history*	Renal biopsy	Gene mutation	cDNA mutation	Predicted protein change	ACMG classification
23	44/F	1	0	COL4A3	c.647G>T	p.Gly216Val	pathogenic
29	72/F	1	1	COL4A3	c.3401G>A	p.Gly1134Glu	likely pathogenic
35	62/F	1	1	COL4A3	c.647G>T	p.Gly216Val	pathogenic
36	68/F	1	0	COL4A3	c.647G>T	p.Gly216Val	pathogenic
37	29/F	1	1	COL4A5 , COL4A6	del Xq22.3	del(X)(q22.3;q22.3)[0.17Mb]	contiguous gene syndrome
60	68/F	1	0	COL4A3	c.1363G>T	p.Gly455Cys	likely pathogenic
63	47/M	1	1	COL4A3	c.1363G>T	p.Gly455Cys	likely pathogenic
64	57/F	1	1	COL4A3	c.1132G>A	p.Gly378Arg	likely pathogenic
77	69/M	1	1	COL4A3	c.1150+1G>T	–	pathogenic
85	61/F	1	1	COL4A5 , COL4A4	COL4A3:c.3221G>A, c.4421T>C, COL4A4:c.3676C>T	COL4A3:p.Gly1074Glu, p.Leu1474Pro, COL4A4:p.Arg1226Cys,	pathogenic, VUS, VUS
92	63/F	1	1	COL4A4	c.4694G>T	p.Arg1565Leu	VUS
108	60/M	0	1	COL4A4	c.1342G>A	p.Gly448Ser	pathogenic
112	57/M	1	0	COL4A3	c.3017G>A	p.Gly1006Glu	pathogenic
116	71/M	1	1	COL4A5	c.3722G>C	p.Gly1241Ala	likely pathogenic
128	55/M	0	1	COL4A4	c.1342G>A	p.Gly448Ser	likely pathogenic

PO1270

Rare Variants in Syndromic Ciliopathy Genes as Novel Causes of Isolated Renal Disease in Adults

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Background: Renal ciliopathies are among the commonest genetic causes of end-stage renal disease (ESRD). Ciliopathies are caused by defects of the primary cilium, an antenna-like organelle with mechanosensory roles, crucial for organ development and maintenance. Disorders of the cilium present early with multi-organ involvement, but some individuals present as adults with organ-specific phenotypes, potentially due to milder mutations and organ-specific effects.

Methods: We identified rare variants in two ciliopathy genes in two unrelated adults presenting with ESRD. ACMG guidelines did not classify these variants as pathogenic, requiring functional validation to establish a causal genotype-phenotype relationship.

Results: Bi-allelic *C2CD3* missense variants were identified in a proband with ESRD, suggestive of an isolated renal ciliopathy. *C2CD3* is essential for ciliogenesis, with complete loss of cilia in knockout mice (*Development* 135:4049 2008). Severe mutations were reported in patients with a syndromic ciliopathy (OFD XIV; OMIM# 615948), but no cases of isolated renal disease have been reported. We detected a moderate but consistent shortened cilia length in skin fibroblasts and renal epithelial cells from our proband, suggestive of a milder ciliary defect. Remarkably, the proportion of ciliated cells was significantly reduced in renal epithelial cells but not in fibroblasts, indicating an organ-specific ciliogenesis defect. Pathogenic variants in *CC2D2A* cause Joubert and Meckel syndrome, with no isolated renal presentations observed to date (*Mol. Genet. Genom.* e1603 2021). We identified a novel homozygous nonsense variant (Arg34*) in *CC2D2A*, classified as not pathogenic due to an alternate start-codon, in a previously healthy 37-year-old male with isolated ESRD of unknown etiology. Using public data (GTEx), we show that protein-coding transcripts harbouring this variant are the predominant trancripts in the kidney when compared to tissues relevant to *CC2D2A*-related phenotypes (e.g., cerebellum, liver).

Conclusions: Rare variants in known syndromic ciliopathy genes cause isolated renal disease in adults due to potential organ-specifc effects. Using variant classification schemes without functional analysis may not accurately capture the genetic contribution to adult ESRD.

Funding: Government Support - Non-U.S.

PO1271

Targeted Exome Sequencing Application for Genetic Diagnosis of Pediatric Patients with Cystic Kidney Disease

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Background: Detection of a monogenic cause of chronic kidney disease accounts for almost 30% of cases in the pediatric cohort. Of these, the highest yield in the genetic diagnosis is currently seen in cystic kidney disease. Nearly 100 monogenic causes of renal cystic ciliopathies have been identified and the genetic diagnostic yield is reported to be approximately 50%. Here, we report the results of genetic testing in a cohort of Korean pediatric patients with cystic kidney disease.

Methods: From July 2019 to February 2021, children under the age of 18 with three or more cysts in both kidneys on imaging studies were recruited from three pediatric nephrology centers in Korea. Genetic identification was performed by targeted exome sequencing (TES) including 89 genes known as cystogenesis-related or causative-ciliopathy.

Results: A total of 46 pediatric patients with cystic kidney disease were recruited. The median age was 9.2 years (IQR, 5.49-14.53) and 60.9% were boys. Twelve patients (27.9%) had a family history of cystic kidney disease. The clinical diagnoses of the patients were 10 patients with autosomal dominant polycystic kidney disease, 5 patients with autosomal recessive polycystic kidney disease, 2 patients with multicystic dysplastic kidney, 1 patient with nephronophthisis, and the others were undiagnosed. The mutation detection rate was 52.2% (24 of 46). *PKD1* was the most common causative gene (16 patients, 34.8 %), followed by *HNF1B* (3 patients), *PAX2* (2 patients), *PKD2* (1 patient), *PKHD1 (*1 patients) and *NPHP3* (1 patient). Genetic mutations were identified in all patients (12 of 12) with a family history of cystic kidney disease. In patients without a family history, genetic mutations were found in 35.3 % (12 of 34).

Conclusions: The mutation detection rate in this cohort of Korean pediatric patients with cystic kidney disease was 52.2% by TES. Mutations in *PKD1* were found most commonly, and the mutation detection rate was higher in patients with a family history of cystic kidney disease. For children with cystic kidney disease, molecular genetic testing is essential for an accurate diagnosis, personalized treatment, and prognosis prediction.

Funding: NIDDK Support

PO1272

The Prognostic Factors of Cyst Infection due to ADPKD

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Background: Renal or hepatic cyst infection is a complication of autosomal dominant polycystic kidney disease (ADPKD), which requires hospitalization and causes death. Cyst aspiration was the gold standard to diagnose this disease. Because of its invasiveness, several diagnostic criteria without using cyst aspiration have been proposed, but prognostic factors of cyst infection have not been analyzed in this setting.

Methods: Inclusion criteria of this retrospective cohort are ADPKD patients who were admitted in Toranomon hospital and Toranomon hospital Kajigaya between 2016 April and 2021 March, and who were diagnosed as cyst infection based on MRI findings, which we previously published. Primary composite endpoint was defined combination of death, septic shock, or hospitalization for more than four weeks, and secondary outcomes were defined by each outcome mentioned above. Logistic analysis was planned to assess the predictors of the outcomes.

Results: One hundred ninety patients were eligible to this study. The average age was 65.0±9.2 years old, 116 (61.1%) were female, and the average height-adjusted total liver volume (htTLV) was 3322±2286 mL per meter, and 164 (86.3%) had hemodialysis therapy. Composite outcome occurred in 109 (57.4%): 25 death, 36 shock, and 98 longer-hospital-stay. Multivariable logistic regression model after adjusted related variables showed that older age (odds ratio(OR) 1.10 (95% confidence interval: 1.10-2.54), p-value=0.02), male (OR 2.49(1.16-5.33), p-value=0.02), higher htTLV (OR 2.29 (1.39-3.77), p<0.01), lower mean blood pressure at admission (OR 0.735(0.5798-0.9319), p=0.01), larger size of infectious cyst (OR:1.42(1.06-1.91), p=0.02) were significantly associated with the composite outcome. Although the culture-positive case or higher white blood cell count were not significantly associated with the primary outcome, they were associated with septic shock due to cyst infection.

Conclusions: Baseline characteristics at admission were associated with the prognosis of cyst infection diagnosed by MRI-based criteria, which was similar to cyst infection diagnosed by cyst aspiration. Culture-positive case or higher white cell count were reported as risk factors requiring more invasive therapies that could lead to septic shock and need longer hospitalization in our study's cohort.

PO1273

ExoGAG, a New Method for Extracellular Vesicle and Glycoprotein Isolation in Urine That Unmasks the Pathophysiology of the Kidney and Identifies New Biomarkers of Kidney Disease

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Background: Glycosaminoglycans (GAGs) are large polysaccharides that interact through glycosidic bonds with proteins and lipids, forming the extracellular matrix; or with secreted proteins, as uromodulin. Glycosylation is altered in pathologies, as cancer or kidney diseases. GAGs are present in extracellular vesicles (VEs), nanometric structures delimited by lipid bilayer that cells release and whose charge (RNA/miRNA, DNA and proteins) is essential in intercellular communication. Our group developed a method for GAG, glycoproteins and VEs isolation in any biological sample, called ExoGAG (commercialized by Nasas Biotech), which led us to identify and characterize new signalling mechanisms, and identify new prognostic/diagnosis biomarkers, for example, in polycystic kidney disease (PKD).

Methods: Urine samples have been collected from patients genetically diagnosed with type I and II PKD at different stages of disease. Using ExoGAG, GAG-glycoprotein-VEs complex has been isolated and characterized by different proteomic techniques (Western Blot, mass spectrometry), gene expression (RT-PCR), and image characterization (electron microscopy, immunofluorescence).

Results: ExoGAG has allowed us to identify a new biomarkers in urine (in protection) in PKD patients, which are altered in disease progression, even anticipating currently used kidney damage markers. The characterization of these complexes has led us to discover signalling mechanisms between the different segments of the nephron, and whose function is altered in different pathologies. These findings have served other researchers deepen knowledge in different specialties such as Oncology and Endocrinology.

Conclusions: This new method for isolating the fraction associated with GAG in urine samples has allowed us to identify prognostic/diagnostic biomarkers of kidney diseases, based on glycoprotein and vesicular profile. Likewise, it has led us to identify new signalling mechanisms of the nephron, which opens a new field for a better understanding of renal pathophysiology. These results uncovered the potential as a method of EVs isolation for its use in the research of new cellular communication pathways or cellular mechanisms.

PO1274

Deposition of an Abnormal Extracellular Matrix as an Initiating Event in Cyst Formation

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Background: Extracellular matrix (ECM) refers to the proteins and other macromolecules outside of cells that provide a scaffolding to maintain tissue architecture. The distinct ECMs to which these cells are attached, epithelial cells to a laminin-rich basement membrane vs. interstitial cells to a collagen/fibronectin (FN) ECM, has profound implications for cell behavior and tissue architecture. These differences in cell behavior are mediated through a family of receptors known as integrins, used by cells to attach to the ECM. Here we provide evidence that cyst formation in ADPKD is a manifestation of abnormal cell behavior in response to an atypical extracellular matrix and changes in integrins.

Methods: To understand the pathological contribution of integrins and FN to ADPKD, we measured their expression and localization *in vivo* using a postnatal murine model of ADPKD and kidney samples from human ADPKD.

Results: We observed increased expression of FN in murine cystic kidneys and also in kidneys from humans with ADPKD. In mice, increased fibronectin expression preceded cyst formation. Moreover, laminin basement membrane underlying cyst lining cells was discontinuous and replaced in some sections by a FN-rich ECM. Some sections were conspicuous for expressing the FN receptor $\alpha5\beta1$ integrin, and for cell morphology being cuboidal instead of flattened. In other areas of the FN rich ECM, αv-integrins, were present on flattened cyst lining cells. $\alpha3\beta1$ integrin was more abundant on cyst lining cells than on non-cystic tubules. Interestingly, *in situ* hybridization revealed that *Fn1* was not expressed in all cyst lining cells but in the specific subset of cells that had a cuboidal appearance.

Conclusions: Our studies presented here identify a distinct subset of cuboidal cyst lining cells that express *Fn1*. They also demonstrate distinct integrin repertoires among subsets of cyst lining cells. As FN deposition precedes cyst formation, these FN-expressing cuboidal cells may have a role in the initiation or early progression of cysts in ADPKD.

Funding: NIDDK Support

PO1275

Uncovering the Role of the Extracellular Matrix in ADPKD Progression

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Background: Polycystic Kidney Disease (PKD) is a genetic disorder due to mutation in either *Pkd1* or *Pkd2* genes and characterized by bilateral cysts formation. We recently uncovered a direct role of PC-1, the protein product of *Pkd1* gene as a mechanosensor of extracellular stiffness. We found that PC-1 interactors mediate inhibition of actomyosin contraction that mediates the cellular response to the rigidity of the Extracellular Matrix (ECM). Based on these findings we speculated that *Pkd1*$^{-/-}$ cells fail to properly respond to the extracellular mechanical force of ECM leading to excessive matrix deposition and proliferation. In line with this, kidneys of end-stage PKD patients show enhanced fibrosis typical of cystic kidney disease and tumors. We then wondered whether PKD ECM is a part of an active Cyst Microenvironment (CME), exerting a key role in the evolution of the disease.

Methods: We characterized CME in the renal tissue of an aggressive *Pkd1*$^{\Delta C/flox}$: Ksp-Cre and a low progressive *Pkd1*$^{\Delta C/flox}$:Tam-Cre inducible mouse models. To study the composition and the mechanical properties of the cystic ECM we decellularized cystic kidneys obtaining ECM-derived kidney scaffolds. Furthermore, we isolated matrix from *Pkd1*$^{-/-}$ fibroblasts *in vitro*.

Results: We have characterized the renal tissue microenvironment of two *Pkd1* inducible mouse models at a late stage of the disease confirming the presence of fibrosis, immune infiltrates and progressive accumulation of collagen I. In line with an active role played by fibroblasts in the deposition and remodeling of the ECM, our data showed the presence of activated fibroblasts in cystic kidneys. We performed a proteomic analysis of cystic kidney scaffolds by Mass Spectrometry (MS). Cluster analysis of MS data showed a clear separation between cystic and control scaffolds. Finally we found that matrix isolated from *Pkd1*$^{-/-}$ cells was able to influence differently key cellular properties such as adhesion, polarization, proliferation and migration.

Conclusions: ECM plays an active role in the progression of ADPKD disease.

PO1276

Abstract Withdrawn

PO1277

17q12 Deletion Syndrome Presenting as Congenital Diaphragmatic Hernia in a 2-Month-Old Infant

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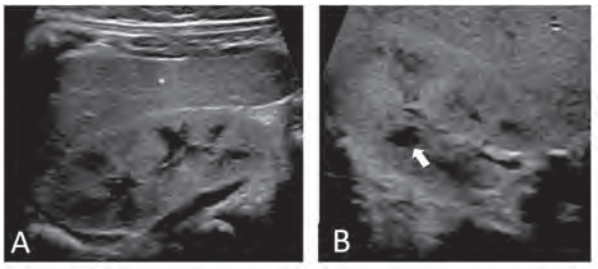
Introduction: 17q12 deletion syndrome results from the loss of as many as 15 genes on the long arm of chromosome 17 including the hepatocyte nuclear factor-1-beta gene (*HNF1B*). Heterozygous pathogenic variants, whole gene deletion, or duplication in *HNF1B* are frequently linked to inherited kidney malformations including hyperechoic kidneys, kidney cysts, solitary kidney, and hydronephrosis as well as extrarenal phenotypic features. 17q12 deletion syndrome has also been linked to congenital diaphragmatic hernia (CDH). We present a case of an infant with hyperechoic and cystic kidneys, diagnosed postnatally with CDH.

Case Description: A 2-month-old female with a history of hyperechoic kidneys on prenatal ultrasound presented to the emergency department with increased work of breathing. A chest x-ray revealed left hemidiaphragm elevation, normal cardiac silhouette, and no focal pulmonary consolidation. Computed tomography of the chest confirmed the diagnosis of CDH. A repeat kidney ultrasound revealed diffuse hyperechoic kidneys and a focal kidney cyst within the right upper pole (**Image 1**). Genetic workup revealed a 1.9 megabase deletion on the long arm of chromosome 17 consistent with the diagnosis of 17q12 deletion syndrome.

Discussion: Pathogenic variants in *HNF1B* or whole gene deletion as part of 17q12 deletion syndrome should be considered in infants with hyperechoic kidneys with cysts, particularly in the context of extrarenal manifestations. Studies have examined the link between *HNF1B* and the development of a CDH. It is proposed that *HNF1B* is involved in the WNT signaling pathway that is critical to mesodermal differentiation and proper diaphragm formation. Only 4 other cases of *HNF1B* mutations associated with CDH are reported in the literature. Two cases describe *HNF1B* deletions, and 2 cases describe *HNF1B* duplications. It is possible that the high prenatal mortality of CDH could explain the paucity of this association.



(A) Grayscale, longitudinal ultrasonographic image of the right kidney demonstrates diffusely increased renal parenchymal echogenicity when compared to the adjacent liver **(asterisk)**. The corticomedullary differentiation is diminished. **(B)** A magnified, transverse ultrasonographic image of the right kidney demonstrates a right upper pole cyst **(arrow)**.

PO1278

Recurrent Pneumothorax in a Marfanoid Adolescent with Autosomal Dominant Polycystic Kidney Disease

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Introduction: Pneumothorax may be a rare extra-renal manifestation of autosomal dominant polycystic kidney disease (ADPKD), and may indicate co-inheritance of other genetic diseases.

Case Description: A 21 year-old man with ADPKD and pneumothoraces presented to nephrology clinic. A screening ultrasound in late childhood was completed due to his family history and confirmed ADPKD. The patient was normotensive and had a tall, thin habitus. His musculoskeletal examination was pertinent for several marfanoid findings, including increased arm span ratios, pes planus, and positive thumb and wrist signs. His eGFR was normal and he did not have proteinuria. He was hospitalized several times between ages 13-20 for recurrent pneumothoraces requiring left apical wedge and lower bleb resections with pleurectomy, and right upper lobectomy and pleurectomy.

Discussion: The patient's lung collapse was attributed to primary spontaneous pneumothorax due to his tall stature and intermittent tobacco use. However, this cannot account for his high rate of recurrence. The extent of pneumothorax burden in this patient should be considered in context of his underlying polycystic renal disease. Pulmonary manifestations of ADPKD are not well understood and have only been described in a handful of case reports. Bronchiectasis and cystic lung disease are thought to occur as a downstream consequence of impaired parenchymal healing. Mutated polycystin-1 in ADPKD prevents normal ciliary function, which is imperative for coordination of cellular repair in bronchial smooth muscle cells. Evolving cystic lung disease in the setting of underlying ADPKD could explain this patient's recurrent pneumothoraces. The possibility of a co-inherited connective tissue disease should also be considered in patients with ADPKD and pneumothoraces. "Overlap" disorders between ADPKD, Marfan syndrome and Tuberous Sclerosis (TSC) have been examined in linkage studies, and have chromosomal proximity. Marfan syndrome and TSC are associated with pneumothorax. Though our patient did not manifest criteria for TSC, his examination is consistent with a Marfan's variant phenotype. This patient may be an example of co-inherited disease, and raises the question of whether it is under this circumstance that rare pulmonary complications become apparent. Clinicians should be aware of these overlap disorders in relation to ADPKD.

PO1279

Ruptured Intracranial Aneurysm as the Initial Presentation of ADPKD in a Pediatric Patient

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is associated with multiple extra-renal manifestations, most notably intracranial aneurysms (ICA). Approximately 10% of ADPKD patients develop ICA during their lifetime. Subarachnoid hemorrhage (SAH) is a major complication of ICA and usually occurs during the end of the 3rd decade. Aneurysm rupture in children <18 years of age is extremely rare. We report a case of a 9-year-old boy presenting with symptomatic ICA rupture as the initial presentation of ADPKD, despite a negative family history of ICA.

Case Description: A 9-year-old boy presented to the emergency department with an abrupt onset of severe headache and lethargy after a fall. His family history was remarkable for ADPKD in his father and grandfather. None of his affected family members developed ICA or intracranial hemorrhage. Initial non-contrast computed tomography scan of the head showed frontal lobe hemorrhage. Additional imaging studies revealed a ruptured anterior communicating artery with SAH. Urgent aneurysm coiling was performed, his bleeding was controlled, and the patient survived. Due to his strong family history for ADPKD, a kidney ultrasound was performed and showed enlarged kidneys with multiple renal cysts bilaterally confirming the diagnosis of ADPKD. The patient's father underwent a screening MRI of the brain at the age of 48 years and was negative for ICA.

Discussion: Our case of SAH due to ICA rupture as the initial presentation of ADPKD, in the absence of a positive family history of ICA or hemorrhage, has not been reported in children. Rare cases of subarachnoid hemorrhage in pediatric patients with ADPKD and a positive family history of ICA or hemorrhage have been described. Based upon available data, it is unclear if either widespread or targeted screening for intracranial aneurysms is beneficial for pediatric patients with ADPKD. Screening is reserved for patients with a family history of hemorrhage, migraine, stroke, patients undergoing major surgery, or patients with high-risk jobs. However, we do not screen children <18 years of age because of the extreme rarity of aneurysmal rupture at that age. Though extremely rare, primary care physicians and pediatricians should stay aware that ICA rupture occurs in children with ADPKD and can lead to devastating complications, even in the absence of positive family history.

PO1280

Congenital Solitary Kidney in ADPKD: A Genotype-Phenotype Correlation

Romina Bucci, Marta Vespa, Maria Teresa Sciarrone Alibrandi, Giancarlo Joli, Giulia Mancassola, Giuseppe Vezzoli, Paolo Manunta. *IRCCS Ospedale San Raffaele, Milano, Italy.*

Introduction: There are a very few cases of ADPKD associated with Unilateral Renal Agenesis (URA). The total amount is currently 9 cases known in the world and their renal function outcome is somewhat undefined.

Case Description: ZG is a pleasant 41-year-old man with a congenital solitary left kidney with multiple cysts and a genetic diagnosis of ADPKD. Familiarity is negative for ADPKD, but positive for URA (present in his sister and her son). Except for hypertension, there are no extrarenal ADPKD manifestations. Poster et al. analyzed 3 patients with a similar phenotype in a cohort of 182 ADPKD subjects, comparing how the volume of the single kidney increased (SKV) over time and how the GFR dropped, stratifying them for sex and age. A greater SKV in time has been recorded in these 3 patients, caused by both compensatory hypertrophy and cyst growth. Surprisingly though, their kidney function was better compared to controls. Late onset kidney failure is probably caused by hyperfiltration, and it is linked with a long-term worse outcome. In our case, ZG's SKV increased less compared to another subject with same age and sex and with controls found in literature. Same goes for kidney function, which was better and more stable in a 10-year time-lapse compared to controls.

Discussion: The reason for this could be found in the PKD1 mutation: ZG has a missense mutation, while the aforementioned 3 cases had truncating ones. ZG's increased SKV is probably more related to hypertrophy than cyst growth itself. Therefore, even in an unorthodox situation like this one, long-term outcome seems to depend on the genotype of the subject.

	Patient ZG (male, 41 y/o)	Matched 2-kidney ADPKD groups (males, y/o 34.3 to 41.4)	Patient with polycystic solitary kidney (male, 38 y/o)
SKV (cm3) baseline	490	546(431-691)	780
Annual SKV progression (%)	2	6.7 (3,9-9,5)	10,2
CCr (ml/min/1.73 m2)	114	91 (85-98)	77

Note: Table shows values of SKV for patient ZG and patient with polycystic solitary kidney. For the matched 2-kidney ADPKD group is reported the SKV mean values with 95% CI. For this last group the volume given is that of the left kidney present in the other 2 cases. SKV is calculated from RMN scans. Creatinine clearance is estimated according to the Cockcroft-Gault formula. In the 2-kidney ADPKD group CCr is estimated by calculating both kidneys.

PO1281

Management of a Patient with ADPKD Who Needs Lithium

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Introduction: N/A

Case Description: A 35-year-old female with borderline personality disorder and schizoaffective disorder presented to nephrology for autosomal dominant polycystic kidney disease (ADPKD). Her biological father had ADPKD and was on dialysis at the time of death. The patient has taken lithium for 10 years, and only lithium allows her to work and live independently. She presented with polydipsia and polyuria, indicating possible nephrogenic diabetes insipidus (DI) from lithium, essential hypertension since age 30, and constant headache; brain MRI was negative for aneurysm. Labs showed a lithium level between 0.3-0.9 mmol/L, creatinine between 0.6-0.75 mg/dL, eGFR of 85-90 ml/min, urine protein:creatinine ratio of 0.27-0.32 g/g, and urine osmolality <100 mOsmol/kg. She has been treated with 2.5 mg lisinopril, 10 mg amiloride, and 1350 mg lithium daily. Abdominal MRI without contrast showed scattered liver cysts and innumerable bilateral kidney cysts. Kidney volume indicated Mayo Class 1C PKD. Her father developed ESRD in his late 50s, suggesting rapidly progressive ADPKD class. Lithium nephropathy is usually characterized by 1-2 mm renal microcysts (Khan et al, *Int J* Psychiatr Med 50(3):290-298). The patient's larger cysts, total kidney volume, and liver cysts suggest ADPKD. Genetic testing showed that the patient has a heterozygous mutation in c.12445-1G>T, expected to cause altered splicing and function of the PKD1 gene.

Discussion: Finding an appropriate agent to slow CKD progression is the current strategy to manage PKD. Her condition is complicated by likely lithium nephropathy. The TEMPO trial (Torres et al, N Engl J Med 367:2407–2418, 2012) showed that tolvaptan helps slow rapidly progressive ADPKD by inhibiting vasopressin's effect, reducing cAMP production, further inhibiting cyst formation and growth (Wang X et al, J Am Soc Nephrol 19: 102–108, 2008; Aihara M et al, J Pharmacol Exp Ther 349: 258–267, 2014). Lithium can also inhibit vasopressin in the kidney, leading to nephrogenic DI (Bokenhauer et al, Nat Rev Nephrol11(10):576-88, 2015). In ADPKD, tolvaptan helps achieve a urine osmolality of less than 300 mOsmol/kg (Torres, Clin J Am Soc Nephrol. 13(11):1765-1776, 2018). Our patient already has polyuria and urine osmolality below 100 mOsmol/kg. Her condition requires agents targeting other pathways. For now, she is on lisinopril, with BP <110/75, and amiloride to limit polyuria.

PO1282

A Case of Mistaken Identity: Alport Syndrome Masquerading as Polycystic Kidney Disease

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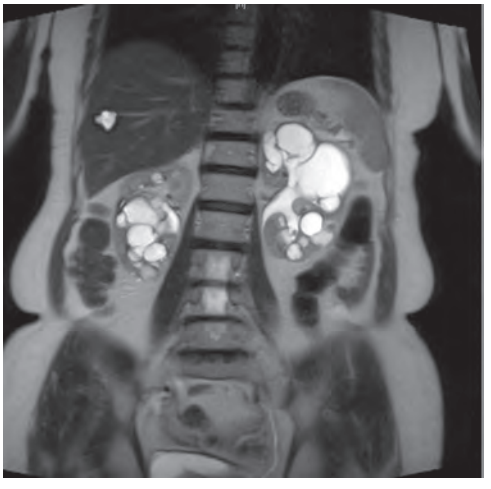
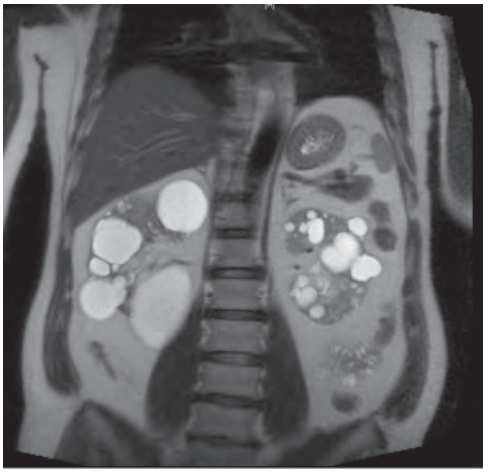
Introduction: Alport Syndrome (AS) is an inherited nephritis caused by a collagen-IV-related mutation leading to abnormalities in the glomerular basement membrane. Patients may present with unexplained hematuria, proteinuria, with or without renal insufficiency. Here, we describe two cases of patients presenting with multiple bilateral renal cysts, initially diagnosed with autosomal dominant polycystic kidney disease(ADPKD), and who were later found to have Alport syndrome via genetic testing.

Case Description: We report two cases of patients followed in our nephrology clinic who were initially thought to have ADPKD. The first patient is a 75-year-old woman who was followed for long-standing hematuria, CKD3bA3, innumerable bilateral renal cysts, few livers cysts, cerebral aneurysms, and a family history of cystic kidney disease. Due to normal kidney sizes, genetic testing was done which revealed a pathogenic COL4A3 mutation, c.1372G>C (p.Gly458ARg). Our second patient is a 64-year-old man with a history of hematuria, CKD3aA2, sensorineural hearing loss, retinal detachment, and family history of hematuria. His genetic testing revealed an X-linked COL4A5 mutation c.367G>C (p.Gly123Arg).

Discussion: Very few cases have described an association with AS and cystic kidney disease. The causal mechanism for renal cyst formation and Alport syndrome is unknown. These cases illustrate the importance of considering alternate diagnosis when suspected ADPKD has atypical features such as normal kidney sizes or kidney dysfunction more than expected for the cyst burden.



Case #1 Bilateral renal cysts in COL4A3-related Alport syndrome



Case #2 Bilateral renal cysts in X-linked Alport syndrome

PO1283

Heterozygous HSD11B2 Gene Mutations and Apparent Mineralocorticoid Excess (AME) in a Patient with Heterozygous ADPKD1

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Introduction: HSD11B2 gene which locates at Chromosome 16q22.1 and encodes the Type 2 isoform of 11-beta-Hydroxysteroid Dehydrogenase that interconverts biologically active cortisol and inactive cortisone. Polycystin-1, encoded by the PKD1 gene, which locates at Chromosome 16p13.3. PKD1 gene forms a complex with polycystin-2 (PKD2) that regulates multiple signaling pathways to maintain normal renal tubular structure and function. We present a new finding of HSD11B2 gene in a patient with polycystic kidney disease.

Case Description: 58-year-old Chinese male presented with bilateral renal cysts and CKD Stage 3 A. PMHx is significant for early onset HTN at the age of 45, Left ICH without residual weakness at the age of 46 years and episode of hypokalemia. Denied Licorice ingestion. Family history is positive for HTN and polycystic kidney disease in his mother and all three siblings. His BP was 145/91 mmHg, not controlled well with daily dose of oral Lisinopril 40 mg and Amlodipine 10 mg. His Na 141, K 4.7, CO2 27, BUN 20, Cr: 1.6, GFR: 46, Hb: 12.5 and Urine protein/ Cr ratio was 0.324. He was started with low dose of Spironolactone 12.5 mg daily for BP control and proteinuria. Renal ultrasound showed Right kidney was 19.5 cm, left kidney was 18.6 cm and presence of multiple bilateral renal cysts. Abdominal CT without contrast disclosed HtTKV: 1724 ml/m. Mayo clinic class was 1 C, estimated frequency of ESRD at 10 years was 37.8%. Kidney gene panels detected the gene of PKD1 (Autosomal Dominant) and HSD11B2 (Autosomal Recessive). BP stable at 125/78 mmHg, 24-hour urine protein was 125 mg per day, Serum cortisol 11 mcg/dl (normal: 8-19 mcg/dl), Serum cortisone: 0.74 mcg/dl (normal: 1.34- 2.65 mcg/dl), Serum cortisol/cortisone ratio: 17.6 (normal: 3.9-11), 24 hours Urine free cortisol: 7 mcg/day (normal 5-64 mcg/day), 24 hours Urine free cortisone: 31 mcg/day (normal 16-128 mcg/day), 24 hours Urine free cortisol/cortisone ratio: 0.22 after spironolactone. However, it was discontinued upon repeated serum K was at the higher side of normal. He is currently treated with oral Tolvaptan.

Discussion: This is an unique case which could be the first case report of HSD11B2 mutations with apparent mineralocorticoid excess associated with heterozygous ADPKD1.

PO1284

A Rare Presentation of Autosomal Recessive Polycystic Kidney Disease in Adulthood

Katerina Hysi, Saira Sajid, James Drakakis. *NYU Winthrop Hospital, Mineola, NY.*

Introduction: Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatorenal fibrocystic syndromes and causes significant renal and liver related morbidity and mortality in children. Renal cysts, congenital hepatic fibrosis, and recessive inheritance characterize ARPKD. The disorder usually manifests infancy, with a high mortality rate in the first year of life. For the patient who survives the neonatal period, the probability of being alive at age 15 ranges from 50-80%, with the majority requiring renal replacement therapy at that age. This diagnosis is rarely made in the adult years with the clinical course and prognosis much less well defined.

Case Description: 57 year-old male with PMHx of gout and long standing CKD with baseline creatnine 1.8 - 2.0 mg/dL, dating back to 2010 with little progression presented for evaluation. Urinalysis was without microscopic hematuria or proteinuria. Historic imaging showed small kidneys and medical renal disease. An updated MRI noted bilateral kidneys cysts with areas of atrophy and scarring, which along with an increase in GGT and family history of a sister with congential hepatic fibrosis, raised possibility of ARPKD. The patient subsequently underwent whole exome sequencing, which confirmed two pathogenic variants (specifically S3018F and R1624W) in the PKHD1 gene, consistent with ARPKD. His brother was eventually tested as well and found to have the same two variants.

Discussion: The classic presentation for ARPKD is systemic hypertension with progression to ESRD by the age of 15. In a typical presentation, a small number of those with ARPKD live to adulthood with some compromise of kidney function; but with significant liver disease. Due to its wide phenotypic variability, the diagnosis of ARPKD may be made during any stage of childhood; in rare cases, it does not present until adolescence or adulthood. A minority of affected individuals present as older children or young adults with evidence of hepatic dysfunction or otherwise unexplained renal cysts as the prominent presenting feature. This case exhibits reveals the silent menace of ARPKD with a delay in recognition of clinical manifestations and thus an unusually older age at the time of diagnosis.

PO1285

HDR: A Novel Mutation in GATA-3 with Variable Expressivity in an Affected Family

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Introduction: Hypoparathyroidism, deafness, and renal disease (HDR) syndrome, also known as Barakat syndrome, is a rare autosomal dominant disorder caused by heterozygous variants in *GATA-3*. *GATA-3* belongs to a family of dual zinc finger transcription factors that is involved in embryonic development of the inner ear, kidneys, and parathyroids. The exact prevalence of HDR syndrome is unknown, but less than 200 cases have been described. The disease has variable expressivity even within the same family. Making a diagnosis can be challenging, more so in individuals with no laboratory abnormalities. Herein we describe a father-daughter dyad with HDR syndrome with variable disease expression.

Case Description: A 7-year-old female with history of congenital deafness, multicystic dysplastic kidney, reflux nephropathy, and multiple urinary tract infections underwent genetic testing. Exome sequencing revealed a heterozygous missense variant in *GATA-3*, a threonine to arginine substitution (c.1058G>C, p.Arg353Thr). The missense variant was ultrarare, predicted pathogenic, and classified as likely pathogenic. Laboratory evaluation demonstrated hypoparathyroidism with hypocalcemia and hyperphosphatemia, fulfilling all criteria for HDR syndrome. Calcium levels normalized on calcium and calcitriol supplementation. Cascade screening revealed that her father carried the same genetic variant. Father's history was pertinent for sensorineural hearing loss diagnosed at 2 years of age with normal renal function, serum calcium, and PTH.

Discussion: Hypoparathyroidism is the most specific symptom of HDR syndrome, absent in 5-7% of affected patients, whereas sensorineural hearing loss is present in 96% of affected patients. Kidney manifestations are variable and may include aplasia, hypoplasia, dysplasia, cysts, vesicoureteral reflux, hematuria, and/or proteinuria. The missense variant described in our patient has not been previously reported, although an alternate amino acid change at the same residue has been reported with HDR syndrome. As the father had isolated deafness, he remained undiagnosed for almost 25 years, until the identification of HDR syndrome in his daughter. Screening family members is important for recognition and treatment of hypoparathyroidism and of renal disease as patients are at risk of symptomatic hypocalcemia and progressive kidney disease.

PO1286

Assessing Genomic Needs

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Background: Interventions must address nephrologists' knowledge gaps, perceived needs and willingness to utilize genomic data to guide more personalized patient care.

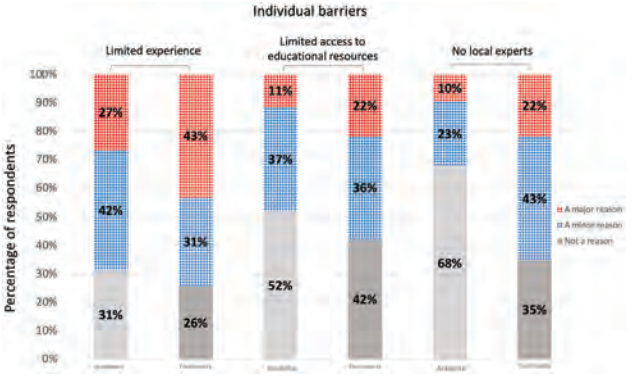
Methods: U.S. Boarded nephrologists were invited to complete an anonymous electronic needs assessment survey on genomic implementation that incorporated multiple themes e.g., objective knowledge, attitudes perceived barriers. Its design was informed by a comprehensive literature review and adapted published tools. Descriptive statistics were used to summarize demographics and baseline characteristics.

Results: Between January-May 2021, 319 complete surveys were eligible for analysis by nephrologists across 47 U.S. States, (86% adult vs. 14% pediatric), with 34% community-based (vs. 66% academic) including 36% who perform transplant evaluations and 75% with prior experience ordering genetic testing; 77% responded that genetic test results have meaningful implications for a patient's care ≤ 50% of cases. Community nephrologists were more likely to cite limited experience, educational resources and access to experts as perceived barriers to implementation of genomics compared to those in academic practice.

Conclusions: Our findings highlight variable levels of experience and comfort using genomics and can inform the design of tailored interventions that address nephrologists' specific needs, including education, workflow and clinical-decision support tools. Together, such tools can promote wider utilization of genomic resources and empower nephrologists to use genomic data.

Funding: Other NIH Support - This publication was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number KL2TR001874, Private Foundation Support

n (col %)		Overall (*n*=319)
Cohort characteristics		
Age group	25-44 years old	149 (37%)
	45-74 years old	161 (50%)
	75 years or older	9 (3%)
Sex	Female	107 (34%)
Race	White	176 (55%)
	Asian	112 (35%)
	Other/Prefer not to answer	41 (13%)
Ethnicity	Hispanic/Latino	29 (9%)
Clinical Role	Adult nephrologist	276 (86%)
	Pediatric nephrologist	43 (14%)
Years in nephrology practice, excluding training	≤ 15 years	199 (62%)
	≥ 16 years	120 (38%)
Practice location	South	110 (35%)
	North-East	102 (32%)
	Mid-West	56 (18%)
	West	38 (12%)
	Hawaii/Alaska	13 (4%)
	Missing	7 (2%)
Practice setting	Academic or Academic-affiliated (including Veterans Affairs)	210 (66%)
	Community-Based	109 (34%)
How are most patients insured?	Government-sponsored insurance	219 (69%)
	Private insurance	49 (15%)
	Other/Uninsured/self-pay/Unsure	51 (16%)
Participate in kidney transplant evaluations		115 (36%)
Prior experience ordering genetic testing		241 (75%)
How often do you think genetic test results have meaningful implications for a patient's care?		
	Never	0
	Rarely (in less than 10% of cases)	58 (18%)
	Occasionally (in about 30% of cases)	99 (31%)
	Sometimes (in about 50% of cases)	90 (28%)
	Frequently (in about 70% of cases)	54 (17%)
	Usually (in about 90% of cases)	13 (4%)
	Every time	5 (2%)
How often are you involved in returning genetic test results to patients?		
	Never/Almost never	140 (44%)
	Occasionally/Sometimes	71 (22%)
	Almost every time/Every time	108 (34%)
Participated in genomic education within last 2 years		119 (37%)
Objective knowledge	Total score: mean (± SD) on a scale of 0 to 8	5.65 (± 1.17)
Perceived barriers to implementation	Total barrier score: mean (± SD) on a scale of 0 to 22	7.60 (± 4.30)
Which workflow do you prefer? (*n*=317)	Nephrologist refers patient to a genomic professional who orders the test and returns the results	146 (46%)
	Nephrologist orders the genetic testing and returns the results	102 (32%)
	Other	69 (22%)



PO1287

Pediatric Nephrologists' Perspectives on Genetic Testing and Return of Results to Children

Hilda E. Fernandez, Marissa Lipton, Olivia Balderes, Hila Milo Rasouly, Fangming Lin, Maddalena Marasa, Ali G. Gharavi, Maya Sabatello. *Columbia University, New York, NY.*

Background: Pediatric (ped) nephrologists care for children with genetic causes of chronic kidney disease (CKD). While genetic testing (GT) is now more accessible in nephrology, little is known about the utility, clinical application, and relevance of GT in determining underlying CKD or other actionable secondary genetic findings for ped nephrology patients. We explored ped nephrologists' views regarding GT in clinical and research settings.

Methods: An online 30-item survey was developed and distributed via professional listservs. Inclusion criteria required self-identification as a U.S. licensed nephrologist. Data collection was from 1//22/21-5/4/202 and analyzed by STATA 15.1. Descriptive statistics are reported.

Results: 85 ped nephrologists completed the survey. Respondents range in yrs in practice (35% 6-15 yrs, 21% 16-25 yrs, 28% > 25 yrs), and 75% practiced in a university hospital. Most had referred > 20 patients for GT (61%). GT was considered clinically important for disease diagnosis (92%), understanding (85%), prognosis (86%), treatment (84%), family counseling (88%), and kidney transplant planning (93%). 68% report they have reliable information for care of patient with genetic results. Top 3 challenges to GT were interpretation of results, selection of test, and ordering test. 86% identified fitting GT into practice as a challenge, and 61% report offering counseling with a genetic expert after return of genetic results. 53% felt patients could not afford GT. Most indicated the importance of having clear guidelines for GT (84%). Majority (70%) would recommend GT for family members, especially in the presence of a tailored lab report (91%). Most

are involved in the return of results in their own practice (60%). Regarding the return of research-based results, most thought diagnostic (92%) and actionable secondary findings (75%) should be returned.

Conclusions: Ped nephrologists report on the importance of GT in CKD. They also report on their personal challenges with GT and structural barriers to the utilization of GT.

Funding: NIDDK Support

PO1288

Attitudes and Perceptions of APOL1 Genetic Testing in Black Patients with Hypertension: A Pilot Study

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Background: A portion of the chronic kidney disease risk in Black persons appears due to polymorphisms in the gene encoding apolipoprotein L1 (*APOL1*). While applications of *APOL1* genotyping for prognostication (e.g. in evaluation of organ donors) are emerging, the interest of Black patients in *APOL1* genotyping and implications for individual kidney risk management are not well defined.

Methods: In this pilot study, we offered *APOL1* genetic testing and assessed attitudes and concerns related to *APOL1* testing and kidney risk management among Black persons seen in the Hypertension & Nephrology clinics at one urban, Midwestern center.

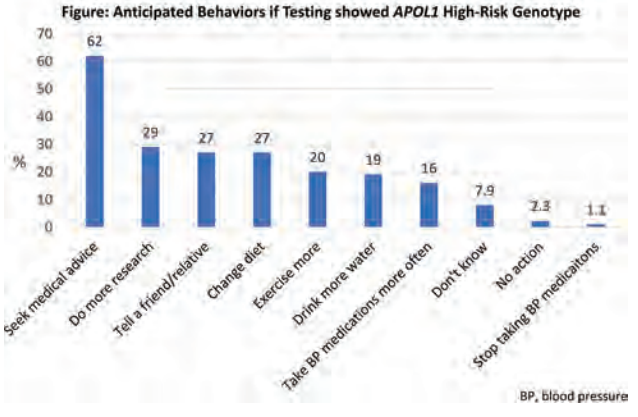
Results: Among 110 participants with genotyping results to date, 56% were women, mean age was 58 years, 72% were obese, and a mean of 3 antihypertensive agents were used (**Table**). 13% had 2 *APOL1* renal risk variants (high-risk genotypes), and 42% had 1 risk variant. At baseline, most participants (86%) reported that they were concerned about kidney disease, 90% thought it was a good idea to be tested for genes that may impact kidney disease, 82% would want *APOL1* testing for their children, and only 26% expected to feel upset if they were *APOL1* high risk. Most participants reported that knowledge of a high-risk *APOL1* genotype would lead to changes in health-related behaviors (**Figure**).

Conclusions: Black patients at a Midwestern medical center were receptive towards *APOL1* genetic testing and believed that testing would motivate changes in health-related behaviors. Ongoing research is needed to determine optimal patient-centered use of this emerging risk assessment tool.

Funding: Private Foundation Support

Table: Baseline Characteristics of Study Cohort

	All (n=110)	Low-risk *APOL1* (n=95)	High-risk *APOL1* (n=15)
Female, %	56 %	56 %	50 %
Age, years, mean (SD)	58 (12)	58 (12)	58 (14)
High school graduate, %	76 %	78 %	67 %
Annual family income, %			
< $15,000	38 %	38 %	42 %
15,000 - $30,000	11 %	11 %	8 %
$30,000 - $45,000	12 %	11 %	17 %
≥ $45,000	19 %	19 %	25 %
Obese (BMI ≥30.0 kg/m²), %	72 %	70 %	83 %
Systolic blood pressure, mm Hg, mean (SD)	146 (24)	146 (22)	138 (29)
Serum creatinine, mg/dl, mean (SD)	2.1 (1.4)	2.1 (1.4)	2.1 (1.4)
eGFR, median [IQR], ml/min/1.73	43 [28-63]	43 [28-63]	47 [27-74]
Urine albumin/creatinine ratio, mg/g, median [IQR]	89 [10-661]	93 [18-758]	95 [7-315]
Antihypertensive agents, %			
ACEi/ARB	67 %	71 %	50 %
Beta blocker	51 %	57 %	75 %
Calcium channel blocker	64 %	66 %	58 %
Diuretic	54 %	53 %	67 %
Vasodilator	18 %	18 %	17 %
Number of antihypertensive agents, mean (SD)	3 (1)	3 (1)	3(1)



(A) Cohort characteristics and **(B)** Anticipated Behaviors if Testing showed *APOL1* High-Risk Genotype

PO1289

Utility of Genetic Testing in Informing Management of Patients with Kidney Disease

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Background: Early identification of monogenic causes of CKD through genetic testing can improve disease treatment, inform management and improve outcomes. Genetic testing can also be useful for families with a history of CKD to plan for the future, including appropriate identification of organ donors. Here we describe the use of genetic testing, with RenasightTM, an NGS-based >380 gene panel for kidney disease, to inform treatment for patients being treated for kidney abnormalities.

Methods: We performed a retrospective analysis of genetic test results using Renasight™ (NGS-based>380 broad kidney gene panel) at a large academic center over an 18-month period. After signed informed consent, broad genetic testing was performed on blood or saliva samples from 31 patients. Genetic testing results were then related to alterations in the management of treatment of these patients.

Results: In this cohort, 41.9% (13/31) were female with an average age 51 years. The most common demographic groups were African American and Caucasian (6 patients [19.4%], each). Nineteen patients (61.3%) underwent Renasight testing due to a CKD diagnosis, 5 (16.1%) due to nephritis/nephritic syndrome, 3 (9.7%) due to proteinuria/nephrotic syndrome, 1 (3.2%) due to thrombotic microangiopathy, 1 (3.2%) due to phosphorus metabolism disorder, and 1 (3.2%) due to hemochromatosis. Positive results were identified in 12.9% (4/31) of the patients in the *COL11A1, COL4A4,* and *APOL1* genes. Genetic testing results led to changes in management for 35.4% (11/31) of patients, confirmed diagnoses for 22.6% (7/31), provided additional diagnoses for 41.93% (13/31), and prompted family testing for 22.6% (7/31). For 4 patients with positive findings, test results impacted treatment management: 1 had transplant management impacted, 1 underwent biopsy to confirm Alport Syndrome, 1 had FSGS diagnosis confirmed and 1 underwent biopsy to confirm FSGS and initiated dialysis. Additionally, negative results led to alterations in management for 48.4% (15/31) of patients.

Conclusions: In this cohort at an academic practice, genetic testing informed nephrologists' management of their patients in multiple capacities. Negative results can rule out genetic causes of disease, and carriers and variants of uncertain significance (VUS) can inform family planning decisions and enable testing in family members.

PO1290

Early Experience with Broad-Panel Genetic Testing in Pre- and Post-Transplant Evaluation of Patients with Kidney Failure

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Background: Genetic testing plays an important role in kidney transplantation (KT). Genetic assessment during the pre-KT workup enables more accurate estimation of the risk of recurrent kidney disease and informs treatment of recurrence living-related kidney donor selection. Testing with a broad genetic panel may be beneficial for patients with advanced disease. Here we describe an academic transplant center's early experience with a >380-gene kidney disease panel using NGS, with variant confirmation via orthogonal methods.

Methods: Twenty-six pre- and post-KT patients underwent genetic testing between June 2020 and April 2021. Patients ranged in age from 28 to 67 years, with a median age of 31 years. Genetic testing results were correlated to clinical histories, including biopsy (when available), ultrasound results, presence of proteinuria and hematuria, demographic factors, family history and comorbidities. Certified genetic counselors interpreted the results and provided consultation to patients on request.

Results: Positive findings were identified in 38.5% (10/26) of patients tested, in *TTR, COL4A3, COL4A4, COL4A5, COL11A1, INF2,* and *PKD1*. Two patients with a pathogenic variant in the *TTR* gene also had 2 *APOL1* risk alleles (G1 and/or G2). Genetic findings confirmed clinical disease in 1 individual, identified a subcategory of clinical disease in 2 individuals, reclassified disease in 3 individuals, and established a molecular diagnosis in 4 individuals. In this cohort, 8 individuals received a KT, of which 6 had no pathogenic variant identified. Of those 6, two had biopsy proven glomerular disease that recurred after early KT, implicating a non-inherited cause of renal disease. Identification of positive pathogenic variants in 75% (3/4) of patients evaluated for a living related donor transplantation, prompted evaluation of the intended donors.

Conclusions: Identification of patients awaiting KT who are at increased risk of a monogenic disease can result in a high yield via a broad-panel testing approach. The implications of a genetic diagnosis in this cohort are multifaceted, with potential to impact care and identify family members who may be at risk for kidney failure, and to enable early diagnosis and intervention.

PO1291

Early Experience with Broad-Panel NGS Testing for Kidney Disease in a Community Nephrology Setting

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Background: Despite the increasing awareness of the value of incorporating genetic testing, its adoption in community nephrology settings is limited. Genetic testing can guide prognostication, targeted treatments, referral to specialists for extra-renal features, and identification of at-risk relatives. For individuals with kidney failure, additional testing can help assess the risk of recurrent kidney disease after transplant and evaluation of suitable living related kidney donors. Broad-panel testing can provide benefits over narrow panels based on clinical presentation.

Methods: Thirty-one patients with kidney disease completed genetic testing with the Renasight™ test (NGS-based >380-gene kidney disease panel) between October 2020 and April 2021. Median age of patients was 49 years (range: 28-78 years). Genetic testing results were correlated to clinical histories, demographic factors, family history (when available) and comorbidities. Certified genetic counselors interpreted the results and provided consultation to patients on request.

Results: Positive findings were identified in 22.6% (7/31) of patients tested in the *APOL1, PKD1, SLC2A9, COL4A4,* and *PKD2* genes (Table 1). Testing resulted in implications for prognosis in 85.7% (6/7) of patients and in changes in clinical management for 28.6% (2/7) of patients. Homozygosity or compound heterozygosity for the *APOL1* high risk alleles G1 and G2 was identified in 9.7% (3/31) of patients and were found primarily in African American patients.

Conclusions: In the community nephrology setting, the utility of genetic testing as part of the diagnostic workup is multifaceted. As compared to selection of a narrow panel based on clinical features, use of a broad panel that includes reporting of the *APOL1* high risk alleles has the additional benefit of identifying genetic causes of kidney disease with ambiguous or non-specific clinical findings.

Findings from Broad Panel Genetic Testing in Patients with Kidney Disease

Genes (# patients)	Associated Genetic Condition	Inheritance Pattern*
APOL1 (3)	Susceptibility to End-Stage Renal Disease & Focal Segmental Glomerulosclerosis 4	Complex
COL4A4 (1)	Alport Syndrome, COL4A4-Related	AD & AR
PKD1 (1)	Polycystic Kidney Disease 1	AD
PKD2 (1)	Polycystic Kidney Disease 2	AD
SLC2A9 (1)	Renal Hypouricemia 2	AD & AR

*Inheritance patterns: autosomal dominant (AD); autosomal recessive (AR); X-linked (XL)

PO1292

KIDNEYCODE: A Genetic Testing Program for Patients with CKD

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Background: Knowledge about the genetic causes of chronic kidney disease (CKD) is one of the key gaps in global kidney research. Recent International Society of Nephrology recommendations encourage the adoption of genetic testing to provide precision medicine based on individual risk. A recent whole-exome sequencing study showed that genetic inheritance may be responsible for up to 10% of CKD diagnoses in adults, many of which may be previously undiagnosed or mis-diagnosed. Continued advances in DNA sequencing technology have made genetic testing applicable to routine clinical diagnoses.

Methods: K**ID**NEYCODE offers no-charge genetic testing for three rare forms of CKD: Alport syndrome (AS), focal segmental glomerulosclerosis (FSGS), and 2 forms of polycystic kidney disease: autosomal dominant polycystic kidney disease (ADPKD) due to *PKD2* mutations and autosomal recessive polycystic kidney disease. Invitae's renal disease panel includes 18 genes (*ACTN4, ANLN, APOL1, CD2AP, COL4A3, COL4A4, COL4A5, CRB2, HNF1A, INF2, LMX1B, MYO1E, NPHS1, NPHS2, PAX2, PKD2, PKHD1,* and *TRPC6).* Patients in the US with eGFR ≤ 90 mL/min/1.73m^2 plus hematuria or a family history of CKD, or with a known or suspected diagnosis of AS or FSGS are eligible for testing. Family members of those with suspected or known AS or FSGS are also eligible. All participants have access to genetic counseling follow-up at no additional charge.

Results: To date, the K**ID**NEYCODE program has results from 1389 genetic tests. Genetic variants were reported in 845 patients. Of those, 574 patients had 613 variants in *COL4A3, 4, or 5* genes (403 Pathogenic/Likely Pathogenic (P/LP), 210 Variants of Uncertain Significance (VUS)), 284 patients had 302 variants in genes associated with FSGS (55 P/LP, 247 VUS), 112 patients had 115 variants in *PKHD1* (15 P/LP, 100 VUS), and 22 patients had a variant in *PKD2* (7 P/LP, 15 VUS), and 75 patients had a VUS in *APOL1*.

Conclusions: Results from the K**ID**NEYCODE genetic testing program demonstrate that combining genetic testing with clinical presentation and medical history can improve accuracy of diagnosis in patients with hereditary CKD.

Funding: Commercial Support - Reata Pharmaceuticals

PO1293

The Emerging Role of Whole-Genome Investigation to Identify Undetected Nephropathies: The HIDDEN Study

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Background: 5% of Australian and New Zealand patients commencing kidney replacement therapy have an uncertain kidney disease aetiology. New approaches and tools are required to resolve such diagnostic odysseys. WGS is an emerging diagnostic technology whose role in this setting is unclear. We sought to determine the diagnostic yield of clinical whole genome sequencing (WGS) in individuals with unexplained end stage kidney disease (ESKD).

Methods: Adult and paediatric patients reaching Chronic Kidney Disease Stage 5 before 51 years of age without an identified aetiology were prospectively recruited through an Australian national network of 18 clinics. Eligibility was determined by a national clinical committee based on pre-specified criteria. Clinically-accredited WGS analysis was undertaken with a curated "KidneyOme" virtual panel of genes associated with Mendelian kidney disorders. A genomic diagnosis constituted a KidneyOme result of pathogenic or likely pathogenic variant/s of appropriate zygosity.

Results: 168 individuals were referred (2018-2021) of whom 147 were approved and 104 consented. Of these, 40 (38.5%) were female and median age was 43yrs; 41 (39.4%) reached ESKD before 30yrs and 63 (60.6%) had undergone native kidney biopsy. Of 50 results returned to date, 7 (14%) were diagnostic, including both autosomal dominant (4/7) and recessive (3/7) inheritance patterns with 6/7 having a family history of CKD. A further 14/50 had variants of uncertain significance. One diagnosis was due to a copy number variation. The KidneyOme virtual panel curation of 384 genes is publicly available in PanelApp-Australia.

Conclusions: One in seven patients with ESKD of uncertain aetiology had an undetected underlying monogenic cause for their kidney disease. Application of KidneyOme with WGS has diagnostic utility and should be considered in younger patients with unexplained renal failure.

Funding: Government Support - Non-U.S.

PO1294

The Utility of an Inherited Kidney Disease Clinic Employing a Broad Range of Genomic Testing Platforms: Experience of the Irish Kidney Gene Project

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Background: Inherited kidney diseases (IKD) are increasingly identified in adult patients. Here we demonstrate the diagnostic and clinical impact of evaluating patients with potential IKD in a dedicated IKD clinic (IKDC) utilising various genomic testing technologies (whole-exome sequencing, comprehensive gene-panel, and dedicated *MUC-1* sequencing) and immunostaining.

Methods: We undertook a prospective cohort study of adult patients referred to an academic medical centre with suspected monogenic cause as part of the Irish Kidney Gene Project (IKGP), between 2014 and 2020. Patients with chronic kidney disease (CKD) who had either a positive family history, extrarenal features, or had CKD of "unknown cause" (uCKD) were recruited from various centres across Ireland. We attempted to identify disease-causing variants and to assess the impact of the IKDC from diagnostic and clinical perspectives.

Results: During this period, genetic testing was performed for 677 adults (n= 501 families). The median age was 53 years (range, 18-93 years) and 73.9% participants had reported a family history of renal disease. We achieved a molecular diagnostic rate of 56.7 % (384/677). Among the identified disease-causing variants, PKD was the largest cohort (n= 183, 47.8% for *PKD1* and *PKD2),* while mutations in three other causative genes were most prevalent among the remaining identified 42 genes encompassing several Mendelian disorders; *MUC-1* (*n*=31, 8.1%); *COL4A5* (n=30, 7.8%); *UMOD* (*n*= 12, 3.3%). In the remaining 167 disease-causing variants, excluding PKD, the clinical diagnosis was confirmed in 60.5% and 18% of cases were reclassified. A molecular diagnosis was established in 27 (36.5%) patients with uCKD, implying the end of their diagnostic odyssey. Clinically, a diagnostic kidney biopsy was unnecessary in 13 (7.7%) patients based on the genomic testing, 80 (47.3%) had their treatment plan altered and further 76 (45%) patients had appropriate cascade testing.

Conclusions: The IKDC is a valuable resource and the implementation of a broad range of diagnostic platforms has a direct clinical and therapeutic impact on treatment of patients with CKD.

PO1295

Characterization of Patients with Alport Syndrome in the United States: A Retrospective Analysis of Medical Claims

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Background: Alport syndrome (AS) is a rare, hereditary genetic condition that often results in chronic kidney disease and may lead to early onset of end-stage kidney disease. The prevalence estimate in the literature is around 30,000-60,000 in the US. However, there are challenges with AS diagnosis (i.e. underdiagnosis and misdiagnosis), hence real-world patient population with AS diagnosis can be less than the prevalence estimates. This study is a retrospective analysis of medical insurance claims aimed to get a real-world estimate of the number of patients with a formal diagnosis of AS in the US, their disease characteristics, and treatment patterns.

Methods: A retrospective, observational cohort analysis was conducted, that leveraged DRG/Clarivate medical claims database, that integrates multi-payer and multi-plan data and covers >220 million annual patients in the US. Patients with at least one ICD-10 code (Q87.81) designated for AS in their medical history between October 2015 to September 2020 were considered diagnosed AS cases. Characteristics of patients and prescription data were analyzed descriptively. Patient interactions with health care professionals (HCP) within the last 24 months of the study window (i.e. October 2018 – September 2020) were used to determine the primary HCP responsible for patient management.

Results: The analysis identified total of 10,387 patients with at least one AS diagnosis code. Of the 42% of the population for whom chronic kidney disease (CKD) stage data were available, 44% had advanced CKD (IV & V). Adult or pediatric nephrologists were the primary HCPs for 59% of patients. Based on the prescription data, 21.6% (2,244 patients) were prescribed ACEs/ARBs, and 10.6% (1,101 patients) were prescribed CYP3A4 inhibitors.

Conclusions: The number of patients our study identified with AS diagnosis is lower than the commonly cited prevalence estimates in the US. The discrepancy can be explained by the fact that the database used covers a majority of but not the whole US population, and our study relies on real-world diagnoses.

Funding: Commercial Support - Reata Pharmaceuticals

AS Population (n)	CKD Stage (%)*				
	CKD I	CKD II	CKD III	CKD IV	CKD V
10,387	13%	11%	32%	17%	27%

* Staging data were available for 42% (4,404 pts) of the diagnosed population.

PO1296

Healthcare Resource Utilization by Patients with Alport Syndrome in the United States: A Retrospective Claims Analysis

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Background: Alport syndrome (AS) is a rare and serious inherited form of chronic kidney disease (CKD) affecting as many as 60,000 persons in the US. In severe cases, patients develop end-stage kidney disease (ESKD) in their 20's. The health and economic burden associated with AS has not been well- characterized in the literature. This study aims to address this evidence gap.

Methods: A retrospective claims analysis (IBM MarketScan® Commercial Database) was conducted to assess the healthcare resource utilization (HCRU) by patients with AS in the US. Patients enrolled in a health plan for a minimum of six continuous months with at least 1 inpatient or 2 outpatient claims with the AS-specific ICD-10 code were considered to have a diagnosis of AS. Patients with AS were further segmented into CKD stages, where such information was available, to understand the impact of disease progression on HCRU. Patients with AS were age- and gender- matched to a comparator group without AS diagnosis in a 1:5 proportion. The analysis included commercial (medical and pharmacy) claims from 2015 to 2019.

Results: 851 patients with AS were identified, of which 518 also had a CKD diagnosis. The mean age was 33.3 years and 51% were males. 16.2% of patients were < 18 years old. Patients with AS required more healthcare services than the matched comparator group. 19.2% of patients with AS and CKD had at least 1 inpatient admission over the course of 6 months, versus 2.1% in the matched cohort; 100% had an outpatient or office visit, versus 61% in the matched cohort; and 26.7% had at least one emergency department visit, versus 6.6% in the matched cohort. The rate of HCRU increased with the increasing CKD stage, the highest utilization being observed in patients with advanced CKD. Approximately 25% of patients with AS were prescribed RAASi's, which is a commonly used treatment in eligible patients with AS.

Conclusions: Patients with AS were observed to utilize inpatient, outpatient, and emergency department services at higher rates than the comparator group, with high utilization largely driven by late-stage CKD. Consequently, delaying or preventing kidney disease may substantially reduce healthcare expenditures among patients with AS, particularly among patients with ESKD.

Funding: Commercial Support - Reata Pharmaceuticals Inc

PO1297

Utilization of Broad-Panel Genetic Testing for Collagen Disorders of the Basement Membrane Disorders in Patients Requiring Kidney Transplantation

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Background: Patients with advanced chronic kidney disease (CKD) are often misdiagnosed. Etiology of end-stage kidney disease (ESKD) significantly impacts the selection of candidates and donors for kidney transplant (KT), and post-KT management. Identification of a genetic etiology can reclassify disease and alter KT planning. Collagen disorders such as Alport syndrome present with heterogeneous phenotypes. However, a recently proposed classification system incorporates genetic variants into the diagnosis of this disease.

Methods: Twenty-two pre- and post-KT patients with a median age of 33 years (range: 26-67 years), completed genetic testing with Renasight™ (a NGS-based >380-gene kidney panel), between June 2020 and April 2021. Test results related to *COL4A* were correlated to clinical histories, including biopsy (when available), ultrasound results, presence of proteinuria and hematuria, demographic factors, family history and comorbidities. Certified genetic counselors interpreted the results and provided consultation to patients on request.

Results: Pathogenic or likely pathogenic variants in a type IV collagen gene were identified in 18.2% (4/22) of patients. All four patients had progressed to ESKD at the time of testing. One patient, with a variant in *COL4A3*, had a right nephrectomy and subsequently developed nephrotic range proteinuria. The second patient, with a variant in *COL4A4*, had genetic testing after a living related KT; the donor was subsequently referred for genetic counseling. The third and fourth individuals, brothers with a family history of CKD, for which the same familial *COL4A5* variant was identified, were both carriers of the *APOL1* G1 risk allele. One brother had biopsy-proven FSGS and did not respond to steroids.

Conclusions: Broad panel testing enables the identification of monogenic causes of CKD that can impact the selection of KT candidates and post-KT management. In this study, molecular diagnosis and genetic subtyping of type IV collagen disorders allowed providers to counsel patients on risk of disease recurrence and donor screening in potential living related donors. KT recipients with causal *COL4A3/4/5* variants have a low risk of recurrence in the allograft and will likely not require extensive therapy during after transplant.

PO1298

Genotype-Phenotype Analyses in Korean X-Linked Alport Syndrome: A Multicenter Study

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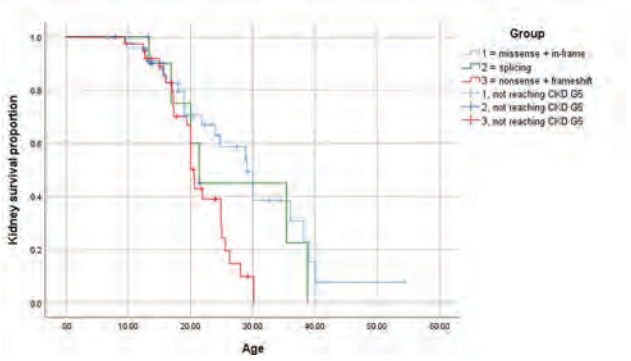
Background: X-linked (XL) inheritance, caused by *COL4A5* mutation, is most common in Alport syndrome (AS). Many clinical studies have elucidated the correlation between genotype and phenotype in male XLAS, whereas no association has been found in female XLAS. Here, we analyzed genotype-phenotype correlation in Korean XLAS.

Methods: This multicenter, retrospective study collected XLAS cases who had been diagnosed from 1985 to Jan 2021 in 13 tertiary centers of Korea. Sanger or next-generation sequencing were conducted in clinically suspected AS patients (male:female 96:42 from 121 Korean families) for genetic confirmation. We divided the cases into three groups according to the genetic variant types: 1=missense or in-frame mutations (n=46); 2=splicing mutations (n=12); 3=frameshift or nonsense mutations (n=38). Kidney survival was compared between the groups using Kaplan-Meier method.

Results: For male XLAS, median age of presentation was 5.1 years (yrs) and onset symptoms were gross hematuria (n=24), asymptomatic urinary abnormality (n=25) or nephrotic syndrome (n=19). At last follow-up, 54 (56.3%) patients had reached CKD G5 (median age 20.0 yrs)) and renin-angiotensin system inhibitors (RASi) were used in nearly all the patients. Hearing loss (HL) was present in 50%. Kidney survival rate was significantly different (median age of group 1, 29.0 yrs; group 2, 21.4 yrs; group 3, 20.6 yrs, p=0.014). HL showed a similar trend by mutant types (group 1, 32.6%; group 2, 58.3%; group 3, 68.4%; p=0.002). Female XLAS presented at median age of 3.0 yrs and 9 (21.4%) patients were reached CKD G5 at median age of 29.2 yrs. HL was present in 14.3%. Kidney survival was not significantly correlated with variant types.

Conclusions: There were strong genotype-phenotype correlation in male Korean XLAS. Both male and female XLAS showed similar results consistent with previous papers according to mutant types, but kidney survival rate was worse for all variant types, despite the appropriate use of RASi. These data could potentially be helpful of counseling in Korean families with XLAS.

Fig 1. Kidney survival proportion according to mutant types in X-linked male patients (p=0.014)



PO1299

Sparsentan, the Dual Endothelin Angiotensin Receptor Antagonist (DEARA), Improves Kidney Function and Life Span and Protects Against Hearing Loss in Alport Mice with Developed Renal Structural Changes

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Background: In Alport syndrome (AS), endothelin type A receptor activation is an important mediator of renal and inner ear pathologies. Sparsentan (SP) administered to COL4A3 $^{-/-}$ mice (AS mice) in prevention mode delayed increases in proteinuria, renal structural changes and hearing loss (HL). Whether these effects translate into preservation of glomerular filtration rate (GFR), increased lifespan (LS) and protection from HL in mice where renal pathology has initiated is unknown.

Methods: Wild type (WT) and AS mice were gavaged daily with vehicle (WT-V or AS-V), 60 or 120 mg/kg SP (AS-SP60 or AS-SP120) starting at 4 weeks (W) of age or at 5, 6 or 7W. Baseline and 10W glomerulosclerosis (GS) were evaluated in kidney sections stained for fibronectin. GFR was measured using a transdermal device (Medibeacon) in mice treated from 4W. The auditory brainstem response (ABR) was used to assess hearing ability and sensitivity to noise at 8-8.75W in AS-V or AS-SP120 mice treated from 5W.

Results: SP begun at 4W abrogated the decline in GFR at 9W compared to AS-V mice (GFR μl/min mean ± SD; WT-V 159 ± 58 (n=6), AS-V 54.0 ± 30 (n=10), AS-SP60 148± 21 (n=6), AS-SP120 145 ± 42 (n=15); p<0.001 AS-V vs AS-SP60 or AS-SP120) and provided protection from GS in mice at 10W (P<0.01 AS-SP120 vs AS-V). For LS studies GS (mean % sclerotic glomeruli) prior to treatment in AS mice was 0 at 4W, 5.2% at 5W, 23.3% at 6W and 47.0% at 7W and SP120 extended median LS (MLS) when dosing began even in 5, 6 or 7W mice with detectable GS (MLS days; AS-V 67.5, AS-SP120 4W start 118.0, AS-SP120 5W start 89.0, AS-SP120 6W start 88.0, AS-SP120 7W start 83.0). SP120 begun at 5W improved post noise thresholds with prevention of HL at 16 (P<0.05) and 24 Hz (P<0.01) (Mean ± SD dB SPL 16 Hz; WT-V 5 ± 6.1, AS-V 23 ± 9.7, AS-SP120 11 ± 4.2).

Conclusions: SP prevents the decline in GFR in AS mice, extends LS and prevents noise-induced HL even in mice with developed renal structural changes. If these results are translated successfully into the clinic, SP may offer a novel treatment approach for reducing both renal injury and protecting hearing in AS.

Funding: Commercial Support - Travere Therapeutics

PO1300

Interim Analysis of the EAGLE Trial: An Open-Label Study to Assess the Long-Term Safety and Tolerability of Bardoxolone Methyl in Patients with Alport Syndrome

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Background: Alport syndrome is a rare genetic disease affecting up to 60,000 persons in the US.

Methods: EAGLE (NCT03749447) is an ongoing, international, multi-center, open-label, extended access trial evaluating the longer-term safety and tolerability of bardoxolone methyl (bardoxolone) in patients with Alport syndrome who completed a prior qualifying clinical trial (CARDINAL Phase 2 and 3; NCT03019185). At baseline patients were 12 to 70 years old with eGFR 30 to 90 mL/min/1.73 m^2 and UACR ≤ 3500 mg/g. Patients receive bardoxolone daily and dose is escalated up to 20 mg or 30 mg (for patients with UACR > 300 mg/g).

Results: As of data cutoff (01/18/2021), 96 patients were enrolled in the EAGLE study, including 79 patients from CARDINAL Phase 3 (placebo: n=46, Bard: n=33), and 17 patients who received Bard in CARDINAL Phase 2. Mean age was 42 years, and 8 (8%) patients were <18. At baseline, mean eGFR was 58.2 ± 21.4 mL/min/1.73 m^2 and mean UACR was 183 ± 40 mg/g. Increases in eGFR were seen in patients who previously received placebo and initiated Bard treatment in EAGLE. Patients who previously received Bard for two years in CARDINAL also continued to experience mean eGFR increases in their third year of treatment. Bard has generally been well tolerated, with no deaths or drug-related severe adverse events (SAEs) reported in EAGLE to date. No drug-related cardiac SAEs were reported and no changes in blood pressure were observed. Nearly all (94%) adverse events were mild to moderate.

Conclusions: In EAGLE, Bard increased eGFR in patients with Alport syndrome, and increases observed in CARDINAL were sustained in the third year of treatment. To date, the longer-term safety profile of Bard is similar to that observed in the CARDINAL trial.

Funding: Commercial Support - Reata Pharmaceuticals

Mean ± SD eGFR Change (mL/min/1.73 m^2)	Week 12	Week 24	Week 48
Placebo to Bard (n=46)	*n=28* 12.4 ± 11.8	*n=14* 9.3 ± 14.7	*n=8* 8.4 ± 11.5
Bard to Bard (n=50)	*n=39* 8.8 ± 15.3	*n=30* 9.9 ± 14.0	*n=19* 7.3 ± 8.8

PO1301

Integrated Analysis of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome

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Background: Alport syndrome is a rare and serious inherited form of CKD. An integrated analysis of efficacy and safety was conducted from the CARDINAL Phase 2/3 (NCT03019185) and EAGLE (NCT03749447) trials of bardoxolone methyl (Bard) in patients with Alport syndrome.

Methods: The CARDINAL Phase 2 trial was open-label and enrolled 30 patients ages 12 to 60 years with Alport syndrome, baseline eGFR values 30 to 90 mL/min/1.73 m^2 and UACR ≤ 3500 mg/g. CARDINAL Phase 3 was an international, multi-center, double-blind, placebo-controlled trial with similar eligibility criteria and randomized 157 patients. EAGLE is an ongoing, open-label, extended access trial that is enrolling patients who completed CARDINAL Phase 2/3 trials.

Results: A total of 218 patients were included in the analysis (placebo: n=80, Bard: n=138). A majority (61%) of patients were female and receiving renin-angiotensin-aldosterone system inhibitor (83%). Mean age was 40 years, and 31 (14%) patients were <18 years old. Mean baseline eGFR was 60.4 and 62.3 mL/min/1.73 m^2 and the maximum duration of exposure was 3.2 and 1.9 years for Bard and placebo groups, respectively. The Bard group had significant increases in eGFR from baseline at the last on-treatment assessment (mean±SE: 3.37±1.21 mL/min/1.73 m^2; p=0.006). Significant decreases in eGFR were seen in the placebo group (mean ± SE: -8.30±1.58 mL/min/1.73 m^2; p<0.0001), resulting in a significant difference between groups after treatment withdrawal (p=0.03 vs placebo). Consistent with prior studies, common adverse events (AE) included muscle spasms, aminotransferase increases, and hyperkalemia. Discontinuations due to AEs were uncommon (9 % of Bard and 5% of placebo groups). Across all studies, no major cardiac events were observed and no changes in blood pressure were observed.

Conclusions: Consistent with individually reported prior trials, an integrated Alport syndrome analysis set showed that Bard preserved kidney function with significant on- and off-treatment eGFR benefits and was generally well tolerated by patients.

Funding: Commercial Support - Reata Pharmaceuticals

PO1302

Novel Keap-Nrf2 Protein-Protein Interaction Inhibitor UBE-1099 Ameliorates the Severity of Experimental Alport Syndrome

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Background: Bardoxolone methyl is an electrophilic agent that induces Nrf2 activation by irreversibly and covalently binding to the cysteine residue of Keap1. Bardoxolone methyl has been shown to improve glomerular filtration rate (GFR) in clinical trials, and is attracting attention as a novel agent for chronic kidney disease. However, there is concern about long-term efficacy due to the unknown mechanism of GFR improvement and transient increase in albuminuria. Moreover, irreversible Keap1 inhibitors such as Bardoxolone methyl may covalently bind to other proteins in a non-specific manner and induce side effects due to off-target activities.

Methods: We developed a reversible Keap1 inhibitor that inhibits Keap1-Nrf2 protein-protein interaction (PPI) and evaluated its efficacy using Alport syndrome mice model (Col4a5-G5X). Development of Keap1-Nrf2 PPI inhibitor was performed by fluorescence polarization and Nqo1 induction test. The obtained novel compound UBE-1099 (30 mg/kg/day) and CDDO-Im (3, 10 mg/kg/day; rodent tolerable Bardoxolone methyl analogue) were orally administrated to Alport mice and efficacy was evaluated.

Results: UBE-1099 showed higher Nqo1 induction efficiency compared with CDDO-Im in mouse renal tissue. While CDDO-Im only improved inflammation pathology in Alport mice, UBE-1099 uniformly improved renal function (GFR and Plasma creatinine, but not albuminuria), podocyte injury, glomerulosclerosis, inflammation and fibrosis. Moreover, UBE-1099 treatment significantly prolonged the lifespan of Alport mice.

Conclusions: This study firstly revealed the efficacy of Keap1-Nrf2 PPI inhibitor for glomerulosclerosis. We will elucidate next the mechanism of renal pathology improvement, which may provide useful information for Nrf2 activators including bardoxolone methyl for clinical application.

Funding: Other NIH Support - Japan Society for Promotion of Science, Commercial Support - Pharmaceutical Research Laboratory, UBE Industries, Ltd

PO1303

Patient Global Impression of Change in Patients with Alport Syndrome in the CARDINAL Phase 3 Trial

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Background: Alport syndrome is a rare and serious inherited form of CKD affecting as many as 60,000 persons in the US with no specific therapies approved for its treatment.

Methods: An international, multicenter, double-blind, placebo-controlled, randomized Phase 3 trial (CARDINAL; NCT03019185) evaluated the safety and efficacy of bardoxolone methyl (Bard) in patients with Alport syndrome 12 to 70 years of age with baseline eGFR 30-90 mL/min/1.73 m^2 and UACR≤ 3500mg/g. As an exploratory endpoint, the trial assessed patient global impression of change (PGIC), a non-disease specific 7-point scale that asks patients to rate how much their illness has changed as very much/much/minimally improved (1, 2, and 3 pts), no change (4 pts), or minimally/much/very much worse (5, 6, and 7 pts) after 48 and 100 weeks of treatment.

Results: A total of 157 patients were randomized to Bard (n=77) or placebo (n=80). In addition to significant on-treatment and off-treatment increases in mean eGFR relative to placebo (between-group differences of 7.7 ± 2.1 [p=0.0005] at Week 100 and 4.3 ± 1.9 mL/min/1.73 m^2 [p=0.023] at Week 104, respectively), Bard improved PGIC scores relative to placebo (lower values) after 48 and 100 weeks. Categorical summaries also showed more patients randomized to bardoxolone (34%) reported their condition had improved compared to those on placebo (19%) after 100 weeks of treatment.

Conclusions: In CARDINAL, Bard significantly preserved eGFR in patients with Alport syndrome and also resulted in improvements in how patients evaluated their wellbeing.

Funding: Commercial Support - Reata Pharmaceuticals

	Placebo	Bardoxolone Methyl	Difference Between Groups
Week 48 Mean ± SE	3.76 ± 0.10	3.59 ± 0.12	-0.17 ± 0.149 (p = 0.26)
Week 100 Mean ± SE	3.90 ± 0.13	3.51 ± 0.14	-0.39 ± 0.186 (p = 0.04)

PO1304

Treatment with Antisense-Oligonucleotide or Splicing Regulating Proteins for X-Linked Alport Syndrome Cases with Deep Intronic Variant

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Background: X-linked Alport syndrome (XLAS) is a hereditary progressive renal disease caused by mutation in *COL4A5*. Some cases of XLAS are caused by deep intronic variants which cause aberrant splicing and produce cryptic exon inclusion. Preventing translation of such cryptic exon has the potential to be an effective therapy. We reported that exon skipping therapy with antisense-oligonucleotide (ASO) was very effective in the XLAS mice model with a truncating mutation. However, an ASO needs very high sequence specificity and few patients can be treated by the same ASO. Therefore, we attempted to modify the splicing pattern not only by ASO but also by proteins important for splicing regulation. U2AF65 is one of the important splicing related proteins binding to polypyrimidine tracts promoting exonization. It has been reported that overexpression of the U2AF65 promotes or suppresses exonization in some circumstances.

Methods: We identified four cases of XLAS caused by the production of the same cryptic exon inclusion (r.[384_385ins385-764_385-617]) by different deep intronic variants: three cases (c.385-756C>G, c.385-749T>A and c.385-645T>A) were ours and 1 (c.385-719G>A) was a reported variant. For these cases, we introduced ASO that could skip cryptic exon. Moreover, using *in vitro* splicing evaluation system (minigene assay), we attempted to reduce the exonization of cryptic exon by overexpression of U2AF65.

Results: We succeeded in preventing the cryptic Exon insertion by introducing ASO treatment for patient's urine derived cells. In addition, in all patients, overexpression of U2AF65 in the minigene splicing analysis system successfully reduced the cryptic exon inclusion.

Conclusions: The cryptic exonization in deep intron region by nucleotide change is often difficult to identify, but there may be more such cases. In addition to ASO treatment, splicing related proteins such as U2AF65 has a potential for the treatment splicing abnormalities with splicing modifications.

Funding: Government Support - Non-U.S.

PO1305

Small Molecule APOL1 Inhibitors Block APOL1 Pore Function and Reduce Proteinuria in an APOL1-Mediated Kidney Disease Mouse Model

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Background: Two genetic variants of *APOL1* (G1 and G2) are associated with increased risk of kidney diseases. Current treatment options for APOL1-mediated kidney diseases are limited and do not address the underlying cause of disease. Here, we report the discovery of a series of novel small molecule APOL1 inhibitors, including the clinical candidate VX-147, that block APOL1 function *in vitro* and reduce proteinuria in a transgenic mouse model of kidney disease.

Methods: Microscale thermophoresis was used to assess binding of small molecule APOL1 inhibitors to recombinant APOL1 protein. HEK293 cells overexpressing APOL1 variants were used to quantify inhibition of APOL1-mediated cell death and ion flux. In addition, activity on APOL1 biological function was assessed using a trypanosome viability assay. Finally, changes in proteinuria following APOL1 inhibitor administration were assessed using a transgenic mouse model homozygous for the APOL1 G2 variant ($G2_{Hom}$).

Results: Small molecule APOL1 inhibitors showed binding to all three forms of APOL1 (wild-type, G1 and G2 variants). In cellular assays, APOL1 inhibitors prevented APOL1-mediated HEK293 cell death and inhibited APOL1-mediated ion flux. Addition of APOL1 inhibitors to trypanosome cultures rescued the parasites from APOL1-induced killing. The potency of VX-147 was consistent across the in vitro functional assays described above (EC_{50} of approximately 2nM). Finally, administration of IFNγ in $G2_{Hom}$ mice induced APOL1 expression, resulting in elevated urine albumin-to-creatinine ratios. Oral administration of VX-147 reduced proteinuria in IFNγ-induced APOL1 $G2_{Hom}$ mice by 74.1%.

Conclusions: Novel small molecule APOL1 inhibitors, including VX-147, bind recombinant APOL1 protein and inhibit its biological function, as demonstrated by trypanosome parasite rescue. These inhibitors block APOL1 pore function, as demonstrated by reduced APOL1-induced death and APOL1-induced ion flux of tetracycline-inducible APOL1 HEK293 cells. Administration of APOL1 inhibitors reduced APOL1-dependent proteinuria in an APOL1-mediated transgenic mouse model of kidney diseases. Taken together, our results strongly suggest small molecule APOL1 inhibitors, such as VX-147, target the underlying cause of disease, and have the potential to treat APOL1-mediated kidney diseases.

PO1306

Inhibition of Endoplasmic Reticulum Stress Signaling Rescues Cytotoxicity of Human APOL1 Risk Variants in Drosophila

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Background: Renal risk variants of the *APOL1* gene are associated with severe kidney disease, putting homozygous carriers at risk. *APOL1* G1- and G2-alleles likely represent gain-of-function (GOF) mutations as human subjects with *APOL1* null alleles have been found to be without renal anomalies. A wide range of mechanisms that are frequently in conflict have been described for *APOL1*-associated nephropathies.

Methods: The genetic tool-kit in *Drosophila* allows unique *in vivo* insights into disrupted cellular homeostasis. To perform a mechanistic analysis in this model, we expressed *APOL1* control and the GOF renal risk variants in the podocyte-like *Drosophila* nephrocytes and a wing precursor tissue.

Results: *APOL1* risk variant expression entailed elevated endocytic function of garland cell nephrocytes while processing of endocytic cargo and slit diaphragm morphology remained unimpaired. All APOL1 variants located to the endoplasmic reticulum (ER) and electron microscopy revealed significantly elevated ER swelling upon expression of risk variant G2-APOL1, indicating stimulation of ER stress. We employed *Drosophila* wing precursor tissue since this epithelial model enables unique recording of relative changes side by side within the same animal to study ER stress. Overexpression of the renal risk variants G1 and G2 caused a markedly stronger upregulation of PDI and apoptosis, while expression of wildtype *APOL1* resulted in milder upregulation. As a control, ER stress was absent upon deletion of 9 aa in the BH3 domain in the G2-APOL1 construct. We further confirmed *APOL1*-dependent ER stress by detection of chaperone induction and an *Xbp1*-reporter in the wing precursor. Both, genetic and pharmacological inhibition of ER stress abrogated apoptosis identifying ER stress as the essential factor of *APOL1*-induced cytotoxicity. This represents the first rescue of *APOL1*-associated cytotoxicity *in vivo*. Direct ER stress induction in nephrocytes phenocopied *APOL1* risk variant expression, supporting that ER stress underlies the gain-of-function in nephrocytes.

Conclusions: Our data reveal ER stress as the essential consequence of *APOL1* risk variant expression *in vivo*, indicating this pathway's central role in the pathogenesis of *APOL1*-associated nephropathies.

Funding: Government Support - Non-U.S.

PO1307

A Cohort Study of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) Started on SGLT-2 Inhibitors

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Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to slow estimated glomerular filtration rate (eGFR) decline in chronic kidney disease (CKD) but have not been tested in patients with ADTKD. We performed a prospective nested cohort observational study and analyzed changes in eGFR and kidney injury marker 1 (KIM-1) in patients who were prescribed SGLT2i by their physicians.

Methods: We obtained baseline and follow-up laboratory studies at 1 week, 1 month, and 4 months after starting an SGLT2i and compared eGFR with baseline function. We also obtained information about adverse events.

Results: 12 individuals were started on SGLT2i by their physicians, with 10 on empagliflozin, 2 dapagliflozin. Table 1 shows the changes in eGFR and KIM-1. For patients with eGFR > 30, mean eGFR increased at 1 month by 3 ml/min. At four months, eGFR was 3 ml/min below baseline (-18.5% due to low baseline eGFR). For eGFR > 30, eGFR decline was 12% from baseline at one month and 8% from baseline at 4 months. Plasma KIM-1 was unchanged, but urinary KIM-1 increased by 100%. One patient stopped empagliflozin at his request after 8 weeks due to decline in eGFR of 14% from baseline. No other adverse events noted. Two patients have been treated for 6 months with stable eGFR

Conclusions: The change in eGFR after treatment with SGLT2i was consistent with prior studies of CKD. The plasma KIM-1 was unchanged, but the rise in urinary KIM-1 was very concerning. Further study is required to determine if these agents are beneficial in ADTKD. An additional 4 months of follow up will be presented at ASN.

Funding: NIDDK Support, Private Foundation Support

Changes in eGFR and KIM-1 in ADTKD Patients Taking SGLT2 Inhibitors

	Baseline	1 week	1 month	4 months
	Mean ± Standard Deviation [count]			
eGFR < 30 (ml/min/1.73m^2)	22.7±4.5 [3]	21.7±3.2 [3]	25.9±7.1 [2]	19.3±5.3 [2]
eGFR ≥ 30 (ml/min/1.73m^2)	42.2±12.1 [9]	37.7±11.2 [6]	34.9±10.5 [8]	34.7±8.6 [6]
Median Plasma KIM-1 (pg/ml)	195.72 [12]		203.74 [12]	-
Median Urine KIM-1 (pg/mg UCr)	2017.9		3395.1 [12]	-
	Percent Mean* Change from Baseline			
eGFR < 30 (ml/min/1.73m^2)	-	-4.1%	5.1%	-18.5%
eGFR ≥ 30 (ml/min/1.73m^2)	-	-5.9%	-11.6%	-7.9 %
Plasma KIM-1 (pg/ml)	-		1.1% [12]	-
Urine KIM-1 (pg/mg UCr)	-		103% [12]	-

*Mean was computed as the average change in eGFR for each individual (at time point), compared to their baseline measurement.

PO1308

A Prospective Observational Study of Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)

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Background: GFR decline in ADTKD due to UMOD or MUC1 mutations has not been well characterized. We have begun an international prospective cohort study to determine genetic and environmental factors associated with progression. We report here on early recruitment.

Methods: Patients with positive genetic testing for UMOD or MUC1 mutations prior to transplantation or starting dialysis are eligible. A baseline collection of health information, serum and urine biomarkers will be performed, with patients then followed longitudinally, with a serum creatinine measurement performed three times per year. There will be a nested cohort study of women who develop pregnancy during the study and patients started on ACE inhibition.

Results: Since March 2021, we have enrolled 57 patients in the prospective observational study, with 20 men, 35 women. The mean age of patients is 43.3 years, the mean baseline eGFR is 39.96 ml/min/1.73m^2. Table 1 shows baseline characteristics of patients enrolled in the study. No patients with CKD Stage 1 or 2 suffered from HTN, and only 39% of patients with CKD Stage 3 had HTN. Only 18% of patients were receiving ACE/ARB inhibition.

Conclusions: Despite significant CKD, there was a relatively low prevalence of HTN. Only 18% of patients were receiving ACE inhibition, indicating a potential therapeutic intervention. Please contact us if you have a patient who may be interested in participating in this prospective study (ableyer@wakehealth.edu).

Funding: NIDDK Support, Private Foundation Support

Baseline Characteristics of Enrolled ADTKD Patients

	ADTKD-*MUC1*	ADTKD-*UMOD*
n	20	37
% male	40%	35%
Mean Age (years)	46.8 ± 14.0	41.7 ± 13.9
Race (% White, Black, Other)	100%, 0, 0	97%, 0, 3%
Mean eGFR (ml/min/1.73m^2)	42.2 ± 25.6	38.8 ± 22.7
Smoking Status	0 current smokers	0 current smokers
Vegetarian Diet	0	1 (4%)
Mean Weight (lbs)	155.5 ± 21.3	175.5 ± 43.5
Systolic Blood Pressure	126.5 ± 8.6	120.4 ± 9.4
Diastolic Blood Pressure	80.1 ± 8.8	75.2 ± 10.7
Diagnosed High Blood Pressure	6 (43%)	15 (53%)
Medication Usage		
ACE Inhibitors	4 (29%)	6 (19%)
Angiotensin Receptor Blockers	2 (14%)	10 (32%)

PO1309

Vasopressin Induces Urinary Uromodulin Secretion by Activating Protein Kinase A

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Background: Urinary uromodulin, secreted by renal tubular cells, protects against urinary tract infections (UTIs) and kidney stones. In contrast, the intracellular accumulation of uromodulin is associated with hypertension and chronic kidney disease (CKD). In addition, uromodulin gene mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD-*UMOD*) via abnormal intracellular accumulation of uromodulin. However, the physiological stimuli for urinary uromodulin secretion remain largely unknown.

Methods: We investigated the acute effect of vasopressin/cAMP signaling on urinary uromodulin secretion in mice and in kidney epithelial cells stably expressing uromodulin. Additionally, we assessed the effect of vasopressin/cAMP signaling in kidney epithelial cells stably expressing mutant uromodulin, which causes ADTKD-*UMOD*.

Results: Desmopressin, a vasopressin type 2 receptor agonist, dramatically increased short-term tubular uromodulin secretion in mice. Immunofluorescence studies and ultracentrifugation-based polymerization assay suggested that desmopressin induced intraluminal polymeric filaments of uromodulin, indicating physiologically functional secretion. As a result of increased excretion, uromodulin abundance in the murine kidney was clearly reduced by desmopressin. In the cellular model, apical uromodulin secretion was increased in response to vasopressin/cAMP signaling, consistent with *in vivo* experiments. We also demonstrated that the response was dependent on cyclic AMP-dependent protein kinase (PKA) signaling pathway. We further showed that cAMP signaling induced excretion of mutant uromodulin. cAMP signaling suppressed PERK phosphorylation, which was upregulated by mutant uromodulin, implying cytoprotective effects.

Conclusions: Our work revealed vasopressin/cAMP/PKA signaling as a physiological stimulus of urinary uromodulin secretion. This finding may provide the basis for novel treatment strategies for UTIs, kidney stones, and potentially hypertension, CKD and ADTKD-*UMOD*.

Funding: Commercial Support - Kyowa Kirin Co., Ltd. Chugai Pharmaceutical Co., Ltd., Government Support - Non-U.S.

PO1310

Standardizing HNF1B-Associated Disease

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Background: Pathogenic variants in *HNF1B* are associated with a variety of inherited kidney diseases ranging from renal cysts and diabetes syndrome and CAKUT to autosomal dominant tubulointerstitial kidney disease. In addition, variable extrarenal manifestations were linked (MIM #189907). Although high throughput sequencing has advanced diagnostic variant detection, there is a lack of specific database analysis gathering both genotypic and phenotypic information from published and unpublished sources in order to establish valid genotype-phenotype correlations. By introducing a novel HNF1B database, we aim at gathering published and unpublished cases for identification of reliable variant-disease association analysis.

Methods: To standardize our own cohort and curate the clinical and genetic spectrum from the literature, we curated a list of 30 clinical features associated with HNF1B-disease based on HPO terms. Next, we developed a web-based application (available on curating. HNF1B.org) for comprehensive data input and analysis from patient histories or published literature within the time span from 1997 - 2020.

Results: We reviewed 968 individuals (152 publications) including 8.4% of prenatal cases and 45.0% of pediatric individuals (<18 years). Among *HNF1B* variants, we found 20.1% whole gene deletions (corresponding to 17q12 microdeletions), 2.3% gene duplications, 54.6% single nucleotide variants or small indels with the remainder represented by either small variants or incomplete/inaccurate descriptions. Reported phenotypes showed a vast variability with more accurate reporting in small case series or case reports. For example, renal function was not reported for 37.0% of cases while in 68.5% of cases with 17q12 microdeletion no neurodevelopmental phenotype was provided despite both phenotypes constitute hallmarks of *HNF1B*-associated disease.

Conclusions: To enhance the understanding of this multi system disorder, we will present out curation effort as an open source clinical and genetic database at HNF1B.org. Based on the literature and unpublished cohorts we will develop a recommendation for standardized reporting and selection scheme for genetic screening. Our effort exemplifies the curation efforts that are required for a better understanding of rare hereditary kidney diseases. The developed tools might serve as starting point for similar efforts.

PO1311

Treatment with 4-Phenylbutyrate Reduces Low-Molecular-Weight Proteinuria in a Clcn5 Knock-In Mouse Model for Dent Disease

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Background: Dent disease-1 (DD1) is a rare X-linked tubular disorder characterized by low-molecular-weight-proteinuria (LMWP), hypercalciuria, nephrolithiasis and nephrocalcinosis. This disease is caused by inactivating mutations in the *CLCN5* gene, which encodes the voltage-gated ClC-5 chloride/proton antiporter. ClC-5 is expressed predominantly in the kidney and participates in the acidification of proximal tubule endosomes. Currently, the treatment of DD1 is only supportive and focused in delaying disease progression. Our group has generated a C*lcn5* knock-in (KI) mouse that presents the main clinical manifestations of DD1 and carries the pathogenic mutation p.V523del, which causes partial ClC-5 retention in the endoplasmic reticulum. Here, we aimed to assess the ability of sodium 4-phenylbutyrate (4-PBA), a small chemical chaperone, to ameliorate DD1 symptoms in this mouse model.

Methods: Twelve-weeks old male *Clcn5* KI mice (n=50) and WT (n=33) littermates were divided into 2 groups, one was treated with 250 mg/kg/day of 4-PBA in drinking water, for 31 days, whereas the other group was given water without the drug for the same amount of time. Mice were placed in metabolic cages before and after treatment for 24h. Urinary β2-microglobulin and serum and urinary creatinine were measured by ELISA. Calcium and phosphate concentrations in urine were estimated using colorimetric kits. Water and food intake and 24-h urinary excretion were also measured, and mice body weights were monitored.

Results: We observed a significant reduction of β2-microglobulin urinary excretion in KI mice treated with 4-PBA compared to non-treated animals (p=0.0004). Glomerular filtration rate was also improved in treated mice (p=0.03). Urine production, urinary calcium and phosphate levels did not show differences compared with non-treated mice.

Conclusions: 4-PBA reduces LMWP in *Clcn5* KI mice, suggesting that this treatment could represent a promising therapeutic option for some DD1 patients.

Funding: Government Support - Non-U.S.

PO1312

Long-Term Efficacy of Migalastat on Renal Function and Outcomes in Patients with Fabry Disease (FD)

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Background: FD, caused by pathogenic *GLA* variants leading to functional deficiency of α-galactosidase A (α-Gal A), can eventually result in key organ damage. Preserving renal function and preventing Fabry-associated clinical events (FACEs) are important treatment goals. Approved therapies include enzyme replacement therapy (ERT) and the pharmacological chaperone migalastat. Stabilized renal function and FACE occurrence up to 30 mo have been reported in migalastat-treated adults with amenable *GLA* variants; here, we extend those analyses up to 8.6 yrs.

Methods: Integrated data from phase 3 clinical trials (FACETS, NCT00925301; ATTRACT, NCT01218659) and open-label extension studies (NCT01458119; NCT02194985) were used to evaluate the eGFR slope using linear regression in pts treated with migalastat for ≥2 yrs (n=78). Incidences of FACEs (predefined renal, cardiac, and cerebrovascular events) were assessed in all pts (N=97). Analyses were stratified by prior treatment and phenotype. Cox regression modeling was used to identify predictors of FACEs.

Results: eGFR remained stable for both ERT-naive and ERT-experienced pts who received migalastat for ≥2 yrs (median [min-max] duration: 5.9 [2.0-8.6]); the mean (SD) annualized rates of change in eGFR (mL/min/1.73 m^2) were –1.6 (3.1) and –1.6 (3.6), respectively. In male pts with the classic phenotype (classification based on multiorgan involvement and [ERT-naive only] α-Gal A level at baseline; n=25), mean (SD) rate of change in eGFR was –2.2 (4.4) mL/min/1.73 m^2. eGFR was also analyzed by baseline renal function and proteinuria levels. In all migalastat-treated pts (median duration: 5.1 yrs), the incidence of composite FACEs (per 1000 patient-years) was 48.3 (65.3 for

classic males) and incidence of renal events was 4.4 (14.5 for classic males). Lower baseline eGFR was a predictor of FACEs in classic males vs all others; however, rate of renal events was too low to analyze predictors.

Conclusions: Results demonstrate long-term efficacy of migalastat in stabilizing eGFR in pts with FD, including male pts with the classic phenotype. FACE incidence in pts receiving migalastat compared favorably to historic reports of ERT. The inverse correlation of eGFR with FACEs suggests the importance of early diagnosis and treatment to preserve renal function.

Funding: Commercial Support - Amicus Therapeutics, Inc.

PO1313

Twenty-Year Renal Prognosis in Patients with Fabry Disease Who Underwent Enzyme Replacement Therapy

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Background: The relationship between long-term renal prognosis and renal histopathology after enzyme replacement therapy (ERT) for Fabry disease (FD) has not been fully investigated.

Methods: Nine patients with FD from our hospital who had participated in a Japanese phase 2 study (August 2000–May 2001) on agalsidase β were eligible for this case-control study. They underwent repeated renal biopsy (before and six months after agalsidase β treatment), and the intra-renal amount of globotriaosylceramide (GL3) was measured at the same time points. Clinicopathological features were compared between the groups with or without developing end-stage kidney disease (ESKD).

Results: Seven patients were included in this study, because two were lost to follow-up. All were males, with a median age at the start of treatment of 30 [quartile 24.5, 31.5] years, and median serum creatinine level (s-Cr) of 1.1 [1.0, 1.2] mg/dL. The podocyte score (International Study Group of Fabry Nephropathy score system) improved in all patients after ERT from that evaluated before ERT. Interstitial fibrosis/tubular atrophy (IF/TA) worsened in three patients. The proportion of foamed tubules improved in five patients. Intra-renal accumulation of GL3 decreased six months after ERT in all patients. All patients continued to receive agalsidase β or agalsidase α after the phase II study. While four patients developed ESKD (median 6.7 years), three patients showed no exacerbation of renal function. The s-Cr level, age, and urinary protein excretion at the start of ERT were higher in the ESKD group. The decrease in the intra-renal accumulation of GL3 was not significantly different between the two groups, but the proportion of foamed tubules in the first biopsy and the degree of IF/TA in the second biopsy were higher in the ESKD group than in the non-ESKD group.

Conclusions: This study suggests that tubulointerstitial injury has a crucial role in the determination of renal prognosis and that earlier diagnosis and intervention in patients with FD may improve the renal prognosis. Further studies are needed on the relationship between tubulointerstitial injury and GL3 accumulation.

PO1314

Systems Analyses of Fabry Renal Transcriptome and Its Response to Enzyme Replacement Therapy (ERT) Identifies a Cross-Validated and Drugable ERT-Resistant Module

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Background: Fabry nephropathy (FN) is a rare disorder caused by mutations in the alpha-galactosidase A gene that can, to a certain degree, be managed with enzyme replacement therapy (ERT). Via understanding the molecular basis of FN and ERT's long-term impact, we aim at providing a framework allowing selection of biomarkers and drug-targets.

Methods: Obtained from controls and two independent FN-cohorts, mRNA-isolates from archival kidney biopsies taken prior and up to 10 years of ERT, were subjected to RNAseq. Combining pathway-centered analyses with network-science allowed computation of transcriptional landscapes from glomeruli, proximal tubuli, distal tubuli and arteries and integration with existing proteome, interactome and drug::target data.

Results: Comparing transcriptional landscapes per cohort revealed high inter-cohort heterogeneity. Especially, with timely treatment initiation, FN seemed well controlled via ERT. Pathways consistently altered in both FN-cohorts pre-ERT vs. N_CTRLs were limited to glomeruli and arteries and commonly pertained to the same biological themes. While keratinization-related processes in glomeruli were sensitive to ERT, a majority of alterations, such as transporter activity and responses to stimuli, remained dysregulated or remerged despite of ERT. Inferring an ERT-resistant genetic module on this basis identified targets suitable for drug repurposing.

Conclusions: Kidney compartments' transcriptional landscapes comprehensively reflected differences in FN-cohort characteristics. With the exception of few key aspects, in particular concerning arteries, early ERT in classical Fabry patients could lastingly revert FN kidney-compartments' molecular state to closely match N_CTRLs. Thus, we identified and cross-validated ERT-resistant modules that, when leveraged with external data, allowed estimating their suitability as biomarkers and potential targets for adjunct treatment.

Funding: Commercial Support - Shire/Takeda, Sanofi Aventis, Government Support - Non-U.S.

PO1315

Resistant Focal Segmental Glomerulosclerosis (FSGS) due to Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency: Is Early Gene Testing the Answer?

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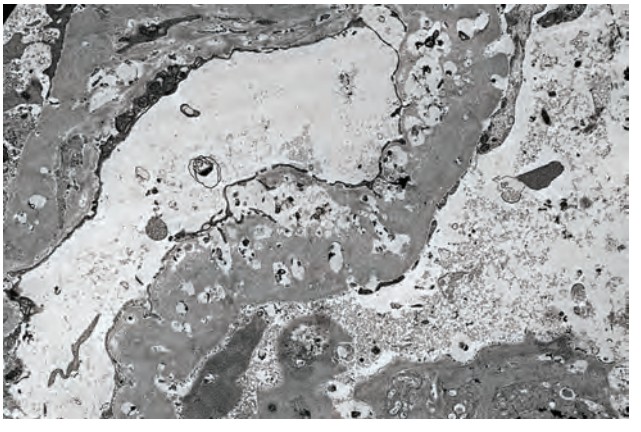
Introduction: LCAT deficiency is a rare autosomal recessive disorder due to mutations in the *LCAT* gene presenting with corneal opacities, anemia, proteinuria, reduced HDL and CKD with progression to ESKD by the 4th- 5th decade. Electron microscopy (EM) is characteristic for abundant partially electron-dense and lucent deposits in the mesangium and basement membrane. Late diagnosis is not uncommon due to its rarity and nonspecific presentations in the early stages. Here we report a case of therapy resistant FSGS later uncovered as LACT deficiency confirmed by gene tests.

Case Description: A 49-year-old male presented to genetic nephrology clinic in 2020 with a clinical diagnosis of *LCAT* deficiency. In 2007, he had presented with hematuria, proteinuria with a serum creatinine of 2.4mg/dl, Hb 11 g/dL, albumin 2.4g/dL, total cholesterol 416mg/dL, HDL 14mg/dL and urine protein of 8.9g/d. Urine microscopy showed fine granular casts and dysmorphic RBCs. Kidney biopsy revealed FSGS with moderate tubulointerstitial fibrosis. EM showed some unexplainable intramembranous and subendothelial lucencies, which were thought to be sequela of prior immune mediated membranous glomerulonephritis. Patient failed treatment with months of steroids, oral cyclophosphamide and mycophenolate. Repeat biopsy in 2010 showed worsening of the prior findings. In 2011, corneal deposits led to a suspicion of LCAT deficiency. He progressed to ESKD in 2011 and kidney transplant in 2020. Genetic testing disclosed a homozygous nonsense variant c.321C>A (p.Tyr107*) in *LCAT* gene. A thorough genetic counseling included risk for his siblings and graft recurrence.

Discussion: LCAT deficiency can present with resistant or atypical appearing FSGS. This case emphasizes the need of early genetic assessment on suspicious biopsies or therapy resistant FSGS cases to timely diagnose and avoid unnecessary immunosuppression.



PO1316

ESKD due to Primary Hyperoxaluria Type I

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Introduction: Primary hyperoxaluria type I (PHT1) is a rare autosomal recessive disease (less than 3 cases per million population). Nephrolithiasis and nephrocalcinosis lead to progressive renal impairment and subsequent oxalate deposition in various tissues. We present a case of PHT1 diagnosed late in life and ultimately requiring definitive management with liver-kidney transplant due to rapid progression to end stage kidney disease.

Case Description: 55 year old male with history of renal calculi at birth, recurrent nephrolithiasis and PHT1 was hospitalized for acute kidney injury following 2 weeks of nausea and poor intake. His admission serum creatinine (Scr) was 11 from baseline of 3.5 four months before. He was diagnosed with PHT1 eight months prior via urinary oxalate measurement and genetic testing. He was started on low oxalate diet, calcium carbonate 1000mg with meals and pyridoxine 500mg daily. Ultrasound at admission notable for

diffuse increased echogenicity and bilateral non-obstructing calculi. Initial serum oxalate level was 63.5micromol/L and 24 hour urine oxalate level was 116mg/24hrs. Scr failed to improve with intravenous fluid administration and renal replacement therapy was initiated with goal serum oxalate level of <30micromol/L. Hemodialysis was performed daily for four hours with high flux membrane. Serum oxalate levels improved to nadir of 40micromol/L. Definitive therapy with simultaneous liver-kidney transplant was ultimately pursued.

Discussion: Our patient required intensive hemodialysis while awaiting liver-kidney transplant following late diagnosis of PHT1 and development of end stage kidney disease. Early diagnosis is key to reduce morbidity and mortality. Progressive kidney impairment leads to inability to excrete the increased oxalate produced by the liver and subsequent systemic deposition of oxalate including in the kidney causing multiorgan dysfunction. Hemodialysis removes oxalate but it is difficult to consistently reduce serum oxalate levels below goal given continued production of oxalate and rebound. Early treatment options include a trial of pyridoxine, hyperhydration, low oxalate diet and novel RNA inhibitors. Patients with advanced disease often require definitive management with liver-kidney transplant. Clinicians need to have a high index of suspicion for PHT1 as patients often go undiagnosed until advanced kidney disease or end stage kidney disease has developed.

PO1317

Real-World Healthcare Utilization and Clinical Markers Preceding Dialysis in Patients with Primary Hyperoxaluria (PH) in the United States

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Background: PH is the accumulation of oxalate resulting in urolithiasis, nephrocalcinosis, chronic kidney disease (CKD), and eventually end-stage renal disease (ESRD) that usually requires dialysis. This study examined demographics, clinical characteristics, and healthcare utilization (HCU) among dialysis-treated PH patients during the time leading up to dialysis start.

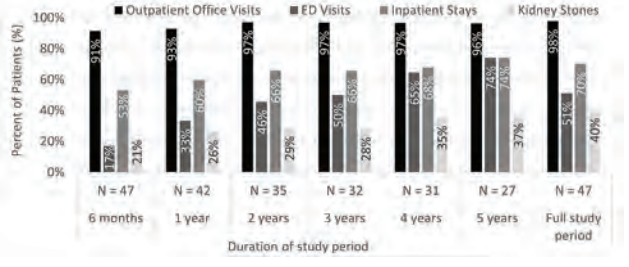
Methods: This was a retrospective study of PH patients (ICD-10: E72.53) initiating dialysis (study entry), on or after October 1, 2018, in TriNetX Dataworks USA, a federated EMR network of 60+ million de-identified patients from 44 healthcare organizations (HCOs). Patient age, sex, race, comorbidities, CKD stage, kidney stone events (KSE), and HCU were examined at least 6 months prior to dialysis, through up to 5 years.

Results: The final study cohort included 47 patients: mean age of 59 years, 53% female, and 85% white. Only 47% had a recorded diagnosis of PH prior to dialysis, and 55% had a diagnosis of ESRD. During the 6 months immediately preceding dialysis, 91% of patients had ≥1 outpatient office visit, 17% ≥1 ED visit, and 53% ≥1 inpatient stay. HCU for the full study period showed 98% of patients had ≥ 1 physician office visit, 51% ≥1 ED visit, and 70% ≥1 inpatient stay (Figure 1). Patients with recorded KSE (n= 19; 40%) had a mean of 4 events during the study period. The frequency of KSEs doubled from 1 to 2 per person per year as patients neared dialysis. In the 6 months prior to dialysis, 70% of patients had CKD of stage III or higher recorded in their EMR.

Conclusions: In this real-world study, more than one-half of patients with PH were undiagnosed prior to initiating dialysis, according to the data reviewed. In addition, high rates of costly HCU, including ED visits and inpatient stays, were observed during the same timeframe. The number of KSEs increased over the study period, which may be indicative of worsening renal function due to PH prior to dialysis.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc.

Figure 1: Resource utilization and clinical outcomes over the study period



PO1318

Association Between Longitudinal Plasma and Urine Oxalate and Time-to-Kidney Failure in Primary Hyperoxaluria Using Joint Models

Lisa E. Vaughan, John C. Lieske, Phillip Schulte. *Mayo Clinic Minnesota, Rochester, MN.*

Background: The association between plasma oxalate (POX), urine oxalate (UOX) and the risk of kidney failure (KF) in patients with the rare disease primary hyperoxaluria (PH) is challenging to study due to small sample sizes and correlations among POX, UOX, and eGFR. To develop better KF models that simultaneously account for all 3 variables we used a novel statistical approach, joint models, modeling longitudinal biomarker processes (eGFR POX, UOX) and survival process (time-to-KF) jointly, using retrospective data from the Rare Kidney Stone Consortium PH registry.

Methods: Repeated eGFR, UOX, and POX after PH diagnosis were obtained from the registry. Time-to-KF was defined as time between PH diagnosis until transplantation, dialysis or eGFR<15 mL/min/1.73m^2. A multivariate joint model was fit with longitudinal sub-models for each biomarker and a survival sub-model for KF. Longitudinal sub-models employed linear mixed effects models with biomarkers on the log scale. Joint models share information between longitudinal and survival sub-models such that eGFR, UOX, and POX were time-dependent variables in the survival sub-model, specifically using subject-specific mean biomarker values. Models were adjusted for age and sex at diagnosis. Results were compared to last observation carried forward (LOCF) analyses.

Results: A total 166 patients (mean 5 POX and 7 UOX per patient) with 60 KF events during follow up were included. With LOCF, POX positively associated with KF risk, both unadjusted and adjusted for other biomarkers (hazard ratio (HR) = 1.14 per umol/L, 95%CI = 1.07, 1.22, p<0.001), while UOX was not associated with KF after adjustment. With joint modeling, POX and KF were not significantly associated after adjustment (HR = 1.12, 95%CI = 0.99, 1.30, p=0.08), while higher UOX was associated with lower KF risk (HR = 0.30 per mmol/1.73m^2/24h, 95%CI = 0.07, 0.92, p=0.04).

Conclusions: When modeling unevenly spaced longitudinal biomarkers and their association with KF, the LOCF time-dependent model makes implausible assumptions about steady-state biomarkers between observations. Implementation of a joint modeling framework allows flexible estimation of the association, which may impact conclusions. These novel methods can be used to inform patient-specific decisions about future KF risk, and the risk-benefit of novel treatment approaches.

Funding: NIDDK Support

PO1319

Modeling the Risk of Progression to Kidney Failure in Patients with Primary Hyperoxaluria Type 1 Treated with Lumasiran Relative to a Natural History Cohort Not Treated with Lumasiran

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Background: In primary hyperoxaluria type 1 (PH1), the risk of kidney failure (KF) is positively associated with urinary oxalate (UOx) excretion. Lumasiran is an RNAi therapeutic to lower UOx levels in patients with PH1. We estimated the risk of progression to KF in patients with PH1 treated with lumasiran, relative to patients not treated with lumasiran.

Methods: A skewed-normal distribution of 24hr UOx values for patients with PH1 was simulated based on reported UOx values from the Rare Kidney Stone Consortium (RKSC) PH Registry among patients who were not in KF at diagnosis and did not receive lumasiran. Data from the ILLUMINATE-A trial of lumasiran were used to build a log-linear model of post-lumasiran treatment steady-state UOx as a function of baseline UOx. The distribution of steady-state, on-treatment UOx values for RKSC patients was then predicted by applying this model to the simulated 24hr UOx values of the RKSC cohort, considered as baseline. A risk model of KF as a function of 24hr UOx excretion, based on Kaplan-Meier curves of renal survival reported from the RKSC, was used to estimate the number of KF events/100 patients in the RKSC PH1 cohort, had all received lumasiran.

Results: The mean (SD) 24hr UOx excretion for the RKSC PH1 cohort was 2.2 (1.1) mmol/24hr/1.73m2 in the absence of lumasiran treatment and was predicted to decrease to 0.62 (0.17) mmol/24hr/1.73m2 in a model that simulated the effect of lumasiran administration (Figure 1). The predicted number of KF events/100 patients (95% CI) using the model for patients not treated with lumasiran at 10, 20 and 30 years, is 10 (4, 23), 32 (19, 50), and 42 (27, 59), respectively. In the model of lumasiran treatment, the estimated cumulative number of KF events/100 patients (95% CI) was 4 (1, 12) at 10 years and remained unchanged at 20 and 30 years.

Conclusions: This analysis predicts a long-term reduction in KF risk among PH1 patients treated with lumasiran, assuming prompt treatment at diagnosis.

Funding: Commercial Support - Alnylam Pharmaceuticals

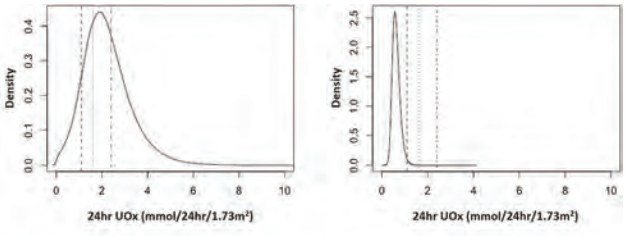

Figure 1. Simulated distribution of 24hr UOx excretion in patients from the RKSC not treated with lumasiran *(left panel)* and the predicted distribution of 24hr UOx excretion had all RKSC patients been treated with lumasiran *(right panel)*. Vertical dashed lines represent 24hr UOx excretion rates of 1.1, 1.6 and 2.4 mmol/24hr/1.73m^2.

PO1320

The Complex Landscape of Factor H and Factor I Rare Variants in Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy

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Background: Complement genetics has been extensively studied to dissect the pathophysiology of atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G) paving the way for highly tailored therapy. However, the assessment of each identified variant's contribution to disease pathogenesis remains a challenge in particular for rare variants detected in patients as well as in healthy individuals in the genome Aggregation Database (gnomAD). In this study we aimed to describe the rare variants in Factor H (CFH) and Factor I (CFI) genes identified in the French cohort of patients with aHUS and C3G.

Methods: We analyzed the distribution of the allele frequency (AF) of rare variants identified in 397 and 398 adult patients with a diagnosis of aHUS without coexisting disease and with C3G/Ig-mediated membranoproliferative glomerulonephritis (Ig-MPGN), respectively. We selected for this study variants with minor AF (MAF) below 0.1% in European healthy individuals.

Results: The frequency of patients with rare variants in CFH (108/398 vs 54/398) and CFI (33/397 vs 17/397) genes was higher in aHUS compared to C3G. A total of 148 variants were identified in CFH (n=98) and in CFI (n=50) genes. Among them, 9 were present in both diseases. We identified 43 (67%) and 20 (66%) novel variants in CFH in aHUS and C3G, respectively. Among them, 98% are pathogenic compared to 44% of the variants reported in gnomAD. The frequency of variants causing FH and FI deficiency is similar in both diseases (70% of the variants). The frequency of CFH variants identified in more than 1 patient is increased in aHUS compared to C3G (11/64 vs 2/30). We identified 12 (12/38; 31%) and 2 (2/12; 16%) novel variants in CFI in aHUS and C3G, respectively. Reported variants in CFI are more frequent in C3G than in aHUS (10/12 vs 26/38). The frequency of variants reported in gnomAD is higher in CFI (80%) compared to CFH (14%).

Conclusions: Our study indicates that novel pathogenic rare variants in complement genes is more frequent in aHUS than in C3G. However, half of the variants reported in gnamAD have a potential impact on gene function. Our results suggest that CFH variants are more damaging than CFI variants, and may contribute more significantly to the pathogenesis of both diseases, as compared to CFI.

PO1321

Phenotypic-Genotypic Relationship of Focal and Segmental Glomerulosclerosis (FSGS)

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Background: FSGS can be of primary, secondary or genetic origin. The objective of our work is to establish in which patients with a histological diagnosis of FSGS a genetic etiology should be suspected

Methods: The study included adult patients with a histological diagnosis of FSGS and with either steroid resistant nephrotic syndrome (SRNS) or proteinuria without hypoalbuminemia in which secondary FSGS was ruled out. The presence of familial kidney disease was not an inclusion criterion. The genetic study was carried out by massive sequencing techniques (NGS) of the coding and flanking regions of the candidate genes associated with glomerular diseases.

Results: Out of 108 samples received, 80 patients met the inclusion criteria. We detected FSGS-related pathogenic genetic variants in 31 (39%) patients, finding no difference between those whose indication was steroid resistance (32 %) or proteinuria with normal albumin (58%). We found 20 pathogenic variants of collagen IV in 17 (55%) patients. NPHS2 mutations were discovered in 7 (23%) patients. The remaining cases had variants affecting INF2, OCRL, HNF1B, WT2. All (3) black patients had high-risk APOL1 alleles. There were no differences between genetic and non-genetic causes in age, proteinuria, GFR, serum albumin, BMI, hypertension, diabetes, or family history. Hematuria was more prevalent among patients with genetic causes.

Conclusions: Genetic testing should be considered in FSGS patients in which a secondary cause has been excluded, to determine the patient's prognosis, treatment and perform familial screening.

Funding: Private Foundation Support

BASELINE CHRACTERISTICS

	Whole cohort n= 80	No genetic diagnoses n= 49	Pathogenic mutations n= 31	Collagen IV n=17	NEPH2 n=7	Other diagnoses n=7
Age	39 (29.3-47.2)	40 (301-47)	39 (30-48)	46 (35-51) *	31 (20-35) *	37 (19-46)
Positive family history	45.0%	46.9%	41.9%	41.2%	42.9%	42.9%
SRNS	33.8%	28.6%	31.9%	23.5%	71.4%	57.1%
eGFR CKD-EPI (ml/min)	70.8 (47.9-110)	68.6 (50-108)	73.3 (42-120)	72.5 (38-102) *	129.1 (116-145) *	62.2 (33-72)
Albuminemia (g/dl)	3.7 (2.9-4.2)	3.8 (3.0-4.2)	3.5 (2.9-4)	3.8 (3.4-4.1) *	2.7 (2.3-3.4) *	2.9 (2.6-4.2)
Proteinuria (g/d)	3.3 (1.7-5.3)	3.3 (1.9-5.0)	3.5 (1.6-6.1)	1.9 (0.3-3.8) *	6.1 (3.3-9.5) *	4.0 (2.2-7.5)
Hematuria	60.0%	46.9% *	80.8% *	88.2%	85.7%	57.1%

* p< 0.01

PO1322

Insight into the Pathophysiology of Hearing Loss and Renal Tubular Dysfunction Through Genetic Testing

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Introduction: In this case report, we present a case of Type 3b Bartter's Syndrome associated with sensorineural hearing loss.

Case Description: A 69 year old caucasian female with a history of hypertension and osteoporosis presented to the emergency department with a worsening dry cough, altered mental status, and paresthesias. Physical examination was positive for Chvostek's sign and hearing loss bilaterally. Laboratory analysis was significant hypolcalcemia, hypokalemia, and hypomagnesemia. EKG on presentation displayed significant QT prolongation (QTc of 482 ms). The patient was treated for symptomatic hypocalcemia and initiated on calcium, potassium, and magnesium supplementation. 24 hour urine collection yielded: potassium and magnesium wasting and normal range calciuria. Parathyroid hormone was found to be inappropriately low in the setting of severe hypocalcemia but attributed to hypomagnesemia. Bartter's vs. Gittleman's was suspected, although profound hypomagnesemia suggested the latter. Renasight, a kidney gene panel employing next generation genome sequencing revealed a heterozygous variant in the basal chloride channel (CLCNKB), associated with Bartter's Syndrome Type 3/4B. This channel is found in the stria vascularis and can lead to sensorineural deafness. Hypoparathyroidism persisted in spite of adequate Magnesium, Vit D levels suggestive of primary hypoparathyroidism of autoimmune etiology.

Discussion: The positivity of CLCKNB heterozygous mutation suggested Bartter's Type 3/4B and this explained hearing loss and aided in the final diagnosis. Individuals who express both type A and B mutations present in infancy or antenatally. In a series of 115 patients w/ type B gene mutation, 26% had a Gitelman-like syndrome which includes late onset of age (1). Our case illustrated the utility of genetic testing in mixed electrolyte wasting presentations. Interestingly, the patient has persistent hypoparathyroidsism for which no genetic basis was identified such as the calcium sensing receptor mutation.

Renal Studies

	Magnesium	Potassium	Calcium	Chloride	Creatinine	PTH
Urine 24 Hour	130 mg/dl	72 MEQ/24hr	346 mg/24hr	95 MEQ/24hr	835 mg/d	
Total Urine Volume	2880 mL	2880 mL	2880mL	2880 mL	2880 mL	
Serum Concentration	1.6 mg/dL	4.5 mmol/L	9.5 mg/dL	95 mmol/L	1.3 mg/dL	27.5 pg/mL
Urine Fractional Excretion of Electrolyte	18%	34.87%				
Potassium/Creatinine Ratio		43 mg/gCr				

PO1323

Whole-Exome Sequencing as a First-Line Diagnostic Tool in Bartter and Gitelman Syndromes

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Background: The clinical diagnosis of Bartter (BS) and Gitelman syndrome (GS) can be challenging, as they are rare and phenotypically overlapping. Thus, genetic testing represents the gold standard for the diagnosis. Next-generation sequencing is increasingly utilized in diagnostics and research of inherited tubulopathies. Sequencing of gene panels achieved high diagnostic yield and new insights into the phenotypic spectrum of these rare disorders. Whole-exome (WES) is not routinely performed for the molecular diagnosis of BS and GS. The aim of our study was to assess the diagnostic performance of WES in BS and GS, to establish genotype-phenotype correlations and to assess cost-effectiveness of this approach.

Methods: We performed WES in all consecutive patients referred for genetic testing with a clinical suspect of BS or GS. Variant prioritization was carried out according to ACMG guidelines. Clinical data were collected retrospectively.

Results: We enrolled 50 patients (22 males) with a clinical diagnosis of BS or GS. All the patients showed hypokalemic metabolic alkalosis at onset. The median age at clinical diagnosis was 7 years (range 0-67). WES showed pathogenic variants in 41/50 patients (82%). A dedicated analytic pipeline allowed us to identify copy number variations (CNVs) in 7/41 patients with a confirmed genetic diagnosis. In details, WES allowed us to confirm the clinical diagnosis in 33/50 patients and to change it 8 additional patients (6 patients from BS to GS, 2 patients outside the BS/GS spectum). Nephrocalcinosis was detected in 38% vs 8% of patients with a genetic diagnosis of BS and GS, respecively. Hypomagnesemia was similarly distributed among BS and GS patients (45% vs. 68%). Finally, patients with GS showed a median age at onset higher than patients with BS, but some overlap did exist, making differential diagnosis challenging at single-patient level.

Conclusions: The results of our study demonstrate that WES ensures a high diagnostic yield in patients with a clinical diagnosis of BS or GS, especially if coupled with analysis of CNVs. This approach showed to be useful in dealing with the phenotypic heterogeneity typical of these rare disorders, improving differential diagnosis by detecting phenocopies also outside the BS/GS spectrum.

PO1324

Examination of the Predicted Prevalence of Gitelman Syndrome by Ethnicity Based on Genome Databases

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Background: Gitelman syndrome is an autosomal recessive inherited salt-losing tubulopathy. It has a prevalence of around 1 in 40,000 people, and heterozygous carriers are estimated at approximately 1%, although the exact prevalence is unknown because most cases are thought to be asymptomatic or have nonspecific clinical findings. On the other hand, it has been reported that the non-specific symptoms can reduce the quality of life of patients, and in practice, we have often experienced cases where patients have suffered from these symptoms since childhood, but were not diagnosed and therefore not treated, and were diagnosed in adulthood. It could suggest that there are far more patients and carriers than expected.

Methods: We estimated the predicted prevalence of Gitelman syndrome based on multiple genome databases, HGVD and jMorp for the Japanese population and gnomAD for other ethnicities, and included all 274 pathogenic missense or nonsense mutations registered in HGMD Professional. The frequencies of all these alleles were summed to calculate the total variant allele frequency in *SLC12A3* which is the responsible gene for Gitelman syndrome. The carrier frequency and the disease prevalence were assumed to be twice and the square of the total allele frequency, respectively, according to the Hardy–Weinberg principle.

Results: In the Japanese population, the total carrier frequencies were 0.0948 (9.5%) and 0.0868 (8.7%) and the calculated prevalence was 0.00225 (2.3 in 1000 people) and 0.00188 (1.9 in 1000 people) in HGVD and jMorp, respectively. Other ethnicities showed a prevalence varying from 0.000012 to 0.00083.

Conclusions: These findings indicate that the prevalence of Gitelman syndrome in the Japanese population is higher than expected and that some other ethnicities also have a higher prevalence than previously been considered.

PO1325

An Off-the-Shelf CRISPR Gene Therapy Approach in Human Kidney Organoids

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Background: Gene therapy offers many opportunities to treat kidney diseases. Targeted, off-the-shelf therapeutics are needed for both loss-of-function (e.g. nephropathic cystinosis) and gain-of-function (e.g. APOL1) disease states. Kidney organoids are complex structures that resemble nephrons and can be used to develop gene therapy approaches. Commonly used gene transfer techniques, such as lentivirus and adeno-associated virus, are size limited, transient, or introduce DNA non-specifically into the genome. While targeted CRISPR gene editing is routinely used in 2D cell cultures, it has been challenging to use this powerful technique in intact organoids.

Methods: To achieve off-the-shelf gene transfer, organoids were transfected with Cas9 and gRNA ribonucleoprotein (RNP) complexes targeting the *AAVS1* safe harbor locus supplemented with knock-in cassettes encoding green fluorescent protein (GFP) or FLAG-tagged cystinosin (deficient in nephropathic cystinosis). Alternatively, to monitor gene knock-out, organoids expressing GFP from *AAVS1* were transfected with RNP and either one or two gRNAs to introduce indels in the coding sequence. Genome editing was detected three ways: by confocal microscopy, PCR, and next generation sequencing.

Results: GFP and cystinosin knock-in events in organoids were detected using microscopy and PCR. Immunofluorescence analysis revealed knock-in in proximal tubule epithelial cells (LTL^+). In knock-out experiments, live confocal microscopy indicated areas of GFP loss within kidney organoids treated with gRNA targeting GFP, but not with a scrambled guide. Mosaic patches of GFP knockout cells expanded over several days. Staining with nephron markers such as LTL and podocalyxin revealed knockout in both proximal tubule cells and podocytes. By next generation sequencing, the two-guide system produced larger deletions and was more efficient (20 % knockout), compared to single guide.

Conclusions: The strategy developed here is efficient for knocking in and knocking out genes in kidney epithelium. It uses commercially available reagents to perform CRISPR gene editing. sgRNA sequences or *AAVS1* knock-in templates can be customized to target or introduce any gene of interest at specific loci. This provides a platform for the development of off-the-shelf gene therapies for diverse kidney disease states.

Funding: NIDDK Support

PO1326

The Kidney Genome Atlas: A Resource to Understand APOL1 and Other Genetic Drivers of Adult Proteinuric Kidney Diseases

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Background: Chronic kidney disease (CKD) affects more than 30 million people in the US with African Americans being particularly at risk. There is an unmet need for pharmaceutical therapies that extend or, ideally, restore kidney function.

Methods: To guide genetically-driven drug development, we have established the Kidney Genome Atlas (KGA), which contains whole-genome sequences (>30X) from adult patients with Focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD) and other, idiopathic, proteinuric disorders as well as public and technically matched controls. By implementing a rigorous quality control procedure, following the gnomAD pipeline, we obtained a high-confidence dataset for downstream analyses. Three genetically inferred ancestries (EUR, AFR, AMR) were included in association testing comparing 1400 cases, including 169 individuals with *APOL1* G1/G1, G2/G2 or G1/G2 high risk haplotypes (*APOL1*-HRH), with 14686 controls (including 485 *APOL1*-HRH individuals).

Results: Overall, our common variant cross-ancestry meta-analysis showed minimal impact of potential confounders, such as ancestry or sequencing center differences (lambda=1.03). Using summary statistics from our EUR analysis, we estimated a SNP heritability of 0.15 (SE = 0.028) in proteinuric diseases. Comparison to a recent CKD GWAS (Wuttke et al., 2019) indicated a weak positive genetic correlation (rg) of 0.097 (SE = 0.053). We identified the previously reported significant disease association of *APOL1*-HRH ($p=2x10^{-10}$) in our study. Recent in vitro data suggests amino acid in position 150 (rs2239785) is critical for the pathogenicity of *APOL1*-HRH (PO1986, ASN 2020) which we confirmed in our cohort of AFR ancestry individuals.

Conclusions: We have built a high-quality, multiethnic cohort that enables understanding of genetic drivers of polygenic proteinuric kidney disease. Future analysis including genetic modifiers of *APOL1* may provide opportunities for novel therapies and patient stratification.

Funding: Commercial Support - Goldfinch Bio

PO1327

Effect of ApoL1 Genotype on Kidney Failure and eGFR Decline in Patients with All-Cause CKD

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Background: *ApoL1* risk variants G1 and G2 associate with an increased risk of kidney failure and a higher rate of eGFR loss. We assess the effect of *ApoL1* genotype in African American and Latino individuals with chronic kidney disease (CKD) in New York City.

Methods: *ApoL1* genotype determined by sequencing. CKD cases with high-risk *ApoL1* genotype (n= 242) were compared to CKD cases with a low-risk *ApoL1* genotype (n=885) and African ancestry per Admixture. Kaplan-Meier survival analyses assessed time to kidney failure followed by Adjusted Cox-proportional hazard model and competing risk regression against death both incorporating covariates. Linear mixed-effects modelling evaluated CKD-EPI $eGFR_{cr}$ decline rate using the same covariates.

Results: Cases with a high-risk *ApoL1* genotype reach kidney failure 10-15 years earlier than low-risk cases. G1/G1 reach kidney failure earliest, followed by G1/G2 and G2/G2 (Fig 1). These data are supported across multiple risk models (Table 1). Cases with a high-risk genotype have a higher eGFR decline rate than low-risk cases with a similar trend per specific genotype (Fig 2). The addition of self-declared or genetically defined ancestry did not confer additional risk.

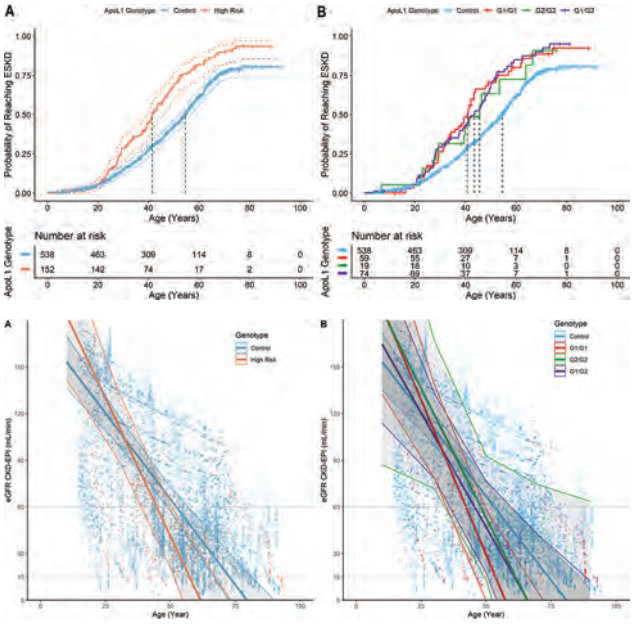
Conclusions: High-risk *ApoL1* genotypes increase the risk of kidney failure at an earlier age, likely due to a higher eGFR decline rate. G1/G1 genotypes appear most affected and G2/G2 least.

Funding: Government Support - Non-U.S.

Table 1. Modelling Results by ApoL1 Genotype

ApoL1 Genotype	Age at Kidney Failure (Median, 95% CI, Years)	Unadjusted HR of Kidney Failure	Adjusted HR of Kidney Failure	Competing Risk HR of Kidney Failure	eGFR Decline Rate (mL/min/year)
Control	54.6 (52 – 56.7)	1	1	1	2.68
High Risk	41.4 (39.4 – 46)	1.83***	1.90***	1.90***	3.89*
G1/G1	40.7 (34.3 – 43.9)	1.89***	1.95**	1.95***	4.56*
G1/G2	43.5 (37.6 – 49.2)	1.84***	2.00	2.01	3.52
G2/G2	45.5 (39.4 – inf)	1.62	1.42***	1.42***	3.91

*p <0.05 **p <0.001 ***p < 0.0001



PO1328

"APOL1-Plus" Genotypes in Patients with CKD

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Background: Inheritance of homozygous or compound heterozygous *APOL1* G1 G2 risk alleles is associated with an increased risk of chronic kidney disease (CKD) including focal segmental glomerulosclerosis (FSGS). The *APOL1* high-risk genotype (HRG) is not completely penetrant; additional genetic and/or environmental factors are thought to be necessary for the development of CKD. While approximately 10% of individuals with CKD have causal variants when tested with exome-based next generation sequencing (NGS), few reports have examined co-occurrence of *APOL1* HRG alongside these variants. Here we examine the co-occurrence of *APOL1* HRG and additional genetic diagnoses ("*APOL1*-plus") using a broad NGS panel of CKD genes.

Methods: Clinical samples were analyzed via an NGS panel of >380 genes associated with isolated or syndromic CKD. Positive results had one pathogenic (P) or likely pathogenic (LP) variant in an autosomal dominant or X-linked gene, two P/LP variants in an autosomal recessive gene, or presence of two *APOL1* risk alleles.

Results: Among 1691 cases with positive results, 25% (n=430) had positive findings in *APOL1*. Other positive findings included variants in *PKD1/2* in 27% (456/1691) of cases, and in *COL4A3/4/5* in 22% (379/1691) of cases. Among positive cases, 7% (119/1691) had >1 positive result, including both dual (n=115) and triple diagnoses (n=4). *APOL1* HRG was present in 50% (59/119) of cases with multiple diagnoses, accounting for 3.5% of all positive cases and 14% of all *APOL1* HRG cases. Among the *APOL1*-plus cases, second positive findings were observed in *COL4A3/4/5* (29%; 17/59), *TTR* (29%; 17/59), and *PKD1/2* (15%; 9/59).

Conclusions: Dual diagnoses comprised 7% of all positive genetic testing results, with *APOL1* HRG present in half of these cases. Future studies are needed to understand how multiple genetic diagnoses, including those with *APOL1* HRG, impact disease presentation and progression. Dual *APOL1* and collagen IV-related diagnoses are of particular interest given the frequency of these glomerulopathies in the CKD population. Genetic testing via broad NGS panels can improve diagnosis and management of CKD and increased testing will contribute to an evolving understanding of genetic etiologies of CKD.

PO1329

Uncovering Mechanisms of Risk-Variant APOL1-Modulated Inflammatory Signaling in Macrophages

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Background: In the United States, Black Americans face a higher risk to develop CKD and progress to end stage kidney disease (ESKD) even after accounting for clinical and socioeconomic factors. Variants in the gene encoding for innate immunity factor Apolipoprotein L1 (APOL1) have been identified as risk factors for focal segmental glomerulosclerosis (FSGS) and HIV-associated nephropathy (HIVAN) in individuals with recent African ancestry. However, the role of immune cells in APOL1 nephropathy is not well understood. In this study we seek to understand the effect of risk variant APOL1 on macrophage function and inflammation.

Methods: Isogenic induced pluripotent stem cell (iPSC) lines expressing the G0, G1, and G2 variants of *APOL1* were generated through CRISPR/Cas9 gene editing. These iPSC lines were used to generate iPSC-derived macrophages (IPSDM). Peritoneal and bone marrow-derived macrophages (BMDMs) were collected from transgenic mice 14-18 weeks of age expressing G0, G1, and G2 variants of *APOL1*. Expression of *APOL1* in cultured iPSDMs, peritoneal macrophages, and BMDMs was induced with IFNγ (5 ng/mL).

Results: We observed that risk-variant *APOL1* expression results in higher *TNF* and *IL1B* gene expression by nine-fold and two-fold respectively, in G1 iPSDM ($P < 0.05$). In *APOL1* transgenic mouse peritoneal macrophages, oil red O staining revealed 2.83-fold increased neutral lipid accumulation ($N = 3$, $P < 0.01$) and 4.84-fold decreased efferocytosis capacity measured with flow cytometry ($N = 5$, $P < 0.05$) in G1 and G2 mice compared to G0. qRT-PCR analysis showed glycolysis genes to be increased in G1 iPSDM compared to G0. Additionally, G2 mouse BMDMs exhibit increased glycolytic rate compared to G0 both at baseline and under mitochondrial stress when *APOL1* was induced with IFNγ.

Conclusions: The findings in this study unveil some mechanisms by which risk-variant APOL1 modulates macrophage inflammatory phenotype and function, relevant to kidney disease progression.

Funding: Private Foundation Support

PO1330

A Multivariate Analysis of Genome-Wide Association (GWAS) Data to Identify Genes Associated with CKD

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Background: Chronic kidney disease (CKD), a major public health burden, is characterised by a progressive loss of nephron function which leads to an impaired ability to filter the blood. Genome-wide association studies (GWASs) have identified single nucleotide polymorphisms (SNPs) and loci associated with the kidney function biomarkers estimated glomerular filtration rate (eGFR) and blood urea nitrogen (BUN) by mostly univariate-based analyses. However, gene-based multivariate-SNP and multivariate-biomarker relationships have typically not been considered so far in this context. The purpose of this study was to highlight the additional insights gained from the statistical power of a multivariate-based approach to identify potential risk factor genes for CKD.

Methods: We used a multivariate statistical approach, canonical correlation analysis (CCA), to identify single nucleotide polymorphisms (SNPs) that showed significant correlation with estimated glomerular filtration rate (eGFR) and blood urea nitrate (BUN) taken jointly. Since attributes were in the form of three published GWAS summary statistics datasets, we used *metaCCA*. The SNPs were filtered using linkage disequilibrium-based pruning. For the significant SNPs and genes we identified, their functions, signalling pathways and cellular expression were investigated using gene set statistical enrichment analyses.

Results: For each of three published GWAS summary statistics datasets of both European and Japanese ancestry groups, we identified sets of 159, 246 and 181 protein-coding genes, respectively, that contained significant SNPs. Using gene set statistical enrichment analyses, these genes showed significant enrichment for kidney development processes, signalling pathways and kidney cell gene expression signatures. In addition, between all three datasets, we identified four significant genes (*CBLB, MACROD2, MECOM* and *SHROOM3)* that overlapped. Between two datasets, we identified a further four significant SNPs that overlapped.

Conclusions: By using a multivariate statistical approach, we have identified both previously reported and additional genes that contained SNPs statistically associated with kidney function. Overall, these findings provide new insights into SNPs and genes potentially involved in kidney function and CKD risk.

Funding: Government Support - Non-U.S.

PO1331

Rare Variants and Risk of ESKD: The Geisinger MyCode-DiscovEHR Study

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Background: Prior studies have reported that up to 1 in 10 patients with end-stage kidney disease (ESKD) have a diagnostic rare genetic variant but have lacked control groups.

Methods: Whole exome sequencing and electronic health records data from 147,750 participants in the Geisinger MyCode-DiscovEHR study, a health system-based cohort, were linked to the US Renal Data System to ascertain ESKD status and attributed cause. We compiled a list of variants in 80 autosomal or X-linked dominant (AD/XLD) genes used in commercial kidney genetics panels previously reported in Clinvar as pathogenic or likely pathogenic (P/LP) (minor allele frequency <0.01, any number of stars). We evaluated the association of these rare P/LP variants with risks of all-cause and cause-specific ESKD in logistic regression models adjusted for age and sex. Additional analyses were performed by subsets of kidney disease genes and by age of ESKD onset.

Results: Prevalence of previously reported rare P/LP variants in AD kidney disease genes was higher in participants with ESKD than those without ESKD (3.0% vs. 1.2%). Rare P/LP variants were most prevalent in congenital/cystic ESKD (12.6%), followed by ESKD attributed to genitourinary/nephrolithiasis disorders (4.9%), hypertension (4.3%), glomerular/vasculitis disorders (3.4%), and early onset diabetic ESKD (<60 years; 3.3%). By contrast, only 0.7% with later onset diabetic ESKD (60+ years) had rare P/LP variants. Individuals with rare variants were at increased risk of all-cause ESKD (OR 2.71, 95% CI: 1.99-3.70) (**Table**). When genes were grouped by specific categories, rare variants in cystic disease, Alport Syndrome, CAKUT, and FSGS gene panels were all associated with increased risk of ESKD.

Conclusions: Individuals in an unselected health system cohort with rare variants had substantially increased risk of ESKD, which was often attributed to hypertension or diabetes.

Funding: NIDDK Support, Other NIH Support - Geisinger Clinic

Associations between rare variants and ESKD phenotypes

	ESKD (n=1415)	ESKD (onset <60 y) due to diabetes (n=301)	ESKD (onset ≥60 y) due to diabetes (n=302)	ESKD due to GN or vasculitis (N=205)	ESKD due to HTN (n=186)	ESKD due to congenital/ cystic cause (n=95)
Category	OR (95% CI) P value	OR (95% CI) P value	OR (95% CI) P value	OR (95% CI) P value	OR (95% CI) P value	OR (95% CI) P value
P/LP variants in any AD kidney disease gene (n=1741)	2.71 (1.99-3.70) P<0.001	2.85 (1.52-5.57) P=0.001	0.57 (0.14-2.29) P=0.4	2.97 (1.40-6.33) P=0.005	3.75 (1.84-7.62) P<0.001	12.08 (6.58-22.17) P<0.001
P/LP variants in AD cystic disease genes (n=417)	4.16 (2.37-7.29) P<0.001	2.83 (0.70-11.43) P=0.1	-	2.09 (0.29-14.94) P=0.5	-	39.92 (19.2-83.1) P<0.001
P/LP variants in AD Alport genes (n=600)	2.90 (1.70-4.97) P<0.001	0.97 (0.14-6.96) P=1.0	-	4.29 (1.37-13.47) P=0.01	7.78 (3.17-19.08) P<0.001	12.93 (4.73-35.36) P<0.001
P/LP variants in AD CAKUT genes (n=209)	2.68 (1.10-6.57) P=0.03	2.38 (0.33-17.05) P=0.4	-	3.64 (0.51-26.13) P=0.2	4.03 (0.56-29.10) P=0.2	-
P/LP variants in FSGS (excluding Alports) genes (n=43)	8.91 (2.67-29.74) P<0.001	-	11.56 (1.50-89.08) P=0.02	19.93 (2.70-147.09) P<0.001	-	12.02 (4.40-32.86) P<0.001

PO1332

Genomic Disorders Are Associated with CKD Across the Life Span

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Background: Genomic Disorders (GDs), caused by pathogenic deletions and duplications (copy number variants, CNV) of large genomic regions of the genome, are a major source of genetic susceptibility for multiple developmental traits and are enriched in pediatric chronic kidney disease (CKD) patients. In the Chronic Kidney Disease in Children Study (CKiD) cohort 1, 4.5% participants carried a GD.

Methods: We extended our previous study in CKiD to cohort 2 and also examined the prevalence of GDs in adults with all-cause CKD enrolled in the Chronic Renal Insufficiency (CRIC, N = 3375), Columbia University CKD (CU-CKD, N=1146) and Family Investigation of Nephropathy and Diabetes (FIND, N=1318) cohorts, comparing them to 30746 controls. CNV calls were based on SNP microarrays and whole exome sequencing and annotated for known GDs. We also performed a phenome-wide association analysis of GDs in the Electronic Medical Records and Genomics (eMERGE, N=11971) cohort.

Results: We found 9/248 (3.6%) CKiD 2 pediatric participants with mild CKD carried a GD, replicating prior findings in pediatric CKD. We next identified GDs in 74/6,679 (1.1%) adult CKD patients in the CRIC, CU-CKD and FIND cohorts, compared to 165/30,746 (0.5%) GDs in controls (OR=1.6, $p=5x10^{-4}$). Recurrent known GDs in adult CKD patients comprised pathogenic CNVs in 1q21.1, 16p11.2, 17q12 and 22q11.2 loci. The 17q12 GD (renal cyst and diabetes syndrome) was most frequent, detected in 1:252 CKD cases with diabetes. In the phenome-wide analysis of the eMERGE cohort, dialysis was in the top three phenotypic associations with GD carrier status ($p<10^{-3}$), replicating the case-control association results. Other phenotypic associations for GDs in CRIC participants included lower serum Mg ($p=2x10^{-3}$) and lower educational achievement ($p=8x10^{-4}$).

Conclusions: GDs are significantly enriched in children and adults with CKD. Undiagnosed GDs can provide a molecular explanation for renal disease in both adults and children and represent hidden genetic links between CKD and other traits such as poorer neurocognitive performance. Systematic detection of GDs can enable a precise genetic diagnosis and inform prognosis and treatment.

Funding: NIDDK Support, Other NIH Support - NHGRI

PO1333

Genome-Wide Association Study in Mice Maps Susceptibility to HIV-Associated Nephropathy to the Ssbp2 Locus

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Background: To gain insight into the pathogenesis of collapsing glomerulopathy, a rare form of focal segmental glomerulosclerosis that often arises in the setting of viral infections, we performed a genome wide association study (GWAS) among inbred mouse strains using a murine model of HIV-1 associated nephropathy (HIVAN).

Methods: F1 hybrids were generated between HIV-1 transgenic mice on the FVB/NJ background and 20 inbred laboratory strains. Histology, BUN, proteinuria and urinary NGAL were assessed in the F1 hybrids. A GWAS in 366 transgenic F1 hybrids generated from these 20 inbred strains was performed.

Results: Six stains (A/J, C3H/HeJ, DBA/1J, KK/HlJ, WSB/EiJ, and LP/J) were highly sensitive to the Tg resulting in severe glomerulosclerosis, 9 strains (129S1/SvImJ, Balb/CJ, C57BL/6J, C57BL/6NJ, C57BL/10J, C57BL/J, C58/J, CAST/EiJ and NZB/BINJ) were resistant to the Tg resulting in limited to no glomerulosclerosis, and 5 strains (CBA/J, DBA/2J, NOD/ShiLtJ, NZO/HlLtJ and FVB/NJ) had intermediate glomerulosclerosis. Analysis of histology, BUN and urinary NGAL demonstrated a marked phenotypic variation among the transgenic F1 hybrids, providing strong evidence for host genetic factors in the predisposition to nephropathy. A GWAS identified a genome-wide significant locus on Chr. 13 and multiple additional suggestive loci. Cross annotation of the Chr. 13 locus, including single cell transcriptomic analysis of wild type and HIV-1 transgenic mouse kidneys, nominated *Ssbp2* as the likely culprit gene. *Ssbp2* is highly expressed in podocytes, encodes a transcriptional cofactor present in LDB1 containing complexes, and interacts with *LMX1B,* a known FSGS gene that requires LDB1 for optimal transcriptional activity. Consistent with these data, older *Ssbp2* null mice spontaneously develop glomerulosclerosis, tubular casts, interstitial fibrosis and inflammation, similar to the HIVAN mouse model.

Conclusions: These findings demonstrate the utility of GWAS in mice to uncover host genetic factors for rare kidney traits and suggest *Ssbp2* as susceptibility gene for HIVAN, potentially acting via the LDB1-LMX1B transcriptional network. Future studies will evaluate the role of *Ssbp2 in vitro* and in *Ssbp2* null mice.

Funding: Other U.S. Government Support

PO1334

Genetics Analysis of IgA Nephropathy-Discordant Monozygotic Twins

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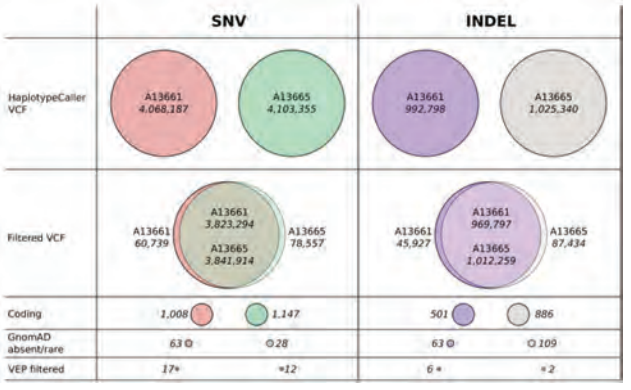
Background: Analysis of monozygotic twins can inform about the genetic and environmental basis of disease. We investigated monozygotic twins phenotypically discordant for IgA nephropathy (IgAN), in order to identify possible postzygotic variants that may provide further insights into IgAN pathogenesis.

Methods: We studied 5 pairs of discordant monozygotic twins, and their family members. Immunological analysis evaluated the in vitro secretion of IgA and Genome Sequencing (GS) was employed to identify germline and somatic variants.

Results: Culture of naïve B-cells and T-follicular like helper cells derived from the IgAN cases yielded 1.74 fold higher IgA production compared to cells from their corresponding healthy twins. Genetic analysis of the samples allowed to call ~4 mln (4,068,187 - 4,103,844) SNPs and ~1 mln (992,798–1,027,413) INDELs for each sample. Of those, ~60,000 (60,739–68,027) SNPs and ~50,000 (45,927–53,052) INDELs were discordant between twin pairs. Slightly lower rate were identified in the technical replicate (57,883 SNPs and 51.415 INDELs). Among discordant variants, only ~1,000 (986–1,147) SNPs and ~500 (401-886) INDELs were in coding regions. Further filtering for GnomAD AF, showed ~50 (43-68) SNPs and ~70 (53-109) INDELs had a minor allele frequency <0.0001, and of those just very few variants (9–22 SNPs and 2–7 INDELs) had potential impact on the gene function. We did not detect discordant variants in the same gene between the twin pairs.

Conclusions: Our analysis identified significant differences in IgA production demonstrating the role of the immune system and genetics in IgAN pathogenesis. Consistent with the literature, GS identified discordant variants between twins pairs, most of which are attributable to background errors in variant calling. Further analysis of twin-specific variants and gene sets may allow the identification of postzygotic variants that may be involved in IgAN pathogenesis.



Affected vs. Unaffected variant differences in one of the IgAN discordant twin pairs under analysis

PO1335

Primary AA Amyloidosis due to a chr11:18287683 T>C (hg19) Mutation in the SAA1 Promoter Linked to the Amyloidogenic SAA1.1 Haplotype

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Background: AA amyloidosis results from deposition of amyloid A (AA), a product of the proteolytic cleavage of serum amyloid A (SAA) proteins. Previously described AA amyloidosis has been due to increased production and deposition of serum amyloid A (SAA) proteins secondary to inflammatory conditions arising from infectious or metabolic causes. We describe for the first time a family with primary AA amyloidosis due to an isolated increase in production of AA protein.

Methods: A family was identified with autosomal dominant transmission of amyloidosis affecting 12 family members and associated with progressive chronic kidney disease (CKD) as well as other systemic manifestations of amyloidosis. Family members underwent measurement of serum SAA1 and whole exome sequencing with targeted sequencing. The luciferase reporter assay was used to determine promoter activity.

Results: Affected individuals developed proteinuria, CKD and systemic deposition of amyloid composed specifically of the SAA1.1 isoform. Affected individuals had a doubling of the SAA1 promoter activity and sustained elevation of serum SAA levels that segregated in an autosomal dominant pattern in 12 genetically affected and in none of 6 genetically unaffected relatives with a LOD score of >5. Genetic evaluation revealed a chr11:18287683 T>C (hg19) mutation in the SAA1 promoter linked to the amyloidogenic SAA1.1 haplotype that segregated completely with affected individuals. Tocilizumab had a beneficial effect when prescribed early.

Conclusions: A mutation in the SAA1 promoter linked to the amyloidogenic SAA1.1 haplotype led to a doubling of production of SAA1, leading to characteristic findings of amyloidosis. This is the first investigation to show that all manifestations of AA amyloidosis in humans are due solely to SAA overexpression. Idiopathic forms represent a significant and increasing proportion (15-20%) of all diagnosed cases of AA amyloidosis. Genetic screening of the SAA1 promoter should be pursued in individuals with AA amyloidosis without an obvious cause of systemic inflammation, especially if there is a positive family history. Contact ableyer@wakehealth.edu for genetic evaluation of familial amyloidosis.

PO1336

Genetic Testing in Focal Segmental Glomerulosclerosis (FSGS): Tale of Three Stories

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Introduction: Genetic testing in kidney disease has improved our understanding of various etiologies of glomerular diseases. FSGS is a histopathological diagnosis with diverse causes and patterns of inheritance. Genetic testing in FSGS has unlocked a treasure of pathogenic mutations that are either limited to the kidney or represent a broader extra-renal manifestation. Here we present 3 biopsy proven cases of FSGS with different genetic polymorphisms and varied presentations.

Case Description: Case 1: 29-year-old female with scoliosis, hearing loss, right optic nerve coloboma presented with 1.5 g/day of proteinuria and normal renal function when she was 16 years of age. Kidney biopsy revealed FSGS with 90% foot process effacement. 13 years later, her renal function worsened, with serum creatinine 1.4 mg/dl (baseline 0.9 mg/dl), and urine protein creatinine ratio of 4 g/g. Her mother had undergone a kidney transplant assumed to be secondary to reflux nephropathy. Genetic testing showed PAX2 truncated mutation c.430>T p.Gln 144* which can lead to FSGS, optic nerve coloboma and papillorenal syndrome. Case 2: 21 year-old male with biopsy proven FSGS when he was 8 years old mentioned that his maternal grandfather suffered from unknown renal disease requiring dialysis and died in his 40's. Genetic testing revealed hemizygous, truncating p.W58* variant in the CLCN5 gene. Variants in CLCN5 gene can cause Dent's Disease manifesting later in life as proteinuria, nephrocalcinosis, hypercalciuria and renal failure. In addition he had variant of unknown significance NPHS1 designated p.T233A, and APOL1G2 risk allele predisposing him to develop FSGS. Case 3: 21 year-old male, born with genital ambiguity, perineal hypospadias, 46 XY karyotype was noted to have 14 g of proteinuria, low albumin and hypertension. Kidney biopsy revealed FSGS, abnormal glomerular basement membrane. Genetic testing was positive for heterozygous intronic variant of WT-1 and heterozygous missense variant of SMARCAL1 p.R820H which are pathogenic variants that cause renal failure due to defective podocyte development and dysfunction respectively.

Discussion: Genetic analysis for FSGS has become an important diagnostic tool in nephrology. We currently have over 50 genes that are known to be involved in FSGS. Reporting of different genetic variants and their occurrence is crucial to yield insight into our current understanding of FSGS.

PO1337

Whole-Exome Sequencing Reveals a Monogenic Cause of Disease in 26% of 335 Families with Steroid-Resistant Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) overwhelmingly progresses to end-stage renal disease. To date, more than 59 monogenic genes have been identified to cause SRNS. We previously detected causative mutations in 25% using whole exome sequencing (Warejko *CJASN* 13:53, 2018) and in 29.5% of patients with SRNS using targeted panel sequencing (Sadowski *JASN* 26:1279, 2015). However, whole exome sequencing (WES) has become more accessible, with the advantage of detecting not only known monogenic causes of SRNS, but also novel candidate NS-causing genes.

Methods: We employed whole exome sequencing (WES) to detect monogenic causes of SRNS in a large international cohort of 335 families with SRNS presenting before the age of 25 years.

Results: Samples were recruited from April, 1998 to December, 2018 (21 years). WES was performed at the Yale Center of Mendelian Genomics. First, we examined the WES data for mutations in 59 genes known to cause SRNS. In 87/335 families (26%), we identified mutations in 22 of the known genes. There were also 7 genes that were identified as phenocopies of SRNS e. g. *COL4A3*. In 58 families (17.3%), we have identified mutations in a potential novel candidate gene for SRNS. We found a 48.1% solve rate in individuals with high homozygosity by decent and 15.4% solve rate in non-homozygous individuals, recapitulating similar solve fractions to what has been previously published (Sadowski 2015; Warejko 2017).

Conclusions: This study confirms that ~26% of families with NS in our cohort are due to monogenic causes. WES is a viable way to diagnose the underlying cause of NS in children and young adults, and to suggest novel monogenic candidate genes of NS.

Funding: Other NIH Support - 5R01DK76683-14.

PO1338

Discovery of Podocyte-Specific Interaction Partners of the Nephrotic Syndrome-Associated Protein NOS1AP

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Background: Recessive *NOS1AP* mutations are a novel Mendelian cause of nephrotic syndrome (NS) in humans and mice (Majmundar *Sci Adv* 2021). The NS patient mutation p.C143Y destabilizes the predicted structure of the NOS1AP phosphotyrosine-binding domain, impairs NOS1AP-dependent actin remodeling in immortalized podocytes, and causes abnormal kidney organoid glomerulogenesis. Here, we aimed to discover podocyte-specific NOS1AP interaction partners, which may mediate NOS1AP functions in the podocyte and whose binding is abrogated by the patient mutation p.C143Y.

Methods: Protein interaction data from candidate immunoprecipitation, mass spectrometry, and yeast two-hybrid studies were queried from the literature and public datasets (Orchard *NAR* 2014; Oughtred *Protein Sci* 2020; Szklarczyk *NAR* 2019). Gene expression was queried from kidney single cell mRNA sequencing (scRNAseq) datasets (Karaiskos *JASN* 2018; Menon *Development* 2018; Wang *Cell Rep* 2018; Wu *JASN* 2018). Protein interactions were validated by co-immunoprecipitation studies using tagged cDNA constructs.

Results: 85 putative NOS1AP-interacting proteins were identified from candidate interaction and proteomics studies. Six interacting proteins (of 85) demonstrated co-expression with *NOS1AP* in podocyte clusters from at least three out of four kidney scRNAseq datasets (% cell expression z-score > 1). Four of six candidates (FYN, GSN, SNTA1, HSPA12A) were cloned into expression vectors for interaction studies. SNTA1 and HSPA12A exhibited bi-directional co-immunoprecipitation with wildtype NOS1AP upon co-overexpression in a podocyte cell line. Co-immunoprecipitation was, similarly, observed with the NS patient mutant NOS1AP^{C143Y}.

Conclusions: Our results suggest NOS1AP is co-expressed with and can physically interact with SNTA1 and HSPA12A in podocytes. These proteins may mediate NOS1AP functions in podocyte biology.

Funding: Other NIH Support - NIH Institutional K12 Child Health Research Center Career Development Award (5K12HD052896-13), Private Foundation Support

PO1339

Synuclein Alpha Accumulation Drives Lysosomal Dysfunction in Fabry Podocytopathy

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Background: Anderson-Fabry disease is an X-linked lysosomal disorder characterized by a multisystemic globotriaosylceramides (Gb3) accumulation due to reduced alpha-galactosidase activity (GLA). Podocyte injury is a major renal manifestation of Fabry disease. Recently, our data indicated Gb3 depletion to be insufficient in repairing podocyte damage seen in an *in vitro* model for Fabry disease. This project, therefore, focused on potential Gb3 independent mechanisms in Fabry podocytopathy.

Methods: We employed CRISPR/CAS9 to generate GLA knock out lines of immortalized human podocytes *in-vitro*. These cells were investigated by (ultra-) structural, transcriptome and proteome as well as functional analyses in the presence and absence of enzyme replacement therapy (ERT). The acquired data sets were integrated through network analysis and connectivity mapping. These data were complimented by the investigation of human biopsies taken sequentially before and after a period of ERT.

Results: We detected that enzyme replacement therapy (ERT) and Gb3 reduction failed to ameliorate signs of podocyte injury in patient biopsies. GLA knockout podocytes depicted high Gb3 levels that were fully reversed upon enzyme replacement. Still lysosomal dysfunction was significantly but not completely reversible with enzyme therapy. Proteomics suggested alpha-synuclein (SNCA) accumulation as a potential driver of lysosomal dysfunction. Transcriptomics-based connectivity mapping further revealed a potential anti-SNCA therapeutic effect of beta-adrenoceptor agonists. Indeed, genetic and pharmacological inhibition of this protein significantly improved lysosomal structure and function in Fabry podocytes beyond the effects of ERT.

Conclusions: This study provides strong evidence of a central role of SNCA in lysosomal dysfunction in Fabry disease independent of Gb3 accumulation. The results offer new options for pharmacological strategies to target Fabry podocytopathy.

PO1340

Drosophila TBC1D8B Promotes Nephrin Endocytosis and Is Required for Endosomal Cargo Processing

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Background: Mutations in *TBC1D8B* were recently identified as a monogenic cause of nephrotic syndrome. TBC1D8B interacts with nephrin and it was implicated as an inhibitory GAP protein for Rab11 which regulates endocytic recycling. However, the functional spectrum of TBC1D8B and its role in trafficking of nephrin remains poorly understood.

Methods: We generated and analyzed a stable genetic deletion of fly *Tbc1d8b* via CRISPR/Cas9. We successfully introduced a c-terminal HA-tag into the *Tbc1d8b* locus using microhomology-mediated end joining. For overexpression of murine *Tbc1d8b*-HA we further generated transgenic flies under control of GAL4/UAS. Endosomal cargo processing was assessed by sequential uptake of two tracers *ex vivo*.

Results: Germline expression of Cas9 and tandem *Tbc1d8b*-guide RNAs resulted in a stable genetic deletion spanning all functional domains while ending with a frameshift. Surprisingly, homozygous mutant animals were viable without any overt phenotype. However, analysis of the podocyte-like nephrocytes of these flies revealed mislocalization and partial loss of slit-diaphragm proteins with incomplete penetrance. This nephrocyte-restricted phenotype recapitulates the phenotype of human mutations that present exclusively with nephrotic syndrome. Overexpression of murine *Tbc1d8b*-HA in nephrocytes caused accumulation of endogenous fly nephrin in large vesicles while its binding partner Kirre (Neph1) was not affected. The vesicles containing fly nephrin co-localized with the late endosomal marker Rab7 and disappeared when silencing the early endosomal regulator *Rab5*. This suggests that mammalian Tbc1d8b specifically promotes nephrin endocytosis. To identify the endogenous subcellular localization of the fly Tbc1d8b we established a knock-in of a c-terminal HA-tag and noted partial co-localization with endosomal markers including Rab7. To investigate the functional role in the endolysosomal pathway we tracked the fate of two tracers sequentially applied *ex vivo*. A background of both, stable and conditional deletion of *Tbc1d8b* was associated with defective cargo processing.

Conclusions: Our findings implicate novel functional roles of Tbc1d8b beyond endocytic recycling: promoting nephrin endocytosis and facilitating processing of endosomal cargo.

Funding: Government Support - Non-U.S.

PO1341

Stable Genetic Deletion of Gapvd1 in Drosophila Results in a Nephrocyte-Restricted Phenotype

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Background: Mutations in the gene GAPVD1 cause of nephrotic syndrome in humans. GAPVD1 interacts with RAB5 and but the subcellular localization of GAPVD1 is unclear. Silencing of Gapvd1 the podocyte-like Drosophila nephrocytes by RNA-interference resulted in mislocalization of fly nephrin.

Methods: We generated conditional knockdowns and a stable genetic deletion of *Drosophila Gapvd1* by CRISPR/Cas9 and used microhomology-mediated end joing to introduce a genomic HA-tag into the Gapvd1 c-terminus. We performed a functional analysis of the novel fly models.

Results: We generated twin frameshift mutations at the second and third exons of the Drosophila Gavpd1 gene. Animals carrying these mutantion were homozygous viable without any overt phenotype. However, the podocyte-like nephrocytes revealed a severly altered slit diaphragm morphology with mislocalization of fly nephrin and the orthologue of NEPH1 and partial loss of both proteins from the surface. This phenotype was similar but considerably stronger than the phenotype observed by RNAi-mediated silencing. This suggests that the homozygous frameshift mutations result in a null allele. The phenotype was further confirmed by conditional CRISPR/Cas-mediated silencing using two different gRNAs. Deletion of *Gapvd1* in the Drosophila model thus results in a phenotype that manifests exclusively in disturbed slit diaphragms formation. This recapitulates the phenotype observed in human patients that was limited to nephrotic syndrome, supporting the use of Drosophila model for this genetic disease. To study the subcellular localization of Drosophila Gapvd1, we introduced an HA-tag into the c-terminus of the Gapvd1 locus. Immunofluorescence of nephrocytes derived from the knock-in lines showed co-localization of the protein with Drosphila Rab5, supporting that Gapvd1 primarily resides in early endosomes. We overexpressed human GAPVD1 in nephrocytes, that equally localized in early endosomes. Gain-of-function of the human gene entailed reduced tracer endocytosis in nephrocytes, suggesting a dominant negative effect.

Conclusions: We established suitable new Drosophila models to study the function of Gapvd1 in nephrocytes as an invertebrate podocyte model.

Funding: Government Support - Non-U.S.

PO1342

Pathogenicity Assessment of Non-Glycine Missense Variants in COL4A5 Collagenous Domain

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Background: *COL4A5*, which encodes type IV collagen α5 chain, is a causative gene of X-linked Alport Syndrome (XLAS). In triple-helical domain on collagen protein (collagenous domain), the amino acid strictly repeats glycine (Gly) in every third position, (Gly-Xaa-Yaa)n, and these Gly contribute to the stability of triple-helical structure. Because of this, within collagenous domain, most Gly missense variants are pathogenic, and most reported missense variants substitutes amino acids from Gly. However, several pathogenic missense variants other than Gly (non-Gly missense variants) have been reported and the mechanisms of disease onset by these variants are not clear until now. The aim of this current study is to investigate the pathogenicity of non-Gly missense variants in *COL4A5* collagenous domain.

Methods: We extracted 18 variants, 13 from the Human Gene Mutation Database and 5 identified in our cohort. Firstly, we conducted a functional splicing assay using a hybrid minigene analysis method to examine the existence of aberrant splicing. Then, variants not causing aberrant splicing were investigated for the characteristics including bioinformatics analysis.

Results: Seven out of eighteen (38.9%) non-Gly variants caused aberrant splicing and then, exhibited XLAS. In addition, three of these variants resulted in both exon skipping and normal splicing, and these three patients showed milder phenotypes. Five of the 12 variants not causing aberrant splicing were missense variants substituted from Proline (Pro) located at Yaa of (Gly-Xaa-Yaa)n. Pro at this position is hydroxylated and results in the stabilization of the triple-helix structure. Bioinformatics analysis showed that Pro missense variants decrease the structural flexibility. Two of the remaining variants were located in the interrupted domains, which are outside of the (Gly-Xaa-Yaa)n repeat. These interrupted domains are related to the flexibility of the collagen molecule or related to network in the basement membrane. Therefore, these 2 variants were considered to influence the triple-helix structure.

Conclusions: We revealed the new mechanisms showing pathogenicity of non-Gly missense variants in *COL4A5* collagenous domain.

Funding: Government Support - Non-U.S.

PO1343

A Human Missense Integrin-Linked Kinase Variant Negatively Regulates Murine Renal Branching Morphogenesis via mTOR Signaling

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Background: Branching morphogenesis is critical to kidney development and the pathogenesis of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Identification of gene variants via genomic sequencing aims to elucidate molecular mechanisms underlying CAKUT. The pathogenic contributions of such variants are largely unknown; functional analyses are required to identify pathogenic mechanisms. Here, we identify pathogenic effects of a CAKUT-associated human missense variant of Integrin-Linked Kinase (*ILK*), a key regulator of renal branching morphogenesis, on ureteric branching.

Methods: Targeted gene panel sequencing was performed to identify gene variants. ILK-T173I function was investigated in mouse inner medullary collecting duct (mIMCD3) cells and mouse embryonic kidney explants transduced with lentivirus expressing ILK-T173I. Gene expression was analyzed by RNA microarray and validated by qPCR and Western analysis. Mutant mice with a *ILK*-c.518C>T point mutation were generated using CRISPR/Cas9. Morphogenic effects of ILK-T173I on ureteric branching were visualized using Hoxb7-driven fluorescent marker (MyrVenus) and quantitated by counts of ureteric bud tips and nephrons.

Results: An ILK missense variant, ILK-T173I, was identified in a CAKUT patient and her mother by targeted gene panel sequencing and verified by Sanger sequencing. mIMCD3 cells expressing ILK-T173I demonstrated dysregulated expression of AKT/mTOR target mRNAs, identified by RNA microarray and qPCR, and elevated levels of phospho-p70-S6Kinase, a mTOR target (n=3, P=0.03). Overexpression of ILK-T173I in embryonic kidney explants increased phospho-p70-S6Kinase expression (n=3, P=0.03) and decreased ureteric tip number by 50% (n=15, P=0.003), both of which were rescued by treatment with Rapamycin, an mTOR inhibitor (n=4, P=0.04). Knock-in mice in which ILK-T173I replaces the ILK-WT allele were characterized by low nephron number (n=6, P=0.04) and decreased ureteric branching (n=5, P=0.006), and increased expression of phospho-p70-s6Kinase (n=3, P=0.014). Treatment of mutant cultured embryonic kidney explants with Rapamycin rescued ureteric branching to levels observed in *Ilk*-WT mice.

Conclusions: Human *Ilk*-T173I variant decreases branching morphogenesis in a mTOR-dependent manner. Increased mTOR signaling disrupts mouse kidney development.

Funding: Government Support - Non-U.S.

PO1344

Whole-Exome Sequencing Identifies FOXL2, FOXA2, and FOXA3 as Candidate Genes for Monogenic Congenital Anomalies of the Kidneys and Urinary Tract

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the most common cause of chronic kidney disease in the first three decades of life. Variants in four Forkhead box *(FOX)* transcription factors have been associated with CAKUT. We hypothesized that other FOX genes, if highly expressed in developing kidney, may also represent monogenic causes of CAKUT.

Methods: We here performed whole exome sequencing (WES) in 541 families with CAKUT and generated 4 lists of CAKUT candidate genes: A) 36 *FOX* genes showing high expression during renal development, B) 4 *FOX* genes known to cause CAKUT to validate list A; C) 80 genes that we identified as unique potential novel CAKUT candidate genes when performing WES in 541 CAKUT families, and D) 175 genes identified from WES as multiple potential novel CAKUT candidate genes.

Results: To prioritize potential novel CAKUT candidates in *FOX* gene family, we overlapped 36 *FOX* genes (list A) with list C and D of WES-derived CAKUT candidates. Intersection with list C, identified a *de novo FOXL2* in-frame deletion in a patient with eyelid abnormalities and ureteropelvic junction obstruction, and a homozygous *FOXA2* missense variant in a patient with horseshoe kidney. Intersection with list D, identified a heterozygous *FOXA3* missense variant in a CAKUT family with multiple affected individuals.

Conclusions: We hereby identified *FOXL2*, *FOXA2* and *FOXA3* as novel monogenic candidate genes of CAKUT, supporting the utility of a paralog-based approach to discover mutated genes associated with human disease.

Funding: Other NIH Support - This research was supported by grants from the National Institutes of Health to F.H. (DK076683 and DK088767).

PO1345

Whole-Exome Sequencing Identifies Likely Deleterious Variants in 50 Families with Spina Bifida

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Background: Spina bifida (SB) is the second most common nonlethal malformation (1/1,000 of live births). Several lines of evidence indicate that SB can be of monogenic origin: i) its congenital nature; ii) familial occurrence; iii) it being part of the phenotypic manifestation of known monogenic syndromes; iv) the knowledge that specific master genes govern neural tube morphogenesis; v) and the existence of monogenic mouse models with SB. We hypothesized that whole exome sequencing (WES) enables identification of likely candidate mutations in a list of 170 candidate genes for SB that we generated, and may allow us to identify potential novel genes for SB.

Methods: We generated a list of 170 candidate genes of four categories: A) 33 known candidate genes from monogenic mouse SB models, B) 33 known candidate genes from human isolated SB, C) 70 known candidate genes from human syndromic SB, and D) 34 known candidate genes considered as risk factors for human SB. We evaluated WES data of 50 families with SB for likely deleterious variants in the 170 known candidate genes, and for potential novel monogenic causes of SB.

Results: Through systematic candidate gene analysis in combination with family-based unbiased evaluation in 50 SB families, we identified 16 likely deleterious variants in 170 SB candidate genes in 14/50 (28%) families: A) 5 variants (5 families) were identified in mouse candidate genes, B) 9 variants (7 families) were identified in human candidate genes for isolated SB, C) 1 variant (1 family) was identified in human syndromic candidate gene, and D) 1 variant was identified in human SB risk candidate gene. In addition, in 11 (22%) of SB families, we have identified mutations in a potential novel gene for SB.

Conclusions: In 28% of individuals with SB we identified likely deleterious variants in 170 candidate genes that we generated. Candidate genes that cause SB in mice can be considered as a potential human SB candidate gene. We additionally identified a potential novel gene in 22% of SB families.

Funding: Other NIH Support - DK076683

PO1346

Pleiotropy of Congenital Anomalies of Kidney and Urinary Tract (CAKUT) Phenotypes in Human 16p11.2 Microdeletion Syndrome Is Recapitulated in Mouse Models of Tbx6 Deletion

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Background: We showed that 16p11.2 microdeletions are a major contributor to congenital anomalies of the kidney and urinary tract (CAKUT), and identified *TBX6* as the most likely culprit. It remains elusive what are the mechanisms by which gene dosage reduction causes CAKUT and what are the TBX6 downstream signaling pathways and targets.

Methods: We studied a *Tbx6* allelic series for gene dosage using two independent alleles: a null allele and a hypomorph allele. We conducted detailed phenotypic analysis of these models across early and late development. We generated gene expression data from E9.5 tailbud mesenchyme and conducted in silico binding site analyses.

Results: Phenotypic analysis showed recapitulation of the whole CAKUT spectrum observed in 16p11.2 patients (renal agenesis and hypodysplasia, hydronephrosis, and duplications of the collecting system) but also profound lower urinary tract defects (rectovesical fistula, persistent cloaca, defects of nephric duct insertion into the urogenital sinus, urethral malformations and failed insertion of the Müllerian ducts). These defects implicate an early effect of Tbx6 in urinary tract development. Tbx6 insufficiency also promoted the occurrence of ectopic neural tubes that impaired the reciprocal interaction between the ureteric bud and metanephric mesenchyme, providing additional mechanisms linking Tbx6 to CAKUT and its pleiotropy. Differential gene expression analysis coupled with supervised and unsupervised geneset enrichment identified somite development and Notch signaling. Binding site and motif enrichment analyses recovered known and novel targets in the Tbx6 interactome including Aldh1a2, Eya1, Fgfr2, Lfng, and Reln.

Conclusions: Phenotypic investigation coupled with gene expression and binding site analyses provides support for causality for TBX6 and CAKUT as well as its pleiotropy; provides a mechanistic reason for causation; and identifies pathways and targets regulated by Tbx6. The involvement of Notch signaling is interesting as mutations in *NOTCH2* cause Alagille syndrome, characterized by CAKUT and skeletal defects observed both in our *Tbx6* mouse models and in patients that carry the 16p11.2 microdeletion. These data implicate loss of TBX6-mediated regulation of Notch as critical to the development of CAKUT and spine defects.

Funding: NIDDK Support

PO1347

Excess Burden of Rare Coding Variants in Mutation Intolerant Genes in Patients with Kidney Malformations

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Background: Renal hypodysplasia (RHD) is one of the most common cause of pediatric kidney failure. Although multiple causative genes have been identified, they only account for 10-15% of cases. The contribution of rare variants has not been systematically examined.

Methods: To evaluate the contribution of rare variants to RHD, we analyzed exome sequencing (ES) data in 1,265 unrelated RHD cases and 13,303 unrelated controls. We used gene-level burden analysis, comparing the proportion of cases and controls carrying rare variants per gene across 20 statistical models.

Results: We observed a 1.63-fold case enrichment for rare variants ($p= 1.5x10^{-6}$) in known genes associated with dominant forms of kidney diseases (165 cases versus 1,075 controls in 172 known genes), including *PAX2* ($7.6x10^{-8}$) and *HNF1B* ($5.6x10^{-6}$). All other known genes did not reach statistical significance (p-value>10^{-3}). Applying a similar approach, we observed a 1.35-fold case enrichment for rare missense variants ($p= 5.8x10^{-6}$) in genes constrained against missenses (misZ >3.09) and a 1.59-fold enrichment for rare protein truncating variants (PTV; $p= 2.4x10^{-9}$) in genes constrained against PTV (pLI>0.9 and oe lof upper<0.35). We particularly identified a 2.38-fold enrichment for PTV in 421 genes constrained against PTV, expressed in the mouse developing kidney (E15.5), and not known to be associated with human kidney disease ($p=1.4x10^{-6}$, Fig.). After curating publicly available databases, we identified at least 23 novel candidate genes, which will require validation in additional human cohorts or analysis of animal models.

Conclusions: We detected a significant excess of rare variants in mutation intolerant genes that are also expressed during early kidney development, suggesting the existence of many yet-to-be identified causal genes. However, owing to the high genetic heterogeneity of RHD, larger-scale investigations will be required to establish causality for individual genes.

Funding: NIDDK Support

PO1348

Reverse Phenotyping Facilitates Disease Allele Calling in Whole-Exome Sequencing of Patients with Congenital Anomalies of Kidney and Urinary Tract (CAKUT)

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the leading cause of chronic kidney disease in children and young adults. To date, 174 genes are known to cause isolated or syndromic monogenic CAKUT. However, incomplete penetrance and broad phenotypic heterogeneity can impair disease allele identification, particularly in syndromic CAKUT. We hypothesized that the yield of a genetic diagnosis can be increased by combining whole exome sequencing (WES) with reverse phenotyping, in which the contributing physician is asked to examine a patient for signs/symptoms that may occur in the suspected clinical syndrome that results from the genetic variant detected by WES.

Methods: We conducted WES in an international cohort of 823 individuals with CAKUT from 732 unrelated families and evaluated WES data for variants in the 174 genes in which variants are known to cause isolated or syndromic CAKUT. In cases in whom the likely causative genotype suggested a syndromic phenotype that was not reported at enrollment, we conducted reverse phenotyping.

Results: In 84/732 (11.5%) families, we detected a likely causative variant consistent with an isolated or syndromic CAKUT phenotype. In 19 of the 84 families (22.6%) with detection of a likely CAKUT-causing variant, reverse phenotyping yielded syndromic findings, thereby strengthening the genotype-phenotype correlation.

Conclusions: We conclude that employing reverse phenotyping in the evaluation of (facultative) syndromic CAKUT genes by WES provides an important tool to establish a more valid and specific diagnosis mitigating the broad phenotypic and genotypic heterogeneity of CAKUT.

Funding: Other NIH Support - This research was supported by grants from the National Institutes of Health to F.H. (DK076683)., Private Foundation Support, Government Support - Non-U.S.

PO1349

Broad Genetic Analysis Reveals Diverse Molecular Causes of Autosomal Dominant Tubulointerstitial Kidney Disease-Not Otherwise Specified (ADTKD-NOS)

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Background: A particularly difficult group of diseases to diagnose are the Autosomal Dominant Tubulointerstitial Kidney Diseases (ADTKD). ADTKD is caused by mutations in one of at least five genes and leads to end-stage renal disease usually in mid adulthood. Families where no mutation can be found are therefore termed ADTKD-NOS (not otherwise specified), who are the focus of this study. Herein we investigated 45 families of our ADTKD-registry.

Methods: The study was approved by the institutional ethics committee (protocol number 251_18B). Detailed pedigree analysis and clinical characterisation of kidney diseases were performed, as well as evaluation of historical kidney biopsies, wherever available. Panel sequencing for all known ADTKD candidate genes was performed, followed by SNaPshot minisequencing for the dupC mutation of *MUC1*. Exome-Sequencing was performed on the HiSeq System 2500 (Illumina) after enrichment by TWIST human core technology (TWIST Bioscience). Initially, 560 genes associated with abnormal renal physiology (Human Phenotype Ontology, https://mseqdr.org/hpo_browser.php?12622, retrieved March 2020) were screened (here termed *nephrome*). If no disease-causing variants were detected, exome-wide analysis was performed.

Results: In 30 of the 45 registry families mutations in known ADTKD genes were found, most frequently *MUC1*. In the remaining 15 families diagnostic gene variants were either detected in the *nephrome* (4x *COL4A5*, 1x *COL4A4*x, 2x *INF2*, 1x *PAX2*) or the exome, where analysis yielded potentially disease associated variants in novel candidate genes for ADTKD. A list of these candidate genes in the respective families will be presented. All variants segregated within families.

Conclusions: In the great majority of our ADTKD registry families we were able to reach a molecular genetic diagnosis. However, a small number of families are indeed affected by diseases, which should in retrospect be seen as glomerular origin. Atypical clinical presentation, (seemingly) autosomal dominant pedigrees (i.e. *COL4*-associated disease) and sometimes decades since onset of disease and genetic evaluation have handicapped the classification towards ADTKD-NOS. The other families investigated by exome analysis have partly led to identification of promising novel candidate genes. However, functional studies will need to follow to determine if these variants are truly pathogenic.

Funding: Government Support - Non-U.S.

PO1350

Prevalence of Autosomal Dominant Tubulointerstitial Kidney Disease in the German Chronic Kidney Disease (GCKD) Cohort

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Background: Exome sequencing (ES) studies in chronic kidney disease (CKD) cohorts could identify pathogenic variants in ~10%. This implies underdiagnosis of hereditary CKD. Tubulointerstitial kidney diseases (TKD), showing no typical clinical/histologic finding but tubulointerstitial fibrosis, are particularly difficult to diagnose. Disorders associated with a tubulointerstitial phenotype include autosomal dominant TKD (ADTKD), mitochondrially inherited TKD (MITKD), nephronophthisis (NPHP) and Collagen4 (COL4) diseases.

Methods: We used a targeted panel (29 genes) and *MUC1*-SnaPshot to sequence 271 DNAs, selected by clinical criteria from 5,217 individuals in the GCKD (German CKD) cohort.

Results: We identified 33 pathogenic small variants. Of these 27 (81.8%) were in COL4 genes, the largest group being 15 *COL4A5* variants with 9 unrelated individuals carrying c.1871G>A, p.(Gly624Asp). We found three typical cysteine variants in *UMOD*, a novel missense, and a novel splice variant in *HNF1B* and the homoplastic *MTTF* variant m.616T>C. Copy-number analysis identified a heterozygous *COL4A5* deletion, and a duplication/deletion of *HNF1B*, respectively. Overall, we found pathogenic variants in 12.5% (34/271 individuals) and variants of unknown significance in 9.6%. This yield is high despite considering the targeted design and PKD1/2 exclusion. To explain this difference we compared our findings to the largest ES study in adults with CKD by random sampling. None of the 10,000 simulations resulted in an equal or higher yield (p<0.0001). Variant classification differences were excluded using automated ACMG classifiers.

Conclusions: Our study shows that >10% of individuals with certain clinical features carry disease variants in genes associated with TKD. COL4 genes constitute the largest fraction, implying that these are easily overlooked when applying clinical criteria for Alport syndrome. We also identified variants easily missed by some ES pipelines. Bioinformatic predictions paired with gold standard diagnostics for *MUC1* (SnaPshot) could not identify the typical cytosine duplication ("c.428dupC") in any individual of this

cohort, implying that ADTKD-*MUC1* is rare. Finally, our results indicate that the filtering criteria applied enriched for individuals with an underlying genetic disorder.

Funding: Government Support - Non-U.S.

PO1351

Ultrabright Plasmonic-Fluor Nanolabel-Enabled Detection of a Urinary Endoplasmic Reticulum Stress Biomarker in Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD)-*UMOD* is one of the most common non-polycystic genetic kidney disease, but it remains unrecognized due to its clinical heterogeneity and lack of screening test. Moreover, clinical feature being a poor predictor of the disease outcome further highlights the need for development of mechanistic biomarkers in ADTKD. However, low abundant urinary proteins secreted by thick ascending limb (TAL) cells, where uromodulin (UMOD) is synthesized, have posed a challenge on detection of biomarkers in ADTKD-*UMOD*.

Methods: We have utilized CRISPR/Cas9-generated mice with *Umod*-C147W mutation, analogous to human *UMOD*-C148W mutation, and ADTKD-*UMOD* patients to discover a novel endoplasmic reticulum (ER) stress biomarker. In addition, we have developed an ultrasensitive, plasmon-enhanced fluorescence-linked immunosorbent assay (p-FLISA) to detect the urinary biomarker in ADTKD patients by harnessing a newly invented ultrabright fluorescent nanoconstruct, termed "plasmonic fluor (PF)" (Nat Biomed Eng 2020).

Results: In the murine model and patients with ADTKD-*UMOD*, we find that immunoglobulin heavy chain-binding protein (BiP), an ER chaperone, was exclusively upregulated by mutant UMOD in TAL and easily detected by Western blot in the urine at an early stage of disease. However, even the most sensitive ELISA failed to detect urinary BiP in affected individuals. We therefore developed the ultrasensitive p-FLISA, which demonstrated that urinary BiP excretion was significantly elevated in ADTKD-*UMOD* patients compared with unaffected controls. Moreover, urinary BiP elevation was positively correlated with decline of kidney function in ADTKD-*UMOD* patients.

Conclusions: By developing the ultrasensitive p-FLISA, we have identified secreted BiP as a novel urinary ER stress biomarker with potential utility in risk stratification, prediction of disease progression and guidance of ER-targeted therapies in ADTKD.

Funding: NIDDK Support, Other U.S. Government Support

PO1352

Genetic Analysis of a Brazilian Nephropathic Cystinosis Cohort Reveals Novel CTNS Variants Mostly of Non-European Origin

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Background: Nephropathic Cystinosis (NC) is a severe autosomal recessive disease caused by intralysosomal cystine deposition. Most *CTNS* variants have been described in Europe and North America, where a specific 57kb deletion (del) is the most frequent one. In this study, we seeked to characterize the *CTNS* variants and their genetic ancestry profiles in a NC Brazilian cohort, an admixed population.

Methods: 61 NC patients were studied, both sexes, ≤21 years old, followed at the University of Sao Paulo Medical Center. Mutation analysis was performed by gel electrophoresis and/or MLPA to assess the 57kb del, and NGS targeted sequencing. To characterize the genetic ancestry profiles, 48 patients were genotyped with a high-density SNP array. The average genomic ancestry was inferred using ADMIXTURE and the ancestry of the *CTNS* gene region using RFMIX.

Results: Two disease-causing variants were identified in 58/61 patients, followed by segregation analysis whenever possible. The detected variants included 9 previously reported and 7 novel ones. All previously reported variants were observed in European genomic segments, except the African ancestry-linked variant c.62-2A>G. Among the novel variants, 4 are in genomic segments of African origin (del exons 2,4,5; c.227delT:p.V76fs; c.T412C:p.W138R and c.A457T:p.K153X), 1 in Native American (c.16_19del:p.L6fs), 1 in a European-ancestry segment (c.*262_*266delinsCGGAC), and 1 could not be determined (c.158delC:p.W53fs). The highest allele frequencies were 57kb del (55.7%), c.C382T (14.0%), c.16_19del (7.4%) and c.611_613del (5.7%). Analyses of LD decay support that 57kb del, c.C382T and c.611_613del originated in Europe at least 1,750 years (250-3,750), 1,050 years (550-1,550) and 275 years ago (75-1,200), respectively, and suggest that c.16_19del likely originated in America 15,025 years ago (5,775-41,000).

Conclusions: 57kb del was the most frequent *CTNS* variant in this Brazilian NC cohort. However, given the admixed nature of the Brazilian population, novel variants with distinct ethnic origins were identified. Indeed, 5 of the 7 novel variants are located in chromosome segments of non-European ancestry. This finding raises the possibility that the novel non-European *CTNS* variants may be present in other South American and African populations.

PO1353

Adult Zebrafish as a Model to Study Renal and Extrarenal Manifestations of Cystinosis

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Background: Cystinosis is a rare autosomal recessive disease caused by mutations in the CTNS gene, which encodes for the cystine transporter cystinosin leading to lysosomal cystine accumulation in all cells of the body, with kidneys being the first affected organs. The current treatment with cysteamine decreases the lysosomal cystine accumulation, but does not reverse the renal Fanconi syndrome, glomerular injury or loss of renal function. We have developed a zebrafish larvae model having truncating mutation in *ctns*, which recapitulates the kidney phenotype of cystinosis. However, long-term disease consequences in adult zebrafish have not been studied so far. In this study, we characterized the adult zebrafish model to evaluate the late effects of cystinosis on kidney and extra renal organs.

Methods: Cystinosis (*ctns*$^{-/-}$) zebrafish of 18 months and wild type (WT) zebrafish were studied. Histologic examinations of kidneys and extra-renal organs were performed. Cleaved caspase-3 staining was used to evaluate apoptosis in the kidney. Cystine accumulation was evaluated via liquid chromatography-mass spectrometry and toluidine blue staining. For the fertility studies, the number of total eggs and fertile eggs produced by breeding female and male *ctns*$^{-/-}$ zebrafish compared to WT zebrafish was evaluated.

Results: *ctns*$^{-/-}$ zebrafish show increased cystine level, glomerular hypertrophy and proximal tubular accumulation of hyaline-like eosinophilic droplets and vacuolated cytoplasm. Moreover, the cystinotic zebrafish exhibit increased cleaved caspase-3, indicating enhanced apoptosis in the proximal tubules. In addition, instead of the typical striped pattern, *ctns*$^{-/-}$ zebrafish present an altered melanin skin pigmentation, resulting in spotted skin. Lastly, male *ctns*$^{-/-}$ zebrafish show spermatogenic cysts enriched in spermatozoa, while female display increased percentage of unfertilized eggs.

Conclusions: The adult *ctns*$^{-/-}$ zebrafish model reproduces several phenotypes of cystinosis, such as altered glomerular and proximal tubular morphology, whole body cystine accumulation, impaired skin pigmentation and decreased fertility. Therefore, this model may be useful for studying long-term effects of cystinosis and for the development of new therapeutic strategies for correcting cystinosis, which is - up to now - incurable.

PO1354

Urine-Derived Kidney Progenitor Cells in Cystinosis: Potential for Disease Modeling and Ex Vivo Gene Therapy

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Background: Nephropathic cystinosis is an inherited multisystem lysosomal storage disorder caused by mutations in the *CTNS* gene. The kidney phenotype is characterized by excessive shedding of proximal tubular cells and podocytes into urine, development of renal Fanconi syndrome and progression to end-stage kidney disease. We hypothesized that, to compensate for epithelial cell losses, cystinosis kidneys undertake a regenerative effort, albeit maladaptive. We aimed to search for the presence of kidney progenitor cells (KPCs) in urine of cystinosis patients, and to explore the feasibility of *ex vivo* gene therapy.

Methods: We isolated undifferentiated cells from urine of cystinosis patients, characterized them as KPCs (Cys-uKPCs) and differentiated these to podocytes (Cys-uKPC-Podo) and proximal tubular epithelial cells (Cys-uKPC-PTEC) as shown by qPCR, RNA sequencing, immunostainings and specific functional assays. Complementation of *CTNS* in Cys-uKPCs was performed via lentiviral vector (LV) transduction.

Results: Cystinosis patients voided high numbers of undifferentiated cells in urine, of which specific clones expressed several kidney progenitor markers, showed a high level of self renewal, and could differentiate into functional podocytes and PTECs. RNA sequencing demonstrated distinctive transcriptomic signatures distinguishing Cys-uKPCs, Cys-uKPC-Podo and Cys-uKPC-PTEC. *Ex vivo* gene therapy using a gene addition approach with wild-type *CTNS* showed significant reductions of cystine levels and altered the perinuclear distribution of the LAMP1^{+} endo-lysosomal compartment.

Conclusions: Kidney progenitor cells are present in the urine of cystinosis patients. These cells can be isolated, differentiated to functional kidney epithelial cells and complemented with wild-type *CTNS* to improve the cellular phenotype. Cystinosis uKPCs are a novel tool for disease modeling, while we provided proof of principle of *ex vivo* gene therapy.

Funding: Private Foundation Support

PO1355

Vascularized Kidney Organoids on Chip for Efficacy and Toxicity Testing of Somatic Genome Editing

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Background: Somatic genome editing has therapeutic potential to cure inheritable disease. Clinical translation requires safety and efficacy analyses. DNA editing may be widely discrepant across species due to genomic differences, necessitating human tissue-based platforms. AAV-based delivery of DNA editing elements is under clinical investigation. If delivered systemically, the kidney may be particularly susceptible to genome editing owing to high blood flow. Kidney organoids have been generated from human stem cells through the co-induction of nephron, stromal, and endothelial progenitor cells that mature to form multicompartment human kidney tissue. We married organoid and organ-on-chip technologies to facilitate the maturation of nephron epithelia and the development of perfusable vascular networks to simulate systemic delivery of genome editing elements.

Methods: Using human recombinant growth factors and defined small molecules, kidney organoids were generated from male and female, embryonic and induced, stem cell lines. To test the efficacy of an AAV2-based delivery system, the tropism of varied capsids, 2/8/9, for kidney compartments was assessed under static and perfused conditions. The AAV receptor expression was evaluated by single nuclear RNA-seq.

Results: The greatest infectivity was with capsid protein 2, whose receptor of heparin sulfate proteoglycan is expressed in proximal & distal tubules and podocytes of kidney organoids by single cellular transcriptomics. Biomarker analysis demonstrated a statistically significant increase in tubular injury markers, KIM-1 and MCP-1, after infection with AAV2/2 as compared to other AAVs. Following treatment with AAV2/2CMVeGFP, the majority of LTL^+ and $CDH1^+$ tubular epithelia were GFP^+, while $PODXL^+$ podocytes were poorly infected. The optimal AAV serotype, MOI, and duration of infection under static conditions were applied to vascularized kidney organoids. Initial on-chip testing supports enhanced infectivity by live-cell monitoring and wholemount immunostaining, including AAV infection in GFP^+PODXL^+ podocytes.

Conclusions: We propose vascularized kidney organoids may simulate the systemic delivery of AAVs across kidney compartments, as a pre-clinical testing platform of the efficacy and safety of somatic cell genome editing.

Funding: Other NIH Support - U01: SCGE Consortium

PO1356

Genotype and Phenotype Analysis in Patients with X-Linked Hypophosphatemia

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Background: X-linked hypophosphatemia (XLH) is the most frequent form of hypophosphatemic rickets and is caused by mutations in the PHEX gene. We analyzed genotype-phenotype correlations in XLH patients with proven PHEX mutations.

Methods: PHEX mutations were detected in 57 out of 81 patients who clinically presented with hypophosphatemic rickets. The patients were grouped into nontruncating (n = 11) and truncating (n = 46) mutation groups; their initial presentation as well as long-term clinical findings were evaluated according to these groups.

Results: Initial findings, including presenting symptoms, onset age, height standard deviation scores (SDSs), and laboratory tests, including serum phosphate level and tubular resorption of phosphate, were not significantly different between the two groups (onset age: nontruncating mutation group, 2.0 years, truncating mutation group, 2.1 years; height SDS: nontruncating mutation group, -1.9, truncating mutation group, -1.8; serum phosphate: nontruncating mutation group, 2.5 mg/dL, truncating mutation group, 2.5 mg/dL). However, at their last follow-up, the serum phosphate level was significantly lower in patients with truncating mutations (nontruncating mutation group: 3.2 mg/dl, truncating mutation group: 2.3 mg/dl; P value 0.003). Additionally, 62.5% of patients with truncating mutations developed nephrocalcinosis at their last follow-up, while none of the patients with nontruncating mutations developed nephrocalcinosis (P value 0.008). Orthopedic surgery due to bony deformations was performed significantly more often in patients with truncating mutations (52.3% vs 10.0%, P value 0.038).

Conclusions: Although considerable inconsistency exists regarding the correlation of truncating mutations and their disease phenotype in several other studies, we cautiously suggest that there would be genotype-phenotype correlation in some aspects of disease manifestation after long-term follow-up. This information can be used when consulting patients with confirmed XLH regarding their disease prognosis.

PO1357

Childhood-Onset Nephrocalcinosis in Twins Caused By Biallelic Mutations in CYP24A1 Gene: A Long Journey to a Genetic Diagnosis

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Introduction: 24-hydroxylase deficiency is a rare autosomal recessive disorder caused by mutations in CYP24A1 gene, characterized by hypercalcemia, hypercalciuria and nephrolithiasis. Establishing a genetic diagnosis, while important to guide management and family counseling, can be challenging. We hereby report a case of twins with childhood-onset nephrocalcinosis and chronic hypercalcemia caused by biallelic mutations of CYP24A1, which took years to be diagnosed.

Case Description: A 26 year-old female presented for preconception evaluation for a history of childhood-onset nephrocalcinosis and chronic hypercalciuric hypercalcemia. Patient reported similar history in identical twin sister. They had exome sequencing (ES) eight years ago after negative genes panel test which revealed a heterozygous variant of unknown significance (c.1186C>T) in CYP24A1. A reanalysis of ES was performed four years ago which demonstrated no changes. Work up revealed hypercalciuric hypercalcemia, low 25(OH)vitamin D, elevated 1,25(OH)vitamin D and 24,25(OH) vitamin D, and suppressed PTH(fig.1). Ratio of 25(OH)D-to-24,25-(OH)2D, a new biochemical test for 24-hydroxylase deficiency, suggested biallelic mutations in CYP24A1 gene. ES reanalysis at this time reclassified the c.1186C>T variant as pathogenic and disclosed a novel intronic variant (c.544-17G>A) which was predicted to cause splicing pattern change with multiple silico algorithms. Parental tests confirmed these two variants were in trans configuration consistent with autosomal recessive inheritance pattern. A thorough counselling included low recurrence risk for her children while high risk for her to develop severe hypercalcemia during pregnancy. She has been closely monitored with low calcium and vitamin D diet, sun avoidance and adequate hydration during current pregnancy with no complications to date.

Discussion: CYP24A1 gene related hypercalcemia is rare and challenging to diagnose even with ES. This case suggests the benefits of ES regular reanalysis for clinically suspected patients with inconclusive genetic findings. The novel intronic mutation identified in this case broadens the genetics spectrum of 24-hydroxylase deficiency.

	Reference range	Results
Calcium *(mg/dl)*	8.5-10.2	9.5- 11.3 ↑
PTH *(pg/mL)*	15-65	4↓
25(OH) vitamin D *(pg/mL)*	31-80	27.1-29.1 ↓
1,25 (OH)vitamin D *(pg/mL)*	15-60	66.1 ↓
24,25 (OH) vitamin D *(pg/mL)*	<20	285 ↑
24 Hour Urine Calcium *(mg/24H)*	100-300	311-872 ↑
Ratio 25(OH)D-to-24,25-(OH)2D	> 80 suggestive of biallelic mutations or deletions in CYP24A1 gene	285↑

Figure 1

PO1358

Refractory Hypocalcemia with Recurrent Nephrolithiasis Related to a De Novo Gain-of-Function Mutation in the CaSR Gene

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Introduction: The calcium-sensing receptor (CASR) serves as the key calcium sensor in the maintenance of systemic calcium homeostasis. Gain-of-function mutations of CaSR-gene, mapped to Ala116-Pro136 region, causes autosomal dominant hypocalcemia and Bartter syndrome type V. Phenotypic manifestations include hypercalciuric hypocalcemia(mostly asymptomatic), hypoparathyroidism, paresthesias, tetany/ epilepsy, nephrocalcinosis/ nephrolithiasis, hypomagnesemia, ectopic and intracranial calcifications. Here we report a case of gravid female who experienced refractory hypocalcemia with recurrent nephrolithiasis related to a de novo gain-of-function mutation in the CASR gene.

Case Description: A 25 year-old G1P0 female at 20 weeks of gestation presented to genetic nephrology clinic due to refractory hypocalcemia. She was incidentally found to have asymptomatic hypocalcemia as part of prenatal evaluation. She was treated with calcium and calcitriol for four months while hypocalcemia persisted. Physical exam was unremarkable. As shown in **Table 1**, her total serum calcium had been persistently low despite calcium and Vitamin D supplementations, and she had low PTH, hyperphosphatemia, hypomagnesemia, and hypercalciuria. Genetic testing revealed a variant (c.398A>T,pGlu133Val) in CASR gene, with negative parental testing consistent with de novo mutation. Given this finding, calcium and calcitriol were discontinued. Renal ultrasound to assess stone burden showed bilateral renal calculi, which patient passed during delivery. Recurrent renal calculi were discovered on post-delivery follow up imaging, necessitating laser lithotripsy and left ureteral stent insertion.

Discussion: This case highlights the importance of early diagnoses by genetic testing which could guide the hypocalcemia management, as routine calcium and vitamin D supplementation exacerbates hypercalciuria and thus risk of nephrocalcinosis/ nephrolithiasis. c.398A>T,pGlu133Val mutation has been described in 1 family cluster of 3 patients with hypoparathyroidism and hypocalcemia to date. De novo mutation, unique to this case, was evidenced by negative parental testing.

	Reference range	Results
Calcium *(mg/dl)*	8.6-10	6.9- 8.0 ↓
Ionized calcium *(mmol/L)*	1.15-1.29	0.99 ↓
Phosphorus *(mg/dl)*	2.5-4.5	5-6.1 ↑
PTH *(pg/mL)*	18.5 -88	<6 -13.4 ↓
24 hour urine calcium *(mg/24H)*	< 200	546 ↑
Magnesium *(mg/dl)*	1.7-2.3	1.5-1.7 ↓

PO1359

TRPV4 Calcium Channel Activity Is Increased by With-No-Lysine Kinase 1 in the Collecting Duct Cells

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Background: Kidneys play a central role in regulation of potassium homeostasis and maintaining plasma K^+ levels within a narrow physiological range. Dietary K^+ load increases circulating levels of the mineralocorticoid aldosterone leading to kaliuresis via stimulation calcium-activated large conductive maxi-K^+ (BK) channel dependent K^+ secretion in the collecting duct cells. WNK1 and WNK4 (With-no-lysine) kinases, have been recognized to regulate K^+ balance, in part, by orchestrating BK-dependent K^+ secretion in the ASDN (aldosterone sensitive renal nephron). Ca^{2+}-permeable TRPV4 channel is essential for BK activation in the distal nephron, as we have recently demonstrated. Also of note, high K^+ diet increases TRPV4 activity and expression largely in an aldosterone-dependent manner.

Methods: Patch-Clamp; $[Ca_{2+}]_i$ imaging; Western blotting;

Results: In the current study, we aimed to test whether WNK1/4 contribute to regulation of TRPV4 by aldosterone. First we treatment of mpkCCDc14 cells with 1 μM aldosterone for 24 h it as expected, increased TRPV4-dependent Ca2+ influx approximately 2 fold. Inhibition of WNK1/4 with the pan-blocker of WNK, WNK463 (100 nM for 24h) decreased basal TRPV4 activity by approximately 30% and virtually abolished stimulation of TRPV4 by aldosterone. Similarly, WNK1 blockade with WNK-in-11 (400 nM, 24 h) produced comparable inhibitory effects on the basal and aldosterone-dependent TRPV4 activity as WNK463. Western blots performed on apical plasma membrane fraction from the same cells showed a complete block of the stimulatory effect of aldosterone after treatment with WNK-in-11 (400 nM, 24 h). Co-expression of TRPV4 and WNK1 into Chinese hamster ovary (CHO) cells increased the macroscopic TRPV4-dependent cation currents from 160±10 pA/pF to 250±22 pA/pF. In contrast, overexpression of TRPV4 with a dominant negative WNK1 variant (K233M) decreased the whole cell currents to 60±5 pA/pF suggesting both stimulatory and permissive roles of WNK1 in regulation of TRPV4.

Conclusions: Overall, we show that WNK1 is essential in controling of basal TRPV4 activity and its activation by aldosterone in collecting duct cells. We propose that this new mechanism is likely contributing to regulation of urinary K^+ levels to maintain systemic homeostasis.

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

PO1360

Cyclin M2 (CNNM2) Is Essential for Development and Systemic Magnesium Homeostasis

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Background: Patients with mutations in the Cyclin M2 (*CNNM2)* gene display hypomagnesaemia and intellectual disability. CNNM2 is highly expressed in the distal convoluted tubule, where it is involved in renal magnesium (Mg^{2+}) reabsorption. However, the complete phenotypical spectrum of the CNNM2-related disorder remains unknown. We characterised a large patient cohort with novel *CNNM2* variants and used transgenic mouse models to investigate the role of CNNM2 in Mg^{2+} homeostasis.

Methods: The identified *CNNM2* variants were found in a cohort of hypomagnesaemic patients and characterised using $^{25}Mg^{2+}$ transport assays in HEK293 cells. In addition, *Cnnm2* deficient mice were developed using CRISPR/Cas9 technology and exposed to deficient or saturated Mg^{2+} diets for two weeks. Using metabolic cages, the 24-hour urinary and faecal excretion for Mg^{2+} was determined.

Results: Eleven patients were identified with novel dominant variants in CNNM2. Using $^{25}Mg^{2+}$ transport assays in HEK293 cells, seven variants showed decreased $^{25}Mg^{2+}$ transport compared to wild type. These pathogenic mutations resulted in decreased membrane expression of CNNM2. The phenotype of these patients was compared with those previously published. Patients with pathogenic *CNNM2* mutations had a mean plasma Mg^{2+} level of 0.54 ± 0.08 mmol/L. Neurological manifestations, such as seizures (79%), intellectual disability (92%) and speech difficulties (91%) were prevalent. Interestingly, obesity was often (80%) found. To elucidate the physiological function of CNNM2, we generated knockout mouse models. Approximately 30% of *Cnnm2*$^{-/-}$ embryos displayed exencephaly and all died shortly after birth. Both *Cnnm2*$^{-/-}$, *Cnnm2*$^{+/-}$ and *Cnnm2*$^{+/-}$ pups, and *Cnnm2*$^{+/-}$ adult mice showed decreased serum Mg^{2+} levels and increased Ca^{2+} levels, independent when fed with deficient or saturated Mg^{2+} diets. At basal level, adult *Cnnm2*$^{+/-}$ mice showed increased faecal Mg^{2+} and Ca^{2+} excretion compared to control.

Conclusions: CNNM2 is important for normal development and Mg^{2+} homeostasis, although the link remains elusive. Our mouse study suggests a putative role of CNNM2 in the intestine, which could have implications for the treatment of patients suffering from CNNM2 mutations.

PO1361

BCS1L Mutations Produce Fanconi Syndrome with Developmental Disability

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Background: Fanconi syndrome is a functional disorder of the proximal tubule, characterized by pan-aminoaciduria, glucosuria, hypophosphatemia, and metabolic acidosis. With the advancements in gene analysis technologies, several causative genes are identified for Fanconi syndrome. Several mitochondrial diseases cause Fanconi syndrome and various systemic symptoms; however, it is rare that the main clinical symptoms in such disorders are Fanconi syndrome without systematic active diseases like encephalomyopathy or cardiomyopathy.

Methods: We analyzed the patients clinically diagnosed with Fanconi syndrome of unknown cause. Patient-1 was a 3-year-old girl and Patient-2 was a 10-months-old boy. They were diagnosed with Fanconi syndrome based on renal tubular dysfunction, rickets, and elevated aspartate aminotransferase and alanine aminotransferase levels. They also had severe developmental disability and growth failure. Patient-1 had twin brothers who were diagnosed with Fanconi syndrome. GDF-15, a mitochondrial disease biomarker, was evaluated as an analysis of mitochondrial dysfunction. The following assays were also performed to confirm the pathogenicity of the novel mutations: oxygen consumption rate (OCR) of mitochondria, the activity of mitochondrial respiratory chain complexes.

Results: Whole-exome sequencing detected compound heterozygous *BCS1L* mutations, which cause mitochondrial respiratory chain complex III deficiency. In Patient-1, we identified missense mutation and frameshift mutation of *BCS1L*, c.268C>T, p.(Arg90Cys) and c.821del, p.(Pro274Argfs*26). These mutations have been reported previously. In Patient-2, we also identified novel missense mutations of *BCS1L*, c.167G>A, p.(Arg56Gln) and c.1195T>G, p.(Tyr399Asp). The level of GDF-15 was elevated in both patients; 1025.5 pg/mL in Patient-1 and 1152.1 pg/mL in Patient-2 (normal: <707.4 pg/mL). In Patient-2 skin fibroblasts, the activities of mitochondrial respiratory chain complexes were normal, whereas the OCR was significantly lower than that in the control.

Conclusions: Mitochondrial diseases with isolated renal symptoms are uncommon; however, this study indicates that mitochondrial respiratory chain complex III deficiency due to *BCS1L* mutations cause Fanconi syndrome with developmental disability as the primally indications.

PO1362

Expression of miRNA from Urinary Extracellular Vesicles in Patients with Gitelman Syndrome

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Background: Gitelman syndrome (GS) is an inheritable renal tubule disorder with defect of sodium chloride cotransporter on distal convoluted tubule, resulting salt-losing, hypokalemia, hypomagnesemia and hypocalciuria. miRNA plays an important role in renal development and physical regulation. However, the miRNA expression from urinary extracellular vesicles (uEVs) in patients with Gitelman syndrome remains unclear.

Methods: miRNA profiling was conducted in uEVs obtained from 20 genetically confirmed GS patients and 20 healthy controls using small RNA sequencing.

Results: Principal component analysis revealed distinct miRNA expression pattern in GS patients (4 groups) compared with healthy controls (4 groups). The biological process from identified miRNA in uEVs included signaling transduction (24.3%), cell communication (22.6%), regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism (18.4%), and transporter (7.7%). Comparing with healthy controls, differential expression of miRNA showed 18 upregulated miRNA (including has-miR-6825-5p, has-miR-4302, has-miR-4458) and 23 downregulated miRNAs (including has-miR-4740-5p, has-miR-4783-5p, has-miR-4508) in GS patients. Biological process conducted by DAVID (Database for Annotation, Visualization, and Integrated Discovery) using target genes from differential expressed up-regulated miRNAs were negative regulation of translation, positive regulation of transcription, and gene silencing by miRNA. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis from upregulated miRNAs also revealed PI3K-Akt, MAPK, ErbB, aldosterone synthesis and secretion, TGF-β, aldosterone regulated sodium reabsorption, and calcium signaling pathways.

Conclusions: The expression of miRNA from uEVs in patients with GS could provide a physiological role in response to defect of NCC. Further validation and functional study will be performed.

Funding: Government Support - Non-U.S.

PO1363

Infantile Hypercalcemia Associated with a Novel Homozygous Mutation in SLC34A1 Gene Encoding Sodium-Dependent Phosphate Transporter 2A

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Introduction: Early-onset and familial hypercalcemia often suggest a genetic etiology which is rare. Infantile hypercalcemia (IH) is a rare, autosomal recessive disorder that occurs due to mutations in the *SLC34A1* gene which encodes a sodium-dependent phosphate transporter 2A(NaPi-IIA) responsible for phosphate reabsorption in the kidney. We report an adult case who carried a clinical diagnosis of familial hypocalciuric hypercalcemia (FHH) since infancy, which is usually a benign condition characterized by autosomal dominant inheritance caused by mutations in calcium-sensing receptor (CASR) gene, while recently uncovered as IH related to a novel homozygous mutation in the *SLC34A1* gene.

Case Description: A 36-year-old Finnish male with a diagnosis of FHH presented to the genetics nephrology clinic for consultation regarding the recurrence risk for his children. He was diagnosed with FHH during infancy in Finland and has been treated with a low calcium diet. Family history was notable for a clinical diagnosis of FHH in his older sister. Physical exam was unremarkable. Labs showed mild hypophosphatemia and decreased glomerular filtration rate (69 mL/min/1.73m^2), with normal serum ionized calcium and intact parathyroid hormone. Twenty-four hour urine analysis revealed hypercalciuria 363 mg/d (normal <250), hypernatriuria 155 mmol/d (normal 50 – 150) and hypocitraturia 420 mg/d (normal >450). Kidney ultrasound showed bilateral medullary nephrocalcinosis. Genetic testing identified a novel homozygous variant in *SLC34A1* gene (c.1483C>T) and was negative in *CASR* gene. Family genetic studies revealed his affected sister is also homozygous for the same variant while his unaffected sister is only a carrier. With the new diagnosis, he was started on potassium citrate and chlorthalidone, and was reassured with the low recurrence risk for his children.

Discussion: Mutations in the *SLC34A1* gene lead to altered NaPi-IIA expression and reduced phosphate reabsorption, leading to hypophosphatemia. Secondary vitamin D activation leads to hypercalcemia, hypercalciuria, and nephrocalcinosis. We identified a novel mutation in the *SLC34A1* gene which broadens the genetic spectrum of IH. This case highlights the importance of early genetic testing for suspected hereditary hypercalcemia that may help improve its diagnosis and treatment.

PO1364

Characteristics and Genetic Defects of Systemic Lupus Erythematosus-Associated Thrombotic Microangiopathy

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Background: Thrombotic microangiopathy (TMA) is a life-threatening complication of systemic lupus erythematosus (SLE). However, the etiology of a considerable number of patients is still unclear and the best treatment is unknown. Sporadic reports suggest that the activation of complement pathway may play a role in SLE-TMA.

Methods: We prospectively enrolled 40 SLE-TMA patients in Peking Union Medical College Hospital, 14 patients with lupus nephritis (LN) and 38 patients with other types of TMA. The clinical data were collected. Peripheral blood concentrations of CFH, cCFB, soluble C5b-9, relative activity of complement pathway, ICAM1, VCAM1 and E-Selectin were measured by ELISA in SLE-TMA patients and control groups. Whole exome sequencing (WES) was performed to analyze the genetic variants in SLE-TMA patients.

Results: SLE-TMA mediated by ADAMTS13 inhibitors had severe nervous system involvement, but less kidney involvement and good response to plasma exchange. Among SLE-TMA with unknown etiology, patients with TMA confined to kidney had lighter hematological manifestations and lower serum creatinine level than SLE-aHUS ($p = 0.005$). Compared with SLE-aHUS, the concentration of CFH in SLE-TMA limited to kidney was higher ($p = 0.026$). The level of E-selectin in patients with SLE-TMA limited to kidney was significantly lower than that in SLE-aHUS patients with MAHA ($p = 0.016$). There was no significant difference in genetic susceptibility among SLE-aHUS, SLE-TMA limited to kidney and SLE-TMA with other causes. In SLE-TMA patients, thrombophilia variants may play a more important role than complement variants. Treatment response of SLE-TMA patients with variants is worse than those without variants. In serological test, VCAM1 level in SLE-TMA patients with complement related genetic variants was significantly higher than that in SLE-TMA patients without variants ($p = 0.001$). Patients with compound complement variants are more likely to detect abnormal level of complement factors.

Conclusions: SLE-TMA with unknown etiology can be divided into two subgroups with different severity according to the presence or absence of MAHA. The detection of complement factor and E-selectin may play a role in differentiating the two subgroups of SLE-TMA. The complement pathway is highly activated in patients with compound complement mutations, resulting in increased complement factors consumption.

PO1365

A Popping Renal Artery

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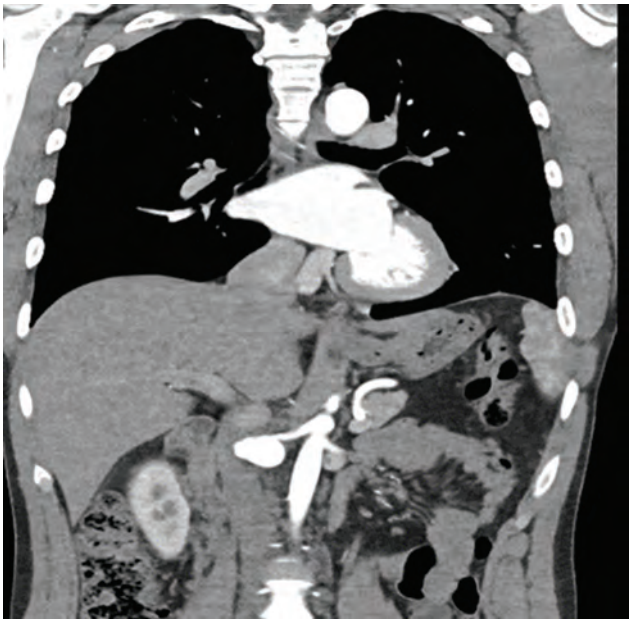
Introduction: The *COL3A1* gene encodes the collagen type III alpha chain, which forms the helical conformation. A mutation on this genec causes vascular Ehlers-Danlos syndrome (v-EDS), a life-threatening disease characterized by arterial fragility, vascular dissection or rupture, and organ perforation are the most common presenting signs in adults with vEDS (1).

Case Description: A 25-year-old man with history of bicuspid aortic valve, shoulder dislocation, chronic hemoptysis presented with severe left flank pain and syncope. A CT scan revealed a right retroperitoneal hematoma and aneurysms on the right renal artery (Image 1). Differential diagnosis were fibromuscular dysplasia, small vessel vasculitis and segmental arterial mediolysis (SAM). An extensive rheumatologic and vasculitis workup was negative. A collagen vascular disease was considered due to the history of bicuspid aortic valve and shoulder dislocation, and genetic testing was ordered. He underwent an urgent aorta-to-right renal artery bypass, and ligation of the aneurysm. Postoperatively, he developed hypotension. Abdominal imaging showed a new aneurysm on the superior mesenteric artery. Genetic testing results showed a *COL3A1 c.593 A* pathogenic variant, confirming vEDS. He now is treated with metoprolol succinate and spironolactone. His fathers genetic testing revealed possible mosaicism.

Discussion: vEDS is an uncommon but severe disease that needs a high degree of clinical suspicion. Patients usually present with unexplained pneumothorax, organ perforations and arterial ruptures. Little data exists about medical management, goals include mantaining low blood pressures (less than 120/80 mmHg). As well, patients should avoid contact sports and isometric exercises. Patients need constant imaging surveillance on the brain, neck, chest, abdominal and pelvic arteries.



PO1366

Mapping Genomic Regulation of Kidney Diseases and Traits at a Cell Type and Variant Level of Specificity

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Background: Although numerous genetically associated loci for kidney function and disease have been identified by genome-wide association studies (GWAS), determining the causal genes and functional variants remains a major challenge. Integration of GWAS results with other data types (such as expression quantitative trait loci [eQTLs]) can help identify causal and functional variants in a tissue- or cell-type specific manner. Further, analysis of disease tissue may uncover context-specific associations that may otherwise not be detectable.

Methods: We integrated eQTL data from micro-dissected glomerular (n = 240) and tubulointerstitial (TI) (n = 311) transcriptomes from individuals with nephrotic syndrome and summary statistics from two large trans-ethnic GWAS meta-analyses for estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). We applied a Bayesian statistical framework for eQTL discovery and multi-SNP fine-mapping (TORUS/DAP). eQTL signals from each renal compartment were integrated with summary statistics to perform a gene-level probabilistic transcriptome-wide association study (PTWAS) and SNP-level co-localization (fastENLOC).

Results: We identified 5,526 glomerular and 9,742 TI eQTLs at < 5% FDR level. For eGFR, we identified 971 gene-trait pairs in the glomerulus and 1,816 gene-trait pairs in TI tissue that were significant (FDR < 5%). For UACR, we identified 194 and 340

significant gene-trait pairs in the glomerulus and TI tissue, respectively. In the SNP-level co-localization, we identified 46 TI and 3 glomerular co-localization signals (regional co-localization probability [RCP] > 50%) for eGFR, including known associations with *UMOD* and *FGF5* expression, as well as novel associations to *LARP4B* and *RRAGD* which can be attributed to single variants. We identified 7 TI and 16 glomerular co-localization signals (RCP > 50%) for UACR. In addition to replicating co-localization signals at *PRKCI* and *TGFB1* in glomerular tissue, we refined the co-localization signal at *PTH1R* to a single variant, rs6787229, which also co-localized with expression of *MYL3*.

Conclusions: Profiling and integrating renal compartment-specific eQTLs with kidney trait GWAS results in a probabalistic framework identified novel gene-trait associations and refined many known associations to a single variant.

Funding: NIDDK Support

PO1367

Factors Contributing to Decisional Conflict in Older Persons Facing Dialysis Decisions

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Background: Dialysis and conservative kidney management are the two main treatment options for elderly persons with end-stage-kidney disease who are ineligible for kidney transplantation. The high stakes of these decisions often force patients to choose between quality versus quantity of life. Thus, they face tremendous conflict while making dialysis decisions. This decisional conflict can adversely affect their mental health-related quality of life and leads to avoidable delays in decision making. Exploring factors contributing to dialysis decisional conflict in older persons with chronic kidney disease is critical.

Methods: Using a qualitative descriptive approach, we purposefully sampled a cohort of 10 patients; 5 with high scores on decisional conflict scale, and 5 with low scores. Patients met with a palliative care physician to discuss dialysis and these visits were audio-recorded. Audio recordings were transcribed verbatim and entered into MAXQDA for data management. Following an iterative process, 2 independent reviewers analyzed the transcripts for common themes contributing to decisional conflict.

Results: The mean age of patients was 83 years. We observed 3 themes in the data of patients with low decisional conflict: (1) clarity in values, (2) good current quality of life, and (3) strong therapeutic alliance with their nephrologist. In the high decisional conflict group, we observed 5 themes: (1) fear of: physical pain, complications from dialysis and its time commitment, loneliness, and losing independence, (2) concerns about being a burden to loved ones, (3) uncertainty about prognosis, (4) worries about transportation to and from dialysis, and (5) poor knowledge of treatment options.

Conclusions: Patients with high decisional conflict worried about their future quality of life, sense of burdensomeness, prognostic uncertainty, and issues related to transportation. They wished for detailed knowledge of treatment options. Future dialysis decision-making interventions should be tailored to identify each patient's unique needs, and incorporate details about treatment options and information about logistics of dialysis. Nephrologists need to discuss the expected quality of life and prognosis. Last, family involvement in these discussions and buy-in for or against dialysis may be helpful in mitigating the patient's sense of being a burden on their loved ones.

PO1368

Shared Decision-Making Among Older Adults with Advanced CKD

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Background: Older adults with advanced chronic kidney disease (CKD) face difficult, preference-sensitive decisions about dialysis. Although shared decision-making (SDM) can help align treatment with patient preferences and values, the degree to which older CKD patients experience SDM and associated factors remain unknown.

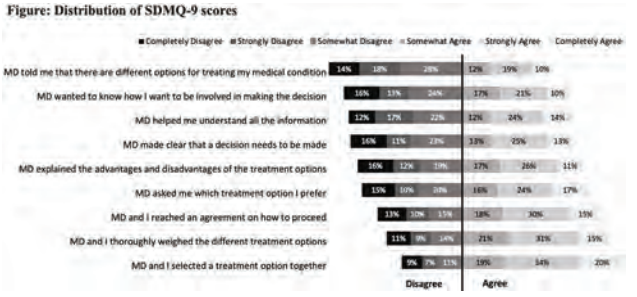
Methods: Using data from the Decision Aid for Renal Therapy Trial, we examined SDM in adults >70 years with non-dialysis CKD stage 4–5 from 4 sites in the US using the validated SDMQ9 measure, with scores scaled from 0-100 and higher scores reflecting greater SDM. We categorized predictors into demographic and clinical factors, cognitive factors (decisional perception and uncertainty), and behavioral and educational factors (resources supporting SDM). Multivariable linear regression assessed predictors of SDM.

Results: Among 350 participants, mean age was 78±6 years, 58% were male, 13% were Black, and 48% had diabetes. Mean SDMQ9 score was 52±28. Responses varied from 73% somewhat, strongly, or completely agreeing that "*My doctor told me that there are different options for treating my medical condition*," to just 41% agreeing that "*My doctor and I selected a treatment option together*" (Figure). In regression analyses, being "very well informed" about kidney treatment options (β=14.9, p=0.02), Black race (β=10.4, p=0.02), attended a dialysis class (β=8.3, p=0.02), diabetes (β=7.9, p=0.007), older age (β=5.2, p=0.04), lower eGFR (β=-2.4, p=0.02), and higher decisional certainty (β=1.5, p=0.002) were associated with higher SDMQ9 scores. In models evaluating behavioral/educational factors, dialysis class attendance (β=8.8, p=0.009) and care satisfaction (β=2.4, p=0.02) were associated with higher scores.

Conclusions: There is room for improvement in SDM for many older CKD patients who face preference-sensitive dialysis decisions. Being well-informed about treatment options, increased decision certainty, and dialysis options class attendance were associated with SDM, suggesting that education is critical to the SDM process.

Funding: Private Foundation Support

Figure: Distribution of SDMQ-9 scores



PO1369

A Qualitative Study of Patient-Clinician Dyads on Perceived Challenges to Shared Decision-Making About Treatment of Advanced CKD

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Background: An important step to implementation of shared decision-making for treatment of advanced CKD is acquiring a deeper understanding of its perceived challenges.

Methods: We performed a qualitative study using in-depth interviews with 29 patients aged ≥65 years with advanced CKD and 10 of their clinicians. We also reviewed patients' electronic health records and abstracted passages containing further information on treatment of their advanced CKD. We used thematic analysis to analyze interview transcripts and note passages and identify emergent themes reflecting their joint experiences with decision-making about treatment of their advanced CKD.

Results: Patients (age 73±6 years) were mostly men (66%) and Caucasian (59%). Of the clinicians (age 52±12 years, 30% male, 70% Caucasian) who participated in interviews, 4 (40%) were non-nephrologists. Four themes emerged from qualitative analysis: 1) *Competing priorities*: patients and their clinicians tended to differ on when to triage CKD and dialysis planning above other priorities; 2) *Focusing on present or future*: patients and their clinicians could be misaligned on their outlook on CKD, with patients being more focused on living well now; and clinicians, on preparing for dialysis and future adverse events; 3) *Textbook approach to CKD*: patients perceived their clinicians as taking a monolithic approach to CKD that was predicated on clinical practice guidelines and medical literature rather than their lived experience with illness, while clinicians were uncertain about how to incorporate patients' personal values and goals into decision-making; and 4) *Power dynamics:* while patients described cautiously navigating a power differential between themselves and their clinicians, clinicians seemed less attuned to these power dynamics.

Conclusions: Improving shared decision-making for treatment of advanced CKD will likely require efforts that explicitly reconcile the differences in mindset between patients and their clinicians on decision-making about treatment of advanced CKD and that address the power imbalances in their therapeutic relationship.

Funding: NIDDK Support

PO1370

Effect of Estimated Glomerular Filtration Rate on Survival in Patients ≥75 Years of Age at Dialysis Initiation

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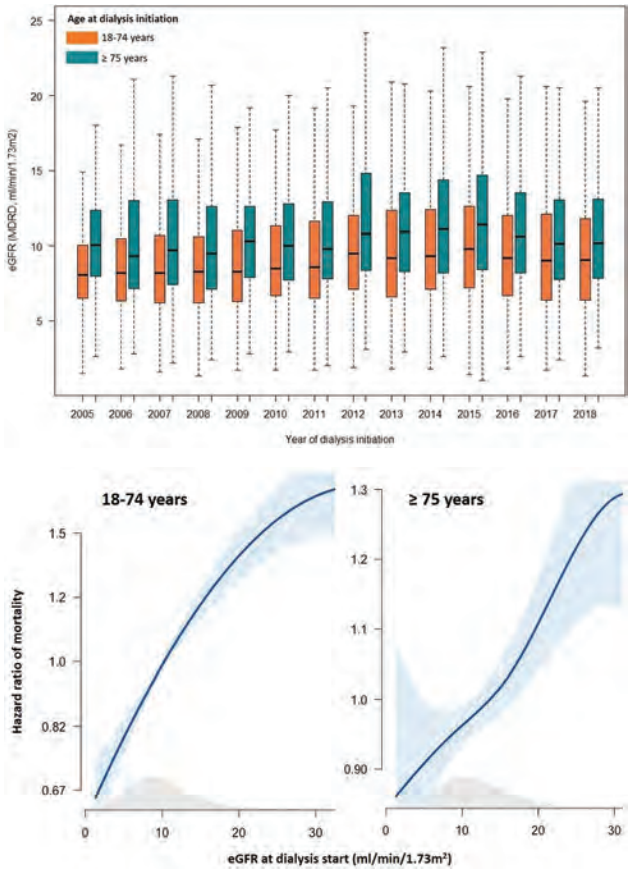
Background: Data regarding the prognostic impact of estimated glomerular filtration rate (eGFR) at dialysis start are discordant, and remain very scarce in elderly populations. The aim of this study is to explore whether the effect of eGFR on survival was similar in elderly incident dialysis patients compared with younger ones.

Methods: We included 4690 patients ≥75 years of age and 7045 patients 18-74 years of age starting dialysis between 2004 and 2018 from a French regional registry. Patients were followed until death or the end of 2019. Survival was assessed by Kaplan-Meier curves and the relative risk of death associated with eGFR (MDRD) was assessed by multivariate Cox regression analysis.

Results: The results showed an increasing trend of eGFR at dialysis start, which was also systematically higher in elderly patients (13.2 [10.1; 17.2] vs 11.2 [8.3; 14.9] ml/min/1.73m^2, p < 0.001) (Fig1). Overall, we found a significant dose-effect relationship between eGFR at dialysis initiation and mortality (HR = 1.33 [1.16; 1.51], 1.47 [1.29; 1.69], and 1.72 [1.49; 1.78] respectively for eGFR [5-10], [10-15], and > 15ml/min/1.73m^2, p for trend < 0.001). The same results were found in subgroup analyses according to age category (Fig2), with a significant interaction in favor of a stronger association in younger patients (p = 0.031).

Conclusions: In incident dialysis patients, our study shows a dose-effect relationship between higher eGFR at dialysis start and mortality, regardless of age category. This association seems to be even stronger in younger patients.



PO1371

Hospitalization Risk Among Advanced CKD Patients Treated with Conservative Management vs. Dialysis

Connie Rhee,[1] Amy S. You,[1] Yoko Narasaki,[1] Csaba P. Kovesdy,[2] Dana B. Mukamel,[1] Susan T. Crowley,[3,4] Alejandra Novoa-Vargas,[1] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh.[1] *[1]University of California Irvine, Irvine, CA; [2]The University of Tennessee Health Science Center VolShop Memphis, Memphis, TN; [3]Yale University School of Medicine, New Haven, CT; [4]Veterans Health Administration, Washington, DC.*

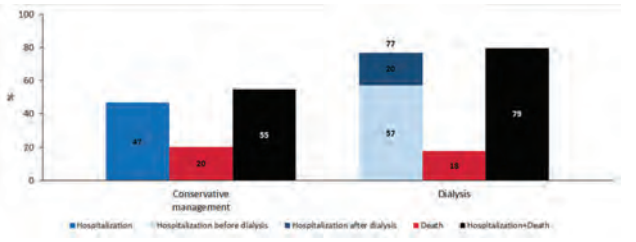
Background: Regarded as the default treatment option for advanced CKD, dialysis has been associated with frequent hospitalizations, functional decline, and loss of independence, particularly in the elderly and comorbid. While there is rising interest in conservative management (CM) as an alternative treatment option, this strategy remains underutilized. We sought to quantify differences in healthcare utilization in advanced CKD patients transitioning to dialysis vs. CM.

Methods: We compared hospitalization risk in 309,188 advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) treated with dialysis vs. CM from 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. We examined hospitalizations within 2-yrs of the index eGFR (1st eGFR <25), which were parsed into pre- and post-dialysis transition hospitalizations in those treated with dialysis. We also examined the composite endpoint of hospitalization+death within 2-yrs of the index eGFR to account for death as competing event for hospitalization.

Results: In the overall cohort, 55% and 20% of patients experienced ≥1 hospitalization(s) and death, respectively, within 2-yrs of the index eGFR. Patients who transitioned to dialysis were more likely to be hospitalized vs. those treated with CM (77% and 47%), with a larger proportion of hospitalizations occurring pre- vs. post-dialysis transition in the former group (57% vs. 20%). While the proportion of deaths across dialysis vs. CM were similar (18% vs. 20%), the composite endpoint was more frequent in patients treated with dialysis vs. CM (79% and 55%).

Conclusions: In a national cohort of advanced CKD patients, while the proportion of death events was similar in those treated with dialysis vs. CM, patients who transitioned to dialysis had higher hospitalization risk. Further studies are needed to compare the components and effectiveness of CM vs. dialysis on CKD outcomes.

Funding: NIDDK Support



PO1372

Mortality Rates in a Nationally Representative Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis

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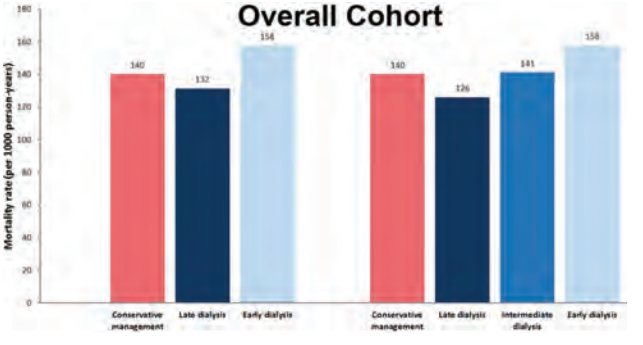
Background: While dialysis has been the prevailing treatment paradigm in CKD patients progressing to ESRD, this treatment approach may not offer survival benefit nor improved quality of life in certain subgroups (elderly, multi-morbid). Hence, there is growing interest in conservative management (CM) as an alternative treatment strategy in advanced CKD.

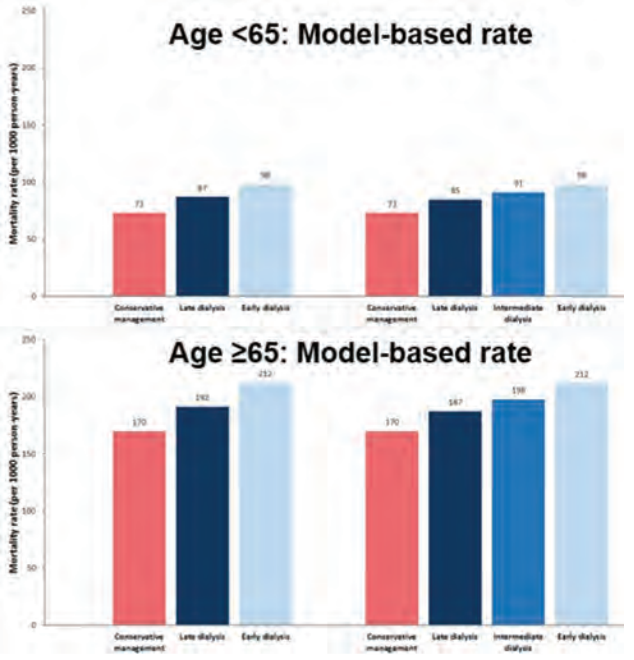
Methods: We compared mortality rates in advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis from 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were categorized according to receipt of dialysis vs. CM, defined as those who did vs. did not receive dialysis within 2-yrs of the index eGFR (1st eGFR <25), with the former group parsed into late vs. early dialysis (eGFRs <15 vs. ≥15 at dialysis transition). Secondary analyses stratified the former group as late, intermediate, vs. early dialysis (eGFRs <5, 5-<10, vs. ≥10 at dialysis transition). Poisson regression was used to compare mortality rates across exposure groups.

Results: Among 309,188 advanced CKD patients, 60% vs. 40% of patients were treated with CM vs. dialysis, respectively. Patients who underwent CM vs. late dialysis had similar mortality, whereas those who underwent early dialysis had the highest mortality rates. In secondary analyses comparing CM and late vs. intermediate vs. early dialysis, a similar pattern was observed (140, 126, 141, vs. 158 deaths per 1000 person-yrs, respectively). In age-stratified analyses, compared to CM, all dialysis groups had higher mortality rates irrespective of timing of initiation in those <65 and ≥65 yrs old.

Conclusions: In a nationally representative cohort of advanced CKD patients, CM vs. late dialysis demonstrated similar mortality, whereas those who underwent early dialysis had the highest mortality rates.

Funding: NIDDK Support





PO1373

Continued Primary Care Use During the Transition to Kidney Failure with Renal Replacement Therapy (KFRT) Is Associated with Reduced Mortality Among Older Hemodialysis (HD) Patients

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Background: Primary care providers (PCPs) are responsible for addressing patients' comprehensive health needs. However, the provision of primary care during the KFRT transition and its contribution to clinical outcomes among in-center HD patients have not been well explored.

Methods: We quantified the associations between PCP use, mortality, and hospitalization among older (age≥67) incident (2008-2014) in-center HD patients using data from the United States Renal Data System. We defined patients' PCP use 1-year prior and 1-year post-KFRT as "continued" for PCP use pre- and post-KFRT; "initiated" for no PCP use pre-KFRT and PCP use post-KFRT; "discontinued" for PCP use pre-KFRT and no PCP post-KFRT; or "never used" as no PCP use pre- or post KFRT. We used Cox proportional hazard models and adjusted for confounding by using inverse probability weighting method to estimate hazard ratios (HRs) for all-cause mortality and first all-cause hospitalization up to 2 years post-KFRT.

Results: Among 111,424 patients, 57% had continuity of PCP care, 10% initiated PCP use, 10% discontinued PCP use, and 23% never used PCP care during the KFRT transition. Compared to those who never used primary care during the KFRT transition, those with continued primary care use had a 14% lower risk of mortality. Continued and initiated PCP care post-KFRT transition was associated with a 5-12% higher risk of hospitalization, respectively.

Conclusions: Continued primary care use during the KFRT transition was associated with lower mortality, but a higher risk of hospitalization. Additional studies are needed to determine the aspects of primary care that may be beneficial and which patients are most likely to benefit from continued PCP use.

Funding: Private Foundation Support

Hazard Ratios for All-Cause Mortality and First Hospitalization by Primary Use during KFRT Transition

	Never used	Discontinued	Initiated	Continued
	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*	HR (95% CI)*
All-cause Mortality	Ref	1.01 (0.96-1.05)	0.97 (0.93-1.02)	0.86 (0.83-0.89)
First all-cause hospitalization	Ref	1.00 (0.98-1.02)	1.12 (1.10-1.15)	1.05 (1.03-1.06)

*Adjusted for age, sex, race/ethnicity, employment, Medicaid, region, %neighborhood-level poverty, %neighborhood urban, Kim's frailty index, Liu's comorbidity index, pre-KFRT nephrology care

PO1374

Vascular Access Type and Survival Outcomes in Elderly Hemodialysis Patients

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Background: The ideal vascular access for elderly hemodialysis (HD) patients remains widely debated. Limited life expectancy and lower arteriovenous access (AVA) maturation rates increase the likelihood of starting HD with a central venous catheter (CVC). The aim of the study was to evaluate the influence of vascular access type in survival outcomes for elderly HD patients.

Methods: Single-center retrospective cohort study of incident HD patients aged > 80 years from January 2010 to May 2021. Patients who recovered renal function or switched to another renal replacement therapy were excluded. Patients were categorized according to their vascular access at the beginning of dialysis: CVC or AVA. Baseline clinical and demographic data were compared among groups. Survival outcomes by the end of follow-up (31st May 2021) were analyzed using Kaplan-Meier survival curves and Cox's proportional hazards model. Statistical analysis was performed using SPSS (Version 23 for Mac OSX).

Results: The study included 99 patients: 48 (48.5%) were male, 44 (44.4%) diabetic, 60 (60.6%) had isquemic heart disease and 15 (15.2%) peripheral artery disease. Mean Charlson Comorbidity Index was 8.41±1.65 and mean age 85.14±3.98 years. Eleven patients (11.1%) were over 90 years old. Eighty patients (81%) started HD urgently as inpatients. The vascular access at dialysis start was a CVC in 75.8% (n=75) and an AVA in 24.2% (n=24). No statistical differences were found in age, gender, or comorbidities among groups. During a mean follow-up of 2.3 years, there were 64 deaths, 27 due to infections (12 access-related infections). All-cause mortality (HR [95% CI]: 1.92 [1.05-3.49], p=0.033) and infection-related mortality (HR: 5.87 [1.38-24.94], p=0.017) were significantly higher among patients who initiate HD with a CVC as compared to an AVA.

Conclusions: The ideal vascular access in elderly patients remains controversial. Our results suggest that patients who start HD with a CVC presented higher all-cause and infection-related mortality when compared with patients who start with an AVA. Our study supports the initiative "fistula first" however more studies are needed to confirm the observations.

PO1375

Predictors of Treatment Discussions in Geriatric Dialysis Patients Who Died

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Background: Geriatric patients on maintenance dialysis often have a high burden of symptoms and comorbidities with limited prognosis. Therefore, in the setting of declining clinical status, goals of treatment (GOT) discussions are important to inform illness expectations and balance the benefits and burdens of ongoing treatment. This study aimed to identify mortality risk factors that prompted nephrologists to have GOT discussions including dialysis withdrawal.

Methods: A cohort of 95 adult patients ≥65 years, cared for by Eastern Health (Victoria, Australia), who died between 1/1/2016-31/12/2019 was analysed using Fischer's exact tests to identify psychosocial variables associated with functional decline and mortality.

Results: Mean age was 78 (SD 7.3), with mean dialysis vintage 5 years and average 3.7 admissions in the 12 months preceding death. Mean Charleston comorbidity index (CCI) was 10 (SD 2.3), with hypertension 78%, T2DM (56%), IHD (56%), cardiac failure (51%), malignancy (34%), peripheral vascular disease (32%) and cognitive impairment (28%) major comorbidities. Almost one third (29%) of patients lived in a nursing facility, 74% used gait aids, and 55% needed assisted transport to dialysis. Median time between needing transport and death was 1.3 years [IQR 0.5, 2.2]. A GOT discussion in the preceding year was documented in 65% of patients, in renal clinics (37%) or on dialysis (12%). Median time between GOT discussion and death was 5 months [IQR 1, 11]. Discussions were more likely if patients had high comorbidity (CCI>5, 57% vs CCI<5, 8%, p<0.05) with no association between GOT discussions and patient age, dialysis vintage, functional status, or specific comorbidities. Advance care plans were completed in 26% and were more likely if a GOT discussion had already transpired (23%v4%, p<0.05), or the patient lived in a nursing facility (16 v12%, p<0.05). Deaths occurred in hospital (50%), hospice (19%), or at home (7%). Dialysis was withdrawn median 8 days before death [IQR 6, 11].

Conclusions: Older patients died with significant comorbidities and functional dependency, though only the former prompted GOT discussions. Despite a long-term relationship, nephrologists could improve documentation of future treatment planning with patients to promote patient centered end of life experiences.

PO1376

Nurse-Driven Advance Care Planning in a Hemodialysis Unit in a Veteran Population

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Background: Patients with end-stage kidney disease (ESKD) face difficult choices near the end of life. Advance care planning (ACP) allows patients and their providers to plan for treatments that align with patients' goals. In the US, only 6-35% of all ESKD patients have advance directives (AD). PREPARE is an interactive ACP website that helps patients complete AD and express their wishes regarding medical decisions. The goal of the study is to assess the feasibility and acceptability of using a nurse to facilitate ESKD patients to completing the PREPARE ACP during dialysis.

Methods: Inclusion criteria include patients without a documented AD within the past 3 years. Exclusion criteria are dementia/cognitive impairment, psychosis, deafness, or blindness. Pre and post engagement surveys were completed. Barriers related to navigating the PREPARE website were documented.

Results: Of 55 patients at the dialysis unit, 25 were eligible and 14 were enrolled. All participants are male with mean age of 69. All participants completed their AD within 1 dialysis treatment. In the pre-PREPARE questionnaire, using the Likert scale of 1 to 5 (1 for "not at all" to 5 for "extremely likely"), patients reported a mean score of 4.07 for readiness to talk about end-of-life care to a close family/friend, 4.23 for readiness to talk to a care provider, 4.46 for readiness to express wishes in writing, and 4.61 for readiness to sign official documentation. In the Post-PREPARE questionnaire, on a scale of 1 (very hard) to 10 (extremely easy), patients scored 7.61 for ease, 7.23 for comfortability, and 8.07 for helpfulness. Analysis of PREPARE AD showed that on a scale of 1 (AD goal mainly to extend life) to 5 (focus on the quality of life), the mean score is 3.06 suggesting that patients value both "extend life" and "maintain quality of life". Five patients expressed wishes for full care, 6 wanted a trial of resuscitation, and 3 requested DNR. Barriers to using PREPARE included patient difficulty navigating the website without help and using a laptop during dialysis when both hands are not always free.

Conclusions: Our study shows that PREPARE is a feasible method in facilitating ACP during dialysis, however, many patients needed assistance to complete the process. Future studies are needed to apply PREPARE and ACP wishes in the ESKD population.

Funding: Private Foundation Support

PO1377

Dialysis Patients' Preferences on Resuscitation: A Cross-Sectional Study Design

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Background: End-stage kidney disease is associated with a 10-100-fold increase in cardiovascular mortality compared to age-, sex-, and race-matched population. Cardiopulmonary resuscitation (CPR) in this cohort has poor outcomes and is often followed by increased functional morbidity. Advance care planning (ACP) is an important aspect of patients' care that is often missed in chronic kidney disease (CKD) and there is growing support for its use. Nephrologists are often involved in end-of-life care decisions for their patients and frequent end-of-life care discussions can provide insight and valuable assistance to patients in the process of decision making.

Methods: 2-center cross-sectional study design. Adults > 18 years undergoing regular dialysis for more than 3 months were included. Patients with severe cognitive impairment or unable to understand discussion secondary to language barrier were excluded. After taking consent, a questionnaire was delivered during a structured interview during a routine dialysis session or clinic visit. Demographic data were collected and baseline Montreal Cognitive Assessment, Patient Health Questionnaire-9, Duke Activity Status Index, Charlson Comorbidity Index, and Willingness to Accept Life-Sustaining Treatment tool were used.

Results: 70 participants were included in this analysis representing a 62.5% response rate. There was a clear effect of treatment burden, nature of clinical outcome, and likelihood of the outcome on patients' preferences. Low-burden treatment resulting in return to baseline (vs death) was associated with 98.5% willingness to accept treatment and 94.2% if it was high-burden. When the outcome was severe functional or cognitive impairment then 54.3% and 71.5% would decline low-burden treatment, respectively. The response changed based on the likelihood of the outcome. In terms of resuscitation, 82.8% and 77.4% of the participants would be in favour of receiving CPR and mechanical ventilation, respectively, at their current health state. Over 94% of patients stated they had never discussed ACP while 59.4% expressed their wish to discuss this with their primary nephrologist.

Conclusions: ACP should be incorporated in managing CKD with an aim to improve communication and encourage patient and family involvement.

PO1378

Evaluation of a Concurrent Hospice-Dialysis Program for Patients with ESRD

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Background: Most dialysis patients are hospitalized in the last month of life, nearly half of whom receive intensive care. Hospice financing poses a major barrier to hospice delivery to dialysis patients, increasing inequities for high-quality end-of-life care. The Concurrent Hospice-Dialysis Program aims to promote timely hospice services for dialysis patients with limited prognosis by offering concurrent hospice and dialysis.

Methods: We conducted a mixed methods study comprised of chart reviews and semi-structured interviews with 10 bereaved caregivers of deceased patients who were enrolled in the Concurrent Hospice-Dialysis Program and 13 clinicians who provided care as part of the program.

Results: Four major themes were identified: 1) Decisional distress regarding stopping dialysis; 2) The option to continue dialysis served as a psychological bridge to hospice; 3) Clear referral process, formal patient education, and care coordination between hospice and dialysis teams facilitated successful implementation; 4) Providing hospice and dialysis promoted goal-concordant care at end-of-life.

Conclusions: Bereaved caregivers and clinicians involved with the Concurrent Hospice-Dialysis Program found the program broadly acceptable and recommended it for patients on dialysis interested in hospice services. They offered suggestions for systematizing and disseminating the program.

Table 1. Key Themes

Theme	Representative Quote
Decisional distress regarding dialysis cessation	"The weight of stopping dialysis is so heavy that it takes so much time and planning and conversation to get a family [..] to see the benefit."
Psychological bridge	"Just knowing that it's an option [...] alleviates a lot of the fear and the sense of abandonment that can come with these really tough decisions."
Facilitator - care coordination	"We communicate far in advance. We set things up [...] so that we're prepared for what might happen. That is the best part of it."
Overall impression	"[...] it was really the best of all worlds." "I think the ones that have gone through this kind of program have done a lot better."

PO1379

Concurrent Hospice Dialysis: Perspectives on Dissemination

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Background: In the United States, people receiving dialysis have traditionally been unable to enroll in hospice without ceasing dialysis treatments due to policy constraints. Therefore, these patients are often denied the full benefits of quality end-of-life care, either dying in hospitals or spending only a few days on hospice after dialysis is stopped. An alternative model would allow people living with end-stage renal disease (ESRD) to receive hospice services concurrently with dialysis treatments.

Methods: We implemented a concurrent hospice-dialysis program in one health system as proof of concept. In this project, we sought to build evidence for feasibility and program requirements for extending such programs to other settings across the country. We conducted semi-structured interviews with people living with ESRD, family caregivers, hospice and dialysis clinicians, and health system administrators from the Pittsburgh area and other regions in the U.S. Interviews elicited perceptions of strengths and weaknesses of a scalable concurrent hospice and dialysis program, including barriers and facilitators of implementation across various settings.

Results: We completed 25 interviews with 2 patients (8%), 3 caregivers (12%), 15 clinicians (60%), and 5 administrators (20%). Preliminary themes include important considerations: 1) Mechanisms and operational definitions for identification of eligible patients; 2) Procedures for decision-making conversations with patients and families; and 3) Protocols for communication between hospice and dialysis teams to coordinate care. Medicare policy and funding restrictions were also frequently discussed as barriers to the program.

Conclusions: Perspectives from patients, caregivers, clinicians and administrators describe critical implementation processes and resources for a successful concurrent hospice and dialysis program. These include the following: clear criteria for patient eligibility, consistent language to use when talking with patients and families, education for both hospice and dialysis teams, and a well-defined plan for care coordination between teams. Future evaluation of such programs may lead to policy change to make concurrent care broadly financially feasible.

Funding: Other NIH Support - Palliative Care Research Cooperative Group (PCRC)

PO1380

Dialysis for the Hospice Patient: A Paradoxical Challenge for Palliative Nephrology

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Introduction: We present a case of a patient who developed anuric AKI who subsequently needed dialysis while patient and family were also simultaneously interested in hospice. Our case addresses the difficult conversation in prognosticating and how hospice eligibility for patients requiring dialysis can be challenging.

Case Description: A 63-year-old woman with hypertension and recently diagnosed metastatic pancreatic adenocarcinoma initially presented for intractable right hip pain and was admitted for emergent palliative radiation. She experienced rapid deterioration including septic and hemorrhagic shock and was managed in the ICU until she was later stabilized off pressors and downgraded to the floors. Unfortunately, she had further complications and quickly experienced anuric AKI from ischemic ATN as her serum creatinine rose from 0.8 to 4.9 mg/dL and became significantly volume overloaded with worsening acidemia. The decision was to start a trial of dialysis by family, but they also wanted hospice. Questions arose including prognosis and if patient could simultaneous be provided with dialysis during hospice. Given the current model of withdrawing from dialysis for hospice eligibility, the daughters agreed to transition their mother to hospice. The patient passed prior to leaving the hospital.

Discussion: We present a difficult scenario for the nephrologist as serious illness conversations remain incredibly challenging. We may opt to not take part in these conversations either due to time commitment, not viewing it as a primary responsibility, or not wishing to upset the patient and their families. Also, so much uncertainty in predicting prognosis makes it intimidating. Here, what also needed to be addressed were hospice benefits for the dialysis patient, if any existed. Usually, one is required to withdraw from dialysis to receive hospice care. There have been suggestions in providing a trial or "as needed dialysis" to focus on a patient-centered type of care but unfortunately that could potentially impact quality metrics and Medicare reimbursement for dialysis centers. As such, these ongoing challenges not only require collaboration between Nephrology and Palliative medicine but also changes at the national broader level.

PO1381

Kidney Palliative Care in Transplant Recipients with a Failing Allograft

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Background: Kidney transplantation provides longer survival and better quality of life than dialysis for patients with end-stage kidney disease. However, when allografts fail, navigating treatment options can be challenging as patients with allograft failure are older and sicker than when they were transplanted. Kidney palliative care, specialized interprofessional medical care working together with nephrology providers, providing communication, coordination, symptom management, and psychosocial support for seriously ill patients, has not yet been well-studied for those with kidney transplants.

Methods: We conducted a retrospective observational study comparing palliative care delivery, patient treatment choices, and clinical outcomes before and after creation of an inpatient kidney palliative care service (KidneyPal) at our institution. We included adult kidney transplant patients (age 18 or greater) who experienced allograft failure or death two years before and after the start of KidneyPal. Allograft failure was defined as imminent indication or chronic need for dialysis for more than 3 months.

Results: Fifty-four and fifty-nine patients were included before and after KidneyPal implementation, respectively. For the patients who experienced death with a functioning graft, inpatient palliative consultation frequency was similar before and after the creation of KidneyPal (40% and 33%, respectively). However, for the patients with allograft failure, palliative care consultation increased from 5.9% to 24.1%. Death in the ICU was common (15% vs. 17%), but death in hospice was more frequent (7% vs. 15%) after KidneyPal was created. While palliative care clinicians addressed code status, symptom management, and psychosocial issues throughout the study period, KidneyPal clinicians held more discussions about treatment options for allograft failure (20% vs. 41%). More patients chose dialysis as a time-limited trial or made a decision to forgo dialysis re-initiation after consultation with KidneyPal (3% vs. 17%).

Conclusions: Our observational study suggests that kidney palliative care may be useful in the context of allograft failure, particularly with regard to ensuring goal-directed shared decision making. Discussing prognosis, goals of care, and care options after graft failure are palliative skills that may be enhanced by collaboration with a specialty kidney palliative care team.

PO1382

Patient Perspectives on Frailty Status Evaluation During Kidney Transplant Assessment

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Background: The concept of frailty garnered attention within nephrology in recent years, given strong associations between frailty status and kidney disease outcomes. There is increased debate on formalizing frailty status evaluation during the early stages of assessment for potential kidney transplant recipients. Studies investigating patient perspectives on frailty and frailty status evaluation during transplant assessment are lacking.

Methods: We conducted a qualitative study using cognitive interviews in English for 25 patients aged 65-85 yrs awaiting initial transplant clinic assessment. The interview enquired on patient understanding of frailty, perspectives on the impact of frailty for transplantation outcomes and whether formalized frailty status evaluation during transplant assessment should be established. An inductive thematic analysis of interviews to identify themes reflecting participants' awareness, understanding and perspectives of frailty and frailty status evaluation in transplant assessment was performed.

Results: There were 14 Male and 11 Female participants and mean age was 69.6 yrs ± 3.4. Participants were mainly white (n=18) and native English speakers (n=20). 3 prominent themes were identified. 1) *Prerequisite awareness of the frailty syndrome and recognition of its strong associations with negative health outcomes.* Most participants understood frailty as a composite of declining physical function, reduced ability to perform daily activities and increased comorbidity status. 2) *Severe frailty status is associated with older transplant recipients.* Many participants felt worsened frailty status is correlated with older age, and older transplant recipients generally do more poorly. 8 participants recognized frailty may be independent of age in which older patients could be fitter transplant candidates compared to younger, frailer patients. *3) Universal support for a formalized screening program to evaluate frailty status during pre-transplant assessment.* All participants voiced support, to assist clinical decision-making on determining suitability for transplantation from an early stage.

Conclusions: Patient education initiatives should continue to expand awareness of frailty and its implications in transplantation. Further work is required to determine an optimal approach to formally evaluate frailty status during transplant assessment.

Funding: Government Support - Non-U.S.

PO1383

Differences in Frailty by Sex in Kidney Transplant Candidates

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Background: Frailty prevalence is higher in women, despite the observed protective effect of female sex on mortality in the general population. Understanding whether there are differences in perceived frailty by sex and the differential impact of frailty on outcomes for males versus females is crucial to avoid a sex disparity within the transplant assessment process.

Methods: We analyzed initial frailty assessments for patients enrolled in a multicenter prospective cohort study across 6 kidney transplant referral centers. Frailty was assessed using the Frailty Phenotype (FP; 3 of slowness, weight loss, low activity, exhaustion, and weakness), a Frailty Index (FI; including 37 variables across the domains of social function/cognition, function, mobility, and comorbidity), and the Clinical Frailty Scale (CFS, based on clinical judgement). Assessments were performed prior to or shortly after waitlisting. Prevalence of frailty as measured by the FP, FI, and CFS was reported. An unadjusted cox survival analysis (separately for males and females) was used to assess the effect of frailty on time to death or withdrawal from the waitlist among activated patients.

Results: A total of 767 unique patients had frailty assessments performed between 2016-2021. Patients were predominantly of male sex (64%), white race (82%) and had a mean age of 54+/-14. The prevalence of frailty for women was not significantly higher by the FP (16% vs 13%, p=0.15) or the FI (48% vs 46%, p=0.38), but was by the CFS (17% vs 12%, p=0.05). Among 325 activated patients, frailty by the CFS was significantly associated with death/withdrawal for men (HR 2.59; 95% CI 1.16-6.79) but not women (HR 1.41; 95% CI 0.48-4.18).

Conclusions: The prevalence of frailty was higher in females when measured by the CFS, but not by a transplant specific FI or the FP. Despite this, frailty was not significantly associated with mortality/withdrawal from the waitlist for female individuals, emphasizing the need to critically evaluate judgement based frailty assessments and their role in the transplant evaluation process.

Funding: Government Support - Non-U.S.

PO1384

Changes in Cognition After Kidney Transplantation

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Background: Longitudinal studies examining changes in cognition pre- to post-kidney transplantation (KT) are small, of short duration and do not include comprehensive neuropsychological (NP) testing or comparison with normative data.

Methods: We analysed pre- to post-KT cognition in 87 ESKD patients listed for KT and compared it to the National Alzheimer's Coordination Center (NACC) data. We used linear mixed models for longitudinal, repeated NP test measurements, adjusted for for age, practice effect, sex, race, transplant status, and level of education, and assessed cognition pre- to post-KT for our primary (Logical Memory I, II, and Digit Symbol tests) and secondary (Mini Mental State Exam (MMSE), Digit span, Category fluency for animals & vegetables, Trail making A & B) outcomes.

Results: Data from 87 ESKD patients (age 55.8±11.7 years) and 6974 controls (age 64.9±7.9 years) were analyzed. Pre-KT, ESKD patients had lower Logical Memory I & II, Digit Symbol, MMSE, Digit Span Backward, and Category Fluency of vegetables test scores (Table 1). There was no difference in scores of Digit Span forward, Category Fluency of animals, and Trail Making A & B between pre-KT ESKD patients and controls. Post-KT, Logical Memory I and II, and Category Fluency animals & vegetables improved, while Digit Symbol, MMSE, and Digit Span backward scores remained lower than controls (Table 1).

Conclusions: Not all cognitive abilities are affected in ESKD. While some test scores improve with KT, others do not. Further studies are needed to understand the mechanisms underlying cognitive impairment in ESKD and to explore interventions to mitigate them.

Funding: Other NIH Support - NIA

Table 1: NP test comparisons in pre- and post-KT recipients and controls

Variables	p-value for any group difference (a)	Pairwise comparisons Estimated difference (p-value) (b)		
		Pre-KT minus Post-KT	Pre-KT minus controls	Post-KT minus controls
Primary outcomes				
Logical Memory I	<0.001	2.14 (<0.001)	-2.28 (<0.001)	-0.14 (0.75)
Logical Memory II	<0.001	2.82 (<0.001)	-2.50 (<0.001)	0.32 (0.49)
Digit Symbol	<0.001	1.50 (0.07)	-7.09 (<0.001)	-5.49 (<0.001)
Secondary Outcomes				
MMSE	<0.001	0.08 (0.61)	-0.83 (<0.001)	-0.74 (<0.001)
Digit Span (Forward)	0.19	0.24 (0.24)	-0.37 (0.08)	-0.14 (0.56)
Digit Span (Backward)	<0.001	0.34 (0.13)	-1.03 (<0.001)	-0.69 (0.01)
Category Fluency (Animals)	<0.001	2.17 (<0.001)	-1.13 (0.05)	1.04 (0.09)
Category Fluency (Vegetables)	0.05	0.92 (0.04)	-0.94 (0.03)	-0.02 (0.96)
Trail Making A	0.66	1.07 (0.40)	0.89 (0.52)	-0.18 (0.91)
Trail Making B	0.22	5.45 (0.21)	7.35 (0.11)	1.89 (0.70)

MMSE: Mini Mental State Exam, a p value for adjusted linear mixed model F-test for any group differences between pre-KT, post-KT, and controls adjusted for age, cumulative number of NP testing sessions (practice effect), race, sex and education level. b p value for adjusted linear contrast of pairwise estimated between group differences t-test.

PO1385

Patients Who Are Treated for Secondary Hyperparathyroidism Have a Lower Risk of Incident Dementia

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Background: Almost all patients with end-stage kidney disease (ESKD) have secondary hyperparathyroidism (SHPT). Elevated parathyroid hormone has been reported as a potential risk factor of cognitive impairment. We aimed to study whether the risk of dementia is improved when patients on dialysis receive treatment for SHPT.

Methods: Using data from the United States Renal Data System and Medicare claims, we studied older (aged≥66) ESKD patients without known pre-ESKD dementia who initiated maintenance dialysis in 2006-2016. SHPT treatment included vitamin D analogs, phosphate binders, cinacalcet or parathyroidectomy and was treated as a time-dependent treatments in the analysis. The study population was followed until transplant, death, end of Medicare coverage or administrative end date (12/31/2016), whichever came first. We used the Cox regression and adjusted for confounding using the inverse probability weighting method to examine the association of SHPT treatment and incident dementia.

Results: Of 189,433 ESRD patients, 65.1% received a treatment for SHPT during the study period. The rate of incident dementia was 11 per 100 person-years among patients with no SHPT treatment and 6 per 100 person-years among those with an SHPT treatment. Among patients on dialysis, the risk of incident dementia was lower after receiving treatment for SHPT compared with not receiving treatment for SHPT (adjusted hazard ratio=$_{0.60}0.62_{0.63}$) after adjusting for confounding.

Conclusions: Receiving treatment for SHPT was associated with a lower risk of incident dementia among older patients with ESKD. SHPT may need to be controlled among older ESKD patients considering the complications of SHPT including cognitive impairment and dementia.

Funding: NIDDK Support, Other NIH Support - NIAID, NIA

Table 1. Risk of incident dementia comparing patients with treatment for secondary hyperparathyroidism during dialysis with those without treatment among older end-stage kidney disease patients (n=189,433).

SHPT treatment	Incident rate (/100 person-years)	Risk of incident dementia (Hazard ratio)	
		Unadjusted	Adjusted[a]
No	11	Reference	Reference
Yes	6	$_{0.61}0.54_{0.55}$	$_{0.60}0.62_{0.63}$

[a]Adjusted for age at incidence, sex, race/ethnicity, employment, geographic region, primary cause of end-stage kidney disease, comorbidities (hypertension, diabetes mellitus, cardiovascular disease, cancer, functional impairment, alcohol dependence, and smoking)

PO1386

Kidney-Metabolic Risk Factors for Cognitive Impairment in Moderate CKD in the BRINK Study: Beyond eGFR and Albuminuria

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Background: Decreased kidney function is a risk factor for cognitive impairment (CI). We sought to identify kidney-metabolic biomarkers beyond eGFR and albuminuria associated with prevalent moderate to severe cognitive impairment (Mod/Sev CI) in a CKD cohort.

Methods: Community-dwelling non-dialysis participants aged ≥ 45 years with CKD (eGFR <60, in mL/min/1.73 m^2) were recruited from four health systems. We examined biomarkers including phosphorus, TNFαR1, PTH, calcium, total cholesterol, hemoglobin A1c%, bicarbonate (CO_2). A neuropsychological battery measured global and domain-specific cognitive performance. Logistic regression analyses estimated cross-sectional associations between kidney-metabolic measures and global and cognitive-domain-specific Mod/Sev CI at baseline, adjusted for eGFR, urinary albumin-creatinine ratio (UACR, in mg/g), demographics, and comorbid conditions.

Results: Among 436 CKD participants with mean age 70 years, 16% were Black, mean eGFR was 34 and median UACR. In adjusted models no kidney-metabolic biomarkers were significantly associated with global Mod/Sev CI. However, in cognitive-domain-specific analyses, low bicarbonate (CO_2 <20 mEq/L) was significantly associated with Mod/Sev impairment in memory [OR (95%CI): 3.04 (1.09, 8.47) P=0.03)] and with language [3.82 (1.12, 13.0; P=0.03). In addition, lower total cholesterol was associated with impaired executive function [1.12 per -10mg/dL (1.02, 1.23; P=0.02].

Conclusions: Low bicarbonate (acidosis) and lower cholesterol levels in older patients with CKD may be modifiable kidney-metabolic risk factors for Mod/Sev domain-specific CI in CKD. Longitudinal analyses are needed to determine whether low bicarbonate and low cholesterol are associated with cognitive decline.

PO1387

Targeting Sedentary Behavior in Older Adults: Subgroup Analysis of a Randomized Clinical Trial

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Background: Sedentary behavior (spending most of the awake hours in sitting/lying posture) is associated with increased mortality in CKD but few studies have examined the feasibility of interventions targeting sedentary behavior in older adults with CKD.

Methods: The Sit Less, Interact, Move More (SLIMM) Study was a 24-week RCT of an intervention to reduce sedenary duration with stepping duration in participants with CKD. Physical activity was measured using a mid-thigh accelerometer worn for 7 days before baseline and q4 weeks in standard of care (SOC) group (N=52) and baseline and q8 weeks in SLIMM group (N=54). Based on the accelerometry data, SLIMM group was provided instructions on reducing sedentary duration. In this post-hoc analyses, we used mixed effect models to compare the effects of the SLIMM intervention in participants age ≥ 70 (N =59) versus age < 70 (N=47).

Results: Age ≥ 70 group compared to age < 70 group had a higher % of Whites and lower % of stage3b-5 CKD (Table 1). While sedentary duration was similar, the older group had lower stepping duration, gait speed and 6-min walk distance (Table 1). In mixed models, there were no significant differences between SLIMM and SOC groups for sedentary (1, 95% CI -39 to 42 min/d) and stepping (-4, 95% CI -18 to 11 min/d) durations and the number of steps/day (-424, 95% CI -1669 to 820) in the age < 70 group. The corresponding numbers for the age ≥ 70 group for sedentary and stepping durations and the number of steps/d were -28, (95% CI -61 to 5 min/d), 13, (95% CI 1 to 24 min/d) and 1330, (95% CI 322 to 2338 min/d), respectively.

Conclusions: It is feasible to decrease sedenaray behavior In older adults with CKD.

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

Baseline characteristics between age group

	Age<70 N=47	Age≥70 N=59	p-value
Age,yrs	58±11	78±5	
Female,%	30	53	0.019
White,%	79	98	0.001
CKD Stages,%			0.019
Stage 2/3a	43	42	
Stage 3b	26	46	
Stage 4/5	32	12	
Sedentary duration, min/d	641±151	653±107	0.62
Stepping duration, min/d	98±61	75±26	0.01
Steps/d	6228 (3146,8446)	4910 (4026,6470)	0.26

PO1388

Association of CKD Stages with Frailty Worsening or Death in Community-Dwelling Older Adults

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Background: Albumin-creatinine-ratio (ACR) and glomerular filtration rate (GFR) have been associated with prevalent and incident frailty. We analyzed the association of the KDIGO CKD stages and frailty status worsening or death in data of the Berlin Initiative Study (BIS).

Methods: Prospective population-based cohort study interviewing participants biannually with a standardized questionnaire. Frailty assessment according to Fried took place at the 3rd and 4th follow-up. Frailty worsening was defined as the transition within a two-year period from robust to prefrail or frail, or from prefrail to frail. Partial proportional odds regression analysis was used to analyze the association between KDIGO CKD stages and the ordinal outcome of no worsening, frailty worsening, or death.

Results: Of 1076 participants with 46% male and mean age 84.3 years, initially 48% were prefrail and 32% frail. After 2.1 (2.0-2.3) years of follow-up 188 (17.5%) had worsened and 111 (10.3%) died. Participants who died were older (88 vs. 83 yrs), were less physically active, had less muscle mass (calve circumference <31: 10% vs. 5%), and were more likely to be cognitively impaired; 92% had a GFR <60 mL/min/1.73m^2 and 59% had an ACR ≥30 mg/g compared to 72% and 24% in participants who did not worsen, respectively. Baseline characteristics of participants who worsened were similar to participants who did not worsen. In the multivariable[1] model participants in CKD stages G1,2/A2,3 and G3/A1 or higher had about 2-fold higher odds of frailty worsening than in CKD stages G1,2/A1. The odds for death increased remarkably with both higher CKD stage and increasing albuminuria. Wide confidence intervals are likely due to limited sample size/events. Additional adjustment for frailty baseline status did not alter the results.

Conclusions: In older adults, advanced CKD stages but also albuminuria independent of GFR were associated with 2-fold higher odds of frailty worsening independent of death.

Funding: Private Foundation Support

Figure: Association between KDIGO CKD stages and Frailty worsening or death

CKD by GFR and albuminuria categories: Adjusted[1] OR (95% CI)			Persistent albuminuria categories	
			A1	A2/A3
			<30 mg/g	≥30 mg/g
GFR categories (ml/min per 1.73m^2)	G1	>=60	Reference	Worsening: 2.16 (1.01 - 4.62) Death: 4.72 (1.20 - 18.62)
	G2			
	G3a	45-59	Worsening: 1.39 (0.90 - 2.17) Death: 2.20 (0.78 - 6.22)	Worsening: 2.19 (1.21 - 3.95) Death: 7.93 (2.70 - 23.31)
	G3b	<45	Worsening: 1.83 (1.10 - 3.05) Death: 5.92 (2.15 - 16.27)	Worsening: 2.67 (1.57 - 4.54) Death: 15.13 (5.63 - 40.67)
	G4			
	G5			

OR: odds ratio; CI: confidence interval;
[1]age, sex, hypertension, diabetes mellitus, polypharmacy, physical activity, calve circumference, smoking, body mass index

PO1389

Role of Klotho in Aging, Relationship with Frailty, Renal Function, and Body Composition

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Background: Reduced expression of the Klotho protein has been associated with premature aging and increased mortality. Our aim is to evaluate the relationships between plasma Klotho levels and frailty, renal function and anthropometric parameters.

Methods: We enrolled a cohort of 1250 volunteers aged > 65 years (FRASNET Study) in recreation centers for the elderly, in hospital's outpatient clinic and in nursing homes. All the volunteers have signed informed consent and subjects with severe cognitive impairment were excluded (MMSE >18). We measured eGFR (CKD-EPI formula) and body composition by impedancemetry. Plasma Klotho was assayed by an ELISA kit on 194 samples. Frailty was classified according to Fried's criteria.

Results: A positive correlation between plasma Klotho and renal function (eGFR) was detected (fig 1). In agreement with what previously observed, in a younger population, we confirmed a reduction of klothemia in the sarcopenic patients (713 vs 791 pg/mL, p=0.0007 in patients with muscle mass <25th centile) and in patients with high visceral fat mass (fig.2). On the other hand, we did not observe different levels of plasma Klotho according to the frailty class or in relation to age.

Conclusions: In our elderly population, the plasma levels of Klotho do not correlate with age. Therefore, our results confirm the relevance of this biomarker in identifying pathological aging, in consideration of its association within the elderly population with CKD, abdominal obesity and sarcopenia (sarcopenic obesity). Klotho expression was demonstrated as an independent predictor of death in a follow up-study and was related to many diseases (e.g.: cognitive impairment, cardiovascular disease). The relation of plasma klotho levels and renal function is debated, and conflicting results have been published. Our findings evidenced a significative association of plasma Klotho with renal function and body composition.

Funding: Private Foundation Support

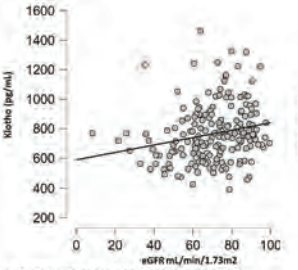

Fig 1: Relationship between eGFR and plasmatic Klotho (Spearman's rho = 0.269, p<0.001)

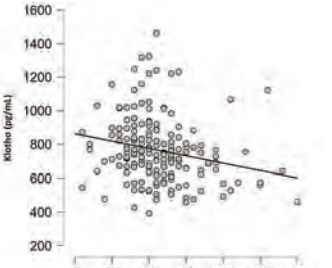

Fig 2: Relationship between visceral fat index at impedancemetry and plasmatic Klotho (Spearman's rho = - 0.276, p<0.001)

PO1390

Shrunken Pore Syndrome: Prevalence and Association with Mortality in a Population-Based Cohort of Elderly Women

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Background: Decreased kidney function results in lower clearance and increased plasma concentration of a GFR marker. So far creatinine has been the commonly used GFR marker but cystatin C becomes more common. Shrunken pore syndrome (SPS) is a recently identified kidney syndrome characterized by disturbed filtration of mid-sized molecules (5-30 kDa) compared to smaller ones (<0.9 kDa) (Fig1). Resulting in increased plasma levels of cystatin C (cysC) compared to creatinine. SPS is associated with increased risk of cardiovascular disease (CVD) and increased mortality risk. So far few data are available about SPS in population-based cohorts.

Methods: 75-yr old **women** (n=849) from the population-based Osteoporosis Prospective Risk Assessment (OPRA-) cohort, with follow-up after 5yr and 10yr were studied. eGFR was calculated with the CKD-EPI equation. SPS was defined as $eGFR_{cysC}$/$eGFR_{crea}$ ratio <0.6 and mortality risk (HR [95% CI]) estimated. Women with sarcopenia or on glucocorticoids were excluded.

Results: Almost 1 in 10 women (9%) had SPS at age 75 but at age 80 the majority of these women had increased their $eGFR_{cysC}$/$eGFR_{crea}$ ratio >0.6 (range from 0.6-1.0). Women with SPS had higher 10-yr mortality risk compared with ratios >0.9 (HR_{adj} 1.7 [95% CI, 1.1-2.6]). Table 1.

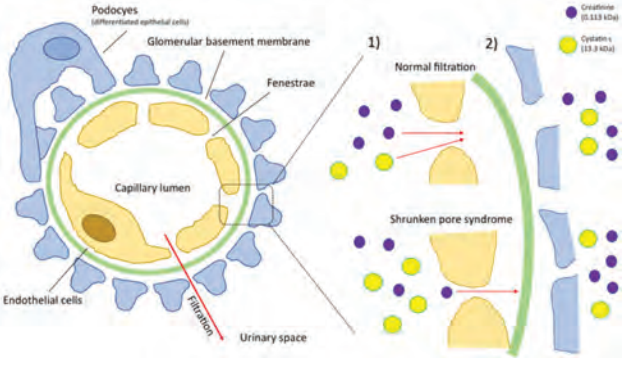
Conclusions: SPS defined as $eGFR_{cysC}$/$eGFR_{crea}$ ratio <0.6 is common in elderly women and associated with increased mortality. While longitudinal data indicate that the state may be reversible. Our results also confirm other studies and suggest that SPS may be a clinically applicable tool to assess mortality risk in the elderly.

Funding: Private Foundation Support, Government Support - Non-U.S.

SPS (eGFRcysC/eGFRcrea ratio <0.6) is associated with increased 10-yr mortality

	eGFRcysC/eGFRcrea Ratio (age 75)				
	n=366 ≥0.9	n=178 0.8-0.89	n=140 0.7-0.79	n=85 0.6-0.69	n=80 <0.6
Model 1*	1 (ref)	1.0 [0.7-1.4]	1.0 [0.6-1.4]	1.3 [0.8-2.0]	1.7 [1.1-2.6]**

*Adjusted for: diabetes, high blood pressure, CVD, smoking. **p=0.016



Possible pathophysiological mechanisms of SPS (1) reduced pore size and (2) thickening of the glomerular basement membrane

PO1391

Molecular Changes Associated with Type IV Collagen Switching in 1-Day-Old Alport Murine Glomeruli

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Background: Alport syndrome (AS) is an inherited disorder caused by pathogenic variants in *COL4A3*, *COL4A4* or *COL4A5*, which encodes proteins that comprise basement membranes of the ear, eye and kidney glomerulus. Type IV collagen chains assemble as heterotrimers and during glomerular development, α1α2α1 (IV) is replaced by α3α4α5 (IV) within the developing glomerular basement membrane (GBM). This "switching" defines the starting point of disease in AS. We aimed to identify the molecular changes at the time of disease initiation in the developing glomeruli of Alport murine kidneys.

Methods: Immunofluorescence (IF) staining was done to identify the GBM distribution of type IV collagen chains in 1 day old *COL4A3* knockout (KO) and wildtype (WT) mice. Urine albumin to creatinine ratio (uACR) was also measured. Subsequently, glomeruli from 1 day old (P1) *COL4A3* KO and WT mice were isolated by cardiac injection of magnetic dynabeads that embolized to glomerular capillaries enabling their extraction from surrounding tissue. Protein was isolated and subjected to liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) analysis.

Results: IF localized type IV collagen α1 in the GBM, Bowman's capsule and mesangial matrix in both P1 KO and WT mice. Type IV collagen α5 was present in short segments of some developing GBM in P1 WT but was absent in KO mice indicating switching. uACR was increased in P1 KO (423.61±396.13 mg/mmol) compared to WT (128.67±69.86 mg/mmol) with a *p*-value of 0.02. LC-MS/MS identified >4300 proteins from glomerular isolates. In males, 2 and 15 proteins were significantly upregulated and downregulated, respectively, in KO compared to WT mice. In females, 543 and 978 proteins were significantly upregulated and downregulated, respectively, in KO compared to WT mice. Pathway analysis revealed alteration in collagen metabolic process, collagen biosynthesis, collagen formation and extracellular matrix organization.

Conclusions: Increased uACR in P1 KO mice showed disease onset at the time of type IV collagen switching. LC-MS/MS analysis revealed dysregulation of matrix turnover pathways in P1 KO mice, identifying potential molecular targets.

Funding: Private Foundation Support

PO1392

PTEN-Induced Kinase 1 Has Association with Renal Aging in the Context of Inflammatory Response

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Background: Among several changes of aging-related human organ system, functional and structural deterioration of kidney is the most dramatic phenomenon, and the role of mitophagy has recently considered important in pro-aging process in CKD patients. PTEN-induced kinase 1 (PINK1), known to be associated with age-related diseases regulates mitochondrial dysfunction. To enhance understanding the function of PINK-1 on aging, we compared whole-kidney RNA sequencing between naturally aging mice (24-month-old) and PINK1 knock out aging mice.

Methods: Kyoto Encyclopedia of Genes and Genomes pathway analysis and gene ontology analysis were performed for gene expression analysis. To investigate the role of PINK1 on aging, we used Pink1-deficient mice and PINK1-overexpressing HKC8.

Results: Compared to naturally aging kidneys, PINK1 knock out aging mice showed prominent expression of the genes related to cytokines, immune system response, and inflammation (Fig 1). We also investigated the function of PINK1 on PINK1 (-/-) aging mice. PINK1 deficiency showed aggravated tubulointerstitial fibrosis on PAS staining (Fig2A), and the Urinary Albumin-Creatinine Ratio increased more prominently according to aging in PINK1 (-/-) mice (Fig2B). The Quantitative PCR analysis validated that the expression of genes associated with aging, fibrosis, and inflammation increased in PINK1 (-/-) mice compared to age-matched controls (Fig2C). Under treatment with H2O2, the expression of aging and pro-inflammatory marker decreased in PINK1-overexpressing HKC8 compared to naturally aging mice (Fig2D).

Conclusions: In conclusion, our results suggest that PINK1 deficiency contributes to renal aging process via proinflammatory change in the kidney.

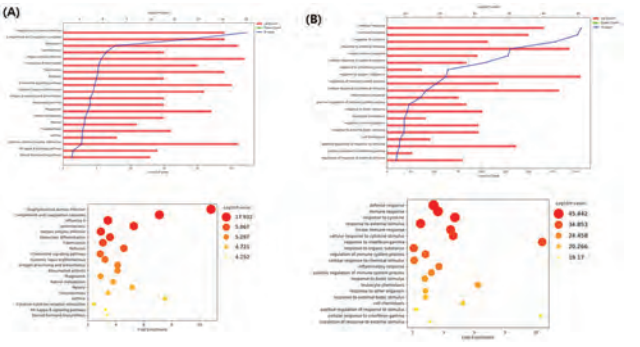

Fig 1

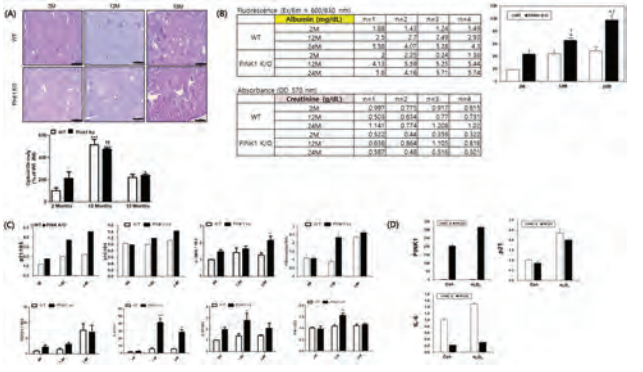

Fig 2

PO1393

TGF-β1/Smad Signaling in Glomerulonephritis and Its Association with Progression to CKD

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Background: Transforming growth factor-β1 (TGF-β1) is a multifunctional cytokine, with diverse roles in fibrosis and inflammation, which acts through Smad signaling in renal pathology. We intended to investigate the expression of TGF-β/Smad signaling in glomerulonephritis (GN) and to assess its role as risk factor for progression to chronic kidney disease (CKD).

Methods: We evaluated the immunohistochemical expression of TGF-β1, phosphorylated Smad3 (pSmad3) and Smad7 semi-quantitatively and quantitatively (computerized image analysis program has also been used) in different compartments of 50 renal biopsies with GN and the results were statistically analyzed with clinicopathological parameters. We also examined the associations among their expressions, the impact of their co-expression, and their role in progression to CKD.

Results: TGF-β1 expression correlated positively with segmental glomerulosclerosis (**p=0.025**) and creatinine level at diagnosis (**p=0.002**), while pSmad3 expression with interstitial inflammation (**p=0.024**). In glomerulus, concomitant expressions of high Smad7 and medium pSmad3 were observed to be correlated with renal inflammation, such as cellular crescent (**p=0.011**), intense interstitial inflammation (**p=0.029**) and lower serum complement 3 (**p=0.028**) and complement 4 (**p=0.029**). We also reported a significant association between pSmad3 expression in glomerular endothelial cells of proliferative GN (**p=0.045**) and in podocytes of non-proliferative GN (**p=0.005**). Finally, on multivariate Cox-regression analysis, TGF-β1 expression (**HR= 6.078; 95% CI 1.168-31.627; p=0.032**) was emerged as independent predictor for CKD.

Conclusions: TGF-β1/Smad signaling is upregulated with specific characteristics in different forms of GN. TGF-β1 expression is indicated as independent risk factor for progression to CKD, while specific co-expression pattern of pSmad3 and Smad7 in glomerulus is correlated with renal inflammation.

PO1394

ANCA Negative Medullary Angiitis

Tarun Kapoor, Daniel Birchmore, Mark Lusco, Juan Pablo Arroyo Ornelas, Gautam B. Bhave. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Medullary angiitis is a rare cause of renal failure. Most cases of medullary angiitis are found to be ANCA positive. We present a rare case of ANCA negative medullary angiitis with no identifiable secondary causes.

Case Description: A 55-year-old male with a medical history significant for uncontrolled diabetes complicated by retinopathy, Chronic kidney disease, HTN, and compensated cirrhosis of unclear etiology, presented to the hospital with shortness of breath and lower extremity edema. Initial workup revealed a creatinine of 7.6 (baseline creatinine 1.5 eighteen months earlier), and significant proteinuria estimated at 8.4g/day along with a urinalysis showing 3 RBC/high power field and 6 WBC/high power field. Serological workup including Hepatitis B/C, HIV, SPEP, serum free light chains, C3/C4, ANA, ANCA was negative. He underwent a renal biopsy revealing medullary angiitis with multifocal medullary hemorrhage with perivascular PMNs and eosinophils along with findings of long-standing diabetes and HTN. In the absence of IgA deposits, infection, or offending drugs, he was started on high steroids and treated similarly to ANCA positive medullary angiitis. His creatinine during the hospitalization peaked at 8.69 before and fell to 7.6 at discharge. He was continued to oral prednisone at discharge. Outpatient follow-up showed a decrease in Cr to 5.8 before slowing climbing back up to 8.5. He is currently maintained on an immunosuppressive regimen to help delay the initiation of renal replacement therapy.

Discussion: Medullary angiitis is a rare renal disorder that has largely been associated with ANCA positivity. ANCA negative medullary angiitis has been documented in the literature with a recent case series showing IgA nephropathy and recent antibiotics use to be the most common etiologies. This is one of the first case reports of ANCA negative medullary angiitis not associated with IgA nephropathy and recent antibiotic use. Currently, we have no standardized treatment options available for these patients. Given the rapid progression of the renal dysfunction, we decided to start our patient on high-dose steroids. Our patient had an initial improvement in his renal function with subsequent decline. However, treatment may have afforded time for AVF creation and patient education before the initiation of hemodialysis, which was the main goal of therapy.

PO1395

Calorie Restriction Ameliorates Obesity-Related Glomerulopathy in Adult Zebrafish

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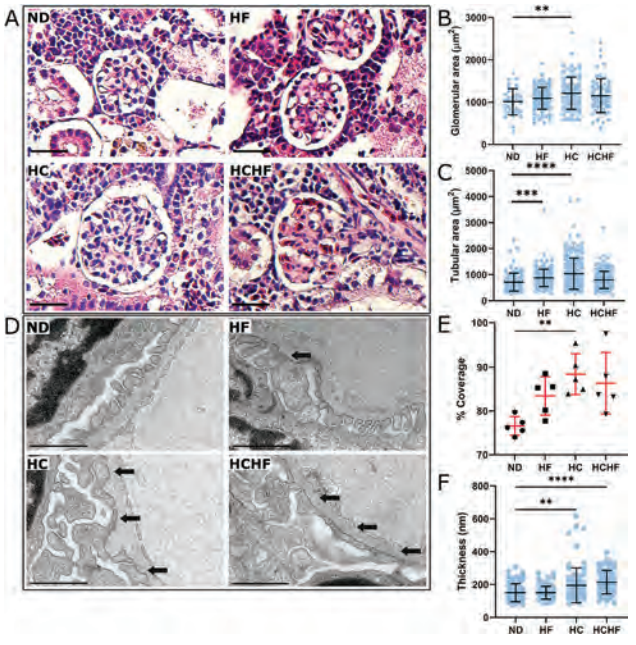
Background: Obesity is a risk factor for chronic kidney disease. The mechanisms by which obesity results in kidney disease are understudied. Zebrafish are an attractive model animal for studying obesity due to their conserved biology and amenability to genetic screening. The effects of obesity on kidney function in zebrafish have not been reported.

Methods: Zebrafish were fed high-calorie and high-fat diets for 8 weeks. Kidneys were evaluated by light and electron microscopy, and the glomerular filtration barrier was assessed by fluorescent dextran permeability. We also tested the ability of calorie restriction to reverse obesity-related defects.

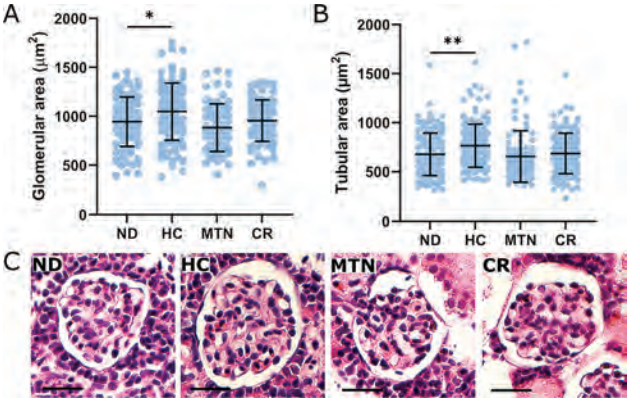
Results: Fish fed a high calorie diet developed glomerulomegaly, foot process effacement, GBM thickening, tubular enlargement (Figure 1) and ectopic lipid deposition after 8 weeks. High calorie feeding resulted in filtration barrier dysfunction. The observed effects resolved after 4 weeks of calorie restriction (Figure 2).

Conclusions: Our study reveals that obese zebrafish recapitulate key aspects of human pathology, and these defects can be reversed with calorie restriction. These findings establish zebrafish as a potential model for the study of obesity-related kidney disease.

Funding: NIDDK Support



ND - normal diet, HF - high fat diet, HC - high calorie diet, HCHF - high calorie+high fat diet.



ND - normal diet, HC - high calorie diet, MTN - maintenance calories, CR - calorie restriction

PO1396

Different Patterns of Renal Fibrosis Are Indicative of Independent Fibrogenic Causes in ANCA-Associated Glomerulonephritis

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Background: Renal fibrosis is a common manifestation and hallmark of a wide variety of chronic kidney diseases (CKD) appearing in different morphological patterns, suggesting different pathogenic causes or consequences. Renal fibrosis with focal injury usually presents with patchy fibrosis whereas diseases affecting renal parenchyma in a diffuse manner lead to a more diffuse fibrotic pattern. In the present study, we aimed to analyze renal fibrotic patters in association with the renal lesions which are considered to directly contribute to renal fibrogenesis in a cross-sectional study.

Methods: A total number of 112 renal biopsies with various renal pathologies including acute interstitial nephritis (AIN), ANCA-associated vasculitis (AAV), membranous GN, lupus nephritis, nephropathy due to hypertension, IgA nephropathy (IgAN), focal-segmental glomerulosclerosis (FSGS) and diabetic kidney disease (DKD) were retrospectively included between 2015 till 2020 in a cross-sectional study.

Results: We here provide evidence that tubulointerstitial fibrosis is either the consequence of nephron damage (dependent or independent of glomerular scaring) or the result of a primary interstitial injury (leading to a diffuse fibrotic interstitial remodeling). Our data also show that focal fibrosis correlated with glomerular damage and irreversible injury to nephrons, confirmed in experimental models of nephrotoxic serum-nephritis and folic acid nephropathy in mice. By contrast, diffuse fibrosis was specifically associated with interstitial inflammation independent of glomerular damage and nephron loss, confirmed in mice challenged with unilateral ureteral obstruction.

Conclusions: In conclusion, we here provide evidence that the majority of renal fibrosis seems to be the consequence of nephron loss and replacement scaring, representing incomplete tissue repair. By contrast diffuse fibrosis appears to be the result of primary interstitial inflammation and injury.

PO1397

Automatic Artificial Intelligence-Assisted Glomerulosclerosis Analysis in Mice Models with Glomerulopathy

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Background: Glomerulosclerosis (GS) is a hall mark pathological feature in glomerular diseases. In preclinical research, GS is recapitulated in a number of experimental mice models with glomerulopathy, and a cross model characterization of GS would add to our understanding of their translatability to human disease. Here, we report GS quantification using an objective and newly developed automated AI assisted image analysis strategy in three mice models with glomerulopathy.

Methods: AI-assisted GS scoring was performed in three mice models with glomerulopathy and to assess drug treatment effects: 1) Diabetic nephropathy in reninAAV-induced hypertensive uninephrectomized db/db mice (DN/HT). Mice received treatment with vehicle, lisinopril, empagliflozin or combination. 2) I.V. injection of nephrotoxic anti-GBM serum (NTS) and 3) Adriamycin (ADR) in healthy mice. Automatic AI-assisted GS scoring was performed as a two-step process on PAS stained kidney sections. Firstly, segmentation of all glomeruli and next, assignment of a GS score to each glomerulus using trained neutral networks. GS was classified on a five-point scale (GS0-GS4) according to the area of capillary tuft involvement.

Results: The automated AI-assisted scoring performed with high degree of accuracy and allowed for a large number of glomeruli to be evaluated pr. section (>100). We show that the mice models had very distinct GS profiles. The DN/HT model was most severely affected with highest average GS score (DN/HT: 2.5, NTS: 1.76, ADR: 0.68, control: 0.1) and the largest percentage of severely affect glomeruli, GS3+GS4 (DN/HT: 54.1%, NTS: 37.2%, ADR: 16.8%, control: 1.1%). The ADR model was the least affected and

NTS was intermediate. AI-assisted scoring was further validated by evaluating the effect of standard of care compounds in the DN/HT model. LIS and the combination treatment with EMPA significantly reduced the average GS score (LIS: 2.1, LIS+EMPA: 1.7).

Conclusions: We here demonstrate an automatic AI-assisted image analysis approach for obtaining GS scores in three mouse models with glomerulopathy, and we show that the models display very distinct GS profiles. An AI-assisted approach allows for rapid and reproducible quantification of GS and, as a tool, could help advance future research.

Funding: Commercial Support - Gubra

PO1398

Increased Glomerular Parietal Epithelial Cell Expression of Cathepsins C and B in Anti-Thy1.1 Mouse Model of FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is characterized by replacement of glomerular capillaries by extracellular matrix (ECM). The collapsing FSGS (cFSGS) variant exhibits a poor prognosis and response to therapy. We recently reported that activated PECs migrate into glomerular tufts in human cFSGS and demonstrate increased cathepsins C and B expression. The absence of cathepsins B and C within normal glomerular tufts suggests these proteases may represent novel mediators of PEC-mediated glomerulosclerosis leading to collapse. We addressed the hypothesis that activated PECs migrate expressing cathepsins C and B migrate into glomerular PECs in a mouse model of cFSGS

Methods: Thy1.1 transgenic mice were injected with either saline (vehicle control) or anti-Thy1.1 antibody (19XE5; 1mg/mouse) to induce FSGS. Mice were sacrificed 4, 7, and 21 days after injection. Kidney sections were subjected to immunofluorescence staining for claudin-1, a marker of PECs, and cathepsin C or cathepsin B. Images were acquired by confocal microscopy.

Results: Claudin-1, cathepsin C, and cathepsin B co-localized to glomerular parietal epithelial cells lining Bowman's capsule in vehicle control mice. On day 4 after anti-Thy1.1 administration, claudin-1 staining showed migration of PECs into glomerular tufts in more than half of the glomeruli. Both cathepsin B and C staining co-localized to claudin-1 positive cells within glomerular tufts. PECs in the Bowman's capsule with hypertrophied morphology, suggesting activation, demonstrated increased expression of cathepsins C and B. Claudin-1 and cathepsins B and C co-localized within glomeruli on days 7 and 21 after anti-Thy1.1 administration, however, the number of stained cells per glomerulus and the percent glomeruli with positively stained cells in the glomerular tuft appeared decreased.

Conclusions: Glomerular PECs migrate into glomerular tufts and show increased expression of cathepsins C and B in the anti-thy1.1 model of cFSGS, recapitulating our findings in human cFSGS biopsies. The Thy1.1 mouse model of cFSGS can be used to define the role of PEC expression of cathepsins B and C in the pathogenesis of human cFSGS.

Funding: Clinical Revenue Support

PO1399

Effects of Enzymatic Cross-Linking and Increased Stiffness on Glomerular Basement Membrane and Podocyte Function

Dan Wang,[1] Nicholas J. Ferrell.[2,1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University, Nashville, TN.*

Background: The Glomerular basement membrane (GBM) is a critical component of the glomerular filtration barrier. Stiffening of the extracellular matrix is an important regulator of cellular function. How GBM stiffening affects podocyte function is not fully understood. This work aims to investigate the effect of GBM stiffening on molecular permeability and the podocyte function using a biomimetic in vitro model directly derived from kidney glomeruli.

Methods: Decellularized glomeruli isolated from porcine kidneys were pressure compacted on a Transwell membrane. GBM stiffness was tuned by crosslinking with transglutaminase (TG). The stiffness of the TG-crosslinked decellularized glomeruli was evaluated using a custom cantilever-based compression system Podocytes cultured on the TG crosslinked GBM were immunofluorescence stained with YAP, phalloidin and the nuclei were counterstained with DAPI. The diffusional molecular permeability was evaluated on native and TG crosslinked GBM with and without podocytes using FITC-Ficoll and AF488-BSA. Effects of GBM stiffening on gene expression of markers of podocyte differentation (NEPH1, WT1, Synaptopodin) were screened by qPCR.

Results: The stiffness of the decellularized glomeruli showed a dose-dependent increase after incubating with TG for 1 day and 4 days. On stiffer GBM, immunofluorescence imaging showed translocation of YAP to the podocyte nucleus. Passive molecular permeability of GBM was similar for native the TG crosslinked GBM. Podocytes cultured on both native and TG crosslinked GBM forms a stringent barrier to large molecules. qPCR results show an upregulation of differentiation markers as podocytes cultured on native and TG crosslinked GBM.

Conclusions: We developed a biomimetic in vitro model that fabricated directly from kidney tissue. mTG crosslinked glomeruli show a dose-dependent increase of stiffness. TG did not significantly effect the diffusive permeabilty of the GBM. GBM stiffness affects the YAP localization in the podocytes. The current in vitro model upregulates the gene expression of podocyte markers.

Funding: Other U.S. Government Support

PO1400

Effect of ANG-3070 in the Unilateral Ureteral Obstruction Mouse Model of Renal Fibrosis

Bert Oehlen, Jingsong Li, Kai Jiang, Latha Paka, Prakash Narayan, Itzhak D. Goldberg. *Angion Biomedica Corp, Uniondale, NY.*

Background: Tubulointerstitial inflammation and fibrosis are strong predictors of progression in all kidney diseases regardless of etiology. Receptor tyrosine kinases such as platelet-derived growth factor receptor (PDGFR) and discoidin domain receptors (DDRs), contribute to renal inflammation and fibrosis. ANG-3070 is an inhibitor of multiple tyrosine kinases receptors including PDGFR and DDR. This study evaluated whether ANG-3070 can slow the progression of fibrosis in the unilateral ureteral obstruction (UUO) mouse model of renal fibrosis.

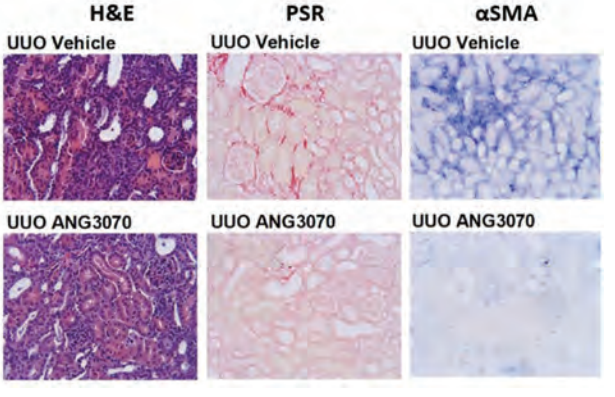
Methods: Male mice were subjected to UUO and randomized to daily oral treatment with vehicle (n=15) or 100 mg/kg of ANG-3070 (n=15) for 10 days after UUO and then sacrificed. Control male animals were age-matched and were not subjected to UUO (n=10). At sacrifice, obstructed and control kidneys were collected and processed for renal damage by hematoxylin-eosin (H&E) staining and scoring (0-8, 0 no damage and 8 damage to >80% of kidney) by blinded observers. Collagen deposition and myofibroblast transformation was determined by quantitative image analysis of picrosirius red (PSR)-stained slides and slides stained for α-smooth muscle cell actin (αSMA), respectively.

Results: Animals treated with ANG-3070 had a statistically significant reduction in histological damage as compared to vehicle (Vehicle, 6.4 vs ANG-3070, 4.3; p-value <0.001) and the histological markers of fibrosis, PSR (% control, vehicle, 1458% vs. ANG-3070, 503%; p-value <0.001), and αSMA (% control, vehicle, 511% vs. ANG-3070, 248%; p-value <0.01) as shown in Figure 1.

Conclusions: Daily oral administration of 100 mg/kg ANG-3070 reduces renal damage and renal fibrosis in a mouse model of renal fibrosis induced by UUO.

Funding: Commercial Support - Angion Biomedica, Inc.

Figure 1



PO1401

Renal Outcome Using New Chronicity Scoring System in IgA Nephropathy: Nationwide Study in Korea

Donghyuk Kang,[1] Tae Hyun Ban,[2] Hyung Duk Kim,[1] Bumsoon Choi.[2] KOGNET group *[1]Seoul Saint Mary's Hospital, Seocho-gu, Seoul, Republic of Korea; [2]Catholic University of Korea Eunpyeong St Mary's Hospital, Eunpyeong-gu, Seoul, Republic of Korea.*

Background: Many new grading systems of glomerulonephritis were proposed, recently. In 2019, new suggestion about standardized classification and reporting of GN is proposed by Mayo Clinic/Renal pathology society. Among the part of this new suggestion, grading the chronicity is an extremely important step and simple scoring system for chronic changes was devised. Therefore, the purpose of this study is predicting renal outcome with new chronicity grading system in IgA nephropathy (IgAN) patients.

Methods: 4,505 IgAN patients were enrolled from Korean GlomeruloNephritis Study Group (KoGNET) registry. Validation of Oxford classification, chronicity index with renal survival (End stage renal disease (ESRD), eGFR decrease rate of 50%, rate of renal function decline) were evaluated, followed by subgroup analysis according to chronic kidney disease (CKD) stages. Additional analysis between immunosuppressive therapy (IST) and chronicity index was performed, that chronicity index might help deciding initiation of IST.

Results: In validation of Oxford classification, both S and T scores were significantly associated with renal outcomes, but M and C scores were not. Multivariate linear regression analysis showed chronicity index was significantly associated with renal outcomes (P<0.05 for all). The severity of chronicity index was well correlated with renal outcomes in multivariate Cox regression analysis: minimal vs mild (HR, 1.95; 95% CI, 1.15 to 3.32; P=0.014), minimal vs moderate (HR, 2.98; 95% CI, 1.66 to 5.34; P<0.001), minimal vs severe (HR, 4.08; 95% CI, 2.27 to 7.35; P<0.001). Hypertension, eGFR, proteinuria and serum uric acid were also well correlated. In subgroup analysis,

chronicity index was still most powerful risk factor (P<0.05 for all) and they showed similar results to whole CKD stages. There was insufficient evidence to initiate IST according to chronicity index.

Conclusions: Among the known prognostic factors of IgAN, pathologic features were relatively abstract compared to other prognostic factors. But the chronicity index, presented as a simple integrated numeric scale, which is independently associated with renal outcome in IgAN, is more easily applicable in estimating renal outcome of IgAN patients.

PO1402

Comparison of Glomerular Proteomics Profiles of Healthy Human Kidney and Minimal Change Disease Identifies Distinct Targets and Pathways

Salem Almaani, Sethu M. Madhavan, John P. Shapiro, Anjali A. Satoskar, Isabelle Ayoub, Brad H. Rovin, Samir V. Parikh. *The Ohio State University, Columbus, OH.*

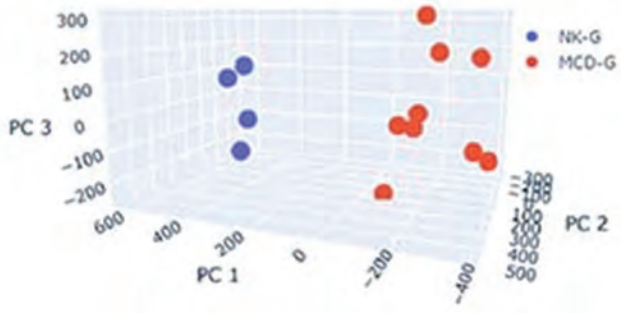
Background: Minimal change disease (MCD) is a common cause of idiopathic nephrotic syndrome and is characterized by diffuse podocyte foot process effacement. The pathogenesis of MCD remains unclear. We hypothesized that proteomics analysis of glomeruli could identify molecular markers that reflect the pathogenesis of MCD.

Methods: We included formalin-fixed paraffin-embedded kidney biopsies from patients with steroid-sensitive MCD (n=9) and normal donor kidneys (n=4). Glomeruli were isolated using laser capture microdissection and HPLC MS/MS was done using Orbitrap eclipse mass spectrometer. After data normalization, groups were clustered using principal component analysis (PCA) and compared by paired *t-tests*.

Results: PCA showed separate clustering of healthy glomeruli and MCD samples (**Figure 1**). Out of the 6729 unique proteins identified in MCD glomeruli, 1088 proteins were significantly differentially expressed compared to controls. Pathway analysis showed upregulation of complement pathway components (C1R, C1S, C1QA, C2, C3, C4A, C4B, C5, C7, C8B, C9) and downregulation of carbohydrate and amino acid metabolic pathway enzymes (FBP1, FBP2, ALDOC, ALDOB, AKR1A1, ALDH4A1, ALDH5A1, ACAT1). MCD glomeruli showed a significant reduction in expression of ECM proteins FREM2, FRAS1, CDHR2. Surprisingly, the expression of podocyte slit diaphragm-associated proteins (SYNPO, NPHS2, CD2AP) was not significantly altered in MCD compared to controls. We did not observe differential expression of MCD associated proteins, KANK, CFL1, CMIP. No peptides from SMPDL3b or ANGPTL4 were identified in MCD glomeruli.

Conclusions: Glomeruli from MCD showed differential proteomic signature compared to healthy human glomeruli. Activation of innate immune pathways including the complement system and loss of extracellular matrix and basement membrane-specific components in glomeruli of MCD are novel observations. The role of these markers in the pathogenesis of MCD needs to be investigated.

Funding: Clinical Revenue Support



PO1403

Effects of ANG-3070 in a Mouse Model of Alport Syndrome

Latha Paka, Natalia Prakash, Kai Jiang, Prakash Narayan, Itzhak D. Goldberg. *Angion Biomedica Corp, Uniondale, NY.*

Background: Alport syndrome (AS) is a hereditary kidney disease that presents in childhood and progresses to end stage kidney disease (ESKD) in adolescence. There are no approved therapies. AS is caused by mutations in type IV collagen genes Col4a3, a4 or a5, that result in reduced structural integrity of the glomerular basement membrane, triggering activation of fibrogenic cytokines, including platelet derived growth factor (PDGF) and transforming growth factor beta (TGFβ1) causing proteinuric disease and fibrosis. We hypothesize that an antifibrotic therapy may decrease proteinuria-induced fibrosis, and evaluated ANG-3070, a novel tyrosine kinase inhibitor, in a Col4a3 knockout mouse model of AS.

Methods: After confirming the Col4a3 mutation by genotyping, 4-week-old male and female Alport mice were randomized to Vehicle (oral, twice-daily) or ANG-3070 (oral, 25 mg/kg, twice-daily) for 5 weeks (n=12/ group). Age-matched, wild-type mice were included (n=9) as a control. Animals were sacrificed after 5 weeks of treatment, after collecting spot urines to measure protein to creatinine ratio (PCR). Renal tissue was analyzed for hydroxyproline (HYP) content, by Western blot for tissue fibrotic markers, and for histopathology using hematoxylin-eosin (H&E) staining for renal damage score and picrosirius red (PSR) staining for fibrosis. All histological analyses were performed blindly by two independent observers using a 0-4 scale (0 being normal, 4 ≥ 75% injured or stained).

Results: ANG-3070 treatment reduced mortality (survivors; Vehicle: 8/12 vs ANG-3070: 12/12). In surviving mice, proteinuria was reduced (mg/ml; Vehicle 6.2 vs ANG-3070 3.1; p<0.05) along with PCR (mg/mg; Vehicle 11.1 vs ANG-3070 5.5; p<0.05). There was a reduction in renal damage (Vehicle: 2.6 vs ANG-3070: 1.2; p = 0.002) along with renal fibrosis (Vehicle 2.4 vs ANG-3070 1.2; p=0.001). When kidney lysates were evaluated, HYP content was reduced (μg/kidney; Vehicle, 132 vs ANG-3070, 57; p <0.002) along with fibrotic markers of collagen-1, TGFβ1, and α smooth muscle actin (αSMA) compared to Vehicle-treated Alport mice (p<0.05). Additionally, PDGFR expression was reduced (p<0.05).

Conclusions: Treatment with a novel tyrosine kinase inhibitor, ANG-3070, was efficacious in AS mice compared to Vehicle. ANG-3070 may represent a novel therapeutic for AS.

Funding: Commercial Support - Angion Biomedica, Inc.

PO1404

Mesangial-Cell Activation by Circulating Immune Complexes Consisting of Galactose-Deficient IgA1 and IgG Autoantibodies from Patients with IgA Nephropathy

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Background: We and others have shown that immune complexes from the circulation of patients with IgA nephropathy (IgAN) that contain galactose-deficient IgA1 (Gd-IgA1) can induce proliferation of mesangial cells (MC) in culture. Here, we assessed cellular responses and signal transduction in MC after stimulation with CIC.

Methods: Quiescent primary human MC were stimulated for 15 min at 37°C, with or without inhibitors, with circulating immune complexes (CIC) isolated from sera of patients with IgAN. Cell lysates were analyzed directly, or after immunoprecipitation (IP) with antibodies specific for integrin β1 or PDGFR-β, by SDS-PAGE/immunoblotting for IgA, IgG, phospho-ERK1/2, phospho-PEGFR-β, talin, and Axl.

Results: Cell lysates from MC stimulated with CIC and the corresponding IP products of integrin β1 contained IgA and IgG. Amounts of IgA and IgG were significantly reduced by an inhibitor of integrin α1β1 (obtustatin), but not by an inhibitor of integrin α5β1 (RGD), and partially inhibited by a tyrosine-kinase inhibitor (dasatinib). CIC induced phosphorylation of ERK1/2 that was inhibited by obtustatin, RGD, dasatinib, and a Chinese herbal medicine, ShenPing decoction (SP) that has been used to treat IgAN patients in China. Dasatinib and SP inhibited CIC-induced phosphorylation of PDGFR-β and Axl. In IP products of integrin β1 from CIC-activated MC, cytoskeleton-associated protein talin, known to activate ERK1/2, was associated with integrin β1. SP blocked binding of talin to integrin β1. In IP products of PDGFR-β, CIC induced association of integrin β1 with PDGFR-β, a process that may subsequently induce activation of MAP kinases. Dasatinib and SP inhibited this association.

Conclusions: Integrin α1β1 mediated activation of MC by IgA-IgG CIC; CIC activated multiple protein-tyrosine kinases in MC, leading to MAP kinase activation and cellular proliferation. Some of the inhibitors in this study may provide information about the mechanism of MC activation by the pathogenic CIC and, thus, inform development of future disease-specific therapeutic approaches.

Funding: NIDDK Support

PO1405

Effect of Mycophenolate and Rapamycin on Pro-Inflammatory and Pro-Fibrotic Mediators in Human Mesangial Cells

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Background: A significant proportion of lupus nephritis (LN) patients develop chronic kidney disease. TGF-β1 expression is increased in renal biopsies from LN patients and it plays an important role in kidney fibrosis. We previously reported that mycophenolate and rapamycin inhibited pro-fibrotic processes in resident kidney cells in murine LN. We proceeded to investigate the effect of mycophenolate and rapamycin on inflammatory and fibrotic processes in human mesangial cells.

Methods: Growth-arrested human mesangial cells (HMC) were incubated with or without exogenous TGF-β1 (10 ng/ml), in the presence or absence of mycophenolic acid (1 μg/ml) or rapamycin (3 ng/ml), for up to 72 h. The effect on inflammatory and fibrotic processes was examined.

Results: TGF-β1 increased IL-6 and MCP-1 secretion, and α-smooth muscle actin, collagen and fibronectin expression, in a time-dependent manner, accompanied by increased ERK, mTOR and PI3K phosphorylation (*P*<0.05, for all). Constitutive IL-6 and MCP-1 secretion was mediated through PI3K phosphorylation, whereas IL-6 and MCP-1 secretion induced by TGF-β1 was mediated through PI3K, mTOR and ERK phosphorylation. Cell activation was mediated through PI3K and mTOR activation, while increased collagen and fibronectin expression was mediated through ERK, PI3K and mTOR. Mycophenolic acid inhibited the secretion of pro-fibrotic and pro-inflammatory cytokines, cell activation, and collagen and fibronectin expression, through suppressing ERK activation. Rapamycin inhibited similar processes through suppression of mTOR and ERK activation. Overall, the inhibitory actions of mycophenolic acid were comparable to that of rapamycin.

Conclusions: Mycophenolate and rapamycin both suppress pro-inflammatory and pro-fibrotic processes in mesangial cells by targeting signaling pathways that overlap partially.

Funding: Government Support - Non-U.S.

PO1406

Collapsing FSGS Is Strongly Associated with Microvascular Injury

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Background: Recent studies have suggested that the collapsing variant of focal segmental glomerulosclerosis (FSGS) might be a common secondary feature in renal disease influenced by microvascular injury. Here, we investigated glomerular and arteriolar microvascular injury in patients with collapsing FSGS, including primary FSGS and HIV-associated FSGS, and compared these lesions to patients with other variants of FSGS.

Methods: Biopsies of patients with FSGS were collected, including primary FSGS in native biopsies or transplant biopsies, as well as HIV-associated FSGS. Cases of FSGS secondary to renal diseases known to be caused by microvascular injury were excluded. We assessed all glomeruli in a biopsy for the presence of lesions associated with FSGS or ischemic injury, assessed microvascular lesions in glomeruli and arterioles, and studied interstitial lesions.

Results: We included 53 cases of FSGS, of which 19 cases with collapsing FSGS, 18 cases with FSGS not otherwise specified (NOS), 11 cases with FSGS tip, 3 cases with perihilar FSGS and 2 cases with cellular FSGS. Compared to other variants of FSGS, glomerular endothelial swelling of the vascular pole was more common in patients with collapsing FSGS (11% vs 0.0%; p=0.05). Associations between thrombotic injury and FSGS variant were not found. Arteriolar abnormalities were seen in 58% of collapsing FSGS and 38% of other variants of FSGS (p=0.17). When evaluating the concomitant occurrence of FSGS lesions and microvascular injury in individual glomeruli, we found that collapsing lesions and FSGS NOS lesions were associated with endothelial swelling in the same glomerulus (OR=22; p<0.001 and OR=3.8; p<0.01, respectively). Endothelial swelling was more common in glomeruli with collapsing lesions than glomeruli with FSGS NOS (OR=2.7; p=0.044). Collapsing FSGS was also associated with endocapillary hypercellularity (OR=4.3; p<0.001).

Conclusions: Here, we demonstrate that collapsing FSGS lesions are strongly associated with microvascular injury such as endothelial swelling and endocapillary hypercellularity, and often co-exist in the same glomerulus. In addition to collapsing FSGS occurring as a secondary phenomenon in renal microangiopathies, these results indicate that endothelial injury could also be involved in the pathophysiology of collapsing FSGS due to primary podocyte injury.

PO1407

Danhong Injection (DHI) Inhibits Lipopolysaccharide-Enhanced Cell Proliferation of Rat Renal Mesangial Cells via NF-κB Signaling Pathway

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Background: To explore the mechanisms of DHI in the treatment of Mesangioproliferative glomerulonephritis (MsPGN), we investigated the effects of DHI on LPS-induced NF-κB activation and its downstream inflammatory mediators, such as ICAM-1, TGF-β1, iNOS and FN protein expression in rat MCs.

Methods: The rat MCs treated with different concentrations of DHI (0, 50, 100, 200, 500, 1000, and 2000 uL/L) for 12 h,then incubated with or without 100 ng/ml LPS for another 24 h. Then, cell proliferation was determined by CCK8. The MCs treated with low-dose DHI (250 uL/L), median-dose DHI (500 uL/L) and high-dose DHI (1000 uL/L) for 12 h or PDTC for 30 min before 24h treatment of LPS. Then the activation of NF-κB was detected by Western blot and immunofluorescence. The protein levels of ICAM-1, TGF-β1, iNOS and FN in rat MCs were detected by Western blot.

Results: DHI significantly suppressed LPS-induced cell proliferation by CCk-8 results (Fig 1). LPS stimulation resulted in a significant increment of p65 contents in nucleus and a decrement of p65 contents in cytoplasm in rat MCs compared with NC. PDTC and DHI exerted potent inhibitory effect on increasing expression of p65 in nucleus and decreasing in cytoplasm compared with LPS-treatment group. The inhibitory effect on NF-κB nuclear translocation of DHI was in a dose-dependent manner (Fig 2). The protein level of IκB-α in cytoplasm treated by LPS decreased significantly compared with that in control (Fig 3) and this decrement was significantly reversed by PDTC and DHI. In addition, the protein expression of ICAM-1, TGF-β1, iNOS and FN was also inhibited by PDTC and DHI (Fig 4).

Conclusions: DHI significantly repressed LPS-induced cell proliferation and FN expression in rat MCs through inhibiting the activation of NF-κB signaling pathway also its downstream inflammatory mediators.

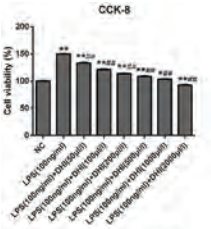

Fig 1 The results of CCK-8 revealed that DHI significantly suppressed LPS-induced cell proliferation

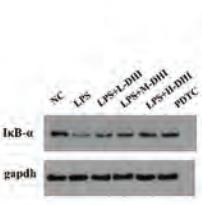

Fig 3 the protein level of IκB-α in cytoplasm treated by LPS

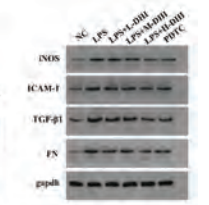

Fig 4 the protein expression of ICAM-1, TGF-β1, iNOS and FN treated by PDTC and DHI

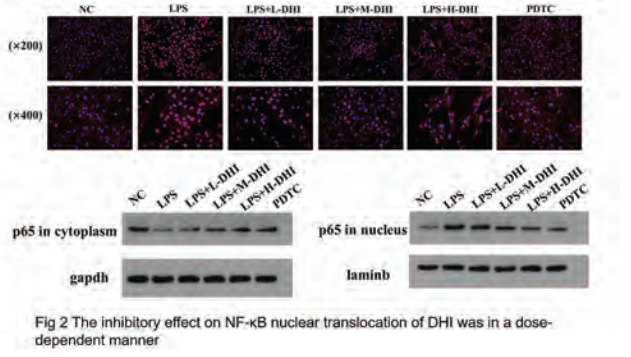

Fig 2 The inhibitory effect on NF-κB nuclear translocation of DHI was in a dose-dependent manner

PO1408

Effect of ANG-3070 in the Passive Heymann Nephritis Rat Model of Primary Proteinuric Kidney Disease

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Background: Primary proteinuric kidney diseases (PPKD) as a group are an important cause of end-stage kidney disease (ESKD). Many receptor tyrosine kinases, including platelet-derived growth factor receptor (PDGFR), contribute to the progression of PPKDs to ESKD. ANG-3070 is a novel and proprietary inhibitor of multiple tyrosine kinases including PDGFR. This study evaluated the effects of ANG-3070 in a passive Heymann's nephritis (PHN) rat model of membranous glomerulopathy.

Methods: Male Sprague Dawley rats (300g) were administered anti-FX1A serum. Treatment groups included 15mg/kg ANG-3070 (n=11), Vehicle (n=11) and Sham (n=5). Animals were dosed orally, twice daily, for 12 weeks, and 24-hour urines were collected biweekly. At sacrifice, kidney tissue was harvested.

Results: Twelve-week treatment with orally dosed ANG-3070 significantly reduced the protein to creatinine ratio as compared to Vehicle (mg/mg; 5.3 vs 9.4; p<0.05). It also led to a significant reduction in total kidney hydroxyproline content (μg/kidney; 952 vs. 1416; p<0.05), indicating a reduction in fibrotic tissue. When periodic acid-Schiff staining from kidney sections were evaluated for glomerular damage by two blinded observers on a scale of 0 (normal/no injury) to 4 (severe injury), ANG-3070 significantly reduced glomerular damage (1.7 vs. 2.6; p<0.05), indicating a reduction in glomerulosclerosis. The evaluation of PDGFRβ levels from total kidney lysates by Western Blot indicated an increase in the Vehicle treated group compared to Sham (PDGFRβ/GAPDH; 2.6 vs 0.7, p<0.05). ANG-3070 treatment significantly reduced these levels when compared to Vehicle (PDGFRβ/GAPDH; 1.0 vs 2.6, p<0.05), which was comparable to the levels observed in the Sham group.

Conclusions: Twice-daily oral administration of the novel tyrosine kinase inhibitor ANG-3070 reduces proteinuria, renal fibrosis, glomerulosclerosis and PDGFRβ expression levels in a rat model of PHN. These data suggest ANG-3070 may be an effective treatment in PPKDs.

Funding: Other U.S. Government Support, Commercial Support - Angion Biomedica, Inc.

PO1409

A Rare Case of Immunotactoid Glomerulopathy Associated with Rheumatoid Arthritis

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Introduction: Immunotactoid glomerulopathy (ITG) is a rare disease that is characterized by nephrotic range proteinuria, hematuria, hypertension, and kidney failure. It is most commonly associated with hematologic disorders. Rarely it presents as a polyclonal process and associated with autoimmune disorders such as rheumatoid arthritis (RA).

Case Description: A 50-year-old woman with a medical history of rheumatoid arthritis without treatment who was recently diagnosed with hypertension (174/82 mmHg) with elevated serum creatinine (Scr 2.2mg/dL). She lost follow-up and returned to emergency department 5 months later complaining of worsening edema, fatigue, foamy urine, and joint pain for which she was taking NSAIDs daily. Further workup showed Scr of 3.0 mg/dL, proteinuria (urine protein to creatinine ratio 14 g/g), hematuria (5 RBCs/HPF), positive ANA (1:160), rheumatoid factor (140), and cyclic citrullinic peptide (30.4), negative for ANCA, dsDNA, cryoglobulins, Hepatitis B and C, HIV, SPEP, UPEP, and serum free light chains with normal complement levels. A renal biopsy showed diffuse thickening of the glomerular basement membranes with focal segmental endocapillary hypercellularity by light microscopy. There is polyclonal IgG-dominant smudgy/chunky capillary loop staining with mesangial extension with lesser IgM and C1q by immunofluorescence and numerous subepithelial deposits and occasional subendothelial deposits, which exhibit a microtubular substructure with hollow cores arranged focally in parallel arrays and measuring 11-72 nm with an average of 34 nm by electron microscopy. A Congo red is negative for amyloidosis. She was treated with low dose prednisone (10mg/day) for her RA. Upon follow up it was noted her Scr decreased to 1.4mg/dL but nephrotic range proteinuria persisted.

Discussion: ITG is a rare glomerulopathy. Determining the clonality and the underlying etiology is essential for the management. This case is associated with RA and presents as a polyclonal ITG. The exact treatment for this condition is unknown. Will continue following her closely as historically ITG caries a poor renal prognosis.

PO1410

Fibrillary Glomerulonephritis: A Rare Entity, Responsive to Rituximab

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Introduction: Fibrillary glomerulopathy (FGN) is a rare proliferative type of glomerular disease with poor prognosis and limited therapeutic options. Literature review showed very few cases of FGN where Rituximab has been used.

Case Description: A 69-year-old Caucasian woman with a history of DM, HTN presented to the hospital with complaints of dyspnea and leg swelling. Lab work revealed BUN/Scr of 34/3.88 mg/dL (baseline Scr of 1.4 mg/dL, proteinuria (7,902 mg/dL). Renal biopsy was performed which showed fibrillary deposits as shown in the picture. Hepatitis panel and work up of malignancy including bone marrow biopsy was negative. She was started on Rituximab 1gm every 14 days for 2 doses. Pt initially required HD but with treatment her symptoms and Cr improved and was taken off HD. Most recent Cr was1.8.

Discussion: The diagnosis of FGN can only be established with kidney biopsy. Most of the patients present with renal insufficiency, nephrotic picture. Mostly idiopathic but can be associated with hepatitis C, dysproteinemia, autoimmune diseases and to lesser extent malignancies. The prognosis is very poor with very limited therapeutic options to date and optimal therapy remains to be ascertained. Rituximab has been used in few cases in literature showing good clinical response. Our patient tolerated and responded very well to Rituximab with significant improvement in kidney function and hence we propose the use of Rituximab in FGN.

PO1411

Renal-Limited Lupus Nephritis Misdiagnosed as Advanced CKD: Addressing the Need for Increasing Renal Biopsies in the Community Setting

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Introduction: "Full-house" nephropathy is characteristic of lupus nephritis, but may be seen in patients without other evidence of SLE. Patient was presumed to have acute renal failure prior to renal biopsy and was placed on dialysis for chronic management of ESRD. Despite no extrarenal or clinical manifestations of SLE, renal biopsy revealed histopathology consistent with lupus nephritis.

Case Description: A 61-year old African American female presented to an outside hospital with complaints of mild abdominal pain, nausea, emesis, and diarrhea. Family history was positive for autoimmune disorders, including SLE and Sjogren's Syndrome. Initial lab work revealed creatinine 8.1 mg/dL, eGFR 7 mL/min, BUN 117 mg/dL, proteinuria, and hyperkalemia with potassium 5.2. Renal biopsy revealed collapsing glomerulopathy with "full-house" immune complex deposition without active glomerular lesions commonly seen with lupus nephritis. Evaluation was positive for anti-nuclear antibody (ANA), but anti-double stranded DNA (anti-dsDNA), serum immunofixation (IFE), hepatitis screen and HIV screen were negative. She was treated for lupus nephritis with a three-day course of Solu-medrol and continued on home peritoneal dialysis and oral prednisone. Renal function recovered with creatinine of 0.64 mg/dL and eGFR 116 mL/min/ leading to discontinuation of dialysis.

Discussion: Renal biopsy revealed collapsing glomerulopathy with "full-house" immune complex deposition without active glomerular lesions. Lupus nephritis is an immune mediated glomerulonephritis with characteristic histological pattern including "full house immunofluorescence" with glomerular deposits that stain for IgG with co-deposits of IgA, IgM, C3 and C1q. "Full-house" immune complex deposits are commonly seen in lupus nephritis, but are not pathognomonic. Nine adult cases of limited renal disease in absence of other evidence of SLE have been reported. Although there are no guidelines on treatment of lupus-like nephritis, all reported patients were treated with regimens of immunosuppressive agents and steroids. To date our patient has not developed additional manifestations of SLE and her renal function remains normal without signs of injury. We advocate for a lower threshold for performing renal biopsies as they can provide valuable information regarding disease diagnosis and treatment.

PO1412

Tissue MALDI-Mass Spectrometry Imaging Reveals the Potential Role of PLPP3 in Regulating Lysophosphatidic Acid Signaling in Aging Kidney

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Background: Increasing evidence suggests that accumulation of lysophosphatidic acid (LPA) and aberrant activation of LPA signaling is implicated in various human diseases such as diabetic kidney disease. However, the role of LPA signaling in aging-related kidney injury remains elusive.

Methods: C57BL/6J male mice at 5 months (Control) and 24 months (Aging), N=10/group, were used in the current study. Kidney pathological changes were evaluated based on PAS-stained images and nephropathy markers including urinary albumin creatinine ratio (ACR) and kidney injury molecule-1 (KIM-1). Gene expression and protein levels of major enzymes/effectors involved in LPA metabolism and signaling were measured in kidney cortical tissues using standard RT-qPCR and western blotting approaches. Matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) was performed for spatial lipidomics analysis of lipids including LPA and other species in kidneys of aging mice and controls. MetaboAnalyst and GraphPad were employed for statistical analyses.

Results: Histological images showed that aging kidney developed glomerulosclerosis at the age of 24 months. Aging mice also had higher levels of urinary albumin, ACR, and KIM-1. Interestingly, both mRNA and protein levels of phospholipid phosphatase 3 (PLPP3), an enzyme that can dephosphorylate and inactivate the signaling functions of LPA, were lower in renal cortical tissues of aging mice. The gene expression level of LPA receptor 1 (*LPAR1*) was upregulated in aging renal cortical tissues. In addition, oscillations of gene expression and protein levels of enzymes involved in LPA metabolism/signaling, mitochondrial biogenesis, and mitochondrial dynamics were observed in aging kidneys. In the MALDI-MSI analysis, we found altered sphingolipid metabolism in glomeruli of mouse aging kidneys compared with controls. In particular, several LPA (e.g., LPA (16:0)) species were increased in aging glomeruli, suggesting the potential role of LPA signaling in the aging kidney.

Conclusions: These findings suggest that reduced PLPP3 contributes to the accumulation of LPA in glomeruli of aging kidneys. Activation of LPA signaling in glomeruli may play an important role in the pathogenesis of aging-related kidney injury.

Funding: NIDDK Support, Other NIH Support - NIA-San Antonio Nathan Shock Center

PO1413

Focal Segmental Glomerulosclerosis: A Rare Cause of Nephrotic Syndrome in Graft vs. Host Disease

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Introduction: Nephrotic syndrome (NS) is a very rare complication of allogeneic hematopoietic cell transplantation (HCT) and is usually associated with chronic graft versus host disease (GVHD). In such patients, membranous nephropathy and minimal change disease are the most frequently observed renal pathology. However, focal segmental glomerulosclerosis (FSGS) is an extremely uncommon etiology of NS in patients with HCT and GVHD. We herein describe a case of a patient with HCT and chronic GVHD who developed NS secondary to FSGS.

Case Description: A 24-year-old man with medical history of Sickle Cell Disease status post splenectomy and HCT, epilepsy, arterial hypertension and chronic GVHD with cutaneous and esophageal manifestations who presented to the emergency department with a one month of evolution progressive lower extremity edema and intermittent hematuria. Vital signs were remarkable for uncontrolled blood pressure. Home medications were lisinopril 20mg daily, levetiracetam 500mg twice daily and prednisone 10mg daily. Physical examination was remarkable for edema of the lower extremities, ascites, and cachexia. Laboratories revealed: BUN 35 mg/dL, serum creatinine 1.15 mg/dL, total protein 3.00 g/dL, serum albumin 1 g/dL, glucose 110mg/dL, total cholesterol 425 mg/dL, triglycerides 335 mg/dL, VLDL 67 mg/dL and LDL 316 mg/dL. Urine protein/creatinine ratio resulted in 30,000mg/g. Laboratory findings of hypoalbuminemia, hyperlipidemia, and nephrotic range proteinuria were consistent with NS. A renal biopsy was performed and revealed findings consistent with a diagnosis of FSGS, not otherwise specified. Partial remission of NS was achieved at 3 months of treatment with mycophenolate mofetil 500mg twice daily and prednisone 15mg twice daily.

Discussion: GVHD is a significant cause of morbidity and mortality in patients after HCT. Renal involvement can be a serious manifestation and prompt recognition is essential for adequate management and prevention of renal disease. FSGS is an extremely rare complication of HCT and very few cases have been reported in the literature linking FSGS to HCT. Further documentation of this phenomenon is important to further characterize the clinical and pathological features of this complication.

PO1414

Catastrophic COVID-19-Associated Nephropathy (COVAN) in an Asymptomatic Patient

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Introduction: Glomerular lesions were reported in a minority of patients with COVID-19, with collapsing focal segmental glomerulosclerosis (FSGS) also called COVID-associated nephropathy (COVAN), This typically occurs in the setting of prominent COVID symptoms. We describe a COVAN occurring in an asymptomatic patient

Case Description: A 48-year-old, African American female patient who had CKD stage 3 a secondary to hypertension, with serum creatinine of 1.2 mg/dl and absent proteinuria at baseline, presented to the hospital for evaluation of an asymptomatic elevation of her serum creatinine to 9.9 mg/dl, discovered during a routine evaluation by her PCP. Her urine Protein/Creatinine was 6.15. Six weeks prior to her presentation, she endorsed 7 days of nausea and intermittent vomiting associated with non-bloody diarrhea without respiratory symptoms. Her GI symptoms has resolved on its own. She had multiple family members, including her husband and daughter, who had tested positive for COVID around the same time. Her nasal PCR for COVID was negative. She had not been vaccinated for SARS COVID. She has no family history of kidney disease; she denied IV drug use and had no risk factors for HIV. She was on Amlodipine for her hypertension. She was afebrile on admission with blood pressure of 170/80 mm Hg. She had 1+ pedal edema with an unremarkable physical exam. A percutaneous kidney biopsy was performed to evaluate the cause of her renal dysfunction. This showed collapsing FSGS. HIV and ANA were negative. A subsequent testing for COVID nucleocapsid and spike protein was positive. Results of APOL1 genotype is pending. She was started on high dose steroids and followed up as an outpatient.

Discussion: COVAN is increasing recognized as a serious complication of COVID. However, the typical presentation is in the setting of prominent respiratory involvement. Recognizing the minor fleeting symptoms of COVID preceding a catastrophic kidney disease and testing for it is an important in patients presenting with features of collapsing FSGS

PO1415

Siglec-9 Agonism Reduces ANCA-Mediated Neutrophil Responses In Vitro

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Background: Sialic acid-binding Ig-like lectin 9 (Siglec-9) is constitutively expressed on neutrophils and monocytes. The expression and potential role of siglec-9 in ANCA-associated vasculitis (AAV) is yet to be determined. We aimed to examine the expression of siglec-9 in patients with AAV and explore the impact of siglec-9 agonism on ANCA-mediated neutrophil responses *in vitro*.

Methods: Leukocytes and serum were isolated from peripheral venous blood of AAV patients and siglec-9 expression was measured by flow cytometry and ELISA, respectively. Immunohistochemistry was performed on kidney biopsies of AAV patients with AAGN and stained for siglec-9 and leukocyte markers. Functional studies were done using healthy donor neutrophils in the presence of ANCA and siglec-9 mAb to investigate its role in apoptosis and ROS production.

Results: We found increased serum siglec-9 expression in active AAV compared to remission AAV and a positive correlation with disease activity. Neutrophils and intermediate (CD14+/CD16+) monocytes from PR3-ANCA patients displayed higher siglec-9 expression compared to MPO-ANCA patients. Siglec-9 expression in AAGN was restricted to areas of active inflammation. We observed increased siglec-9 shedding in neutrophils following ANCA stimulation. Siglec-9 agonism in these neutrophils was associated with increased apoptosis and reduced ROS production compared to isotype control and unstimulated neutrophils.

Conclusions: Our study suggests that siglec-9 is expression correlates with disease activity in AAV. Our functional studies support a potential role for siglec-9 in modulating ANCA-mediated neutrophil responses. Further evaluation is required to determine the relevance of these findings on neutrophil-endothelial interactions.

Funding: Government Support - Non-U.S.

PO1416

The Proteinase 3-Alpha1-Antitrypsin Connection in PR3-ANCA Vasculitis

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Background: PR3 is a major autoantigen in ANCA-associated vasculitis (AAV) and a neutrophil serine protease inhibited by alpha1-antitrypsin (AAT). Increased PR3 and decreased AAT were suggested as disease mechanism for PR3- but not MPO-AAV

Methods: We assessed PR3 and AAT in 100 AAV patients and 50 healthy controls (HC) and produced recombinant wt- and mut-AAT to study the effect on proteolytic PR3 activity, membrane PR3 (mPR3) by flow cytometry and surface plasmon resonance (SPR), and neutrophil activation.

Results: In active PR3- and MPO-AAV, plasma PR3 concentration increased approximately 5-fold and plasma AAT 1.8-fold shifting the PR3:AAT ratio significantly towards PR3. Both parameters normalized with remission. Notably, only one PR3-AAV remission patient showed strongly decreased plasma AAT. The PR3 neutrophil content was approximately 50% higher in active PR3- and MPO-AAV accompanied by increased PR3 transcription. The resulting total PR3 pool (plasma PR3 concentration x plasma volume + neutrophil PR3 x neutrophil number) was approximately 3-fold larger in active AAV and normalized with disease remission. In active PR3-AAV but not MPO-AAV, the total PR3 pool correlated with kidney injury, hemoglobin, and PR3-ANCA ELISA. Membrane-PR3 (mPR3) correlated negatively with plasma AAT in HC, was increased in AAV patients with a compromised plasma AAT correlation. Mechanistically, extracellular AAT dose-dependently reduced mPR3 by competing with PR3 for the PR3-presenting CD177 receptor. Consequently, AAT reduced neutrophil activation by PR3- but not MPO-ANCA. Neutrophils from AAV patients and HC showed similar mPR3 reduction with AAT. However, in contrast to HC plasma, neutrophil incubation in active AAV plasma increased the AAT concentrations required to lower mPR3, an effect that was recapitulated by adding inflammatory mediators to HC plasma. Finally, oxidative AAT modification resulted in less PR3 interaction and diminished mPR3 reduction

Conclusions: We found a strongly increased PR3 pool in active PR3-AAV and exclude decreased plasma AAT as the general underlying disease mechanism, as previously proposed. However, AAT controls mPR3 expression and subsequently PR3-ANCA induced neutrophil activation, suggesting adjunctive AAT administration may have beneficial effects in acute PR3-AAV

Funding: Government Support - Non-U.S.

PO1417

Serum Soluble CD206 Complements Urinary Soluble CD163 in Detecting Active ANCA-Associated Glomerulonephritis

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Background: Early detection of active glomerulonephritis (GN) in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is crucial to minimize renal damage, but accurate biomarkers are currently lacking. Urinary soluble CD163 (usCD163) has been shown as a potent biomarker for active ANCA GN. However, false negative rates can be as high as 29%. Here, we investigated whether serum soluble CD206 (ssCD206; macrophage mannose receptor), complements usCD163 in the detection of active ANCA GN.

Methods: Three independent cohorts (C1-Maastricht University Medical Center, C2-University Medical Center Groningen & C3-Trinity College Dublin) with available serum, urine, and renal biopsy samples (C1 only) were included. usCD163/creatinine (ng/mmol) and ssCD206 (ng/ml) were assessed by ELISA in urine and serum, respectively. The performance of usCD163 and ssCD206 to detect ANCA GN was assessed using receiver operating characteristics (ROC) curves. Biopsies from ANCA GN patients were immunohistochemically (IHC) stained for CD163 and CD206. Colocalization of CD163 and CD206 was assessed by immunofluorescence (IF).

Results: Patients (C1/C2/C3) had active ANCA GN (n=42/17/47), active non-renal AAV (n=3/3/12) or were in remission (n=4/8/38). Healthy controls (HCs; n=6/34/0) were included. usCD163 was significantly higher in active ANCA GN compared to active

non-renal AAV and remission in all cohorts, and healthy control urine in C1 (Kruskal-Wallis, $P<0.001$). ssCD206 was significantly higher in active ANCA GN compared to HCs in cohorts C1 & C2 (Kruskal-Wallis, $P\leq0.01$). usCD163 had a specificity of 100% in all cohorts, whereas sensitivity was 71 (C1), 88% (C2) and 64% (C3). The addition of ssCD206 increased the sensitivity to detect active ANCA GN in all cohorts to 83% (C1), 100% (C2) and 81% (C3). IHC revealed $CD163^+$ and $CD206^+$ cells in the kidneys of active ANCA GN patients (n=8). IF showed glomerular presence of $CD163^+CD206^-$ cells, whereas $CD163^+CD206^+$ and $CD163^-CD206^+$ cells were mainly found in the tubulointerstitium.

Conclusions: ssCD206 complements usCD163 and reduces false negative rates in the detection of active ANCA GN. Histological assessment revealed distinct glomerular and tubulointerstitial populations of $CD163^+$ and $CD206^+$ cells.

PO1418

Urine and Plasma Complement Ba Levels During Flares of Nephritis in Patients with ANCA-Associated Vasculitis

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Background: The alternative complement pathway has been implicated in the pathogenesis of ANCA-associated vasculitis (AAV), however it is not clear whether activation of complement occurs systemically or in affected organs such as the kidney. This study measured levels of urinary and plasma complement fragment Ba (uBa and pBa respectively) at multiple timepoints in patients with AAV.

Methods: Ba was measured by ELISA in serial samples of urine (uBa) and plasma (pBa) from 20 AAV patients who developed a renal flare, 20 who developed a non-renal flare, and 20 in long-term remission. Changes in Ba levels were modeled using linear mixed effect models.

Results: Cohort characteristics are given in **Figure.1**. uBa levels increased at renal flare, but did not increase at non-renal flare, and remained stable in long-term remission (**Figure 2a**). pBa levels were stable over time in all groups (**Figure 2b**). uBa correlated with renal AAV activity measured as the renal component of the BVAS score (R^2= 0.33, p<0.01), but did not correlate with the overall BVAS score during renal flare (R^2= 0.13, p=0.12) or non-renal flare (R^2= 0.10, p=0.22).

Conclusions: Urine, but not plasma, Ba levels increase at the time of a flare of renal disease in AAV, suggesting intra-renal alternative complement pathway activation. uBa has the potential for use as a surveillance biomarker of renal vasculitis.

Funding: Other NIH Support - Supported by the Vasculitis Clinical Research Foundation

	Long-Term Remission (n=20)	Non-Renal Flare (n=19)	Renal Flare (n=21)	p-value
Male	8 (40%)	8 (42%)	16 (76%)	0.03
White	18 (90%)	19 (100%)	19 (90%)	NS
Non-Hispanic	18 (90%)	19 (100%)	17 (81%)	NS
Age (years)	52 ± 15	54 ± 20	55 ± 13	NS
Disease duration at visit 1 (years)	11.1 ± 8.8	7.3 ± 5.9	4.9 ± 3.8	0.02
Granulomatosis with polyangiitis	14	14	16	
Microscopic polyangiitis	4	1	3	
Eosinophilic granulomatosis with polyangiitis	2	4	2	
ANCA Type				
cANCA/pANCA/unmeasured	10/2/8	9/4/6	12/4/5	
PR3/MPO/unmeasured	12/3/5	8/5/6	14/4/3	
BVAS	0	8 (5-10)	14 (12-18)	
rBVAS	0	0	10 (6-12)	
eGFR	74 (61-101)	83 (74-104)	50 (38-59)	

Figure 1. Patient demographics and disease characteristics.
Data depicted n (%); mean ± standard deviation; median (inter-quartile range) as appropriate.
Fisher's exact test used to compare group memberships and ANOVA used to compare continuous variables. Data obtained at flare visits for the non-renal flare and renal flare groups; and at the last visit for the long-term remission group.
ANCA: anti-neutrophil cytoplasmic antibody; cANCA: cytoplasmic ANCA; pANCA: perinuclear ANCA; PR3: proteinase 3; MPO: myeloperoxidase; BVAS: Birmingham Vasculitis Activity Score;
rBVAS: active renal disease per BVAS; eGFR: estimated glomerular filtration rate.

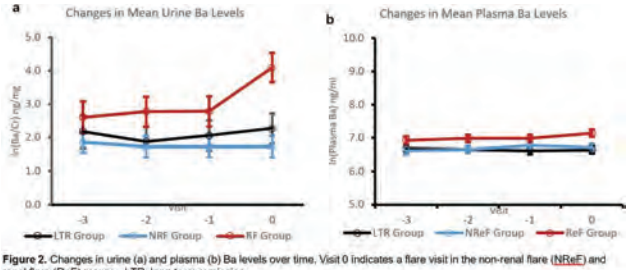

Figure 2. Changes in urine (a) and plasma (b) Ba levels over time. Visit 0 indicates a flare visit in the non-renal flare (NReF) and renal flare (ReF) groups. LTR: long-term remission.

PO1419

Alterations in Amino Acid and Lipid Metabolism in ANCA-Stimulated Monocytes

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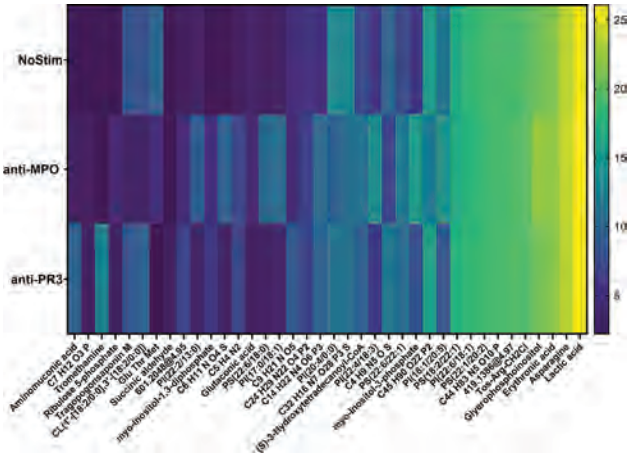
Background: Multiple metabolic pathways and intermediates are involved in inflammation. Altered immune cell metabolism is involved in the pathogenesis of autoimmune diseases such as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). In particular, monocytes stimulated with ANCA show increased oxidative phosphorylation and glycolysis, with a more profound response to myeloperoxidase (MPO) ANCA than proteinase-3 (PR3). The aim of this work was to profile the metabolome of ANCA-stimulated primary monocytes.

Methods: Monocytes from healthy donors (n=24) were isolated and stimulated with monoclonal anti-MPO, anti-PR3 for 4 hours. Metabolites were extracted using an optimised extraction protocol and analysed by liquid chromatography–mass spectrometry (LC–MS). Targeted and untargeted analyses were carried out using Agilent MassHunter Profinder and Mass Profiler Professional. Cytokine production was measured by ELISA and flow cytometry was used to assess surface expression of MPO and PR3.

Results: Targeted metabolomic analysis showed increases in several amino acid and TCA cycle metabolites relative to unstimulated cells, notably phenylalanine, isomers leucine & isoleucine, and fumarate. Untargeted analysis confirmed alterations in amino acid and lipid metabolism in ANCA-stimulated monocytes (Figure 1). These metabolic differences did not correlate with the increased cytokine expression observed in anti-MPO-treated monocytes. Anti-PR3 stimulation did not induce major changes in metabolism or cytokine production. Monocytes expressed high levels of surface MPO and PR3, with MPO expression showing a significant inverse correlation with age.

Conclusions: Inflammatory and metabolomic activation of primary human monocytes occurs with anti-MPO, but not anti-PR3 stimulation. Early increases in amino acid and lipid metabolism are evident in anti-MPO treated cells. Further work is needed to validate these findings and determine their physiological relevance in AAV.

Funding: Commercial Support - Agilent Technologies Ireland Limited



PO1420

LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) Are Important for Mediating Myeloperoxidase-ANCA Glomerulonephritis in a Preclinical Mouse Model

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Background: Neutrophils play a critical role in the pathogenesis of necrotizing crescentic glomerulonephritis (NCGN) caused by anti-neutrophil cytoplasmic autoantibodies (ANCA). LFA-1 and Mac-1 are β2-integrins that have critical synergistic roles in neutrophil-mediated inflammation. In this study, we investigated the role of LFA-1 and Mac-1 in murine NCGN induced by mouse anti-mouse MPO, which is histopathologically indistinguishable from human ANCA NCGN.

Methods: Anti-MPO IgG was purified from sera of MPO knock out (KO) mice immunized with murine MPO. Mice with KO of LFA-1 or Mac-1, and normal wild-type C57BL/6j mice (WT B6) were injected i.v. with 50ug/g body weight anti-MPO IgG. Circulating anti-MPO IgG (MPO-ANCA) was monitored by ELISA. Proteinuria, hematuria and leukocyturia were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for pathologic examination. MPO-ANCA-induced neutrophil activation was assayed *in vitro*.

Results: At day 6, WTB6 (n=8), LFA-1 KO (n=8) and Mac-1 KO (n=9) mice that received anti-MPO IgG had similar levels of circulating MPO-ANCA. All WT B6 mice developed hematuria and NCGN with mean 13.9% glomeruli with crescents and 5.3% with necrosis. In contrast, LFA-1 KO mice and Mac-1 KO mice had normal urine and substantially reduced NCGN (Table). *In vitro* assays showed that anti-MPO IgG caused similar activation of neutrophils from LFA-1 KO, Mac-1 KO and WT mice.

Conclusions: Depletion of LFA-1 or Mac-1 blocks MPO-ANCA induced NCGN in mice, thus both of these β2-integrins are required for ANCA disease induction. Depletion of LFA-1 or Mac-1 does not block MPO-ANCA induced neutrophil activation. These observations indicate that blockade of either of these β2-integrins abrogates MPO-ANCA NCGN by inhibiting the recruitment of neutrophils that is required to induce inflammatory vascular injury in ANCA disease. These data suggest that pharmacologic blockade of β2-integrins may have a therapeutic role in ANCA disease.

Funding: NIDDK Support

Anti-MPO IgG-Induecd Glomerular Lesions in Different Strains of Mice

	Crescents/glomerulus	Necrosis/glomerulus
B6 WT (n=8)	13.9%	5.3%
B6 Mac-1 KO (n=9)	2.9% (p<0.001)	0.7% (p=0.003)
B6 LFA-1 KO (n=8)	0.9% (p<0.001)	0.0% (p<0.001)

PO1421

Drilling into a Potential Correlation Between ANCA-Associated Vasculitis and Natural Gas Wells

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Background: ANCA-associated vasculitis (AAV), a systemic necrotizing disease affecting small and medium blood vessels, is caused by antineutrophil cytoplasmic autoantibodies which target intracellular proteinase 3 (PR3) or myeloperoxidase (MPO). The incidences of PR3-AAV and MPO-AAV vary geographically with PR3-AAV most commonly reported in the United Kingdom and MPO-AAV the predominant type seen in Japan. Environmental exposure has been implicated in the pathophysiology of MPO-AAV. The aim of this study is to evaluate a potential relationship between AAV and environmental factors in north central West Virginia.

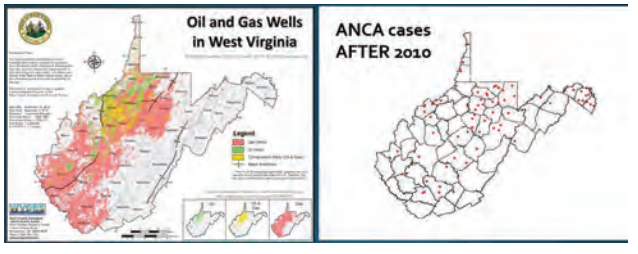
Methods: This is a retrospective cohort study of 212 patients diagnosed with AAV at West Virginia University and its affiliated hospitals from January 1, 1990 to December 31, 2019. Patients were mapped by zip code and prevalence of AAV assessed over time.

Results: The proportion of MPO-ANCA cases increased (37.5% before 2010 vs 71.7% after 2016 (p=0.008)) with a resultant increase in the prevalence of AAV overall after 2010 (Table). During this time, the production of natural gas through fracking increased with barrel production rising more than 5-fold after 2010. Regional heat mapping reveals that the increase in cases of AAV occurred in areas of increased fracking activity (Figure)

Conclusions: The increase in prevalence of MPO-ANCA AAV correlates temporally and geographically with escalations in fracking activity. These findings suggest that exposure to toxins from fracking could be operative in the pathophysiology of AAV and the increase in case numbers seen in north central West Virginia.

Prevalence of ANCA before and after 2010

Prevalence per 100,000	Before 2010	After 2010	p- value
Overall	4.84 (N=24)	11.73 (N=61)	<0.001
PR3-ANCA	3.25 (N= 16)	4.42 (N=21)	0.41
MPO-ANCA	2.24 (N=8)	7.66 (N=40)	<0.001



Pictured on the left is a map of all the gas fracking wells (pictured in red) and gas and oil fracking wells (pictured in yellow) (WVGES Maps and GIS Data Menu [wvnet.edu]). Pictured on the right is a map of the ANCA cases diagnosed after 2010.

PO1422

Maintenance of ANCA Vasculitis Remission by Intermittent Rituximab Dosing Based on B Cell Reconstitution vs. a Serologic ANCA Flare (MAINTANCAVAS)

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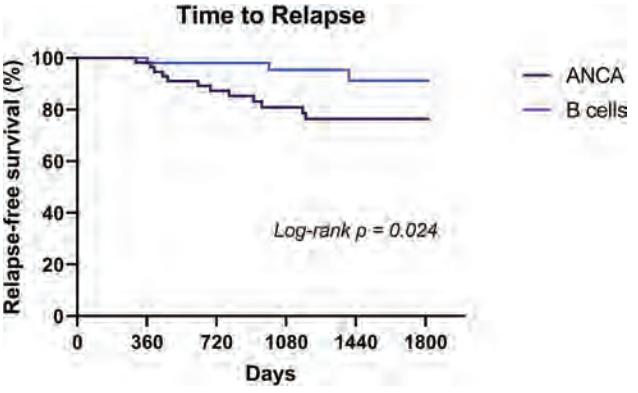
Background: ANCA vasculitis is caused by autoantibodies to proteinase 3 (PR3) or myeloperoxidase (MPO). Rituximab (RTX), an anti-CD20 monoclonal, is effective at induction and maintenance of remission. However, RTX is associated with adverse events; hypogammaglobulinemia, infections, and late onset of neutropenia. The ideal strategy for long-term maintenance of remission remains unknown.

Methods: This is an interim analysis of an open-label, single center, randomized, two-arm controlled trial (ClinicalTrials.gov Identifier: NCT02749292) to evaluate maintenance of remission strategies that provides the best relapse-free survival in patients with ANCA vasculitis at 36 months. We enrolled subjects with ANCA vasculitis on RTX-induced continuous B cell depletion for a minimum of two years to one of two arms as follows: intermittent B cell depletion with RTX re-dosing upon (1) B cell return (≥ 10 B cells/mm^3) or (2) upon a significant ANCA titer increase. The primary outcome was number of relapses defined by a Birmingham Vasculitis Activity Score (BVAS/WG) ≥ 2. Other outcomes, including serologic relapse and serious adverse events are not included in this analysis.

Results: From May 2016 to June 2021, 113 patients (mean age, 61 years; 48% women) were randomized, 57 to the ANCA arm and 56 to the B cell group. 52 patients were positive for anti-MPO, and 61 for anti-PR3. Relapse-free survival estimates at month 60 were 76% (95% CI, 62% to 86%) and 91% (95% CI, 74% to 97%) in the ANCA and B cell groups, respectively (hazard ratio of 3.85 (CI, 1.40 to 10.60) (P = 0.024 by logrank).

Conclusions: B cell driven RTX dosing appears to be highly efficacious at preventing relapses compared to ANCA titer driven dosing. Full trial analysis, including differences in adverse events, is needed to balance the benefit of reduced relapses against the infectious complications that may be associated with increased RTX use.

Funding: Private Foundation Support



PO1423

Pulsed Steroids Impede T Memory Cell Recruitment to the Kidney in Human and Experimental Crescentic Glomerulonephritis

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Background: Despite undesirable side effects and understudied modes of action steroids still constitute a cornerstone of therapeutic regimes for autoimmune kidney diseases presenting as rapidly progressive glomerulonephritis (RPGN), e.g. anti-neutrophil cytoplasmatic antibody associated glomerulonephritis (ANCA-GN). However, if the rapid clinical effects of steroids are due to a direct impact on leukocytes, i.e. CD3$^+$ T cells, or mediated indirectly by attenuation of an inflammatory environment is still unknown.

Methods: Kidney biopsies of patients with ANCA-GN with and without pulsed steroids before biopsy were analysed by immunohistochemistry, flow cytometry and single cell RNA sequencing. Furthermore, corresponding studies were conducted in untreated or steroid pulsed mice with crescentic glomerulonephritis (cGN), respectively. Additionally, steroid effects were studied in mice lacking the glucocorticoid receptor specifically in T cells and in CD4$^+$ T cell transfer experiments in nephritic recombination activating gene 1 (RAG1) knockout mice.

Results: Combined high-dimensional single-cell analysis and IHC showed that intravenous steroid pulses rapidly reduced renal T-cell infiltrate in human ANCA-GN patients but did not significantly regulate the immune response of a specific T-cell subset (e.g., Th1, Th2, Th17, Treg). Almost identical effects were observed in a murine cGN model (nephrotoxic nephritis), including reduced glomerular crescent formation, after steroid pulse treatment. Functional studies using CD4+ T-cell-specific glucocorticoid receptor-deficient mice showed that T-cell reduction was not caused by T-cell-intrinsic factors. Mechanistically, we demonstrated in CD4+ T-cell transfer experiments that steroid-induced attenuation of intrarenal effector T cells in cGN was a consequence of reduced expression of the T-cell-attracting chemokines CCL5, CCL20, CXCL9, and CXCL10 by resident kidney cells, which was further confirmed by in vitro and ex vivo trafficking experiments.

Conclusions: Our findings demonstrate that pulse steriod therapy rapidly reduce renal T-cell infiltrate in human and murine cGN by inhibiting the production of T-cell-attracting chemokines by resident renal cells. In summary, we have identified a previously unrecognized therapeutic mechanism of steroids in immune-mediated glomerular disease.

Funding: Government Support - Non-U.S.

PO1424

Immune Checkpoint Molecule BTLA Attenuates Inflammation and Glomerular Damage in Experimental Glomerulonephritis

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Background: An imbalance of pro- and anti-inflammatory signals in the kidney can result in irreversible damage and destruction of glomeruli leading to end stage kidney disease. Current treatment of the glomerulonephritis (GN) consists of unspecific, highly toxic immunosuppressive therapies with detrimental adverse effects. More specific therapies are therefore warranted. T Lymphocytes are not only key players in the nephrotoxic nephritis (NTN) model in rodents but also during GN in humans, representing potential targets for tailored therapies. As an immune checkpoint molecule, B and T lymphocyte attenuator (BTLA) is crucial in the regulation of T Lymphocyte activation and has been shown to mediate anti-inflammatory effects in other T cell-mediated disease models.

Methods: NTN was induced in BTLA knock out mice (BTLA-KO) and littermate controls. Regular urine analysis (ACR) was performed throughout the course of the disease. 14 days after NTN induction, blood, kidneys and spleens were harvested for further analysis. Histological assessment of the kidneys was used to evaluate the severity of NTN. Local immune response in the kidney and systemic immunity was analyzed via flow cytometry and qPCR.

Results: Wild type mice (WT) showed an increased BTLA expression on renal T cells and dendritic cells throughout the course of NTN. No immuno-phenotype was observed in unstimulated BTLA-KO and WT mice. However, BTLA-KO resulted in aggravation of NTN compared to WT. Quantification and characterization of renal immune cells revealed an increase in proinflammatory cells. Interestingly, especially T Lymphocytes were significantly expanded in BTLA-KO mice.

Conclusions: BTLA attenuates inflammation in experimental GN through suppression of proinflammatory T Lymphocytes. These results build the foundation of a checkpoint inhibitor based therapy of inflammatory glomerular disease.

PO1425

Collapsing FSGS or Crescentic GN or Both: A Diagnostic Challenge

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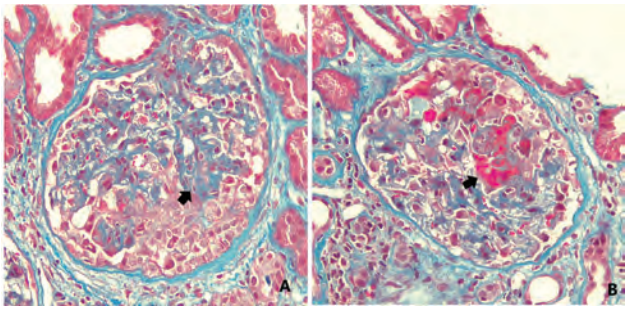
Introduction: The finding of an ANCA associated necrotizing & crescentic GN with collapsing FSGS is a rarity with only few reported cases in literature.

Case Description: A 53-yr-old AA female was admitted to hospital with difficulty in swallowing, poor oral intake, hemoptysis & AKI superimposed on CKD-III with hx of HTN & use of NSAIDs. Urine analysis showed hematuria, proteinuria & UPC ratio of 4.15. Blood analysis showed S.Cr 8.7mg/dl, BUN 60mg/dl, Albumin 2.4gm/dl, positive MPO ANCA & ANA titers. By light microscopy 36 glomeruli were present, 20% showed cellular/fibro-cellular crescent formation with underlying tuft fibrinoid necrosis & 20% showed collapsing FSGS. ATI, moderate IF/TA & moderate to severe arteriosclerosis were present. EM showed global podocyte activation with foot processes effacement.

Discussion: Collapsing FSGS and ANCA associated GN can both present with abrupt onset AKI & proteinuria. No specific test exists to separate crescents from collapsing FSGS; therefore this daunting differentiation requires a high level of suspicion, often relegated to experience. Most useful morphologic features are summarized in table 1. In our case, AA race (possible $APOL_1$ risk variants) & underlying severe arterionephrosclerosis (ischemia) are the most likely etiologies for the collapsing FSGS.

Morphology	Collapsing FSGS	Crescentic GN
Tuft Collapse	++	-
Podocytes hyperplasia/hypertrophy	++	-
Parietal epithelial cell hyperplasia	-	++
Tuft fibrinoid necrosis	-	++
Fibrin in extra capillary space	+/-	++
Podocytes protein resorption droplets	+++	+/-
Inflammatory cells in extra capillary proliferation	-	+
Spindle cell elements/Myofibroblasts	-	+
Extracellular matrix deposition	+	+
Interstitial inflammation	+	-/++
RBC casts	-	++
ATI	+	+
Tubular microcystic dilation	+++	+/-



A-Tuft collapse(arrow), podocytes hyperplasia/hypertrophy. B-Fibrinoid necrosis (arrow) & crescent formation(Trichrome stain x20)

PO1426

CD11b Activation Suppresses Pro-Inflammatory IL-1β in Myeloid Cells and Protects Against Lupus Nephritis

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Background: Lupus nephritis (LN) is a debilitating glomerular disease and a comorbidity of systemic lupus erythematosus (SLE). CD11b, the alpha-chain of integrin CD11b/CD18, plays a critical role in cell signaling. Mutations in the ITGAM gene, encoding CD11b, are associated with LN and reduce integrin function. Interleukin-1β (IL-1β) is produced by myeloid cells as a proprotein and cleaved by caspase-1 where it mediates the inflammatory response. IL-1β is downstream of toll-like receptor and IL-1β receptor signaling. We previously showed that activation of CD11b suppresses TLR-dependent pro-inflammatory signaling. Here, we investigate if this mechanism includes control of IL-1β and/or if CD11b influences IL-1β by another mechanism, which may provide novel therapeutic options for proinflammatory diseases.

Methods: To investigate TLR-dependent signaling affected by CD11b activation, we utilized in vitro assays using primary macrophages. Cells were treated with TLR agonists, IL-1β protein, or IL-1β antibody and changes in protein expression was assessed by western blot and proinflammatory cytokine levels were assessed by ELISA. For complementary in vivo studies, we utilized our newly generated mouse model, where we incorporated a constitutively active CD11b point mutation (I332G) globally in mice to generate a model for CD11b activation – CD11b knock-in model. C57BL/6 wild type mice, CD11b knock-out, and CD11b knock-in mice were used to determine the effect of CD11b activation on circulating IL-1β levels.

Results: TLR-stimulation increased IL-1β levels in vitro and in vivo. Importantly, CD11b activation resulted in significantly reduced IL-1β levels in both systems, suggesting a novel mechanism for controlling inflammation in glomerular diseases. Additional mechanistic studies are on-going to define the exact molecular mechanism of action. Murine models of SLE and LN display significant decreases in IL-1β when CD11b is activated, both genetically or pharmacologically, showing potential protection against LN.

Conclusions: Using these models, we have identified a possible link between CD11b activation and IL-1β secretion in myeloid cells. These studies will provide understanding of the influence CD11b has on signaling pathways and inflammation associated with inflammatory diseases such as LN.

Funding: NIDDK Support

PO1427

Deletion of Smad3 Worsens Lupus Nephritis by Promoting B Cell Activation

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Background: TGF-β signaling has been shown to play a critical role in many autoimmune diseases. However, its regulatory role in lupus nephritis remains unknown, which was investigated in the present study in a mouse model of lupus nephritis (LN) in which Smad3 gene was deficient.

Methods: To investigate the role of Smad3 in LN, we generated Smad3 knockout (KO) lupus mice by cross-breeding Smad3$^{+/-}$ mouse with B6.NZMSle1-3 lupus mice (C57BL/6J background) mouse. We then determined the regulatory role of Smad3 in the pathogenesis of LN and investigated the regulatory mechanisms of Smad3 in T cell and B cell activation and autoantibody production in Smad3 KO LN and Smad3 WT LN mice and B cells in vivo and in vitro.

Results: We successfully deleted the Smad3 gene from B6. NZMSle1-3 mice with unexpected findings that Smad3KO-LN mice developed much more severe LN with higher mortality rate (50%), higher circulating anti-dsDNA (60%), higher levels of serum creatinine (Cr, 30%) but lower creatinine clearance rate (Ccr, 20%), more severe glomerular necrosis (50%), massive renal immune complex deposition and complement activation, and progressive renal inflammation and functional injury. Mechanistically, we observed that lupus mice lacking Smad3 largely promoted Th1, Th2 and Th17 populations while suppressed Treg immune responses in the kidney. Unexpectedly, deletion of Smad3 largely increased macrophage inducible lectin-receptor (Mincle) expression by B220^{+} B cells (80%). Further studies showed that B cells lacking Smad3 were largely promoted Cytosine-phosphorothioate-guanine oligodeoxynucleotides (CpG ODN)-induced but failed to response to the inhibitory effect of TGF-β1 on Mincle-Syk-NFκB signaling, MHC II and CD86 expression, and autoantibody production. Importantly, silencing Mincle inhibited CpG ODN-induced Syk-NFκB signaling and IgG production by splenic B cells.

Conclusions: TGF-β/Smad3 signaling plays a protective role in LN by maintaining the balance of T cell immunity and B cell function. Loss of Smad3 worsens LN by shifting Treg to Th1, Th2 and Th17 and promoting B cell activation and autoantibody production via the Mincle-Syk-NFκB-dependent mechanism. Thus, outcomes from this study will be of great significance both scientifically and clinically.

Funding: Government Support - Non-U.S.

PO1428

Intrarenal B Cells in Systemic Lupus Erythematosus Upregulate Na+-K+-ATPase to Facilitate Survival in a High-Sodium Environment

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Background: The kidney is a unique microenvironment characterized by high sodium concentrations, yet susceptible to infiltration by lymphocytes in autoimmune diseases such as systemic lupus erythematosus. The effects of sodium-immune cell interactions on tissue injury in autoimmune disease and the mechanisms used by infiltrating lymphocytes to survive the high sodium environment of the kidney are not known.

Methods: We investigated the mechanisms utilized by B cells from lupus-prone mice to survive in a high Na^+ environment *in vitro* and *in vivo.* We also utilized biopsies from lupus nephritis patients to confirm our key findings.

Results: Here we show that numbers of kidney infiltrating B cells in murine lupus are significantly decreased when exposed to elevated sodium concentrations [Na^+] *in vivo* and that the expression of sodium potassium ATPase (Na^+-K^+-ATPase) correlates with the ability of infiltrating B cells to handle sodium stress. Pharmacological inhibition of Na^+-K^+-ATPase and a genetic knockout of the Na^+-K^+-ATPase gamma subunit, newly shown by us to be expressed in B cells, resulted in decreased kidney B cell infiltration and amelioration of proteinuria. Na^+-K^+-ATPase gamma subunit expression was also observed in renal B cells in human lupus nephritis.

Conclusions: These studies reveal that kidney-infiltrating B cells in lupus adapt to environmentally regulated sodium stress and identify Na^+-K^+-ATPase as a novel organ-specific therapeutic target in lupus nephritis.

Funding: Other NIH Support - NIH grants R37 AR40072 and R01 AI152443, Private Foundation Support

PO1429

Environmental Factors Influence Site and Magnitude of Myeloperoxidase and DNA Autoimmunity in BXSB Murine Lupus

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Background: SLE is a systemic autoimmune disease with devastating clinical manifestations and complex origins linked to gene-environment interactions. To better understand the role of environmental factors, we exposed lupus-prone female mice to crystalline silica (Si) or vehicle (V) by oropharyngeal aspiration (OPA), mimicking an inhalational exposure compellingly linked to human autoimmunity. Si but not V exposed mice developed chronic lung inflammation, tertiary lymphoid structures (TLS), and elevated autoantibody (autoAb) levels. Si-exposed BXSB mice, a strain that develops vasculitis and glomerulonephritis, uniquely demonstrated elevated anti-myeloperoxidase (MPO) as well as anti-DNA Ig levels in bronchoalveolar lavage fluid (BALF). Herein we extend our studies in BXSB lupus to quantify local autoAb production and assess the impact of environmental co-exposure, using Toll-like receptor ligand (TLR-L) stimulation to mimic microbial infection.

Methods: BXSB mice were exposed to Si or V by OPA and organs harvested 2-3 months later. A subset of mice were injected with TLR4-L i.p. 1-2 days prior to harvest. Lung injury and TLS were quantified and autoAbs in serum, BALF, and cell culture supernatants (±TLR4 or TLR7/9 L) measured by ELISA; mean±SD.

Results: Si but not V exposed BXSB mice developed chronic lung injury (scores 5.0±4 vs 0.1±0.4) and lung TLS (counts 36±19 vs 0±0), n=13/grp, p<0.0001. Levels of anti-DNA and anti-MPO IgM and IgG in BALF and anti-DNA IgG in serum were elevated in Si vs V exposed mice (p<0.05, for each). Splenocytes produced little anti-MPO or anti-DNA Ig when cultured with medium and abundant anti-MPO IgM and anti-DNA IgM after TLR-L stimulation, regardless of Si vs V exposure (p=NS; n=13/grp). Anti-DNA IgG levels were higher from stimulated splenocytes of Si-exposed mice (OD 0.082±0.054 Si vs 0.035±0.011 V, TLR4-L, p=0.0009). Lung cells from Si but not V exposed mice produced abundant autoAb after TLR-L stimulation (OD 1.232±1.100 Si vs 0.025±0.043 V, anti-MPO IgM; OD 0.212±0.310 Si vs 0.001±0.001 V, anti-DNA IgG, TLR7/9-L, p<0.05).

Conclusions: Inhalational Si exposure enhances local and systemic autoimmunity in lupus-prone BXSB mice. Autoreactive B cells with diverse disease-relevant specificities, including anti-MPO and anti-DNA Ig, are recruited to the lungs, where they can be activated by co-exposure to exogenous or endogenous TLR-L.

Funding: Other NIH Support - NIEHS, Veterans Affairs Support

PO1430

Anti-SOD2 Antibodies in Lupus Nephritis as Second Wave Antibodies

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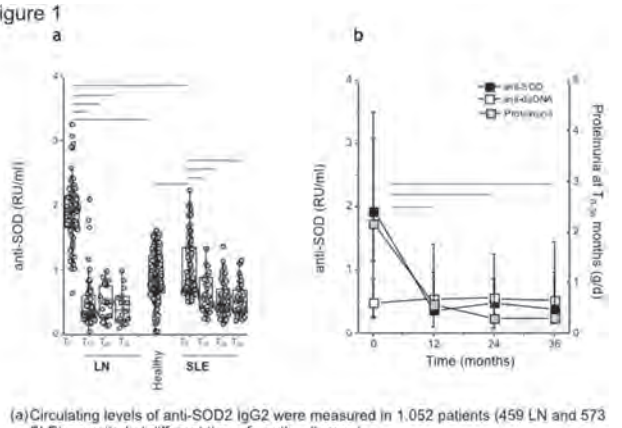
Background: Superoxide dismutase-2 (SOD2) is an enzyme with antioxidant action. Anti-SOD2 antibodies (anti-SOD2 IgG2) were recently described in the serum of subjects with Membranous Nephropathy, as antigens of a possible second wave injury. The presence of anti-SOD2 IgG2 correlated with worse outcomes in terms of response to treatment [1]. The presence and role of anti-SOD2 IgG2 in Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN), a secondary autoimmune glomerulonephritides, are to be clarified.

Methods: We measured serum levels of anti-SOD2 IgG2 (Homemade designed ELISA), every six months, in 1.052 patients (459 LN and 573 SLE) enrolled at different times from the diagnosis (i.e., 0-1 month, 2-12 m, 13-24 m, 25-48 m, 49-96 m, and >96 m). We also evaluated the main markers of the SLE activity, such as serum complement C3 and C4, ANA, ENA, anti-dsDNA and proteinuria. Of note, 91 LN and 130 SLE had a relevant follow-up of 36 months.

Results: As main characteristics, we report median age of 40 (IQR 28-54) years, the predominance of females (88%), disease activity (SLEDAI) of 4 (IQR 2-8). At the cross-sectional analysis, serum levels of anti-SOD2 IgG2 at T0 are significantly higher in LN than in SLE (**Fig 1a**). Considering LN, the serum levels of anti-SOD2 IgG2 at T0 were significantly higher than the other time points (**Fig 1a**). No correlation with the histological class of LN is reported. In LN, the reduction of anti-SOD2 IgG2 was in accordance with proteinuria. Anti-dsDNAs did not result as a valuable marker of disease activity (**Fig 1b**).

Conclusions: Circulating anti-SOD2 IgG2 are elevated in active LN. Serum levels of Anti-SOD2 IgG2, also considering the concomitant negative serum levels of anti-dsDNAs in all phases of LN, support the hypothesis of direct involvement of anti-SOD2 antibodies in LN as second wave antibodies that actively contribute to the manifestations of autoimmune glomerulonephritides.

Figure 1



(a) Circulating levels of anti-SOD2 IgG2 were measured in 1.052 patients (459 LN and 573 SLE), recruited at different times from the diagnosis.
(b) 91 LN and 130 SLE patients recruited at the time of the diagnosis were followed for 36 months. Anti-SOD2 and anti-dsDNA antibody levelsweredetermined every 6 months during the follow up. In both cases, antibodies were of the IgG2 isotype and levels were calculated as relative intensity value (RU/ml) given the absence of WHO international standards.

PO1431

Altered Propanoate Metabolism and gut Lachnospiraceae Composition in Lupus Nephritis Patients

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Background: There are growing evidence for the role of gut microbiota in the pathogenesis systemic lupus erythematosus (SLE), especially lupus nephritis (LN). Recently, high abundance of Ruminococcus gnavus belonging to the family Lachnospiraceae has been noticed in fecal sample of LN patients. However, the functional role of gut microbiota and its metabolic pathway which affect host metabolism in LN are less understood.

Methods: Shotgun sequencing of fecal samples from biopsy-proven LN patients and matched controls was performed. We used Kraken2 for taxonomic analysis and humann2 with customized KEGG database for genefamily analysis. Comparison of taxonomic abundance and genefamilies were assessed by Maaslin2.

Results: Control and LN group were included 24 and 20 patients, respectively. Both groups had similar age, sex, and eGFR. In the comparison of relative abundance of major species, Roseburia intestinalis, Butyricimonas faecalis, and Eubacterium eligens were significantly decreased while Ruminococcus gnavus was significantly elevated in LN group, respectively. Interestingly, 3 of these 4 species were included in the same Lachnospiraceae family showing a significantly different composition between the two groups (PERMANOVA p=0.042). Furthermore, we found 161 differentially expressed genefamilies including 65 metabolism-associated and 29 carbohydrate metabolism-associated genes. Considering Lachnospiraceae is known to play a role in propanoate (esters of propionate) formation, we further assessed the propanoate pathway (ko00640). As a result, LN patients revealed more prone to propanediol pathway rather than in succinate pathway in the propanoate pathway. This tendency was more pronounce in the contribution to the pduE gene by R. gnavus having well-known pathogenetic linkage with SLE.

Conclusions: LN patients showed altered propanoate metabolism associated with the differential species composition of Lachnospiraceae including R. gnavus. Functional role of this alteration on the pathogenesis of LN should be clarified by further investigations.

PO1432

Gut Microbiome Changes in NZBWF1/J Murine Lupus Nephritis

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Background: Lupus nephritis is an important cause of acute kidney injury and chronic kidney disease. There is preliminary data that gut dysbiosis may be involved in the pathogenesis of lupus nephritis. We investigated gut microbiota burden in murine lupus nephritis.

Methods: Eight-week old NZBWF1/J mice were randomized to receive drinking water alone or containing ampicillin (1.0 mg/ml) and neomycin (0.5 mg/ml) for 18 weeks. Renal and colonic histopathology was examined, and intestinal mucosal permeability investigated with LPS-FITC. Quantitative changes in gut microbiota were assessed by 16S rRNA sequencing.

Results: Serum LPS and urea levels, and proteinuria were significantly lower in antibiotic-treated mice ($P<0.05$, for all). Histopathologic manifestation of active nephritis and podocyte foot process effacement were associated with increased LPS-binding protein, CD14 and TLR-4 expression in proximal renal tubular epithelial cells, and increased interstitial α-smooth muscle actin, fibronectin and collagen expression. Mice with active nephritis showed increased gut permeability to LPS-FITC given orally, and decreased ZO-1 expression in the colonic epithelium. 16S rRNA sequencing data showed that active nephritis was associated with a progressive decrease in Gram-positive bacteria phyla *Actinobacteria* and *Firmicutes* and increased Gram-negative bacteria phyla *Bacteroides* and *Proteobacteria*. Antibiotic treatment significantly decreased *Bacteroides*, which was associated with lower levels of serum LPS and urea, proteinuria, and ameliorated histopathologic features in the colon and kidney.

Conclusions: Murine lupus nephritis is associated with gut dysbiosis, which may contribute to the pathogenesis of nephritis progression.

Funding: Government Support - Non-U.S.

PO1433

The Significance of Glomerular Galactose-Deficient IgA1 in Patients with Systemic Lupus Erythematosus (SLE)

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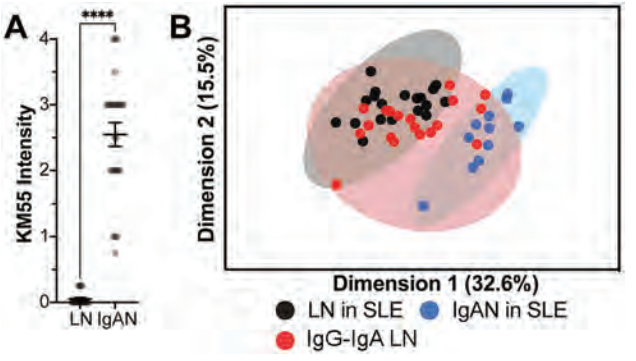
Background: Approximately 0.3% of end stage kidney disease in SLE patients is due to non-lupus nephritis. IgA nephropathy (IgAN) is rarely reported in SLE patients. As galactose-deficient IgA1 (Gd-IgA1) plays a key role in the pathogenesis of IgAN but not SLE, the aim was to investigate whether KM55, a Gd-IgA1 specific monoclonal antibody, might identify IgAN in patients with SLE.

Methods: Immunofluorescence (IF) staining of KM55 was performed on 77 native kidney biopsies from 25 non-SLE (IgAN or IgA vasculitis (IgAV)) and 52 SLE patients, the latter including lupus nephritis (LN) with IgG dominant full house staining (LN; n=20), IgAN without features of LN (IgAN; n=11), concurrent LN class V and IgAN (n=2), and LN with dominant/co-dominant IgA (IgG-IgA-LN; n=19). In SLE patients, principal component analysis was carried out on LN, IgAN, and IgG-IgA-LN cases.

Results: KM55 staining intensity >0.5 (trace) on a scale of 0-4 discriminates IgAN/IgAV from LN with a sensitivity of 1.00 [0.86-1.00] and specificity of 1.00 [0.82-1.00] ($p<0.0001$) (Fig 1). KM55 staining with mean 2+ intensity was detected in all SLE patients with lgAN and no features of LN. IgAN had no difference in KM55 intensity or distribution in non-SLE vs SLE patients. Mesangial KM55 staining was detected in cases with dual LN class V and IgAN. Of 19 IgG-IgA-LN biopsies, 9 (47%) showed positive KM55 staining in the same distribution as IgA.

Conclusions: Our results demonstrate that IF staining of KM55 is valuable in distinguishing IgAN from LN. In SLE patients, negative KM55 staining argues against the presence of IgAN while >0.5 (trace) KM55 staining with dominant/co-dominant IgA staining is suggestive of IgAN as the sole lesion or a co-occurring component of dual glomerulonephritis.

Funding: Other NIH Support - NHLBI [F30HL151138 to BIG]



A) KM55 staining intensity in LN and IgAN/IgAV. B) Principal component analysis shows LN with dominant/co-dominant IgA (IgG-IgA-LN; pink) with overlapping features with LN (grey) and/or IgAN (blue).

PO1434

Tertiary Lymphoid Tissue Development Is Associated with Impaired Renal Function in Lupus Nephritis

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Background: Lupus nephritis (LN) is one of the most serious complications of systemic lupus erythematosus (SLE) and the pathophysiology is heterogenous. Recently, the careful assessment of not only glomerular but tubulointerstitial lesions has been proposed for more precise evaluation of the disease activity, which leads to better management. Tertiary lymphoid tissues (TLTs) are inducible ectopic lymphoid tissues formed in the kidney interstitium under chronic inflammation. Several studies have reported TLTs in LN, though the frequencies, clinical characteristics and relevance in LN have been undefined.

Methods: We examined the presence of TLTs in 205 kidney biopsy samples of patients with LN and investigated the clinical characteristics of patients with renal TLTs. TLTs were defined as organized T and B cell aggregates with sign of proliferation. Histological activity and damage at biopsy were calculated as the National Institute of Health (NIH) activity and chronicity indices (CI).

Results: 43 patients (21%) exhibited TLTs in the kidneys. There were no significant differences in ISN/RPS classification between LN patients with TLTs and those without TLTs. TLT development was not associated with disease activity indicators, such as SLEDAI, dsDNA titer, proteinuria, or complement factors, but it was associated with reduced eGFR (60.2 versus 83.8 ml/min/1.73m^2, P = 0.001) and higher histological kidney injury scores (P = 0.0038). A higher prevalence of TLTs was observed with age over 40 years old and non-treatment history of immunosuppressive drugs. Additionally, TLT development was associated with incidence of hypertension.

Conclusions: Association between TLT development and reduced eGFR and higher histological injury suggest the potential of TLTs as an additional histological marker for evaluation of LN disease activity. Dissociation between TLT development and SLE disease activity indexes such as SLEDAI and dsDNA antibody titers also suggest that TLTs development are, at least partly, independent of the severity of glomerulonephritis.

Funding: Government Support - Non-U.S.

PO1435

New Drugs and Evolving Treatment Patterns in Lupus Nephritis: How Nephrologists and Rheumatologists Are Responding Differently to New Treatment Options

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Background: Early uptake and experience with recently approved lupus nephritis (LN) drugs belimumab and voclosporin reveal different perceptions, comfort levels, and prescribing intentions between nephrologists and rheumatologists.

Methods: Data were collected over four waves of research between February and May 2021 via online surveys with 50 US nephrologists and 50 US rheumatologists who are actively treating LN patients, followed-up with a subset of qualitative interviews.

Results: In a notable trend, rheumatologists deem more of their LN patients as candidates for belimumab, while nephrologists increasingly see their patients as better suited for voclosporin. Rheumatologists tend to rate belimumab higher overall than voclosporin, particularly on safety and tolerability, thanks to long term history with the product in SLE patients. Both physician types generally use belimumab as later-line therapy in mild-to-moderate LN, often to reduce steroid burden. It is generally used with at least one other advanced agent like an antimalarial, steroid, or MMF. Recently initiated patients are most often in CKD Stage 3, with proteinuria and fatigue. Nephrologists favor voclosporin, likely due to their familiarity with the CNI drug class. Both physician-types are using voclosporin even later-line than belimumab for moderate-to-severe LN patients given the drug's perceived quicker onset of action, efficacy, and steroid-sparing effect. Voclosporin is nearly always used concomitantly with advanced drugs like antimalarials, steroids, or MMFs. Rheumatologists appear to be initiating voclosporin most often in CKD Stage 2, while nephrologists are initiating most often in CKD Stage 3. Rheumatologists are the leading prescribers of belimumab, and currently have a slight edge with voclosporin patient initiations as well. Nephrologists are tending to wait longer to initiate, due to cost- and risk-benefit uncertainty compared to other options like tacrolimus. Rheumatologists currently view both drugs as a greater treatment advance than nephrologists; nephrologists believe voclosporin is more of an advance in LN treatment than belimumab.

Conclusions: Physician understanding and comfort level with belimumab and voclosporin MOAs are driving early use and perceptions of the two new LN drugs.

PO1436

Treatment of Crescentic Lupus Nephritis with Voclosporin

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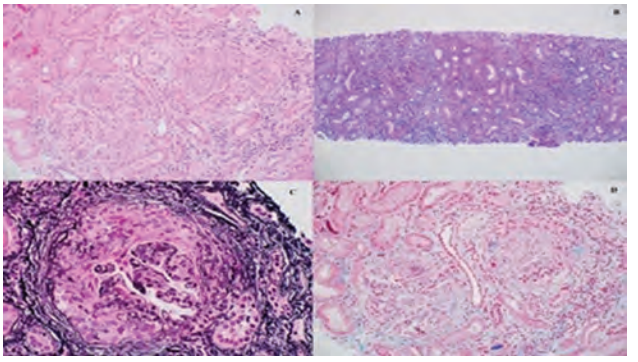
Introduction: Crescentic glomerulonephritis (CGN) is a rare complication of Lupus nephritis (LN) and carries a worse prognosis. There is paucity of data regarding effective treatment options for CGN. We present a case of crescentic ANCA negative LN treated with voclosporin (VSN).

Case Description: 19-year-old African American female with 2-year history of Class II LN, treated with hydroxychloroquine 200 mg/day, prednisone 10 mg/day, mycophenolate mofetil 1 gm twice daily and Belimumab, presented with a 2-week history of anasarca and generalized bullous skin rash. On exam BP 126/78 mm Hg, HR 96/min, afebrile, RR 18/min, O2 saturation 97% on room air. Investigations revealed hemoglobin 9.2 g/dL, serum creatinine (SCR) 1.2 mg/dl (baseline 0.6), albumin 1.9 g/dL, hypocomplementemia, microscopic hematuria and proteinuria of 4.3 gm. A kidney biopsy showed diffuse crescentic immune complex LN and membranous LN (Figure 1). The patient received IV methylprednisolone 1gm for 3 days, however, became anuric, SCR peaked at 5 mg/dl and was commenced on hemodialysis and 7 sessions of plasma exchange. She was started on VSN 15.8 mg BID and after 10 days of therapy, SCR improved and dialysis was discontinued. On discharge, SCR was 2.0 mg/dl and proteinuria 0.9 gm. C4 normalized and C3 improved.

Discussion: There has not been any published case report of Crescentic LN being treated successfully with VSN. Given poor prognosis of CGN, early diagnosis and treatment is imperative. Our patient had rapid recovery of renal function and resolution of proteinuria following treatment with VSN. VSN may be effective in combination with plasma exchange in ANCA negative Crescentic LN. Larger studies with longer follow-up are needed to assess the efficacy of VSN in CGN.



A. H&E stain shows diffuse segmental endocapillary hypercellularity and glomeruli with cellular crescents (60%), segmental necrosis and subendothelial deposits. B and C. PAS and Silver stains show no glomerular basement membrane remodeling. D. Trichome stain with moderate interstitial fibrosis and tubular atrophy (35%).

PO1437

Healthcare Resource Utilization and Costs over 5 Years for a Systemic Lupus Erythematosus (SLE) Cohort Newly Diagnosed with Lupus Nephritis: Evidence from a US Administrative Claims Database

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Background: Lupus nephritis (LN) occurs in ~40% of adults with SLE. Despite the high burden of LN, current care management and utilization data are limited. This longitudinal study evaluated US healthcare resource utilization (HRU) and costs over 5 years in patients (pts) with SLE newly diagnosed with LN.

Methods: This retrospective cohort study (GSK Study 214102) used data from the Optum Research Database. Index date was the first claim with a renal diagnosis code indicating LN during the identification period (Aug 1, 2011–Jul 31, 2018). Inclusion criteria: age ≥18 years; ≥2 renal diagnosis codes during the identification period; ≥1 inpatient or ≥2 outpatient SLE diagnosis codes in the 12 months pre index; and continuous enrollment of ≥12 months pre and post index. HRU and costs for the cohort with 5 years of continuous enrollment post index are reported.

Results: Overall, 2159 pts met the study criteria (mean [standard deviation, SD] age, 58.5 [14.9] years; 86.7% female) and 335 had ≥5 years of continuous enrollment post index. HRU and costs were highest in the first year post LN diagnosis (**Figure**). Mean healthcare costs were $44,205 in Year 1 and ~$30,000/year in Years 2 through 5. Approximately 50% of patients incurred an inpatient stay in Year 1, with ~25% of patients hospitalized in each subsequent year.

Conclusions: Patients with newly diagnosed LN incur substantial HRU and costs, which were highest in the year of diagnosis. These data highlight the need for interventions to prevent renal worsening in SLE.

Funding: Commercial Support - GSK

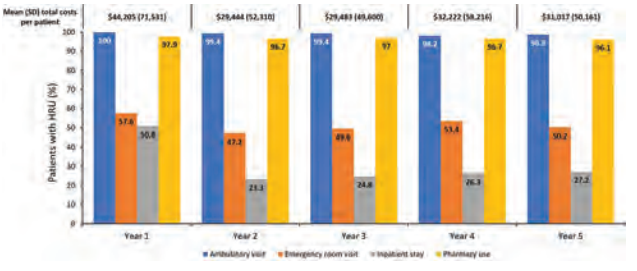

Figure. Longitudinal HRU and costs among patients with ≥5 years of follow-up (N=335)

PO1438

Association of TNIP1 Variants with Disease Severity and Progression and IP-10 Chemokine Levels in Lupus Nephritis Patients

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Background: African American SLE patients experience higher rates of LN, increased progression to ESKD, and higher mortality when compared with white patients, but etiology for this disparity in unclear. We reported that a TNIP1 polymorphism, rs4958881, is a risk variant for lupus nephritis (LN) in African American patients. TNIP1 encodes the protein ABIN1, which negatively regulates the transcription factor NF-κB. Transgenic mice with impaired ABIN1 function (ABIN1[D485N]) spontaneously develop autoimmunity and LN. IP-10 is a pro-inflammatory chemokine and NF-κB target.

Increased tissue levels of IP-10 have been implicated in pathogenesis and as a diagnostic marker of LN, but the mechanism is unknown. The current project tested a hypothesis that LN severity and enhanced IP-10 levels are associated with the TNIP1 rs4958881 risk allele.

Methods: All endpoints were compared for LN patients w/wo TNIP1 variant rs4958881. LN pathology classifications were compared for 125 African American and 133 White American LN patients. Urine and serum IP-10 levels were measured in 33 LN patients using ELISA. Progression of disease was assessed and compared from follow up (mean = 3 yrs) for 33 LN patients. Urine, plasma, and kidney levels of IP-10 were compared in wildtype and ABIN1[D485N] mice.

Results: A higher percent of African Americans with Class IV LN had the TNIP1 variant (68%) versus 42% for Whites with Class IV and 93% of African American with Class V LN had the variant versus 38% for Whites with Class V. 26.3% of patients with the variant vs. 7.1% of patients without the variant reached the endpoint of doubling of creatinine or ESKD. Proteinuria at follow up was higher in variant (2800 mg/g) vs. non-variant (1175 mg/g) patients, suggesting refractory disease in variant patients. There were significantly higher levels of IP-10 in serum and urine from African American versus White LN patients and a trend for association in patients with the variant. Urine, plasma, and kidney levels of IP-10 were significantly enhanced in ABIN1[D485N] versus wildtype mice.

Conclusions: Our findings suggest that TNIP1 variant genotyping and IP-10 measurement could provide precision diagnostics for African American LN patients and that inhibition of NF-κB or neutralization of IP-10 is a promising personalized therapeutic direction for these patients.

Funding: NIDDK Support, Other U.S. Government Support, Clinical Revenue Support

PO1439

Inflammatory Dendritic Cell and Th17 Polarization in Mouse Model of Lupus Nephritis

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Background: We have recently identified inflammatory dendritic cells (InfDC) in human lupus kidneys. These cells are over expressed in LN patients compared to healthy controls. Knowledge on how the infDC interact with intra-renal T cells and their role in pathogenesis of LN kidney is crucially needed

Methods: We examined infDC and T cells in the kidneys of NZM 2410 (NZM), from proteinuric (prot-NZM) mice (proteinuria ≥300mg/dl) and pre-proteinuric NZM (pre-prot-NZM) mice by Immunofluorescence (IF). To quantitatively assess infDC and various T cells, we analyzed single cell suspensions obtained by enzymatic digestion followed by gentle MACS dissociation from prot-NZM kidneys and pre-prot-NZM kidneys by multi-color flow cytometry using specific markers for infDC and T cells.

Results: The immunofluorescence studies recapitulated the human LN robust infiltration of the infDC marked by FcRγ in the periglomerular and tubulointerstitium in prot-NZM compared to pre-prot-NZM. The infDC were also identified to be in close proximity to CD3+ T cells constant with an immunological synape. Further characterization by IF revealed infDC in mice LN were $FcR\gamma^+$, $MHCII^+$, $CD11c^+$, $CD163^-$, $CD11b^+$, $Ly6C^+$. Interestingly, 2 subtypes of infDC were identified in NZM mice, $FcR\gamma^+MHCII^+CD11c^+$, $CD11b^+$ and $FcR\gamma^+MHCII^+CD11c^-$, $CD11b^+$ and differentiated by the presence or absence of CD11c. Flow cytometry analysis of T helper cell phenotypes shows that Th17 expression, but not Th1 was upregulated significantly in prot-NZM compared to pre-prot-NZM in parallel to infDC.

Conclusions: Similar to human LN, infDC are abundant in prot-NZM LN kidneys compared to respective pre-prot NZM and healthy control kidneys; 2) infDC synapse with CD3+ T cells in LN kidneys; and 3) Th17 cells, but not Th1 cells, correlate with infDC's expression in LN kidneys. These data suggests that infDC regulate the intra-renal Th17 cell response in LN and contribute to IL-17 mediated kidney injury. Ongoing studies will examine if these infDC are necessary or sufficient to cause LN.

Funding: Other NIH Support - Department of Internal Medicine MPI grant, The Ohio State University

PO1440

SeqStain Is a Novel, Multiplex Imaging Method for Spatialomic Profiling of Human Kidney Tissues

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Background: Chronic Kidney Disease (CKD) is the ninth leading cause of death in the United States, an emerging global health challenge affecting 10-15% of the population. Lack of reliable biomarkers precludes early diagnosis of CKD. The progression of CKD is known to be dictated by renal tissue changes. For instance in Diabetic Nephropathy, disease progression is accompanied by considerable changes to the glomeruli, reduced podocyte number, inflammation in the renal tissue, influx of immune cells that ultimately lead to tissue damage. Understanding these tissue-centered events on a deeper level is imperative for early diagnosis

Methods: To understand molecular and cellular composition of tissues and their relative organization in three-dimensional space, we developed a novel multiplex staining method called SeqStain. The SeqStain multiplex platform uses fluorescently labeled DNA oligonucleotides (termed "SeqStain antibodies") to stain while endonucleases are used to achieve gentle de-staining after each round. This methodology can fluorescently label primary antibodies, secondary antibodies and Fabs of secondary antibodies to efficiently analyze complex tissues. We generated a SeqStain multiplex panel with antibodies that would probe different histological regions relevant to the kidney

Results: Normal kidney was stained with SeqStain antibodies and de-stained using endonucleases. Using SeqStain methodology, we built >20-plex panel on kidney tissue and provided a simple, gentle and rapid technique for multiplex imaging. Strikingly, de-staining using the SeqStain method was rapid and removed ~99% of the signal in <1min without affecting tissue integrity. The method was implemented using a simple perfusion setup with readily available components, allowing staining of tens of antigens on a single tissue section. Alignment of images and their analyses provided spatialomic data on multiple cell types in tissue

Conclusions: The SeqStain method offers a gentle, easy-to-use, and effective multiplex imaging technique that provides a unique platform for obtaining spatialomic insights. SeqStain method can profile the CKD kidney tissues and comprehend the tissue-centered events that could play a role in disease progression. Currently, we are profiling the CKD tissues in multiplex staining experiments in comparison to healthy human kidney to generate spatial maps

PO1441

A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AT1501

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Background: CD40L is a costimulatory receptor for CD40 found on T helper cells. Binding of CD40L on T cells to CD40 on antigen presenting cells induces downstream immune and inflammatory responses. Inhibition of CD40L signaling can abolish inflammation, prevent the progression of autoimmunity, and instill transplant tolerance. AT-1501 is a humanized anti CD40L antibody lacking Fc effector function and high affinity binding to CD40L. Purpose: Execute a phase 1 study of AT-1501 to assess safety, pharmacokinetics, and functional activity.

Methods: The study employed a placebo-controlled, sequential, dose-escalation design. 28 healthy subjects and 4 adults with ALS were enrolled. Five sequential ascending doses of AT1501 (0.5, 1, 2, 4, or 8 mg/kg) or placebo were administered by IV infusion. The primary endpoint was the safety and tolerability of AT1501. The secondary endpoint was to determine plasma pharmacokinetics (PK) and anti-drug antibody (ADA) responses to AT1501. An exploratory endpoint was to examine the ability of AT1501 to block an immune challenge in subjects who received a Keyhole Limpet Hemocyanin (KLH) challenge.

Results: Dose proportionality was achieved over the AT-1501 dose range of 0.5 to 8 mg/kg for C_{max} and AUC_{0-t}. The mean AT-1501 $t_{1/2}$ in healthy volunteers was 18 to 26 days. AT1501 had a safety profile comparable to placebo and was well tolerated in healthy subjects and subjects with ALS. 54% of subjects treated with AT-1501 had at least 1 TEAE and 62% of subjects treated with placebo had at least 1 TEAE. The most commonly reported TEAEs overall were headache, somnolence, and upper respiratory tract infection. There were no meaningful laboratory abnormalities, vital sign assessments, ECG assessments, or physical examination findings. Positive ADA responses to AT-1501 were observed in 6 of 30 subjects in the study. There was no dose dependence with respect to the incidence of positive ADA titers. ADA did not appear to affect AT-1501 plasma PK profiles or parameters suggesting they were not neutralizing. 8 mg/kg AT-1501 successfully blocked an immune response to KLH challenge in 2 of the 3 subjects tested.

Conclusions: Our results support further clinical development of AT-1501 for transplantation and autoimmune indications

Funding: Commercial Support - Eledon Pharmaceuticals

PO1442

High Expression of Mincle in Intermediate Monocytes of Patients with Autoimmune Diseases

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Background: Macrophage-inducible C-type lectin (Mincle) is a transmembrane C-type lectin receptor that is predominantly expressed on macrophages' surface and recognizes a broad range of self and foreign antigens as part of innate immune sensing, thus playing a pivotal role in tailoring immune response. Mincle's function associates with its expression levels on immune cells' surfaces. However, the differential expression of Mincle in various types of immune cells between patients with autoimmune disease (AD) and normal controls (NCs) is yet to be examined, and its clinical relevance remains unclear. Therefore, this study aimed to investigate Mincle expression and distribution in different types of immune cells in patients with AD and NCs, and to explore the clinical relevance and potential mechanisms of Mincle expression levels in immune cells of peripheral blood in patients with systemic lupus erythematosus (SLE).

Methods: Mincle expression levels in leukocyte subgroups and monocyte subsets of peripheral blood from all participants were analyzed using flow cytometry and real time PCR, and the clinical characteristics of patients with SLE were collected for correlation analysis. Intermediate monocyte (IM) were co-cultured with naïve T cells, and the differentiations of naïve T cells were detected by flow cytometry.

Results: Mincle was expressed predominantly in myeloid cells, both in peripheral blood and cell lines. Moreover, monocytes expressed higher levels of Mincle than granulocytes in both patients with AD and NCs, and Mincle expression levels were higher in IMs of patients with AD, including patients with SLE, than in those of NCs;

however, Mincle was not differentially expressed in granulocytes, lymphocytes, classical monocytes, and nonclassical monocytes between the two groups. In addition, Mincle expression was positively correlated with immunoglobulin G and κ-LC levels in serum but negatively related to serological renal function index (serum urea and creatinine levels) in patients with SLE. IMs increase the differentiation of toward Th1, Th2 and Th17, but IMs decrease naïve T cells toward Treg.

Conclusions: High expression levels of Mincle in IMs were associated with elevated immunological indicators in patients with SLE. IM influences the differentiation of T cells in patients with SLE.

PO1443

Development of Kidney Resident and Recruited Macrophages

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Background: Macrophages are part of the phagocyte mononuclear system constantly replaced by the circulating blood monocytes. In the steady state, the myeloid cell compartment is highly heterogenous, and contains cells of different origins and functions. These cells include macrophages and dendritic cells, and each play important roles in tissue maintenance, including development, homeostasis, immunity and repair following tissue injury. The composition of kidney macrophages is not well known.

Methods: A multi-parameter flow cytometry approach was used to identify the resident and recruited macrophage population in the kidneys of male and female C57BL/6J mice aged -7, -21 and -84 days in the steady state. Resident and recruited macrophage populations were characterized based on 33 cell surface and intracellular markers.

Results: Both resident and recruited macrophages were identified in the kidneys of male and female mice aged -7, -21 and -84 days in the steady state. We observed two distinct resident macrophage populations in young mice (7 and 21 days old) but by 84-days, male and female mice displayed 4 and 5 resident populations, respectively. The resident macrophage population in 7-day old mice displayed low surface expression of MHC class II and began to shift to an increased expression of MHC class II at 21 days, and high MHC class II expression at 84 days. We detected three recruited macrophage populations in 7- and 21-day-old mice, and two populations by 84-days of age. The recruited macrophage population displayed low MHC class II at all ages in both sexes. Analysis of the global macrophage populations at 84 days of age revealed female mice had twice as many recruited compared to resident macrophages, whereas male mice had an equal distribution.

Conclusions: The data indicate a dynamic change in the kidney macrophage population, leading to an activated resident macrophage phenotype. The composition of macrophage populations also differs by sex and age. These data suggest each population plays a role in kidney homeostasis. Future studies will be directed towards elucidating the functions of each of the identified macrophage populations.

Funding: NIDDK Support

PO1444

Activation of the Integrated Stress Response Regulates the Production of IL-17 in Tissue Resident Memory T Cells

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Background: CD4-positive T cells produce cytokines and play a central role in immunity. Tissue-resident memory T (Trm) cells remain in organs after infection and contribute to efficient host defense by immediate production of cytokines, such as IL-17A. More recently, it was demonstrated that Trm cells also promote autoimmunity. Therefore, the regulation of cytokine production by Trm cells is of great importance to achieve efficient host defense without excessive inflammation. However, the control mechanisms of cytokine production by Trm cells are not well understood.

Methods: Human and mouse T cells including renal Trm cells were analyzed by single cell RNA sequencing (scRNAseq), polysome profiling combined with bulk RNA sequencing, RT-PCR, flow-cytometry, immunocytochemistry, and mRNA FISH. Mouse models for *Staphylococcus aureus* infection and crescentic glomerulonephritis were used to induce and study Trm cells *in vivo*.

Results: Combined scRNAseq, polysome profiling and tissue signature analysis of human and mouse tissue samples revealed that resting $CD4^+$ Trm cells in the kidney express *IL17A* mRNA but do not produce or secrete the cytokine protein without re-stimulation. Mechanistically, we demonstrate that the phosphorylation of eIF2a, a key feature of the integrated stress response (ISR) activation, resulted in recruitment of *IL17A* mRNA into stress granules, which are organelles crucial for regulating mRNA translation during ISR, thereby inhibiting mRNA translation in resting Trm cells. Finally, we show that re-stimulation of human renal Trm cells through T cell receptor resulted in eIF2a dephosphorylation, leading to efficient translation of *IL17A* mRNA and subsequent IL-17A secretion.

Conclusions: Tissue-resident memory $CD4^+$ T cells in the kidney express high levels of IL-17A cytokine mRNA. Under homeostatic conditions the cytokine mRNA is stored in stress granules and not translated into protein. In contrast, these Trm cells rapidly produce IL-17A upon re-stimulation. Our study identifies a novel mechanism of how “poised Trm17 cells” use the integrated stress response - stress granules pathway to regulate IL-17A cytokine mRNA translation. Dysregulation of this pathway might have a pathogenic role in chronic relapsing and remitting inflammatory diseases.

Funding: Government Support - Non-U.S.

PO1445

Differential Cell Cycle and Kinase Activation in IgA1-Producing Cells from IgAN Patients and Healthy Controls Mediated by Cytokine Stimulation

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Background: Some cytokines increase production of galactose-deficient IgA1 (Gd-IgA1) in immortalized IgA1-producing cells derived from peripheral blood of patients with IgAN. Previous work has indicated dysregulated cytokine induced signaling may be responsible, but minimal work investigating the overlapping pathways has been performed. Using single-cell transcriptomics, we analyzed pathway responses in immortalized IgA1-secreting cells derived from IgAN patients and healthy controls (HC) before and after response to a mixture of cytokines.

Methods: A mixture of cytokines mimicking those produced by T-follicular helper (Tfh) cells (IL-4, IL-6, IL-21, CD40L; 50 ng/mL) was used to stimulate immortalized IgA1-producing cells for 30 min before single-cell transcriptomic analysis. Gd-IgA1 level was determined by lectin ELISA. Standard data processing using Seurat was performed along with Alteryx for IgA1 separation. Differential markers for genes in unstimulated and stimulated conditions were analyzed for pathway differences using the GSEA MSig database, and kinase-transcription factors were imputed using X2K analysis.

Results: Tfh cytokines mediated overproduction of Gd-IgA1 in IgAN cells but not HC. IgA1-secreting subpopulations were separated, and UMAP was used for unsupervised dimension reduction analysis. Within these UMAP groups, pathway analysis found multiple significant associations, including down-regulation of cell cycle processes ($FDR<6X10^{-25}$) in IgAN IgA1 cells compared to an increase in HC ($FDR<4.7X10^{-6}$) cells after Tfh cytokine stimulation. Analysis of imputed kinases changed in IgAN stimulated IgA1 cells compared to HC identified MAPK14 ($p<1X10^{-20}$ and AKT1 ($p<1.1X10^{-17}$), which have been associated with controlling *O*-glycosylation expression.

Conclusions: Significant changes in imputed kinases previously associated with *O*-glycosylation were found in IgA1-secreting cells in IgAN compared to HC in response to Tfh cytokine stimulation. When stimulated with cytokines, there were significant decreases in cell cycle and proliferation pathway responses in the IgA1-secreting cells from IgAN vs. HC samples. Further investigation is needed to determine the role of cell cycle and MAPK14 pathways in driving Gd-IgA1 overproduction mediated by cytokine stimulation.

Funding: NIDDK Support

PO1446

Serum and Glomerular Complement Components as Biomarkers in the First South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort (GRACE-IgANI)

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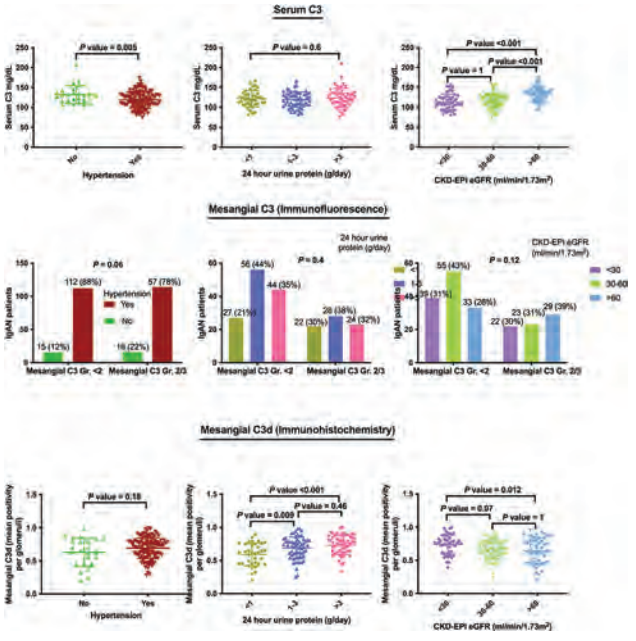
Background: The **G**lomerular **R**esearch **A**nd **C**linical **E**xperiments- **IgA** **N**ephropathy in **I**ndians is a prospective longitudinal cohort. The study protocol has been published and is registered with WHO trial id: ISRCTN36834159. The role of serum and glomerular complement components in South Asian IgAN is unknown.

Methods: 201 consenting adult IgAN patients were consecutively recruited post kidney biopsy. 192 (97%) patients completed 3 years. Serum complement C3 and C4 levels and glomerular C3d, C4d and C5b-9 by IHC were quantified at baseline in IgAN patients. Composite outcome (CO) was defined as ≥50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m² or RRT/death.

Results: 195 patients (97%) completed 3 year longitudinal follow-up. Lower serum C3 was significantly associated with S1, T1/T2 according to the Oxford MEST grading and with global glomerulosclerosis (GS>33%) whereas higher C4 levels were associated S1 scores. Increased mesangial C3d deposition correlated with increased mean arterial pressure, proteinuria, decreased serum albumin, decreased eGFR and with GS>33%. Similar to C3d, increased mesangial C4d correlated with increased systolic blood pressure, decreased serum protein and decreased eGFR and with GS>33%. Mesangial deposition of C5b-9 did not have any clinical associations. Lower serum C3, higher serum C4 and incrased mesangial C3d was significantly associated with CO over three years.

Conclusions: Serum and tissue complements could be potential biomarkers for severity and progression n the GRACE-IgANI cohort. This requires furhter validation.

Funding: Government Support - Non-U.S.



Associations with clinical variables

PO1447

Immune Complexes Containing Galactose-Deficient IgA1 Deposit on Mesangium Through Damage to Endothelial Cells

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Background: Galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the pathogenesis of IgA nephropathy (IgAN). However, the pathogenic role of mesangial Gd-IgA1-containing immune complexes (ICs) remains unclear. The endothelial surface glycocalyx modulates microvascular function. Loss of the glomerular endothelial glycocalyx is known to be involved in albuminuria. Here, we examined whether the deposition of Gd-IgA1-containing ICs in the mesangium may lead glomerular endothelial cell dysfunction in this disease.

Methods: Gd-IgA1 and recombinant anti-glycan IgG were used to form ICs to inject into nude mice. The renal microvascular endothelial glycocalyx removal of the injected nude mice was evaluated by real-time glycocalyx imaging. Human renal glomerular endothelial cells (HRGECs) were used to assess the potential capacity of Gd-IgA1-containing ICs to activate endothelial cells.

Results: After co-culture of Gd-IgA1-containing ICs with HRGECs, mRNA expression levels of endothelial adhesion molecules (ICAM-1, VCAM-1 and E-selectin) were significantly upregulated (P<0.01). Expression levels of proinflammatory mediators (TNFα and IL-6) that are able to induce the expression of the adhesion molecules on endothelial cells were also increased (P<0.01). Nude mice injected with Gd-IgA1-containing ICs showed podocyte and endothelial injuries with IgA, IgG, and C3 co-deposition along the glomerular capillaries and in the mesangium. Moreover, albuminuria and hematuria were also induced. Real-time glycocalyx imaging showed that renal microvascular glycocalyx was decreased immediately after the injection of Gd-IgA1-containing ICs and then mesangial IgA deposition was increased.

Conclusions: Present data suggest that Gd-IgA1-containing ICs may induce glomerular endothelial injuries resulting in mesangial deposits.

PO1448

Immune Complexes in the Peripheral Blood of Patients with IgA Nephropathy Contain Polymeric Galactose-Deficient IgA1 Associated with IgG and Complement C3

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Background: IgA nephropathy (IgAN) is an autoimmune disease wherein immune complexes (IC) consisting of IgA1 with some hinge-region *O*-glycans deficient in galactose (Gd-IgA1) and IgG autoantibodies deposit in the kidneys and induce injury. Although the glomerular immunodeposits are enriched for Gd-IgA1, not much is known about the distribution of different molecular forms of Gd-IgA1 in circulation.

Methods: Total serum IgA1 was isolated from 7 Caucasian and 10 African American patients with IgAN by jacalin -affinity chromatography. Different molecular forms of IgA1 were then separated by size-exclusion chromatography (SEC). Gd-IgA1 was detected by lectin ELISA. IgA1-IC were isolated by SEC from sera of 4 IgAN patients. Biological activity of the isolated IC was assessed measuring the proliferation of cultured primary human mesangial cells (MC). IgA1, IgG, and complement C3 were analyzed by SDS-PAGE/immunoblotting.

Results: Total serum IgA1 included monomeric and polymeric forms and IgA1 bound in IC. Monomeric IgA1 represented ~88-92% of total IgA1, whereas polymeric IgA1 represented ~8-12%. IgA1 in IC was the least abundant form, representing <0.4% of total IgA1. Relative representation of Gd-IgA1 was highest in IC, followed by polymeric forms, and lowest in monomeric forms. Gd-IgA1 in IC had minimally sialylated *O*-glycans, whereas polymeric and monomeric forms were substantially sialylated. Caucasian patients had higher content of Gd-IgA1 in polymeric and monomeric forms of IgA1 compared to those of African American patients (P<0.03 and P<0.05, respectively). IgA1-IC in sera of IgAN patients had molecular mass >700 kDa and stimulated proliferation of MC. These IC consisted of polymeric IgA1, IgG, and complement C3.

Conclusions: Biologically active IC in the circulation of IgAN patients contain polymeric, minimally sialylated Gd-IgA1 associated with IgG and C3. These findings support the pathogenic role of Gd-IgA1-IgG IC in IgAN.

Funding: NIDDK Support, Private Foundation Support

PO1449

Propensity of Immunoglobulin A Self-Aggregation via "Tailpiece" Cysteine 471 and Therapeutic Use of Existing Drug Cysteamine to Treat IgA Nephropathy

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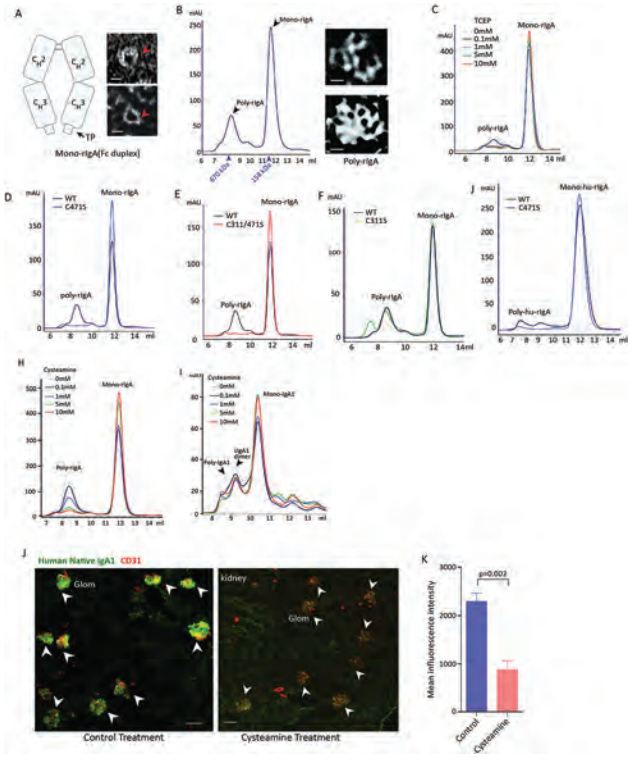
Background: IgA nephropathy (IgAN) is caused by deposition of circulatory IgA1 in the kidney. Hypo-galactosylated IgA1 has the propensity to form poly-IgA1 complexes that are prone to deposition. In IgA1 protein sequence, there are features required for the assembly of dimeric mucosal IgA1, including "tailpiece" Cys471 residue of the heavy chain in participating disulfide bonds with J-chain subunit in IgA1 dimer. In monomeric IgA1 with the absence of J-chain, this free Cys471 is susceptible to oxidation-induced disulfide with other IgA monomers.

Methods: Poly-IgA1 isolated from the plasma of IgAN patients was analyzed for intermolecular disulfide connections. Cysteine residues of Cys311 and Cys471 of IgA1 were mutated to determine their participation in IgA1-IgA1 disulfide bond formation. Cysteine-reducing drugs cysteamine and WR-1065 were tested for effects on IgA1 aggregation and on kidney deposition.

Results: High-molecular-weight IgA1 complexes were susceptible to reducing condition, suggesting disulfide-linkages in poly-IgA1 complexes. Mutagenesis confirmed Cys471's participation in IgA1 self-aggregation, which could be disassembled by aminothiol drugs cysteamine and WR-1065. Administration of cysteamine to murine models of IgAN reduced the level of IgA1 deposition in the glomerulus.

Conclusions: IgA1 tailpiece contributes to the propensity of IgA1 monomer to self-aggregate via intermolecular disulfide bonds. Our results revealed a novel molecular mechanism for aberrant formation of IgA aggregates, to which repurposed cystinosis drug cysteamine was efficacious in preventing renal IgA deposition.



'Tailpiece' Cysteine-471 involved in IgA self aggregation, cysteamine treatment lowers poly-IgA contents *in vitro* and its renal deposition *in vivo*.

PO1450

Structural Characterization of Autoreactive IgG Antibodies in the Context of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most prevalent glomerulonephritis in the world. The pathology of IgAN is characterized by deposition of immune complexes in the kidneys. These complexes can trigger inflammation and mesangial cell proliferation in patients, where up to 40% of cases progress to renal failure. The pathogenic immunodeposits in kidneys of IgAN patients have been shown to contain IgA1, which has *O*-linked glycans in the hinge region of the heavy chain that are deficient in galactose (galactose-deficient IgA1; Gd-IgA1) and IgG autoantibodies to Gd-IgA1. Sequencing of IgG heavy chain variable regions from IgAN patients has identified a correlation between a serine residue, introduced by somatic hypermutation into the framework leading into the third hypervariable loop of the heavy chain, with an increased association of IgG autoantibodies with Gd-IgA1. We set out to understand how this single amino acid mutation affects the IgG Fab structure and antigen recognition with the aid of protein crystallography, reverse engineering, and binding studies.

Methods: Recombinant IgG constructs (rIgG) based on IgAN patient sample sequences and site-specific mutants were expressed in 293F cells and purified. Fabs were cleaved from IgG, purified, crystallized, and their protein structures determined. Binding differences between Gd-IgA1 and intact rIgGs were determined with ELISA-based experiments.

Results: Comparisons of rIgG Fabs structures derived from a healthy control patient and an IgAN patient showed conformational differences that possibly influence the recognition of Gd-IgA1. Using this structural data and bioinformatics to guide antibody design, we reverse engineered the IgG from a healthy patient control to modulate binding to Gd-IgA1. Site-directed mutagenesis and binding studies indicated that residues in our selected regions of the variable domains alter Gd-IgA1-IgG complex formation.

Conclusions: We have determined the structures of Fabs from IgGs that form complexes with Gd-IgA1, and we have further identified residues in the Fabs that are important for Gd-IgA1-binding. This knowledge could inform future strategies to inhibit pathogenic immune complex formation.

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

PO1451

Histopathologic Association of Lambda Light Chain Predominance in IgA Nephropathy

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Background: A relative predominance of lambda (λ) over kappa (κ) light chain deposition has long be recognized in IgA Nephropathy (IgAN), which is unlike any other glomerular disease. The reason for this predominance is unknown but may be related to a purported predominance of λ chain expression by gut associated lymphoid tissue B cells. There is limited information regarding the histopathologic findings, if any, associated with predominant λ light chain deposition. Utilizing the CureGN IgAN cohort, we evaluated if predominant λ chain deposition was associated with histologic markers of disease activity by examining MEST characteristics and other variables.

Methods: We divided the CureGN IgAN cohort into two groups based on the intensity of light chain deposition by immunofluorescence. The λ dominant group (LD) was defined by a difference in intensity score of staining of λ minus κ ≥ 1+, and the λ-κ codominant group (KL) by a difference of λ minus κ < 1+. Fisher's exact test was used to compare the histopathologic changes between the groups with respect to M, E, S, T, scores, total crescents, percent (%) of globally sclerotic glomeruli, % of glomeruli with fibrinoid necrosis, degree of interstitial inflammation, and the intensity of IgG, C1q, and C3 staining.

Results: Among 695 IgAN patients, the kidney biopsy digital images of 269 patients were reviewed by CureGN pathologists and 234 patients had reported λ and κ staining intensity. Of these, 96 (41%) patients were classified as LD (including 7 patients (3%) with λ monotypic staining) and 138 (59%) classified as KL. The two groups did not differ significantly in age, sex, or race. Compared to the KL group, the LD group had a greater frequency of endocapillary hypercellularity (E1, 51.1% vs 36.3%, p=0.04) and IgG staining intensity ≥ 1+ (37.3% vs 21.9% ; p=0.01). There were no significant differences between groups with respect to any other histologic finding.

Conclusions: In IgAN, patients with predominantly λ mesangial deposition are more likely to have increased endocapillary hypercellularity and IgG deposition, two findings previously linked with greater histologic disease activity and possibly worse prognosis. Further studies are needed to elucidate if the predominance of λ chains represents a unique pathogenesis in a subset of patients, or if it imparts a more severe disease course.

Funding: NIDDK Support

PO1452

Plasmacytoid Dendritic Cells from Murine IgA Nephropathy Have a Capacity to Enhance IgA Production Through TLR9/APRIL Signaling

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Background: Our recent study revealed that chronic Toll-like receptor 9 (TLR9) stimulation induce a proliferation-inducing ligand (APRIL) expression on naïve B cells and such APRIL$^+$B cell may contribute to nephritogenic IgA production in IgA nephropathy (IgAN). On the other hand, APRIL from TLR9 activated dendritic cell (DC) is generally known to be involved in B cell maturation and IgA class switching. In this study, we evaluated IgA production through TLR9/APRIL signaling by DCs from murine IgAN.

Methods: Splenic B cells and DCs from grouped ddY (gddY) mice, which are known as the spontaneous IgAN model, and Balb/c mice were isolated using magnetic cell sorting system. In addition, DCs were further divided into three DC subsets; i.e., plasmacytoid DCs (pDCs), CD8+ conventional DCs (cDCs), and CD11b+ cDCs by cell sorter. We co-cultured these isolated DCs and B cells with or without CpG-ODN, a synthetic oligonucleotide TLR9 ligand, and IgA in the culture supernatants was measured by ELISA. We also measured the expressions of TLR9 and APRIL in each DC.

Results: The gddY-derived, but not Balb/c-derived, DCs could dramatically enhance IgA production by co-culture with B cells derived from both gddY and Balb/c mice, and further enhance under CpG-ODN stimulation. Moreover, pDCs from gddY mice strongly induced the IgA production in B cells, compared with cDCs. The expressions of APRIL and TLR9 in the pDCs were higher than those in cDCs.

Conclusions: Present findings suggest that the gddY DCs, especially pDCs, strongly enhance IgA synthesis from B cells through TLR9 and APRIL signaling.

PO1453

Targeted Release Formulation Budesonide (Nefecon) Selectively Reduces Circulating Levels of Chemokines Critical to Immune Cell Trafficking to Peyer Patches in IgA Nephropathy

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Background: Evidence supports a pivotal role of gut-derived chemokines in the direction of immune cell trafficking to the intestine in homeostatic and inflammatory conditions. It is well established that chemokines and their receptors control the influx

of T cells and B cells into Peyer's patches (PP). T-cell homing to the PP depends on CCR7 and its ligands, CCL19 and CCL21, whereas B-cell homing to PP depends on the coordinated signaling of CCR7, CXCR4, CXCR5 and CCR6. The PP are believed to be a major source of the poorly *O*-galactosylated IgA1 in IgA nephropathy (IgAN). The therapeutic potential of targeting PP was demonstrated in the Phase 2 NEFIGAN trial (NCT01738035), which assessed the safety and efficacy of a novel targeted-release investigational formulation of budesonide (TRF-budesonide [Nefecon]), designed to deliver budesonide to the PP-rich distal ileum in patients with IgAN. The trial comprised a 6-month run-in, 9-month treatment, and 3-month follow-up phase: 49 patients received Nefecon 16 mg/day, 51 patients received Nefecon 8 mg/day and 50 patients received placebo. Nefecon 16 mg/day, added to optimized renin–angiotensin system blockade, reduced proteinuria and stabilized eGFR in patients with IgAN. This study investigated whether Nefecon treatment altered serum levels of chemokines.

Methods: Serum levels of a panel of 20 chemokines were measured by Luminex. Changes in log-transformed levels of each biomarker with treatment were compared by one-way ANCOVA. Significance was p<0.05.

Results: A significant, dose-dependent modulation in serum levels of key chemokines directing T and B cell trafficking to the intestine (CXCL5), and more specifically to the PP (CCL11, CCL19, CCL20) was seen with Nefecon, which reversed on cessation of Nefecon. These observations paralleled significant reductions in the levels of soluble CD23, CD27 and CD30, and are consistent with our previous reports describing a dose-dependent reduction in BAFF, soluble BCMA, TACI, IgA–IgG immune complexes, secretory IgA and galactose-deficient IgA levels with Nefecon.

Conclusions: Nefecon, which targets the PP-rich distal ileum, modulates key chemokine signals which direct immune cell trafficking to the intestine in IgAN.

Funding: Commercial Support - Calliditas Therapeutics

PO1454

The Dual Endothelin Angiotensin Receptor Antagonist (DEARA) Sparsentan Protects from Glomerular Hypercellularity and Associated Immune/Inflammatory Gene Network Activity in a Model of IgA Nephropathy

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Background: IgA Nephropathy (IgAN) is an autoimmune glomerulonephritis wherein immune complexes (IC) composed of galactose-deficient IgA1 (Gd-IgA1; autoantigen) and Gd-IgA1-specific IgG autoantibodies (AuAb) deposit in the glomeruli (gli) and cause injury. In a mouse model of IgAN induced by IC formed *in vitro* from human Gd-IgA1 and a recombinant AuAb, we used whole-kidney RNAseq profiling to assess how Sparsentan (Sp) affects the gene expression of pathways dysregulated by IC.

Methods: IC were injected into ~7-week-old nude mice every other day for a total of 6 doses (n=5/group). Sp (60 or 120 mg/kg) or vehicle (V) were given by gavage once daily from the first day of IC injections. Negative-control mice received only V. Kidney tissue for histopathology and RNAseq was harvested on day 12. RNAseq raw data processed using DESeq2 identified differentially expressed genes. WGCNA was used for network-level profiling and to identify co-expressed genes associated with hypercellularity and Ki-67 positivity of gli. GSEA and X2K assessed changes at the pathway level and imputed correlated upstream cell-signaling networks. Pathway enrichment p-values were adjusted with FDR.

Results: Sp ameliorated IC-induced hypercellularity (P<0.01) and Ki-67-positive gli (P<0.05). WGCNA clustered genes into co-expressed modules associated with hypercellularity and Ki-67 positivity. GSEA-identified top-5 pathways were enriched for immune processes (FDR <1x10^-20), the top being cytokine signaling pathways. The expression pattern of 95% of the top module genes dysregulated by IC, was corrected by Sp. X2K analysis revealed correlated expression of top hub genes, kinases MAPK14, GSK3B, CSNK2A1 (z-score <1x10^-12) and transcription factors SP1 and RUNX1 (z-score <0.05), highlighting the role of the ERK1/2-SP1 axis known to regulate cell proliferation.

Conclusions: In a mouse model of IgAN, kidney transcriptomics revealed gene networks, enriched in immune/inflammatory functions, correlating with IC-induced hypercellularity. The top dysregulated genes were normalized by Sp and were linked to kinases and transcription factors with correlated functional activity. These data suggest a potential anti-inflammatory role for Sp in IgAN.

Funding: Commercial Support - Travere Therapeutics, Inc., San Diego, CA

PO1455

Treatment with Targeted Release Formulation Budesonide (Nefecon) Modulates the Complement System in Patients with IgA Nephropathy

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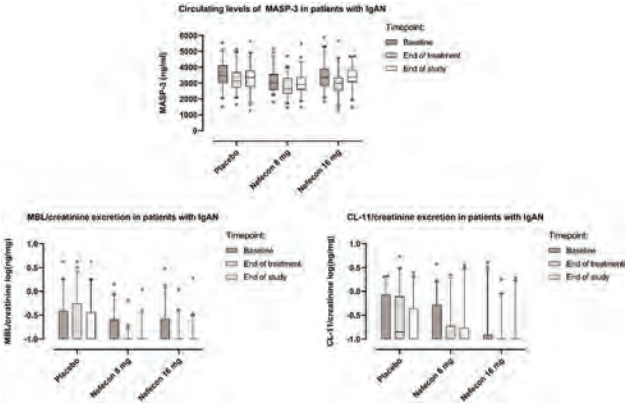
Background: The NEFIGAN trial (NCT01738035) evaluated the effect of a novel targeted-release investigational formulation of budesonide (TRF-budesonide [Nefecon]) in the treatment of IgA nephropathy (IgAN). Participants in this Phase 2b trial were randomly assigned placebo, Nefecon 8 mg or 16 mg/day, and samples were collected at baseline (0 months), at the end of the treatment (9 months) and at the end of the study (12 months). In this exploratory study we evaluated the effect of Nefecon treatment on the circulating levels and urinary excretion of a panel of complement components.

Methods: Plasma and urine levels of complement proteins (C4c, C3bc and soluble C5b-9) and ficolin-1, -2 and -3, MBL, CL-11, MASP-3, MAP-1 and PTX-3 were measured using in-house sandwich-ELISAs. Treatment differences between baseline, end of treatment and end of study were assessed by mixed-effects model analysis. The effect of the treatment correcting for the baseline was assessed by multiple linear regression. Significance: $p < 0.05$. Urinary proteins were adjusted for creatinine excretion.

Results: Circulating levels of MASP-3 were decreased in a dose-dependent manner after treatment (p=0.0313 Nefecon 8 mg/day, p=0.0080 Nefecon 16 mg/day). MBL/creatinine was significantly reduced in the urine by both doses of Nefecon compared with placebo (p<0.0001 Nefecon 8 mg and 16 mg/day). CL-11/creatinine levels were also significantly reduced in a dose-dependent manner after Nefecon administration (p<0.0411 Nefecon 8 mg/day, p<0.0095 Nefecon 16 mg/day). Complement activation markers and ficolin-3 levels were detectable in urine but levels remained unaltered.

Conclusions: Treatment with Nefecon modulates components of both the alternative (MASP-3) and lectin (MBL and CL-11) pathways of complement, two pathways known to be important in mediating kidney damage in IgAN. These initial observations warrant further investigation.

Funding: Commercial Support - Calliditas Therapeutics



PO1456

Defining Cell Type Specificity of TNF Targets in Nephrotic Syndrome

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Background: Mechanistic, targeted therapies are needed for patients with FSGS and MCD, as diverse biological processes produce similar histologic injury patterns. Bulk transcriptomic data from kidney biopsy tissue can be used to find subgroups with shared molecular features, but cellular signaling networks need to be defined.

Methods: Consensus clustering was applied to bulk RNA sequencing data from the tubulointerstitial (TI) compartment of 220 participants from the NEPTUNE cohort, a study of children and adults with nephrotic syndrome enrolled at the time of kidney biopsy. Clusters were assessed for association with clinical outcome. Differential gene expression analysis was analyzed for enrichment of canonical pathways and functional groups between patient clusters. Nuclei were extracted from renal biopsies, processed, and quality control analyzed to remove low quality nuclei. Nuclei identity were assigned by comparisons of enriched genes in a cluster to previously identified cell type-specific gene profiles.

Results: One cluster of 59 patients was associated with a higher risk of loss of kidney function over time and observed TNF activation. To test the cellular source of the TNF pathway biomarker candidates, we performed snRNA-seq on 10 NEPTUNE biopsies, 5 with high TNF activity scores and 5 with moderate to low TNF activity scores in TI gene expression profiles. We pooled 45,175 nuclei into 15 clusters, which included all major kidney cell types. *TNF* expression was found in nuclei from immune clusters and in a proximal tubule and loop of Henle cluster. *TNFRSF1A* was universally expressed across cell clusters, while *TNFRSF1B* showed more restrictive expression. TNF targets *CCL2* and *TIMP1* had higher levels in all patients with activated TNF scores with maximal increase in epithelial cells (proximal and podocytes). Kidney organoids confirmed MCP1 (encoded by *CCL2*) and TIMP1 upregulation by TNF treatment.

Conclusions: TNF, TNF receptors, and TNF-responsive biomarkers reflect alterations in inflammatory and intrinsic kidney cell populations in patients with a TNF-associated signaling profile and are currently assessed as TNF target engagement biomarkers in a clinical trial of FSGS patients (NCT04009668).

Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases Research; National Center for Advancing Translational Sciences, Private Foundation Support

PO1457

Dysregulated T Cell Metabolomic Profile in Patients with Steroid-Resistant Nephrotic Syndrome

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Background: We have recently reported early relapse following rituximab in patients with minimal change disease was associated with baseline reduction in regulatory T-cells and T-cell hyporesponsiveness to activation, suggesting chronic T-cell activation. This study aimed to compare T-cell activation and characterise the metabolic alterations associated with T-cell hyporesponsiveness in patients with steroid-dependent (SDNS) and steroid-resistant nephrotic syndrome (SRNS) in relapse.

Methods: A total of 48 patients with childhood-onset SDNS (n=31) and SRNS (n=17) were recruited during relapse. T-cell activation assay was performed on whole blood while metabolomic profiling was performed on purified stimulated CD4 T-cell culture supernatants (n=23) using GC-MS/MS and analysed using Shimadzu Smart Metabolites Database. Differences in the metabolomic profile between SDNS and SRNS were identified using PLS-DA (SIMCA), and pathway analysis was performed using MetaboAnalyst 4.0. Metabolomic validation assay was performed using Glucose 6 Phosphate Dehydrogenase (G6DP) assay kit.

Results: SRNS patients had significant lower T-cell expression of CD69 (88±2.3% vs 91±3.1%, P=0.024) and IFNγ (1.9±0.73% vs 6.6±1.35%, P=0.016) compared to SDNS patients. PLS-DA modeling of the 93 metabolites identified in CD4 culture supernatants yielded one fitted component, in which 24% of the variability in metabolites measured (R^2X) could explain 58% of the variation in steroid-response (R^2Y). Of note, 85% of the metabolites tended to be lower in SRNS compared to SDNS patients. Pathway analysis of the 38 metabolites with VIP>1 implicated the biosynthetic pathways glyoxylate and dicarboxylate metabolism, ascorbate and aldarate metabolism as well as galactose metabolism (Benjamini-Hochberg P<0.05). Interestingly, the 2 metabolites with the highest VIP score have been implicated as downstream products in the pentose phosphate pathway and were reduced in SRNS compared to SDNS patients (P<0.001). G6DP activities in SDNS patients in relapse negatively correlated with T-cell expression of CD69 (r=-0.58, P<0.047).

Conclusions: We demonstrated that muted T-cells response to *in vitro* stimulation in SRNS patients was associated with metabolic quiescence, with dysregulated biosynthetic pathways including the pentose phosphate shunt.

Funding: Government Support - Non-U.S.

PO1458

Blocking the IL-1β/IL-1R1 Signaling as a Potential Therapy for Multidrug-Resistant Nephrotic Syndrome

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Introduction: In idiopathic nephrotic syndrome (NS), Steroid-resistant patients with complete or partial resistance to the combination of prednisone and steroid sparing-agents are at high risk to progress to end-stage kidney disease. Considering the toxicities associated with chronic use of these drugs, alternative interventions are urgently needed. IL-1β/IL-1R1 has been recently suggested as a possible mechanism of complement-mediated progression of Focal Segmental Glomerulosclerosis.

Case Description: A 26-year-old white woman had FSGS (kidney biopsy) presenting with NS and kidney failure. Serum creatinine level was 1.6 mg/dL, urinary protein excretion 20.4 g/d and serum albumin 0.9 g/dL. She received methylprednisolone, 1g rituximab, and CNI with partial remission. Three months later, she presented relapse of NS and acute kidney failure requiring 5 HD: CNI was switched to MMF. Immunoglobulins IV were administered. After 3 months, serum creatinine was 5.1 mg/dL, urinary protein excretion was 18 g/d. Given the lack of improvement/worsening of proteinuria, wet started anakinra, the anti-IL-1R1 (subcutaneously, 2 mg/kg/d for the first week and then 4 mg/kg/d). After 1 year, serum creatinine is 3.4 mg/dL, urinary protein excretion is 5.2 g/d and serum albumin level was 1.3 g/dL. No side effects were reported (**Fig 1**).

Discussion: We administered Anakinra in MRNS due to FSGS and CKD Stage IV. After Anakinra, multiple ongoing immunosuppressive treatments were stopped. We acknowledge that Anakinra did not promote full disease remission, but it was associated with a significantly amelioration of the disease clinical. By slowing the rapid progression of kidney failure, the young patient better faced all future perspectives: a pre-emptive kidney transplant in case kidney function worsens is now available. In conclusion, our data indicate that Anakinra, by antagonizing IL-1β/IL-1R1 signaling, may represent a useful therapeutic option to prevent the progression of kidney injury in advanced forms of nephrotic syndrome.

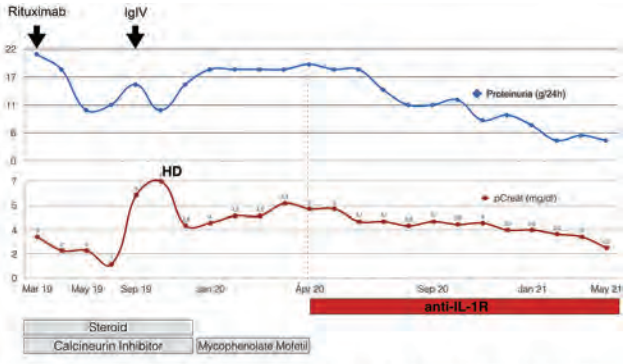

Figure 1. Proteinuria and serum creatinine course pre and post anakinra administration in 26-year-old white woman with Focal Segmental Glomerulosclerosis multidrug-resistant.

PO1459

More Severe Mitochondrial Injury at the Time of Diagnosis Is Associated with Poor Prognosis in Minimal Change Disease

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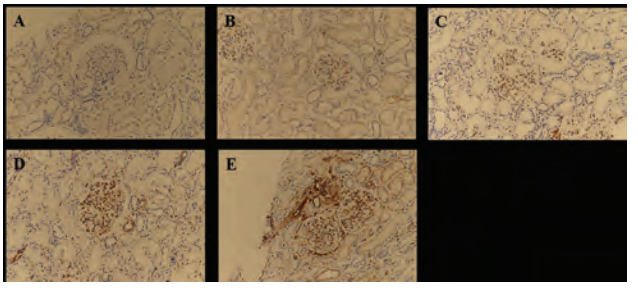
Background: We hypothesized that the pathogenesis of minimal change disease (MCD) may be associated with mitochondrial injury and that the degree of mitochondrial injury at the time of diagnosis may serve as a prognostic marker in MCD.

Methods: We retrospectively enrolled patients with MCD who were followed up for more than 5 years and IgA nephropathy (IgAN) patients as controls (n = 20 each). Focusing on the stimulator of interferon genes (STING) pathway activated by mitochondrial injury, immunohistochemical (IHC) staining for STING was performed on kidney tissue at the time of diagnosis. The IHC stain site and signal intensity for STING were analyzed. Time-averaged proteinuria (TA-proteinuria) was calculated as the average of the mean of proteinuria measurements were obtained by 24-hour urine collection every 6 months for each patient. A relapse after treatment was defined as proteinuria >3.5 g per 24 hours after complete or partial remission.

Results: In patients with IgAN and MCD, kidney tissue from 13 patients each showed positive IHC staining for STING. While various kidney structures including glomerulus and tubulointerstitium were stained in IgAN patients, the glomerulus was exclusively stained in MCD patients (Figure). MCD patients were divided into the high (n = 6) and low (n = 14) intensity subgroups according to the signal intensity based on 2+ and more or less, respectively. TA-proteinuria and frequency of relapses during the follow-up period were higher in the high intensity group than in the low intensity group (1.18 ± 0.54 vs. 0.57 ± 0.45 g/day, p = 0.022; and 0.72 ± 0.60 vs 0.09 ± 0.22 episodes/year, p = 0.022, respectively).

Conclusions: These findings suggest that more severe mitochondrial injury, as represented by a high signal intensity of IHC stain for STING at the time of diagnosis, could be used as a prognostic marker to predict poor prognosis in MCD.



IHC staining for STING on kidney tissue obtained from MCD patients (classified into negative (A), 1+ (B), 2+ (C), and 3+ (D) according to the signal intensity) and IgAN patient (E).

PO1460

Maturation of Decay Accelerating Activity Response Across the Natural History of C3 Glomerulopathy

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Background: C3 Glomerulopathy (C3G) is an ultra-rare complement-mediated renal disease characterized by dysregulation of the alternative pathway (AP) of complement. Dysregulation is often driven by a nephritic factor (C3Nef), an autoantibody to the C3 convertase (C3BbB) of the AP. We hypothesized that the properties of Nefs change

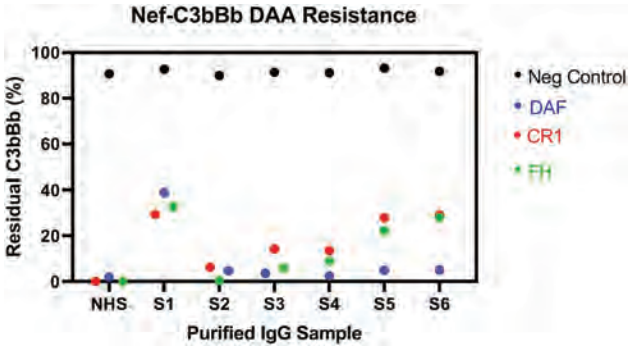
over time and that changes will be associated with changes in underlying complement dysregulation.

Methods: IgG was purified from normal human serum and from sera collected across six time points of a well characterized C3G patient. Using SPR (Biacore), the C3 convertase (C3bBb) was formed on a CM5 sensor chip. Purified test or control IgG was injected to form the Nef-C3bBb complex. The ability of native complement regulators to decay the Nef-C3bBb complex was assessed by injecting Decay Accelerating Factor (DAF), Complement Receptor 1 (CR1), Factor H (FH), or control reagent. Residual C3bBb was determined by the ratio of post- to pre-regulated convertase. Data were compared to time-associated complement biomarker results.

Results: The presence of Nef conferred resistance to the normal decay accelerating activity (DAA) by DAF, CR1, and FH. Resistance to DAA was highest in the earliest sample (S1, p= 0.0001), with a reduction in subsequent samples. This change was independent of Nef titer and coincident with reduced complement activity. Low DAF resistance was maintained in later samples, whereas CR1 and FH resistance gradually increased.

Conclusions: Nef-stabilized C3bBb resistance to native DAA proteins matures over time and is independent of Nef titer. Changes in response to regulators is accompanied by a relative change in underlying complement dysregulation as reflected by complement biomarkers. How this variance (in time and across regulators) impacts disease course and outcome in patients with C3G or whether the phenomenon represents a novel treatment target warrants further study.

Funding: NIDDK Support



	C3CSA (<20%)	C5CSAP (<20%)	CH50 (>70 Eq/mL)	C3 (0.9-1.8g/L)	Bb (<2.2 mg/L)	C3c (<1.5 mg/L)	FH (130-420 mg/L)	C5 (13.5-27.0 mg/dL)
S1 (10/15/2016)	50	48	39	0.8	2.3	3.4	57	9.9
S2 (12/1/2017)	30	19	129	1.04	1	0.7	241	14.5
S3 (11/6/2018)	25	17	153	1.1	1.1	0.9	305	13.9
S4 (1/10/2019)	26	19	118	1.2	0.8	0.9	309	14.4
S5 (10/2/2019)	20	17	129	1.1	1.2	0.6	209	11.2
S6 (4/16/2020)	17	14	143	1.4	1.2	0.7	276	30.5

PO1461

C3 Glomerulonephritis with Nephritic Factor Treated with Rituximab

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Introduction: C3 Glomerulonephritis (C3GN) is a well described cause of kidney disease that results from dysregulation of the alternative complement pathway. Kidney biopsy demonstrates a membranoproliferative pattern of injury and mesangial C3 staining with minimal or no staining of immunoglobulins on immunofluorescence. C3GN can be due to genetic mutations, autoantibodies against the alternative complement regulators, or monoclonal gammopathy. C3 nephric factor (C3NeF) is an auto-antibody that stabilizes C3 convertase which leads to an increase in activity of the alternate complement pathway. Steroids, mycophenolate mofetil (MMF), rituximab, and eculizumab have been used with varying results. We present a patient with biopsy proven C3GN with C3NeF who was successfully treated with rituximab after failing therapy with MMF.

Case Description: Patient is a 64-year-old male diagnosed with biopsy proven C3GN after being found with decreased kidney function with a peak creatinine of 1.97 mg/dL and nephrotic range proteinuria with a maximal urinary protein excretion of 4.3 g/d. Evaluation revealed low C3 and C4 at 60 mg/dL and 5 mg/dL respectively, negative monoclonal testing, and a C3NeF of 21 unit/mL (reference range 0). Patient was initiated on prednisone 60 mg/day with taper, MMF with a maximal dose 3 grams/day, and valsartan for 2 years with little improvement in clinical parameters. Therapy was switched to rituximab 1 gram on weeks 0, 2, 26. Within 3 months patient had; normalization of complements, negative C3NeF, 0.7 urine protein-to-creatinine ratio (UPCR), and serum creatinine 1.5 mg/dL. Since his initial rituximab regimen 2 years ago, he remains off maintenance therapy, with negative C3NeF, normal complements, 0.1 UPCR, and serum creatinine 1.04 mg/dL.

Discussion: C3GN was successfully treated with rituximab based on the disappearance of C3NeF and improvement in clinical parameters. Rituximab was chosen to target CD20 cells to halt the production of the C3NeF autoantibody. Laboratory response (complements and C3NeF) was seen within 3 months of initial rituximab dosing, and UPCR and serum creatinine required a longer follow up for a nadir. Reoccurrence of relapse is being monitored using serial C3NeF measurements. We believe that targeted B cell therapy should be considered in the treatment of C3GN cases which are C3NeF antibody mediated.

PO1462

Complement-Activated Polymorphonuclear Neutrophils Contribute to C3G Pathogenesis

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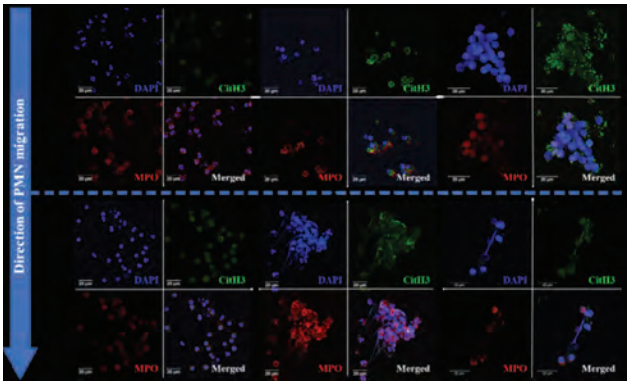
Background: C3G is caused by dysregulation of the complement alternative pathway, but there is a gap in the pathogenetic cascade from complement activation (intravascular space) to inflammation and complement deposition in the glomeruli (extravascular space). Recently, biopsies have shown the presence of (activated) polymorphonuclear neutrophils (PMNs) in C3G glomeruli indicating an underappreciated role for PMNs in C3G pathogenesis.

Methods: PMNs were investigated in a transwell chamber allowing for different environments. Conditions were chosen to resemble the intravascular space (top well; serum containing) versus extracellular space (bottom well; serum-free conditions). PMNs were stimulated in the top well via various agonists, including complement, and allowed to transmigrate to the bottom well where they were monitored for the formation of Neutrophil Extracellular Traps (NETs) via immunofluorescence and SYTOX assay. Circulating C3G patient PMNs were examined for priming via flow cytometry.

Results: Upon complement stimulation, PMNs showed evidence for priming in serum conditions (top well). PMNs travelled to the bottom well following chemoattractant fMLP where they then completed the process of NET formation (NETosis) in serum-free conditions (bottom well). Results were validated ex vivo using C3G patient PMNs and autologous serum (Figure). In addition, incubation of control PMNs in C3G patient serum revealed a correlation between serum-albumin levels and the degree of NET formation. C3G patient PMNs showed upregulation of CD11b compared to controls.

Conclusions: Assigning a pathogenetic role to PMNs in C3G identifies a new treatment and monitoring strategy with the potential for improved long-term outcomes and quality of life.



PMNs were seeded in the top well of a transwell system and allowed to transmigrate for 12 h. PMNs from both wells were stained for IF with DAPI (blue), Citrullinated histone 3 (CitH3; green) and Myeloperoxidase (MPO; red). Scale bar 20 um. 63x magnification.

PO1463

Differential Expression of Complement and Non-Complement Proteins in C3 Glomerulonephritis and Dense Deposit Disease

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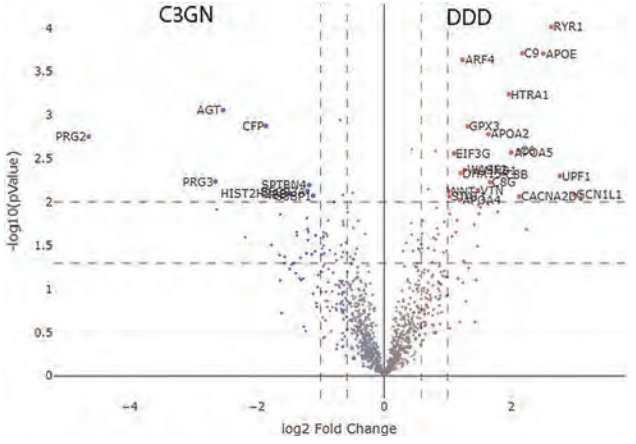
Background: C3 glomerulopathy comprising dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) results from overactivation of the alternative pathway of complement. Mass spectrometry (MS) studies have previously shown accumulation of complement proteins in C3GN and DDD. However, complete MS analysis of non-complement proteins and comparison of complement proteins in C3GN and DDD has not been done.

Methods: We performed laser microdissection of glomeruli followed by MS in 12 cases each of biopsy-proven C3GN and DDD, and 6 control cases of time 0 transplant biopsies.

Results: Compared to the controls, C3GN showed increased intensity based absolute quantification (iBAQ) values of C3 (20-fold), C5 (52-fold), C6 (76-fold), C7 (90-fold), C8 (66-fold), C9 (30-fold), CFHR1 (146-fold) and CFR5 (65-fold). Similarly, DDD showed also increased iBAQ values compared to controls of C3 (26-fold), C5 (365-fold), C6 (473-fold), C7 (261-fold), C8 (353-fold), C9 (159-fold), and CFHR1 (73-fold). When DDD was compared to C3GN, there was a 2-5 fold increase in iBAQ values in C5, C6, C7, C8 and C9 ($p<0.001$), although there was no significant difference in C3. Among the non-complement proteins Apolipoprotein E (APOE) and A-II and V (APOA-II and V), Serine protease HTRA1, Ryanodine receptor 1 (RYR1), and Translational activator GCN1 were expressed 3-7 fold higher in DDD compared to C3GN ($p<0.001$). On the other hand, proteoglycan 2 and 3 (PRG2 and 3), angiotensin (AGT) and properdin (CFP) were expressed 2-5 fold higher in C3GN compared to DDD ($p<0.001$).

Conclusions: MS of C3GN and DDD show high iBAQ values of complement proteins. DDD shows a higher iBAQ vaules in terminal complement proteins compared to C3GN. In addition, proteins such as APOE and APOA II/V are increased in DDD compared to C3GN, while PRG2/3 and properdin are increased in C3GN compared to DDD suggesting a role for the proteins in the pathophysiology of C3GN and DDD.



Volcano plot showing differential expression of proteins in C3GN and DDD.

PO1464

Clinical and Histological Features of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: A Single-Center Retrospective Study from China

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Background: PGNIMID is a new entity of monoclonal gammopathy affecting the kidney characterized by intact monoclonal immunoglobulins (mIg) deposits that result in membranoproliferative pattern of glomerular injury. In this study, clinical and histological of PGNMID cases were evaluated.

Methods: A total of 23 patients with biopsy-confirmed PGNMID in native kidney diagnosed between December 2015 to April 2021 were enrolled in this study. Clinical, histological, hematologic, and follow-up data were abstracted from the medical record.

Results: Of 23 cases, majority were male (65.2%), and the mean age was 49.5 years with 8 cases (34.8%) under 40 years old. At the time of biopsy, 19 cases had proteinuria with a mean 24h urine protein of 3.99g (0.28 to 8.96), 11 of 22 cases had nephrotic syndrome, and 18 of 22 cases had hematuria. The mean serum creatinine was 1.52mg/dL (0.6 to 7.8), 15 cases (65.2%) had eGFR<90 mL/min (CKD-EPI), and 4 cases had eGFR <60 mL/min. Eleven of 23 cases (47.8%) showed MPGN, 6 cases showed EPGN, 2 cases showed MesPGN, and 2 cases showed MN. By IF, 21 cases (91.3%) showed mIgG deposits (12 IgG3κ, 5 IgG1κ, 1 IgG1λ, 1 IgG3λ, and 2 IgGκ without determined subclass) and 2 cases (8.7%) showed mIgAλ deposits. All cases showed C3 co-deposits, and 6 of 18 cases (33.3%) had a low serum C3 level. EM revealed unorganized and granular deposits in the mesangial area (17 of 17), subendothelial area (15 of 17), and subepithelial area (12 of 17). Three of 4 cases whose eGFR<60 mL/min showed EPGN. SIFE showed mIg that matched the renal deposits in 2 of 13 cases (15.38%). After mean follow up of 3 months in 3 cases, 1 patient treated with bortezomib+ CTX+DXM and another patient treated with rituximab both achieved partial renal remission. But the third patient treated with rituximab had a persistent renal dysfunction. Of note, previous or concurrent infections by fungi, HIV, HBV, HPV or other undetermined pathogen, were observed in 5 cases (21.7%). We also found 1 patient with autoimmunity and another with malignancy.

Conclusions: Compared with previous reports, our PGNMID cases showed similar clinical and histological features. EPGN pattern seems to be associated with more severe renal function damage. Previous or concurrent infections, autoimmunity and malignancy were observed in 21.7% of cases.

PO1465

Diagnostic and Risk Factors for Deregulated Complement in Thrombotic Microangiopathy

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Background: The syndromes of thrombotic microangiopathy (TMA) are diverse and represent severe endothelial damage caused by various etiologies. The early recognition of complement-mediated (C-)TMA is of utmost importance to select patients for complement inhibition. Whether or not clinicopathologic features at presentation can distinguish C-TMA from secondary TMA and/or predict the response to complement inhibition remains unknown.

Methods: Fifty-seven patients with TMA on kidney biopsy and a normal activity of von Willebrand factor cleaving protease were screened for deregulated complement using *ex vivo* C5b9 formation on the endothelium and genotyping. Massive *ex vivo* C5b9 formation and/or rare complement gene variants defined C-TMA. Clinicopathologic features that may distinguish C-TMA from secondary TMA were studied. Regression models were used to assess the prognostic value of chronic damage on kidney biopsy.

Results: C-TMA was diagnosed in 30 patients (coexisting conditions, n=26 [87%]), including 16 (53%) cases with rare complement gene variants; 27 patients had secondary TMA related to autoimmunity (n=13), hypertension (n=10), and other etiologies (n=4). Patients presented with acute kidney injury, while systemic hemolysis was uncommon in both groups (n/N=14/30 vs. n/N=6/27; P>0.05). C-TMA was linked to younger age (37 [±14] vs. 46 [±15] years; P=0.04), low plasma C3 (n/N=16/29 vs. n/N=3/22; P<0.01), and glomerular thrombosis (n/N=19/30 vs. n/N=8/27; P=0.02) as compared to secondary TMA; glomerular thrombosis, however, was common in patients with autoimmunity (n/N=6/13; P>0.05 vs. C-TMA). These characteristics, when combined, had a specificity and sensitivity for C-TMA of 100% and 33%, respectively. Eculizumab treatment was associated with clinical remission in C-TMA (n/N=12/14; P<0.01 vs. n/N=3/16 untreated patients). Morphologic features of chronic damage, i.e., glomerulosclerosis, interstitial fibrosis/tubular atrophy, and arteriosclerosis, did not predict prognosis; 5 out of 6 patients with C-TMA and moderate-to-severe chronicity scores treated with eculizumab recovered and/or improved kidney function.

Conclusions: Patients with TMA, low plasma C3, and glomerular thrombosis who present at younger age (i.e., <45 years) are at high risk for C-TMA. Although a kidney biopsy is often needed to detect the TMA, morphologic features of chronic damage cannot predict prognosis.

PO1466

Limited Therapeutic Arsenal for the Thrombotic Microangiopathy Spectrum

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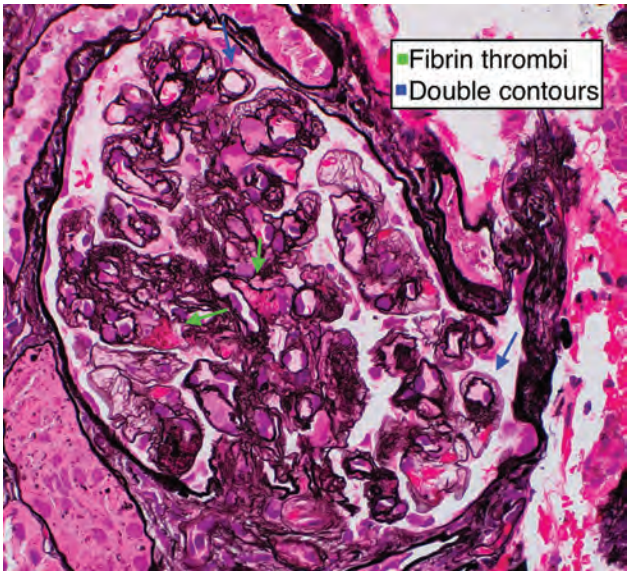
Introduction: Thrombotic microangiopathy (TMA) is a common renal pathologic finding with an associated broad spectrum of clinical diseases. Complement-mediated TMA (C-TMA) is a frequently recognized cause of TMA due to uncontrolled complement activation. Terminal complement inhibitors such as Eculizumab have been shown to improve renal function in C-TMA. Multiple case reports have demonstrated a benefit in patients without identifiable complement disorder.

Case Description: 41-year-old Ethiopian female with a history of metastatic ovarian cancer treated with omentectomy, partial hepatectomy, salpingo-oophorectomy, splenectomy one year before admission was admitted for renal biopsy for evaluation of an increasing creatinine and proteinuria. Following her surgery she had been treated initially with paclitaxel and carboplatin and subsequently she had received bevacizumab and doxorubicin; the last doses of these latter agents were six months before admission. Four months prior to admission she developed new onset hypertension and her creatinine began to increase with subsequent development of nephrotic range proteinuria. All serologies were negative. Kidney biopsy demonstrated TMA. Despite the discontinuation of all chemotherapeutic agents and adequate blood pressure control, her creatinine continued to increase, peaking at 6.8 mg/dl 2 months after the biopsy She was started on Eculizumab with an improvement in creatinine to 3.49 mg/dL 2 months later.

Discussion: There are no randomized trials evaluating terminal complement inhibitors for c-TMA. The indication for these medications becomes even more unclear when we factor in drug-induced TMA, cancer-associated TMA, malignant hypertension, and other TMAs without readily identifiable complement disorders. More research on the use of genetic testing and complement inhibition is warranted for the entire spectrum of TMA.



PO1467

Hematopoietic Stem Cell Transplant Membranous Nephropathy Is Associated with Protocadherin FAT1

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Background: Membranous nephropathy (MN) is a common cause of proteinuria in patients with a hematopoietic stem cell transplant (HSCT). The antigen(s) responsible for MN in HSCT-associated MN is unknown.

Methods: We performed laser microdissection and mass spectrometry (MS/MS) of glomeruli of 230 cases of PLA2R-negative MN to detect novel proteins/antigens in MN. These included PLA2R-negative MN developing in the setting of HSCT and *de-novo* MN in the kidney transplant.

Results: We detected a novel protein Protocadherin FAT1 (FAT1) in 9 cases of PLA2R-negative MN. Of the 9 FAT1-associated MN cases, 7 patients followed HSCT and 2 followed kidney transplant (*de-novo* MN). HSCT was done for treatment of AML (5 cases), MDS (1 case) and essential thrombocytopenia (1 case). All 9 cases were negative for known antigens of MN including PLA2R, THSD7A, NELL1, PCDH7, NCAM1, SEMA3B and HTRA1. Baseline PLA2R spectral counts were detected in 7 of the 9 cases. The FAT1 total spectral counts ranged from 27 to 70 (mean 44.1 ± 13.1). FAT1 was not detected by MS/MS in 115 control cases that included time 0 transplant, minimal change disease, FSGS, diabetes and IgA nephropathy. FAT1 was also not detected in 28 cases of PLA2R-positive MN. No case of FAT1-associated MN was detected in a non-transplant setting. The mean age of patients with FAT1-associated MN was 56 ± 9.7 yrs, 7 patients were females and 2 were males. MN occurred 2.5 ± 0.8 yrs and 7.5 ± 1.2 yrs after HSCT and kidney transplant, respectively. The mean serum creatinine and proteinuria at kidney biopsy was 1.9 ± 1.2 mg/dL and 7.4 ± 5.4 gms/L, respectively. Kidney biopsy showed IgG (2-3+) and minimal C3 (0-1+) along glomerular capillary walls; electron microscopy showed stage II MN in 8 out of 9 cases.

Conclusions: FAT1 appears to be a unique protein found in MN developing in the setting of HSCT and *de-novo* MN following kidney transplant. Further studies to localize FAT1 on the glomerular basement membranes and detect circulating antibodies are ongoing.

Proteomic identification of FAT1 in 9 cases of PLA2R-negative MN. All 9 cases show large spectral counts of FAT1 and only baseline spectral counts of PLA2R. Case 3 and 5 are de-novo MN in kidney transplant, the remaining are following HSCT.

PO1468

Netrin G1 Is a Novel Target Antigen in Membranous Nephropathy

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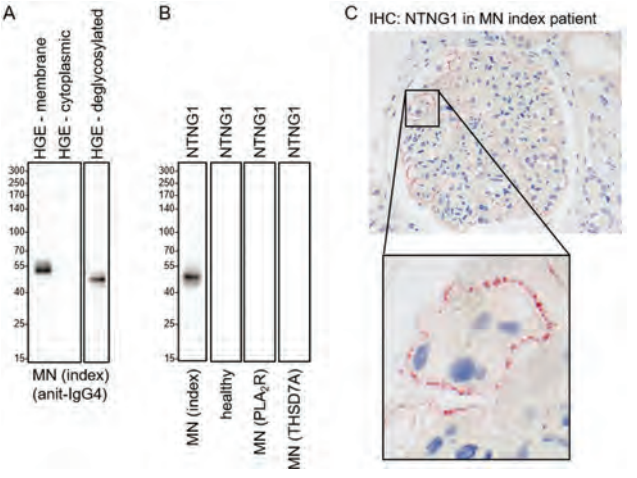
Background: PLA_2R is the main target antigen in membranous nephropathy (MN), representing 70-80% of cases. In the past years a number of confirmed, or potential target antigens, such as THSD7A, NELL1, HTRA1, Sema3B and PCDH7 have been reported, showing that the pathophysiology of PLA_2R-antibody (ab) negative MN represents a diverse repertoire of antigens with low frequency.

Methods: Western blot (WB) analysis was used to identify sera of MN patients with IgG4 specific signals binding to antigens in the membrane fraction of human glomerular extracts (HGE). Only sera which were negative for PLA_2R- and THSD7A-ab were used. IgG4-ab from the serum of an index patient was purified and used to immunoprecipitate the corresponding target antigen from the membrane fraction of HGE. The purified antigen in the eluate was identified by mass spectrometry. Recombinant protein was used to confirm the reactivity of patient sera by WB and identify other patients in a large cohort of MN patients. The deposition of the target antigen in the glomerular immune deposits was confirmed by immunohistochemistry (IHC).

Results: Using this approach, we identified Netrin G1 (NTNG1) as a novel target antigen in MN. NTNG1 is a 50 kDa secreted glycoprotein, which is attached to the cell surface by a GPI anchor (Fig. A, B). We identified NTNG1-ab in two out of 110 PLA_2R- and THSD7A-ab negative MN patients. A follow-up of 5 years was available for the index patient. During this time, both proteinuria and NTNG1-ab persisted while renal function was stable. Further, a granular positivity for NTNG1 along the glomerular capillary wall was confirmed in the kidney biopsy by IHC (Fig. C), but was undetectable in the negative control (PLA_2R-ab positive MN).

Conclusions: We report NTNG1 as a novel target antigen in MN, occurring with low frequency and expanding the repertoire of antigens in patients with MN. Its prevalence, pathogenetic and clinical roles remain to be defined.

Funding: Government Support - Non-U.S.



PO1469

Contactin 1: A New Antigen in Membranous Nephropathy Associated with Chronic Inflammatory Polyneuropathy

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Introduction: In recent years, several new antigens have been characterized in membranous nephropathy (MN), but those involved in association with demyelinating neuropathy remain elusive. Although several antibody specificities were identified in this group of autoimmune neuropathies with or without glomerular involvement, there is no evidence for the deposition of the relevant antibodies in glomeruli. We investigated a patient with such association.

Case Description: A 73 y/o woman was referred to the neurology department for weakness and ataxic gait. Romberg's manoeuvre was positive. On examination, thermal and nociceptive hypoesthesia and hypopallestesia were found. Electromyography demonstrated sensory-motor axonal polyneuropathy, compatible with a chronic inflammatory demyelinating polyneuropathy (CIDP). Blood tests showed normal kidney function (eGFR 73 ml/min) and hypoalbuminemia (2.89 g/dl); 24h proteinuria was 3.6 g/24h. Autoantibodies (ANA, ENA, DNA, LAC, anti-cardiolipin, ANCA) were undetectable, serum immunoglobulins and C3 and C4 complement components were normal. A kidney biopsy (KB) demonstrated a picture of MN. Anti-PLA2R antibody was negative in the serum and PLA2R and THSD7A antigens were not detected in the KB. Three CIDP-associated autoantibodies (anti-contactin 1 (CNTN1), anti-contactin associated protein 1 and anti-neurofascin) were tested by ELISA which revealed the presence of anti-CNTN1 at 1:100 serum dilution. CNTN1 antigen was revealed by immunohistochemistry in the subepithelial immune deposits in the patient's paraffin biopsy sections but not in control PLA2R-positive KB (figure 1).

Discussion: CNTN1 should be added to the armamentarium of antigens involved in MN and tested in PLA2R negative MN associated with CIDP. Further studies are needed to determine the prevalence of CNTN1-associated MN among patients with CIDP, and in those without CIDP and as yet unidentified antigen.

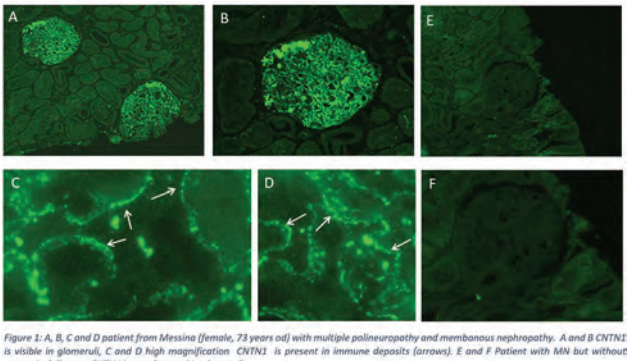

Figure 1: A, B, C and D patient from Messina (female, 73 years od) with multiple polineuropathy and membanous nephropathy. A and B CNTN1 is visible in glomeruli, C and D high magnification CNTN1 is present in immune deposits (arrows). E and F Patient with MN but without neurogical disease. CNTN1 is not detected in glomeruli

PO1470

Epitope Spreading and Immune Complex Rearrangement in Membranous Nephropathy

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Introduction: We present a rare case of ANA and anti-dsDNA negative, anti-GBM positive lupus nephritis (LN) patient with two biopsies demonstrating LN Class III+V with possible immune complex (IC) rearrangement and/or epitope spreading (ES).

Case Description: A 62-year-old white male who presented with a year-long history of purpuric rash and hematuria. His hospital admission laboratory data is detailed in Table 1. The first renal biopsy showed crescents in 2/4 glomeruli with mild (+) granular and segmentally linear deposits by immunofluorescence (IF). The patient received cyclophosphamide, corticosteroids and one session of therapeutic plasma exchange due to rapidly worsening renal function and an initial presumptive diagnosis of anti-GBM disease. The second biopsy demonstrated no crescents but features of combined class III + V LN with IF findings suggestive of a full-house pattern with a change in the deposits from segmentally linear to pure granular. He began therapy with mycophenolate mofetil and prednisone resulting in a decrease in his UPCR from 2.3 to 0.3 mg/mg (complete remission) over the next four months and significant improvement in renal function.

Discussion: A link has been reported between anti-GBM histopathology and membranous nephropathy. Evidence suggests IC rearrangement and/or ES as possible explanations. ES refers to the molecular conformational changes of secondary, non-dominant epitopes leading to propagation of autoimmunity. Circulating anti-GBM antibodies may continually stimulate the upregulation and alteration of anti-GBM epitopes leading to the development of granular deposits and membranous nephropathy. We believe our case suggests this possible pathogenic mechanism. More research is needed to improve understanding of the sequential change observed on immunofluorescence microscopy.

Laboratory Data

Laboratory Test	Result	Units	Reference Interval
White Blood Count	8.3	x10 3/mL	4.0-10.5
Hemoglobin	12.8	g/dL	14.0-18.0
Platelets	342	x10 3/mL	140-415
Creatinine	2.35	mg/dL	0.7-1.3
Complement - C3	39	mg/dL	88-201
Complement - C4	2	mg/dL	15-45
Anti-Neutrophil Antibody (ANA)	1:20		Titer < 1:40 (negative)
Double Stranded DNA Antibody (dsDNA Ab)	3.0	IU/mL	<30.0
Anti-Glomerular Basement Membrane (anti-GBM)	63	AU/mL	0-19
Urine Protein-to-Creatinine Ratio (UPCR)	2.3	mg/mg	<0.2

PO1471

Generation of Anti-THSD7A Antibodies Using a Human Antibody Phage Display Library

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Background: Membranous nephropathy (MN) is an antibody-mediated autoimmune renal disease. In the majority of cases, autoantibodies target podocyte membrane proteins such as PLA2R1 and THSD7A. We could previously demonstrate that autoantibodies in THSD7A-associated MN cause disease and recognize several extracellular domains of the target antigen. However, it remains unclear how this antibody polyreactivity relates to disease pathogenicity. The aim of this study was the generation of anti-THSD7A antibodies using a human antibody phage display library for further diagnostic and pathomechanistic studies.

Methods: In the antibody phage display technology, antibody fragments are displayed on the phage particle and the corresponding gene fragment encoding the antibody fragment is packaged in the phage particle. A selection process called panning enables the selection of antibody fragments against virtually any target structure *in vitro*. In this project, a naïve antibody gene library was used to select binders to the extracellular part of human and mouse THSD7A. Binders were sequenced, cloned into scFv-Fc format - an IgG like format - and produced in HEK293 cells. Binding of scFv-Fc to human and mouse THSD7A was investigated using Western blot, ELISA and indirect immunofluorescence testing (IFT). Epitope regions were mapped using an ELISA.

Results: Four binders (SAK79-B1, SAK78-C12, SAK78-E6, SAK78-F8) could be obtained. While SAK78-F8 exclusively bound human THSD7A, the other binders reacted with both human and murine THSD7A in Western blot, ELISA and IFT. A domain-specific ELISA revealed binding of SAK78-C12, SAK78-E6 and SAK78-F8 to the regions d8_d9, d1_d2 and d6_d7, respectively. SAK79-B1 did not react with any domain combination, but showed strong binding to murine and human d1_d21. We suspect a conformational epitope that is not conserved in the coated domain fragments. SAK78-C12 and SAK78-E6 were succesfully cloned into human IgG subclass backbones IgG 1-4.

Conclusions: Antibody phage display represents a powerful method to generate recombinant antibodies. The antibodies selected in our study show different binding characteristics *in vitro*. *In vivo* binding characteristics, pathogenicity and potential as a diagnostic tool, e.g. to stain THSD7A in patient biopsies, need to be determined.

Funding: Government Support - Non-U.S.

PO1472

A Comparison of aPLA2Rab Assays on Treatment with Cyclophosphamide and Steroids

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Background: Anti-PLA2r antibodies (aPLA2r) are present in ~75% of patients with primary membranous nephropathy (MN). A qualitative immunofluorescence test (IIFT) allows accurate detection of aPLA2r, additionally ELISA and ChLIA provide quantitative analysis. Sensitivity of the two latter methods after start of immunosuppressive therapy is not well studied.

Methods: We retrieved stored samples of patients with aPLA2R associated MN, who were treated with cyclophosphamide and steroids(CP), collected at baseline and 8 weeks after start of therapy. Assays were performed by the EUROIMMUN researchlab, Lübeck, Germany. All samples were analysed by IIFT, ELISA and ChLIA. We categorized ELISA results to cut-off values used in literature: 2, 14, and 20 RU/ml resp.

Results: We included baseline samples of 50, and 8 week samples of 51 patients. At baseline, all patients tested IIFT positive; ELISA test was positive in 94% or 98% of samples using cut-off values of 20 RU/ml or 14 RU/ml resp., indicating high sensitivity. Agreement between IIFT and ChLIA was 100%. After 8 weeks on CP, 37/51 patients had immunological remission by IIFT. ELISA test results are given in Table1. In the IIFT positive samples collected after 8 weeks, ELISA titers were < 20RU/ml or < 14 RU/ml in 9/14 and 5/14 patients respectively, suggesting lower sensitivity. All IIFT negative samples had ELISA titers < 14 RU/ml. When analysing IIFT negative patients with ELISA titer <2 U/mL (N=23) vs. 2-14 U/mL (N=14), persistent immunological and clinical remission was better in the first group (74% vs 58%), however not statistically different. With ChLIA only 4/51 (8%) had different results (2 IIFT+/ChLIA-, 2 IIFT-/ChLIA+); resulting in a sensitivity of 86% and a specificity of 95%, when compared to IIFT.

Conclusions: Using immunological remission as treatment target, as described here after 8 weeks of CP, requires evaluation of the applied assay for this purpose. Of the examined quantitative methods, ChLIA demonstrated the highest agreement with IIFT. ELISA titers below the recommended cut-off for initial diagnosis still show a tendency towards the clinical outcome, which could be investigated by further studies.

Funding: Commercial Support - EUROIMMUN researchlab, Lübeck, Germany

	ELISA titer	<2	2-14	14-20	>20	Sum
Baseline samples (total 50)	IIFT + / ChLIA +	0	1	2	47	50
8 weeks sample (total 51)	IIFT + / ChLIA +	0	3	4	5	12
	IIFT + / ChLIA -	0	2	0	0	2
	IIFT - / ChLIA +	0	2	0	0	2
	IIFT -/ ChLIA -	23	12	0	0	35

PO1473

The Classical Pathway Triggers Pathogenic Complement Activation in Membranous Nephropathy

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Background: Membranous nephropathy (MN) is characterized by severe proteinuria, circulating autoantibodies against podocyte antigens such as PLA2R1 and THSD7A, and glomerular deposition of IgG and complement components (CCs). However, the pathways triggering the complement cascade (classical, alternative or lectin) and the significance of local glomerular complement action for podocyte damage and proteinuria are poorly understood.

Methods: Complement activation was investigated in 20 biopsies from patients with PLA2R1- and THSD7A-associated MN using immunofluorescence and proximity ligation assays to visualize the assembly of CCs/convertases. Experimental autoimmune MN (EAMN) was established in 12-week-old BALB/c mice by immunization with THSD7A. Anti-THSD7A antibodies, proteinuria, serum parameters, and histological signs of MN were analyzed. The role of the complement system was studied by induction of EAMN in *C3*$^{-/-}$ mice. The efficacy of complement-targeted treatment was evaluated by weekly injection of a C3-silencing siRNA after the onset of proteinuria.

Results: The assembly of the classical/lectin convertase was identified in 19/20 MN biopsies, which was accompanied by detection of IgG and C1q in the majority of cases. The alternative convertase and MBL deposits were detected in fewer cases. Upon immunization, mice developed clinical and histopathological features of MN. Proteinuria ranged from mild to severe nephrotic syndrome and histopathological features included granular glomerular deposition of IgG and CCs including C1q and C3 as well as loss of the integral podocyte proteins neph1 and nephrin. Strikingly, severe disease with ascites was prevented in *C3*$^{-/-}$ mice and overall proteinuria was reduced in comparison to WT littermates. Finally, treatment with C3-silencing siRNA after the onset of proteinuria attenuated disease.

Conclusions: The complement system is dominantly activated via the classical pathway in MN patients. Experimental data in the first autoimmune model involving an antigen that is pathogenically relevant in patients suggest complement-targeted treatment as a promising strategy for MN patients with severe disease, but also hint at a role of complement-independent mechanisms in the pathogenesis of MN.

Funding: Government Support - Non-U.S.

PO1474

Positive PLA2R Detection by Mass Spectrometry but Negative PLA2R Staining on Immunofluorescence Microscopy

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Background: Detection of PLA2R along the glomerular basement membranes by immunofluorescence (IF) studies using antibodies directed against PLA2R is considered the gold standard for diagnosis of PLA2R-positive MN on the kidney biopsy. Laser microdissection of glomeruli followed by mass spectrometry (MS) of PLA2R-positive MN also detects high total spectral counts of PLA2R confirming the IF studies. However, correlation of PLA2R-negative MN cases by both IF and MS has not been done.

Methods: We performed laser microdissection and mass spectrometry in 230 cases PLA2R-negative MN in search of novel proteins that may represent new target antigens in PLA2R-negative MN. All 230 cases were negative for PLA2R by IF staining.

Results: We detected high total spectral counts of PLA2R in 8 (3.5%) of the 230 PLA2R-negative MN cases by IF. The mean total spectral count of PLA2R in the 8 cases was 57 (range 24 to 83, SD ± 25.0) (Figure 1). This is comparable to the mean total spectral counts in PLA2R-positive MN (57.7 ± 23.7). The baseline mean total spectral count of PLA2R in 6 time zero transplant biopsies (control cases) was 6. Interestingly, all subtypes of IgG were present in the 8 cases that were postivie for PLA2R by MS with IgG1 being the dominant (total spectral count 57 ± 16.9) followed by IgG3 (50.0 ± 11.5), IgG4 (46.3 ± 18.1) and IgG2 (39.3 ± 11.4). On kidney biopsy, 3 of the 8 cases showed findings for secondary autoimmune MN such as C1q positivity or full house Ig staining. Electron microscopy showed stage I MN in 2 cases, stage II MN in 5 cases and stage III in 1 case. Clinical details at presentation were as follows: 3 females and 5 males, mean age 53.6 years (± 20.7), mean serum creatinine 1.38 mg/dL (± 0.6), and mean proteinuria 6.8 gms/24 hours (± 6.2).

Conclusions: IF is negative for PLA2R-staining in a small (3.5%) number of PLA2R-postive MN. These cases can be detected by MS. Thus, MS is an alternative to IF staining and the new gold standard to detect PLA2R on the kidney biopsy.

MS studies showing high total spectral counts of PLA2R in 8 cases that were PLA2R-negative by IF. Baseline mean levels of PLA2R in 6 controls (Ctrls) are shown in first column.

PO1475

Can the Use of the Serum Anti-PLA2R Antibody Negate the Need for a Renal Biopsy in Primary Membranous Nephropathy?

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Background: Since the emergence of the anti-PLA_2R antibody test, nephrology practice has not changed dramatically, and most nephrologists are still relying on performing a kidney biopsy in diagnosing membranous nephropathy. In this study, we sought to examine how anti-PLA_2R antibody tests using ELISA can be utilized in clinical practice.

Methods: We have conducted a retrospective analysis for 187 patients between 2003 and 2020 correlating their renal biopsy findings with their anti-PLA_2R antibody test when performed. We have recorded all patient's demography, urine protein creatinine ratios, serum albumin, and treatment commenced whether using RAS blockade or immunosuppression treatment. Using a statistical analysis model, we have calculated the positive and negative predictive values of the anti-PLA_2R ab test carried out during that period.

Results: The mean levels of anti-PLA2R antibody titer in primary membranous nephropathy were 217 RU/ml, whereas the mean level was only 3 RU/ml for both secondary membranous nephropathy and other diagnoses. The majority of our cohort who had a positive anti-PLA_2R antibody test had a confirmed renal biopsy diagnosis of primary membranous nephropathy with a PPV of 97.3%. Also, we found that the test sensitivity was 75.5%. On the other hand, we found that the NPV was 79.8% and the specificity was 97.8% at a level of >20 RU/ml

Conclusions: The anti-PLA_2R antibody test is a highly specific test for diagnosing membranous nephropathy. Experience from our center supported by some evidence from the literature suggests that we can rely solely on a positive test without the need to perform a renal biopsy. More prospective trials are required to further validate that notion.

Funding: Private Foundation Support

PO1476

Complement Activation and Suppression Profile Reveals Distinct Subtypes in C3 Glomerulonephritis

Nicholas J. Steers, Kelsey O. Stevens, Judy Liang, Anna Mo, Debanjana Chatterjee, Jason Zheng, Iman Ghavami, Rafael Gras, Maria M. Morban, Xueru Mu, Stacy E. Piva, Vanna M. Nicasio, Maddalena Marasa, Andrew S. Bomback, Pietro A. Canetta, Jai Radhakrishnan, Gerald B. Appel, Ali G. Gharavi. *Columbia University Irving Medical Center, New York, NY.*

Background: The complement pathway is an innate immune defense mechanism, and uncontrolled activation can cause damage to host tissues including the kidney. C3GN is characterized by deposits in the glomerulus made up entirely of complement C3 protein without the presence of immunoglobulins.

Methods: The activity of the alternative complement pathway (ACP) was determined in serum derived from C3GN patients, IgA Nephropathy (IgAN) and Polycystic Kidney Disease (PKD) and heathy controls (HC) by measuring the lysis of rabbit red blood cells (rRBC). Complement factor H (CFH) was added to the serum of C3GN patients to establish if CFH is capable of inhibiting the ACP in C3GN.

Results: Analysis of the ACP using the serum of C3GN, IgAN, PKD patients and healthy controls can be calculated by the lysis of rRBC. The percent lysis at specified time points (5, 10 and 15 minutes) was calculated using the maximal lysis for each sample. Serum from C3GN patients result in more significant lysis (one way ANOVA $P < 0.01$) at 5 and 10 minutes (22.9% ± 11% and 42.7% ± 12%, respectively) compared to HC (7.1% ± 3% and 21.7% ± 6%, respectively), IgAN (10.9% ± 7% and 27.3% ± 15%, respectively) and PKD (8.6% ± 6% and 24.4% ± 12%, respectively). However, at 15 minutes, there were no significant differences in the lysis of the rRBC between these groups, suggesting that the ACP is more rapidly activated in C3GN patients, leading to faster depletion of C3. Addition of CFH to the serum of C3GN patients reduced the ACP activity to control levels in 6 out of 14 patients. We did not detect CFH specific antibodies in the serum of patients who did not respond to CFH, indicating additional mechanisms are involved with the rapid activation of the ACP in C3GN.

Conclusions: The ACP is rapidly activated by the serum of C3GN patients compared to other kidney diseases and HC. Although the addition of CFH to the serum reduced the ACP activation comparable to controls in 42% of C3GN patients, not all the serum samples responded to CFH. Future work may elucidate additional mechanisms of the continued ACP activation in C3GN patients and have implications for therapy of these patients.

PO1477

Preexisting Autoimmune Dysregulation Unmasks a Role for Silica Dust Exposure in Nephrotropic Autoantibody Production

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Background: Pathogenic autoantibodies (autoAb) promote severe glomerulonephritis in ANCA vasculitis and lupus. Genetic susceptibility and environmental exposures, particularly inhalation of silica (Si) dust, are implicated in dysregulated autoimmunity and are targets for therapeutic intervention. Using a mouse reporter system expressing a regulated nephrotropic autoAb transgene (Tg) targeting basement membrane (BM) and instilling Si by oropharyngeal aspiration (OPA), we demonstrated that central B cell tolerance and anergy to BM are preserved in multiple lupus strains despite induction of lung inflammation and ectopic lymphoid tissue. Nonetheless, Si exposure increased local and systemic anti-DNA Ig levels in wildtype (WT) B6 and lupus mice, suggesting subversion of alternative regulatory checkpoints. Herein we leverage the aberrant M7 anti-BM Tg lineage that demonstrates partial escape from tolerance and evidence of glomerular Ig deposition to study the interaction of Si exposure with preexisting defects in autoreactive cell regulation.

Methods: M7 Tg mice (WT at Ig light chain, or LC, locus) were exposed to Si or vehicle (V) by OPA, organs harvested at 5-6 weeks, and cells cultured ±Toll-like receptor ligand (TLR-L). To restrict Ig specificity, a subset of mice (Tg/KI) was bred to heterozygosity for the Vk8/Jk5 V8R Ig LC knock-in. Tg autoAb were measured by ELISA; mean OD±SD.

Results: Presence of serum Tg autoAb and induction of high levels of autoAb by TLR-L-stimulated splenocytes (OD 2.612±0.49, TLR7/9, vs 0.063±0.03, medium, $p<0.0001$) confirmed Tg phenotype, and bronchoalveolar lavage fluid cell counts confirmed exposure (237.1±130 vs 1.8±1.7, x1000, Si vs V, $p<0.05$). Among Tg/WT mice, more autoAb were produced by TLR7/9-stimulated lung cells from Si vs V exposed mice (OD 0.131±0.15, Si, vs 0.032±0.01, V, $p<0.05$), indicating that Tg B cells recruited by Si exposure contribute to local autoAb production. Among Si-exposed mice, Tg autoAb levels were higher in Tg/W vs Tg/KI mice: OD 1.239±0.47 for TLR4-L stimulated splenocytes, Tg/W, vs 0.515±0.13, Tg/KI, $p<0.05$.

Conclusions: An autoAb reporter system reveals that anti-BM autoreactive lymphocytes that escape tolerance can be recruited to the lung after exposure to inhaled silica dust. Anti-BM cell activation by superimposed stimuli, such as TLR-L, can lead to secretion of nephrotropic autoAb.

Funding: Other NIH Support - NIEHS, Veterans Affairs Support

PO1478

Characteristics of Membranous Nephropathy Patients with IgG and IgA Co-Deposits on Capillary Wall

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Background: Membranous nephropathy (MN) is characterized by immune deposits on glomerular capillary wall, predominantly IgG. There have been several reports of MN combined with IgA nephropathy with features of IgA immunofluorescence staining in the glomerular mesangium. However, we found that IgA can also be deposited on the capillary wall with IgG. This study aimed to investigate the prognostic, clinical and renal histopathological characteristics of adult MN patients with IgG and IgA co-deposits on capillary wall.

Methods: A retrospective study was conducted in biopsy-proven MN patients of our renal department during January, 2007 to May, 2020. Clinical data were collected at time of biopsy and the latest followed-up. Pathological parameters included immunofluorescence staining, pla2r staining, membranous Churg's stages, sclerosis, crescent, focal segmental sclerosis lesion, chronic tubulointerstitial injury and et al. Indirect immunofluorescence experiment was conducted in 293T cells transfected with pla2r plasmid.

Results: Out of 531 cases diagnosed with MN, 53 patients have moderate IgA deposit on capillary walls with IgG. 19 cases were determined to be secondary MN, which were 10 cases of autoimmune disease, 4 cases of Hepatitis B, 3 cases of kidney transplation, 1 case of chemical explosure and 1 case of AL amyloidosis-associated secondary MN. 31 Idiopathic MN patients with both IgA and IgG depositing along capillary wall were followed up for a median interval of 49months (interquartile-range, 17-82) and 3 withdrew. 3 (9.8%) patients progressed to ESKD or death, 2 (6.5%) patients had their eGFR declined by half, 11 (35.5%) patients had no remission and 15 (53.6%) patients underwent immunosuppressive therapy. 72.4% idiopathic MN patients with IgA deposit were pla2r associated. Indirect immunofluorescence study revealed that both IgG and IgA isoform of anti-pla2r autoantibody in MN patients' serum.

Conclusions: IgA and IgG could be co-depositing along glomerular capillary wall in MN patients, secondary causes should be screened with cation. IgA and IgG type of autoantibodies linked to MN co-existed in serum of idiopathic MN patients, whose prognosis might be poor.

PO1479

Humanistic Burden of Rare Kidney Diseases; Understanding the Impact of FSGS and IgAN on Patients and Caregivers: The HONUS Rationale and Study Design

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Background: While both Immunoglobulin A Nephropathy (IgAN) and Focal Segmental Glomerulosclerosis (FSGS) conditions have been shown to be associated with significant clinical and economic burden to healthcare systems, less is known about the humanistic burden associated with these diseases. Here we describe the **H**umanistic Burden **o**f Rare Kid**N**ey Diseases: **U**nderstanding the Impact of FSGS and IgAN on Patients and Caregivers **S**tudy (HONUS), which aims to elucidate the impact of these conditions.

Methods: HONUS is being designed in consultation with patient and clinical community members as a multi-national, cross-sectional survey recruiting adult patients, caregivers (care-partners) and parents/care-partners of youth with FSGS or IgAN. Participants complete a comprehensive survey covering demographic and clinical information, health-related quality of life (HRQoL), and the impact these diseases have on education, career, employment, relationships, mental wellbeing, personal finances, lifestyle, and fear and uncertainty for the future.

Results: Humanistic burden considers the impact of illness on patient HRQoL, activities of daily living, caregiver health and HRQoL, and is commonly quantified in population health context as Disability- or Quality-Adjusted Life Years (DALYS or QALYS). Quantifying humanistic burden is foundational for value assessment of new therapeutic options, but also has broader benefits. For patients and care-partners, insights can validate and support individual experiences and coping. For patient advocacy groups, information can be used to raise awareness, facilitate education and develop resources for affected families. For the clinical community, evidence supports patient/family communication, education of the broader clinical community and contributes to informed decision making. For industry, data supports value assessments and ensures the patient and care-partner voice is heard. This begins with engagement of patient and clinical community members at inception of study design, ensuring the right elements are included in the study, the design fits with the evidence generation goal, and results are disseminated in a comprehensive and useful way.

Conclusions: HONUS will provide evidence quantifying the humanistic burden of FSGS and IgAN from patient and care-partner perspectives.

Funding: Commercial Support - Travere Therapeutics

PO1480

Mystery Cryoglobulinemic Glomerulonephritis Treated with Rituximab

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Introduction: Cryoglobulinemic Glomerulonephritis (GN) is characterized by the deposition of immunoglobulins (IG), also known as cryoglobulins (CG), in the kidney. We report a case of idiopathic mixed cryoglobulinemic GN treated with rituximab and prednisone.

Case Description: A 42-year-old tri-athlete with a history of pediatric meningitis with hydrocephalus requiring placement of a ventriculoperitoneal shunt presented with lower extremity swelling limiting his ability to exercise. He denied non-steroidal anti-inflammatory drug and illicit drug use, and was not on any prescribed medications. Laboratory workup showed serum creatinine: 1.2 mg/dL (normal 0.7 – 1.2), serum albumin: 2.1 mg/dL (normal 3.9 – 4.9), CG: 140 μg/mL (normal 0 – 50), C3: 39 mg/dL (normal 86 – 166), C4: 7 (normal 13 - 46), and a urine protein to creatinine ratio (UPCR) 5.9 g/g. Kidney biopsy showed diffuse proliferative GN with polyclonal IgM deposits consistent with mixed cryoglobulinemic GN (figure 1). An infectious workup, including human immunodeficiency virus (HIV), viral hepatitis, blood and urine culture, and a lumbar puncture were unremarkable. Computed tomography of the chest, abdomen, and pelvis revealed splenomegaly. Echocardiogram and bone marrow biopsy were non-diagnostic. He was treated with rituximab and prednisone with normalization of CG, C3, and C4, a reduction in UPCR to 0.5 g/g and return to full exercise capacity five months later.

Discussion: Mixed cryoglobulinemic GN is a rare disorder caused by polyclonal deposition of IG in the kidney. Autoimmune disease, hematological malignancies, and infectious etiologies such as endocarditis, HIV, and viral hepatitis should be ruled out prior to immunosuppressive therapy. Our patient elected to proceed with treatment due to his poor quality of life and evidence of end-organ involvement. Although workup for hematological malignancies was unremarkable, it is unclear if his splenomegaly could be reflective of an underlying indolent lymphoma, which could have simultaneously responded to rituximab treatment.

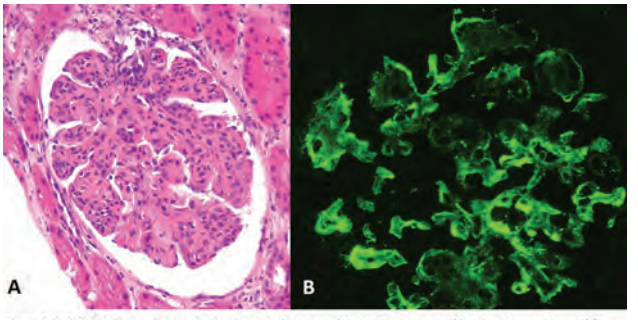

Figure 1. A: H & E stain showing lobular hypercellularity suggestive for membranoproliferative glomerulonephritis, B: Immunofluorescence showing polyclonal IgM kappa and lambda staining.

PO1481

Does SARS-CoV-2 Activate the Alternative Complement Pathway? A Case Report of C3-Dominant Proliferative GN in a Patient with SARS-CoV-2 Infection

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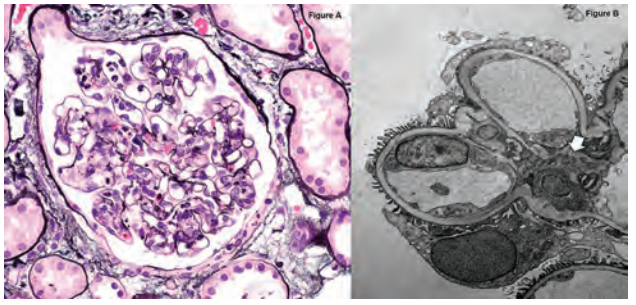
Introduction: C3-glomerulopathy is a rare kidney disorder due to dysregulation of the alternative complement pathway. C3 glomerulonephritis (C3GN) has been associated with a variety of diseases including connective tissue disorders and infections. Here we present the first case report of C3GN in a patient with SARS-CoV-2 infection.

Case Description: A 54-year-old man with no known renal disease presented to the hospital with fever, cough, dyspnea and worsening edema. His SARS-CoV2 PCR test was positive and he was treated for COVID-19 pneumonia. His blood cultures remained negative and no bacterial infection was identified. He was also noted to have worsening renal function with a peak serum creatinine of 3.9 mg/dL. His serologies including Hep B, Hep C, HIV, ANA, ANCA, RF, and Cryoglobulins were all negative. His serum complement levels were low. A renal biopsy was performed. Light microscopy showed mild mesangial and endocapillary hypercellularity (Figure A). IF revealed mesangial and endocapillary wall staining positive for C3. Electron microscopy confirmed electron dense deposits of C3 (Figure B).

Discussion: Several mechanisms have been suggested in the pathogenesis of SARS-CoV-2 related tissue injury including classical and alternate compliment pathways. C3GN is rare renal disorder due to dysregulation of alternate complement pathway. C3GN is characterized by mesangial deposits, endocapillary hypercellularity under light microscopy, and C3 deposits in mesangial and endocapillary wall on IF, in the absence of other significant findings. We present the first case report of C3GN in a patient with SARS- CoV-2 infection. Although this case does not establish a cause-effect relationship, but does raise the possibility of activation of the alternative complement pathway in SARS-COV-2 infection.



Light microscopy showed mild mesangial and endocapillary hypercellularity (Figure A). Electron microscopy confirmed electron dense deposits of C3 (Figure B).

PO1482

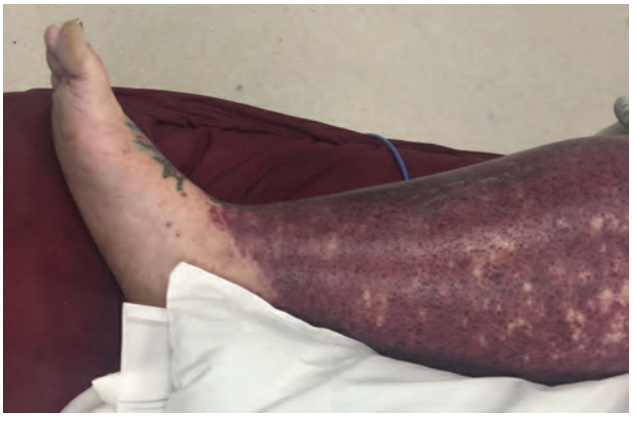
Vancomycin-Induced Thrombotic Microangiopathy: A Rare Association

Gaurav Rajashekar, Anuja Java. Washington University in St. Louis *Washington University in St Louis, St Louis, MO.*

Introduction: Thrombotic microangiopathies (TMAs) are life-threatening conditions characterized by hemolytic anemia, thrombocytopenia and AKI. Drug-induced TMA (DITMA) is a diagnostic challenge because specific tests to identify a drug etiology are not available.

Case Description: A 40 yr-old female with history of neurofibromatosis type 2 underwent resection of a T10-11 schwannoma. The surgery was complicated by wound dehiscence which was treated with incision and drainage followed by intravenous vancomycin and cefazolin. The next day, she developed fever, altered mental status and a diffuse purpuric rash (Fig 1). Labs showed anemia (Hgb, 6.2 g/dl), thrombocytopenia (PLT, 15 k/µl), elevated LDH and anuric AKI requiring dialysis. C3 and C4 were low. Coombs test was negative. She subsequently developed disseminated intravascular coagulation and elevated liver enzymes. Skin biopsy revealed a leukocytoclastic vasculitis with IgG and complement deposition within vessel walls. Given the concern for DITMA versus thrombotic thrombocytopenic purpura, vancomycin was discontinued. Treatment with prednisone and plasmapheresis was initiated which led to improvement of renal function, mental status and hematologic parameters within 48 hrs. Renal biopsy confirmed TMA. ADAMTS-13 activity and complement genetic testing came back normal. Unfortunately, later during the hospitalization, she developed acute respiratory failure leading to cardiac arrest.

Discussion: This is a rare case of vancomycin-induced TMA. We speculate the mechanism is immune-mediated given the presence of low complement levels (although we did not test for vancomycin-dependent antibodies). Patients with immune-mediated DITMA present with sudden onset of severe systemic symptoms after a short exposure to the implicated drug. Greater awareness with improved methodology for diagnosis of DITMA is critical for clinicians evaluating such patients. Recognition of DITMA and documentation of the drug etiology are essential for patient safety.



Diffuse purpuric rash

PO1483

Post-Transplant Thrombotic Microangiopathy due to a Pathogenic Mutation in Complement Factor I

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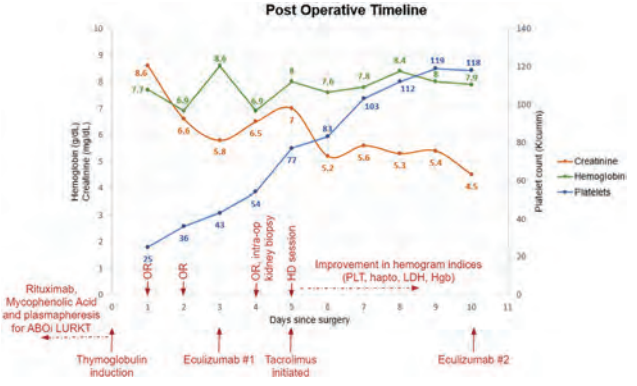
Introduction: Thrombotic microangiopathy (TMA) is characterized by hemolytic anemia, thrombocytopenia, and AKI. Atypical hemolytic uremic syndrome (aHUS) is a classic complement-mediated TMA that occurs when genetic variants in complement proteins result in a dysregulated complement system. Genetic variants in complement Factor I (*CFI*) have been reported in 5–15% of patients with aHUS.

Case Description: 28-year-old African American man with ESKD secondary to biopsy-proven PLA2R-positive membranous nephropathy underwent a 2/2/1 mismatch ABO incompatible living-unrelated kidney transplantation. Induction immunosuppression included methylprednisolone and Thymoglobulin. Post-op course was complicated by bleeding and he was taken back to the OR on POD 1. Labs showed anemia (Hgb 7.7 g/dL), thrombocytopenia (PLT 25 k/µl), low haptoglobin (< 10 mg/dL), high LDH (580 Units/L), low C3 and normal C4. ADAMTS-13 activity and coagulation profile were normal. Graft function was delayed. This raised concern for a TMA. Tacrolimus was not initiated. Allograft biopsy performed on POD 4 confirmed the diagnosis. Eculizumab was administered, resulting in resolution of thrombocytopenia and hemolysis, and gradual renal recovery. Genetic testing for complement revealed a 'variant of uncertain significance' in *CFI* (Iso357Met). This variant is located in the serine protease domain of Factor I which contains the catalytic site. Functional analysis of the variant using recombinant proteins revealed that it had defective complement regulatory activity. This work established that the *CFI* variant was deleterious and thus defined the etiopathogenesis of TMA in the patient.

Discussion: This is a case of de novo post-transplant aHUS due to a pathogenic complement mutation, likely triggered by transplant surgery. Our strategy of recombinant protein production followed by detailed functional assessment defined the functional repertoire of the variant protein and provided critical guidance relative to the underlying pathophysiology and appropriate therapeutic regimen.



PO1484

Cryoglobulinemic Vasculitis in a Patient with Known Thrombotic Microangiopathy

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Introduction: Acute kidney injury (AKI) is a ubiquitous presentation, but thrombotic microangiopathy (TMA) and cryoglobulinemia are uncommon causes that are not easily diagnosed. We highlight a case of AKI that was found to be cryoglobulinemic vasculitis, an unexpected diagnosis in a patient with history of TMA.

Case Description: A 68-year-old female was diagnosed with giant cell arteritis, with temporal artery biopsy showing inflammation of the adventitia consistent with small vessel vasculitis. She received prednisone and tocilizumab. 6 months later, she was admitted for hypertensive crisis with thrombocytopenia and schistocytes, with creatinine (Cr) elevation to 3.5 from baseline of 1.0. Renal biopsy showed TMA. Tocilizumab was discontinued. She was transitioned to eculizumab, eventually resulting in renal recovery (Cr 1.5) after 1.5 months. However, she continued to feel poorly and returned to the hospital, where she was found to have Cr 4.0. Physical exam was significant for hypertension and tender retiform purpura. Urine studies were consistent with cellular casts. Dermal biopsy showed dermal necrosis but no intravascular thrombi. Renal biopsy ultimately revealed cryoglobulin deposition, resulting in a diagnosis of cryoglobulinemic vasculitis. She was treated with prednisone, rituximab, and cyclophosphamide with good renal response, and discharged with Cr 2.4.

Discussion: The finding of cryoglobulin on this patient's renal biopsy was subtle, causing a near-miss in her diagnosis. Her history and repeat clinical evidence of TMA further confounded her presentation. Therefore, when TMA is on the differential, workup should also evaluate for cryoglobulinemia. Her prior diagnosis of GCA also acted as a confounder, though absence of panarteritis and large vessel involvement on temporal artery biopsy may have hinted at underlying systemic vasculitis. While eculizumab is a standard therapy for TMA, there is limited evidence for its use in treating cryoglobulinemic vasculitis. This patient's positive renal response to eculizumab supports the potential role of complement inhibitors in treating cryoglobulinemia. It remains possible that the patient could have had TMA and cryoglobulinemia concurrently, with renal biopsy during this presentation only capturing the latter. Therefore, further research into the role of complement inhibitors for cryoglobulinemia is needed.

PO1485

Minimal Change Disease as a Novel Manifestation of Cytomegalovirus

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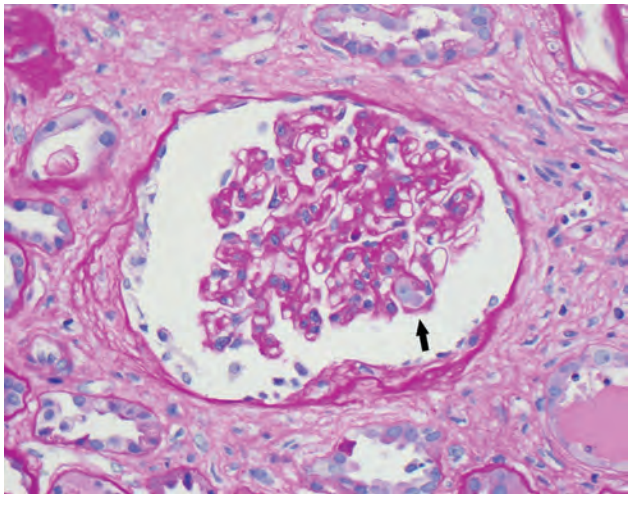
Introduction: Cytomegalovirus (CMV) infection is typically asymptomatic among the immunocompetent or can cause a mononucleosis. Among immunosuppressed patients common presentations are colitis, hepatitis, encephalitis, retinitis and even Guillian-Barre syndrome. This case is a rare disseminated presentation of CMV manifesting as acute glomerulopathy.

Case Description: A 67 year-old female with past medical history of lupus, rheumatoid arthritis, and Sjogrens syndrome on maintenance steroids presented with a prolonged cough, joint swelling, shortness of breath and rash consistent with livedo reticularis. She developed worsening weakness in the arms and legs. High dose IV steroids were initiated for presumed rheumatoid vasculitis. Nephrology was consulted for worsening renal function with urine protein to creatinine ratio of 42 g, later requiring hemodialysis for volume management. Work up for nephrotic range proteinuria including hepatitis B/C, HIV, SPEP, UPEP, and complement screen was unrevealing. Renal ultrasound demonstrated an 11.7 cm right kidney and 14 cm left kidney. Renal biopsy demonstrated diffuse podocyte effacement and large atypical mononuclear cells within the glomerulus. No immune deposits seen on electron microscopy. Immunohistochemical staining confirmed glomerular CMV. Six weeks after starting treatment with ganciclovir and tapering steroids, CMV viral load was undetectable and renal function recovered to baseline.

Discussion: CMV involvement of the kidney is unusual aside from tubulointerstitial nephritis. Rare cases of collapsing glomerulopathy and focal segmental glomerular sclerosis are found in literature. We report a novel presentation of CMV glomerulopathy with minimal change disease and renal failure. To prevent tissue invasive CMV in a chronically immune suppressed patient one needs to maintain clinical suspicion for infectious pathogens and perform tissue biopsy.



PAS of glomerulus showing giant cell

PO1486

Minimal Change Disease Following the mRNA-1237 Vaccine in a Kidney Transplant Recipient

Juanly N. Rodriguez, Shobana Sivan, Mariella O. Goggins. *University of Miami School of Medicine, Miami, FL.*

Introduction: Kidney transplant recipients (KTR) are susceptible to post-transplant glomerulopathies. Minimal change disease (MCD) seen rarely. Few cases have been reported post-immunization, recently with the Pfizer-BioNTech vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report a case of *de novo* MCD after mRNA-1273 vaccine in a deceased donor KTR, with sudden onset nephrotic syndrome (NS) and acute kidney injury (AKI) a week after the first dose.

Case Description: 45-yo woman with history of ESKD from lupus nephritis, underwent DDKT on 09/2019 from a 20-yo Caucasian male, kidney donor profile index 16%, calculated panel reactive antibody 0%. Complicated by delayed graft function. On day 27 post-transplantation serum creatinine (Scr) improved to 0.8 mg/dl. Maintenance immunosuppression tacrolimus and mycophenolic acid. 11 months post-KT contracted COVID-19 pneumonia, managed conservatively. 6 months later developed anasarca 4 days post-mRNA-1273 vaccine. Initial Scr 2.10 mg/dl, urine analysis 4 + protein / 2 RBCs, urine protein to creatinine ratio (UPCR) 9.6 g/g, albumin 2.1 g/dl consistent with NS. SARS-CoV-2 PCR negative. Positive IgG antibody, titer 3.87 s/co (0-0.99), tacrolimus 4.7 ng/ml. Normal C3/C4 levels, anti-DNA antibody 5 IU/m. Allograft biopsy showed mild tubulitis and interstitial nephritis on light microscopy (LM), immunofluorescence negative for C4d, electron microscopy with moderate foot process effacement and no electron dense deposits, suspicious for MCD. Prednisone 1mg/kg/day was started. 4 weeks later UPCR 1.12 g/g, Scr 0.8 mg/dl and albumin 3.3 g/dl.

Discussion: This is a seropositive SARS-CoV-2 KTR from previous COVID-19 pneumonia who developed NS and AKI following the mRNA-1273 vaccine. Biopsy consisted with MCD. Immunogenicity to mRNA vaccines in transplant recipients is blunted after the first dose but higher in seropositive patients. Timing from vaccine exposure to development of MCD ranges from days to months, our patient mounted an immune response in 4 days. The acute tubular injury seen in LM is atypical, unclear if this is a cell mediated process from allograft rejection or part of the pathogenesis post-immunization. In cases of AKI with NS, days to weeks following either class of mRNA vaccine a prompt initiation of steroids and further investigation with kidney biopsy is warranted.

PO1487

COVID-19-Associated Collapsing Focal Segmental Glomerulosclerosis During Pregnancy in a Woman with Lupus Nephritis

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Introduction: Lupus nephritis (LN) is a common clinical entity in patients with systemic lupus erythematosus (SLE). LN is classified on the basis of renal biopsy findings. We present a woman with a history of LN who was diagnosed with COVID and AKI during pregnancy. Kidney biopsy showed collapsing FSGS and class V LN with APOL1 gene mutation.

Case Description: A 32-year-old G4P0212 African American female presented to a multidisciplinary Nephrology Maternal-Fetal Medicine program at 12 weeks gestation for management of LN in pregnancy. She was diagnosed with SLE at age 8, previously treated with rituximab and belimumab for rash, and other extrarenal manifestations. Three years prior, she was diagnosed with LN Class 3 + Class V treated with MMF with partial remission. She was switched from MMF to azathioprine at pregnancy diagnosis. She was diagnosed with COVID 4 days prior to the telemedicine office visit with GI symptoms and fever and admitted to the hospital. Her creatinine was 3.9 mg/dl, increased from the prior baseline of 1.3 mg/dl. Urinalysis showed proteinuria, and 24-hour urine collection contained 13.6 grams of protein. Her renal function continued to worsen despite intravenous fluid administration. Laboratory results included anti-Ds DNA titer 1:80, C3 61 mg/dl (90-180 mg/dL), and C4 34 mg/dl (10 -40 mg/dL). Kidney biopsy revealed class V LN and FSGS potentially related to COVID. As per biopsy finding and ethnicity, we sent APOL1 genetic analysis which came back positive. Treatment was started with IV steroids. The creatinine peaked at 4.7 mg/dl on hospital day 8 and subsequently improved. She did not require RRT and was continued on her maintenance IS. Unfortunately, she had fetal demise at 18 weeks 3 days of gestation with stable renal function.

Discussion: This is a case of COVID-associated FSGS in a pregnant woman with a history of LN. The initial impression included prerenal azotemia, LN flare, and COVID-associated kidney injury. Serologies were consistent with an LN flare, but renal biopsy showed both class 5 LN and FSGS potentially related to COVD. Kidney biopsy should be considered in pregnant patients with hematuria, proteinuria, to rule out alternative etiologies, even when LN is suspected on clinical grounds. The threshold of RRT is very narrow in pregnancy and requires increasing dialysis frequency for adequate pregnancy outcomes.

PO1488

Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis (SAPHO) Syndrome and IgA Nephropathy

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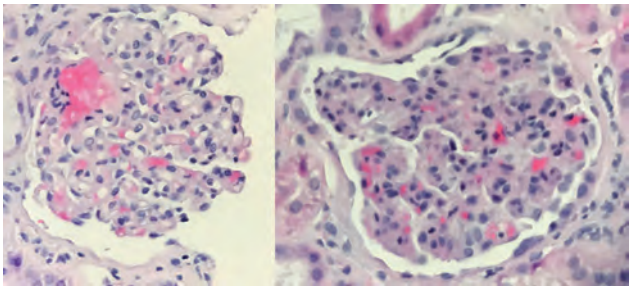
Introduction: Immunoglobulin A nephropathy (IgAN) is the most common form of glomerulonephritis (GN). It is characterized by IgA-dominant or codominant immune deposits within glomeruli, classically caused by poorly galactosylated immunoglobulin A1 that trigger autoantibodies. Other forms of IgA nephropathy include IgA vasculitis with nephritis (Henoch-Schönlein purpura) and secondary forms arising from chronic liver disease, chronic infections and neoplasms.

Case Description: Patient is a 50 year old female with anemia, hypothyroidism and chronic joint pain who presented for rising creatinine and hematuria. Baseline creatinine was 0.9 mg/dL but increased to 1.8 mg/dL within 2 months. She follows with a rheumatologist for polyarthralgias and hives where labs showed rheumatoid factor of 18 IU/mL, CRP elevated to 125 mg/L, sedimentation rate of 81 mm/hr but normal complement levels and negative ANA titers. Workup for lymphoma or myelodysplasia was negative and she was eventually diagnosed with SAPHO syndrome. Her urinalysis showed active sediment with mixed WBC/RBC casts, dysmorphic RBCs and nephrotic range protein to creatinine ratio of 7.4 g/g Concerning for a rapidly progressive GN, she was admitted to nephrology for expedited biopsy.

Discussion: Labs were negative for pauci-immune GN, phospholipase A2 receptor antibody, hepatitis panel and blood cultures. Kidney biopsy showed a membranoproliferative pattern of injury with IgA dominant GN and diffuse endocapilllary proliferation. This case may represent a rare association between SAPHO and IgA nephropathy which has only been reported in a few case reports. For the proteinuria, she was started on lisinopril and for the IgA, she was given pulse dose steroids and maintenance prednisone. Her creatinine has stabilized to 1.4 mg/dL and urine protein to creatinine ratio has also improved.



Kidney biopsy for IgA case depicting membranoproliferative pattern of glomerular injury in patient with SAPHO syndrome

PO1489

Crescentic Pauci-Immune Glomerulonephritis in a Patient with Sickle Cell Anemia and Cocaine Abuse

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Introduction: Levamisole is an anthelminthic agent and a common contaminant found in cocaine. It has been linked to ANCA-associated vasculitis with cutaneous, and more rarely, renal and pulmonary manifestations. This is the case of a patient with sickle cell anemia and cocaine abuse presenting with acute kidney injury (AKI) and nephrotic-range proteinuria, initially attributed to sickle cell nephropathy, but with kidney biopsy revealing pauci-immune glomerulonephritis, demonstrating the importance of having a high level of suspicion in patients with known cocaine use.

Case Description: A 58-year-old male with history of sickle cell anemia, CKD Stage 3, hypertension, and cocaine abuse, was admitted for epididymitis and found to have AKI. He presented with testicular pain, as well as right knee and back pain. Initial work up revealed a creatinine of 2.45 mg/dL, from baseline of 1.8 mg/dL. Urine toxicology was positive for cocaine. His urine studies were consistent with intrinsic renal disease. He received red blood cell exchange transfusion, but he continued with worsening renal function following the procedure. His 24-hr urine collection revealed 6.2 g proteinuria. Extensive workup included normal C3 and C4, positive rheumatoid factor, negative UPEP, free kappa/lambda light chain ratio 1.8, negative HIV and anti-HCV, hepatitis B immunity, negative c-ANCA, but positive p-ANCA and anti-MPO. Patient chronically smoked cocaine, sometimes cut with levamisole, which is associated with vasculitis. A kidney biopsy was performed, with pathology showing a pauci-immune necrotizing and crescentic glomerulonephritis, transmural arteritis, and sickle cell nephropathy. He was treated with pulse dose steroids and rituximab, followed by maintenance prednisone and additional doses of rituximab after discharge. His renal function improved, but did not return to baseline, which could have been due to his degree of kidney injury and ongoing cocaine use after discharge.

Discussion: This case demonstrates the importance of keeping a broad differential diagnosis in the evaluation of AKI and nephrotic-range proteinuria in sickle cell anemia, particularly in the setting of cocaine use and its known association with levamisole. Although sickle cell nephropathy could have explained this patient's presentation, a broader workup was key to arrive to the correct diagnosis, and therefore prompt treatment.

PO1490

A Case of Rapid Progressive Glomerulonephritis Associated with Disseminated Gonococcal Infection

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Introduction: Disseminated gonococcal infection (DGI) results from bacteremic spread of the sexually transmitted pathogen, Neisseria gonorrhoeae. Direct and immunological damage of multiple organs can be seen. We are reporting a case of sterile DGI with RPGN as part of the initial presentation.

Case Description: A 60-years old male with a 5-year history of seronegative spondyloarthropathy, hypertension, heart failure, poor dentition who presented to the hospital with shortness of breathing, diarrhea, joint pain, and palpable purpura ongoing for several weeks. Work-up revealed severe anemia and rapidly progressive acute renal failure (Baseline creatinine unknown, peaked at 7.2 mg/dl on admission), urine showed 9.3 g of proteinuria, hematuria, and pyuria. Serological w/up showed low C3 with normal C4, ASO, ANA, ANCA and anti GBM. Negative HIV, hepatitis B, C, syphilis serologies, monoclonals and cryoglobulins. Skin biopsy showed leukocytoclastic vasculitis which improved with steroids. Kidney biopsy showed crescentic glomerulonephritis (GN) with 10% IFTA likely due to infectious GN (RPGN). Patient completed 3-day course of solumedrol but left before cyclophosphamide could be initiated. A week later he presented with persistent hematuria and oliguria. Echocardiogram showed tricuspid endocarditis and leaflet perforation. Blood cultures were negative. Patient started on vancomycin and Rocephin for culture negative endocarditis. Extensive infectious disease workup, metagenomics test showed Neisseria gonorrhea as the cause of endocarditis. Kidney function improved. Due to disseminated GC and concern for complement deficiency, he was referred to Adult Immunology clinic.

Discussion: DGI is estimated to occur in up to 3 percent of patients infected with N. gonorrhoeae. The probability that a localized gonococcal infection will spread to joints and other tissues depends upon specific host, microbial, and possibly immune factors. RPGN is unusual presentation, the immunopathogenesis is uncertain but immunological and hypersensitivity damage is postulated based on the frequent lack of N. gonorrhoeae growth from blood, skin, and synovial fluid cultures during disseminated infection. Congenital or acquired complement deficiencies (C5, C6, C7, or C8) predispose to DGI as a result of decreased complement-mediated killing of N. gonorrhoeae.

PO1491

Proliferative Glomerulonephritis with Monoclonal IgM Deposits in ANCA Vasculitis

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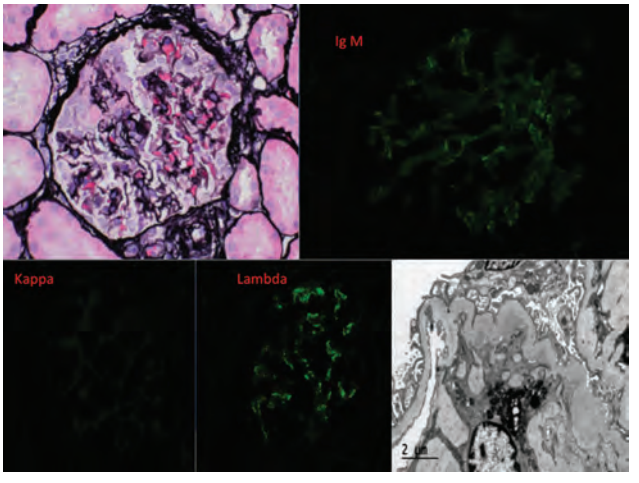
Introduction: Proliferative glomerulonephritis with monoclonal immunoglobin deposition (PGNMID) is a rare entity of unclear etiology that can be occasionally associated with an underlying hematological malignancy. We report a case of PGNMID in a patient with ANCA vasculitis.

Case Description: A 78 yr old female with hypertension presented with a history of recurrent sinusitis over 6 months that was treated with steroids and antibiotics. She had progressive weight loss, fatigue, cough, and dyspnea. Chest X-ray was normal prompting a CT chest, which showed bilateral pulmonary nodules. Her creatinine was 0.96mg/dL. Urine analysis was notable for hematuria. Antineutrophil cytoplasmic antibodies were positive at 1: 640 with myeloperoxidase Abs IgG of 199. Serum protein electrophoresis showed a normal pattern with no monoclonal spike on immunofixation electrophoresis. Her Kappa/Lambda light chain ratio was normal at 1.04, infections were ruled out, and cryoglobulin was not detected. She was started on prednisone 60 mg and had a renal biopsy. Renal biopsy showed focal segmental necrotizing glomerular lesions, mesangial hypercellularity with deposition of IgM with lambda light chains restriction on immunofluorescence and occasional mesangial and subendothelial granular electron densities on electron microscopy. She was referred to hematology for concern with monoclonal gammopathy of renal significance and had a negative evaluation on serological tests, bone marrow biopsy and PET CT scan. She was treated with Rituximab. Her creatinine had remained stable with resolution of hematuria and respiratory symptoms.

Discussion: PGNMID is an immune complex glomerulonephritis that is occasionally associated with a hematological malignancy. The pathophysiology remains elusive and treatment can be challenging. We present a case of PGNMID with monoclonal IgM with light lambda chain restriction with an unusual association with ANCA vasculitis.



PO1492

A Case of ANCA-Associated Vasculitis (AAV) in Mixed Connective Tissue Disease (MCTD) Manifesting as Pulmonary Renal Syndrome

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Introduction: Newly diagnosed microscopic polyangiitis (MPA) with positive anti-MPO in the background of MCTD is quite uncommon. Not every patient with positive Anti-MPO titers develops clinical manifestations of microscopic polyangiitis. Prompt diagnosis and early intervention is necessary to prevent end organ damage.

Case Description: 56-year-old malnourished AAF with history of MCTD (diffuse systemic sclerosis and SLE since 2005), restrictive lung disease, recurrent URI, CKD stage 3, diastolic heart failure with moderate MR, and pulmonary hypertension was transferred to ICU for worsening pneumonia and acute on chronic kidney injury. Admission serum creatinine was 2.6mg/dl (baseline s. creat 2.0mg/dl) which increased to 4.7 mg/dl during the hospital course. Lab was significant for Hgb 6.3 gm/dl, ESR 120 mm and CRP 30. Non-contrast CT chest showed bilateral interstitial opacities with superimposed consolidation. Evaluation for infectious etiologies and malignancies were negative. Bronchoscopy was concerning for diffuse alveolar hemorrhage. UA was positive for large blood with proteinuria >200mg/dl. Vasculitis work up came back positive for p- ANCA (1:1280) and anti-MPO 4 AU/ml (reference range <19) but negative for anti-PR3 and anti-GBM antibody. Renal biopsy revealed focal crescentic and necrotizing glomerulonephritis with

severe interstitial fibrosis and tubular atrophy indicating MPA. Patient was treated with pulse steroid and plasma pheresis initially, later received Rituximab. Patient improved clinically with therapy. Later, serum creatinine plateaued around 3.6 with eGFR 15.6 indicating patient's CKD had progressed to advanced CKD stage 4/ 5.

Discussion: Though the presence of AAV is not common in MCTD, this case illustrates the importance of considering AAV for worsening pulmonary and renal function in overlap syndrome. Microscopic polyangiitis is one of the most common cause of pulmonary- renal syndrome, often manifested as diffuse alveolar hemorrhage and RPGN. Prompt diagnosis and early intervention can dramatically improve the patient outcome.

PO1493

Nephrotic Range Proteinuria due to ANCA-Associated Vasculitis in a Diffuse Systemic Sclerosis Patient: A Rare Presentation

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Introduction: Scleroderma renal crisis (SRC) is a severe complication of SSc and typically presents with new-onset hypertension and a reduction in renal functioning. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare co-occurrence with SSc. We present a rare case of diffuse systemic sclerosis who presented with features of SRC and AAV with nephrotic range proteinuria without significant renal failure.

Case Description: The patient is a 32-year old woman with diffuse systemic sclerosis complicated by pulmonary fibrosis who had been treated with Mycophenolate mofetil but she discontinued treatment in order to conceive. She reports having an uncomplicated pregnancy without proteinuria or hypertension, but she delivered 7 weeks early. After delivery, she began experiencing weakness of her lower extremities and given steroids for suspecting demyelinating neuropathy and restarted treatment with Mycophenolate mofetil. She had improved but few weeks later (3 months after delivery), she was readmitted with hypertensive encephalopathy in setting of suspected scleroderma renal crisis. She also developed a rash and swelling in her legs after her pregnancy. Her urinalysis was remarkable for proteinuria and numerous RBCs and quantification of the urine protein revealed nephrotic range proteinuria (4.6 g/24 hours) but her serum creatinine (0.6 mg/dl) remained normal. She was found to be positive for antinuclear antibodies, rheumatoid factor, myeloperoxidase antibodies, MPO-ANCA (> 8.0 IU/mL). Her complement levels were within normal limits. She underwent a renal biopsy, which revealed an acute necrotizing vasculitis consistent with AAV.

Discussion: Clinicians should remain vigilant for concomitant autoimmune disorders in patients with scleroderma. In the background of systemic sclerosis, our patient developed AAV with neurologic and renal manifestations. Thus, renal injury, proteinuria or rapid onset of hypertension should not be assumed to be due to scleroderma renal crisis, particularly when there is nephrotic range proteinuria or an active urine sediment.

PO1494

Filgrastim-Induced ANCA-Associated Glomerulonephritis in the Presence of Membranous "Full House Nephropathy"

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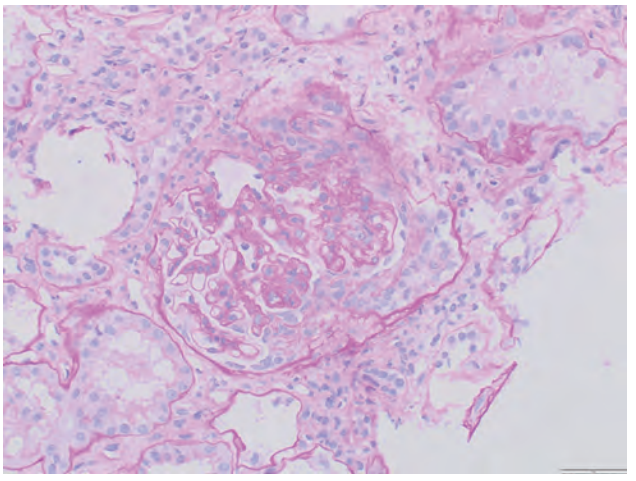
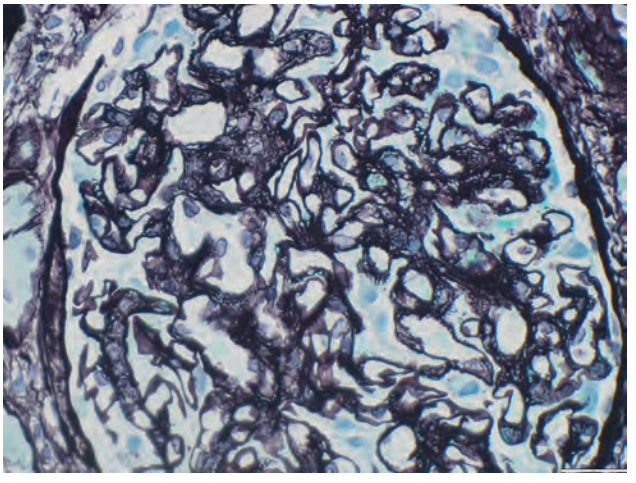
Introduction: G-CSF is commonly used to stimulate progenitor cell collection for bone marrow transplantation . We present a seemingly healthy altruistic bone marrow donor who developed glomerulonephritis secondary to G-CSF treatment.

Case Description: A 34-year old man presented after altruistic bone marrow donation. During G-CSF treatment he developed headache, epistaxis, painless macrohematuria and AKI (creatinine- 2.91mg/dL). Seven years and one year prior to this event he had similar presentations of macrohematuria, AKI and proteinuria . In between episodes he had persistent microhematuria . At this admission, Myeloperoxidase antibodies (MPO) were found to be elevated to 97 IU/ml. all other serologies were unremarkable. A kidney biopsy revealed glomeruli with cellular crescents (Figure 1). Capillary loop "spikes" were seen on silver staining (Figure 2). On immunofluorescence, there was a "full house" granular pattern. PLA2R and IgG4 stains were negative. Electron Microscopy revealed mainly subepithelial electron dense deposits. His current creatinine, without immunosupression, is 1.19 mg/dL.

Discussion: G-CSF induced ANCA associated glomerulonephritis developed on top of silent membranous "full house nephropathy ". Bone marrow donors should be asked about prior glomerulopathies and screened for proteinuria and hematuria before bone marrow donation is authorized.



A glomerulus showing a cellular crescent (PAS stain x100)



By silver stain, spikes are identified (Silver stain x400)

PO1495

Ivermectin-Induced ANCA Vasculitis

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Introduction: Ivermectin is an antiparasitic agent that has demonstrated antiviral potential against HIV1, Dengue, Zika viruses and most recently, COVID-19. But the rampant self-medication and off-label use for COVID prophylaxis in some countries is cause for concern. Here, we present what may be the first reported case of ANCA-associated vasculitis(AAV)from Ivermectin use.

Case Description: A 56-year male with no significant past medical history presented with dark urine, epistaxis, conjunctival redness, arthralgias, and malaise. His mother was on dialysis for the past few years for ESRD of unknown etiology. For several months, he had been taking Ivermectin imported from Peru for COVID prophylaxis per family advice. He was on no other medications. His creatinine, normal at baseline, was now 4.5mg/dL. He had hematuria, 3g/d proteinuria, dysmorphic RBCs and RBC casts. Serum C3, C4, ANA, anti-dsDNA, anti-GBM, hepatitisB&C screen, SPEP&UPEP were negative. Atypical and p-ANCA were negative, but c-ANCA was 1:640. Kidney biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis. He soon developed pulmonary hemorrhages. Ivermectin was discontinued. He received prednisone 1mg/kg, 3 biweekly doses of intravenous cyclophosphamide, 10 doses of plasmapheresis, and was initiated on dialysis. Four weeks later, he has no epistaxis or pulmonary hemorrhages and is off oxygen. He does remain dialysis-dependent.

Discussion: Drug exposure can trigger ANCA formation against myeloperoxidase(MPO) and, less commonly, proteinase 3(PR3). Drug-associated AAV can't be discerned from primary AAV based on clinical and pathological findings. Clues suggesting drug-associated AAV include a temporal relationship of symptom onset with suspected drug, a high ANCA titer, and positive autoantibodies like elastase and lactoferrin. Drug-associated AAV has a better prognosis than its primary counterpart, with symptoms often resolving with drug withdrawal. Though this may not suffice in cases with pulmonary and renal involvement, outcomes in drug-associated AAV remain comparable even with shorter induction and often no maintenance regimens. Commonly implicated drugs are hydralazine, levamisole-contaminated cocaine, propylthiouracil, allopurinol.

Although no case of Ivermectin-induced AAV has been reported, we recommend a high index of suspicion as prompt cessation of the offending drug can significantly improve prognosis in drug-associated AAV.

PO1496

Myeloperoxidase-ANCA and Takayasu Arteritis Overlap Syndrome Presenting as Rapidly Progressive Glomerulonephritis

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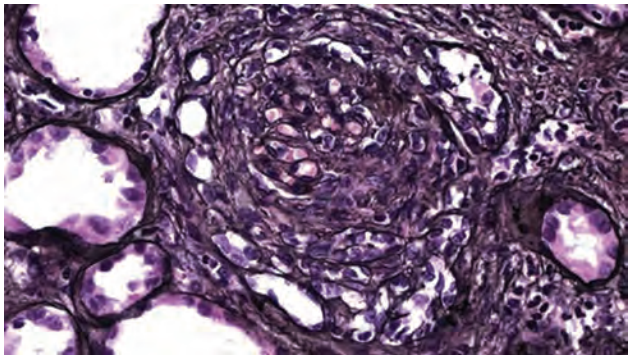
Introduction: The spectrum of vasculitides is classified according to the size of the vessels involved and the clinical and histopathological findings. The simultaneous involvement of Takayasu arteritis and myeloperoxidase-ANCA vasculitis is extremely rare

Case Description: A 12-year-old female with no previous medical history. In the last three years the patient developed lower limb claudication and unexplained intermittent fever. In recent weeks she developed edema and oliguria, she was admitted in another hospital where she was started on renal replacement therapy. Large vessel involvement was suspected so a contrast enhanced CT was ordered and was compatible with Takayasu arteritis. The patient was referred to our hospital for evaluation. During nephrology assessment she was found to have acute kidney disease with massive proteinuria (16 g/g), so work up was directed towards rapidly progressive kidney disease. Percutaneous kidney biopsy was performed, and it revealed pauci-immune crescentic glomerulonephritis. ANCA and glomerular basement membrane antibodies were ordered, with a positive MPO-ANCA result. She was then started on IV methylprednisolone pulses and 5 cycles of plasma exchange therapy. After this, rituximab was started on a weekly basis. The patient has not recovered kidney function and is still dependent on hemodialysis therapy, pending to finish the final two rituximab doses.

Discussion: This an extremely rare case which highlights the diagnostic and therapeutic difficulties in patients presenting with overlap clinical and serological features of different forms of systemic vasculitis.



Cellular crescent. Silver methenamine stain

PO1497

Granulocyte Colony Stimulating Factor-Associated Vasculitis: Adding Fuel to the Fire

Nilam Patel, Ahmed Siddiqui, Pravir V. Baxi. *Rush University Medical Center, Chicago, IL.*

Introduction: Granulocyte colony-stimulating factor (G-CSF) is commonly used with chemotherapy to stimulate bone marrow production and prevent neutropenia. Although usually well tolerated, G-CSF can exacerbate underlying autoimmune diseases with the development or progression of glomerulonephritis (GN). We present a case of pauci-immune necrotizing GN that developed in a patient with rheumatoid arthritis (RA) after receiving G-CSF therapy.

Case Description: A 61 y/o man with ampullary adenocarcinoma and RA without prior renal involvement presented with AKI. One week prior to admission he had received his 5th cycle of FOLFOX and a first dose of G-CSF. His creatinine (Cr) was 4.8 mg/dL from a baseline of 0.9 mg/dl. His urinalysis was notable for hematuria and urine protein-creatinine ratio (UPC) of 5.2 g/g. Workup showed: +p-ANCA (1:320), +anti-histone Ab, + SSA and +ANA (1:1280 speckled pattern). A renal biopsy revealed necrotizing GN with necrosis or crescents in 75% of the glomeruli (Fig 1). There was no evidence of immune-deposits c/w pauci-immune GN. He received steroids and rituximab for induction. His Cr peaked at 6.0 mg/dl but improved down to 1.1 and UPC improved to 0.6 g/g after 3 months.

Discussion: G-CSF is used to prevent neutropenia and reduce infection risk by activating mature neutrophils and preventing neutrophil apoptosis. G-CSF can also have inflammatory effects including the release of proinflammatory cytokines and tissue infiltration by activated neutrophils with the potential of end-organ damage. In patients with a preexisting GN or an autoimmune disease (eg RA, SLE), G-CSF administration can exacerbate or even initiate a de-novo GN. Pauci-immune GN is a rare but well established complication of RA. In our case, the almost immediate temporal relationship between the development of the GN and the G-CSF administration supports G-CSF as etiologic. This case demonstrates the importance of considering the possible renal complications and need for close monitoring while giving G-CSF in patients with autoimmune diseases.

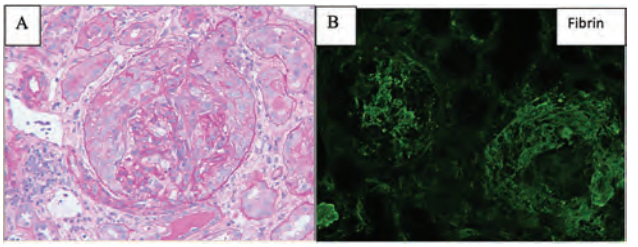


Figure 1: A) H&E Stain B) IF stain

PO1498

Spontaneously Resolved Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is thought to be a progressive disease, with early studies showing 38% of patients with persistent renal dysfunction and 22% progressing to ESKD within a 30 month follow up period. We present two cases of PGNMID who achieved spontaneous remission without directed therapy.

Case Description: Case 1: A 53 yo woman with hypertension and diabetes presented for evaluation of proteinuria with UPCR 3.86 g/g and normal creatinine. She was asymptomatic, but had an upper respiratory infection 1 month prior. Serologic evaluation for nephrotic range proteinuria was unrevealing. Renal biopsy showed PGNMID with IgG λ light chain deposits. Serum paraprotein was not detected. Bone marrow biopsy showed no concern for malignancy. UPCR decreased to 0.63 within 4 months with no treatment but an ACEi. Case 2: A 53 yo man with primary biliary cholangitis presented with edema and new hypertension. He was found to have AKI with SCr 1.83 mg/dL, UPCR of 12.9 g/g, and microscopic hematuria. While serum autoimmune markers were notable for mildly elevated anti-dsDNA (75 IU/mL), normal C3 and low C4 (8 mg/dL), renal biopsy revealed PGNMID with IgG λ light chain deposits. A low titer IgM κ was detected in the serum. The patient had diffuse lymphadenopathy on imaging, and two excisional biopsies showed reactive follicular hyperplasia. Bone marrow biopsy was normal. UPCR decreased to 1.23 g/g within 2.5 months of presentation and SCr down to 1.22 without any therapy.

Discussion: These unique cases demonstrate that PGNMID is likely a heterogeneous disease whose pathogenesis and natural history is poorly understood. We hypothesize that an infectious antigen or autoantigen may induce clonal proliferation of B-cells and the formation of transient monoclonal antibodies leading to complement activation and proliferative glomerulonephritis. When the stimulus is controlled, the associated immune response is regulated. Our patients did not require any immunomodulatory therapy, contrary to most recent case series. Recognition of the potential for spontaneous remission in PGNMID has important implications on treatment paradigms for this emerging diagnosis.

PO1499

PLAR2-Positive Membranous Nephropathy: A Renal Manifestation of Scleromyxedema

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Introduction: Scleromyxedema (SMX) is a rare primary cutaneous mucinosis that usually occurs in association with a monoclonal gammopathy. Systemic manifestations may involve the musculoskeletal, cardiovascular, gastrointestinal, pulmonary, nervous and renal systems and may lead to significant morbidity and mortality. Renal manifestation has been reported, but histopathologic description of renal involvement has been vague and histopathologic classification has not been implemented. Therapeutic management of the renal disease has included plasmapheresis and cyclophosphamide, but the roles of each of these is not determined.

Case Description: We report a case of a 53-year-old male with SMX and monoclonal gammopathy who developed renal manifestation of sclerodermoid disease. His skin manifestations of SMX had been previously controlled with intravenous immunoglobulins (IVIG) until he developed presumed central nervous system involvement manifestating as an isolated seizure. He failed a series of treatments including lenalidomide, melphalan, and bortezomib. He subsequently underwent an autologous stem cell transplant with initial improvement in cutaneous manifestations for 6 months but experienced a relapse thereafter. In addition, he developed acute kidney injury associated with minimal proteinuria (<1000 mg). A kidney biopsy demonstrated thrombotic microangiopathy (TMA) and tissue phospholipase A2 receptor antibody (PLAR2) positive membranous nephropathy. Ravulizumab was instituted but had to be abandoned as the patient was hospitalized on two occasions with fever and culture negative pulmonary infiltrates after each infusion. Alternatively, he was treated with intravenous cyclophosphamide, oral prednisone and plasmapheresis with improvement in skin disease and stabilization of proteinuria and renal function.

Discussion: Renal manifestations of SMX are poorly defined and treatment is unknown. Membranous nephropathy has been rarely reported in SMX, but PLA2R status has not been available. Most cases focus on treatment of the underlying monoclonal

gammopathy but outcomes with conventional therapy remain poor. We report a patient with SMX who developed TMA and PLA2R positive membranous nephropathy who failed clone directed therapy but was successfully treated with IV Cytoxan (an accepted option for PLA2R+ MGN), steroids and plasmapheresis.

PO1500

Pemphigus Vulgaris and PLA2R-Associated Membranous Nephropathy: Two IgG4-Related Diseases in the Same Patient

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Introduction: The relationship between bullous skin diseases and glomerulopathies has been increasingly recognised. Other bullous diseases were previously reported in association with membranous nephropathy (MN), but the association between MN and pemphigus vulgaris (PV) has not been reported in the literature yet.

Case Description: A 39-years-old smoker woman presented with trunk blisters and worsened mouth ulcers after stopping the treatment for MN. One year before she had nephrotic syndrome and the kidney biopsy was positive for anti-PLA2R and IgG4 (and negative for THSD7A) in the immunohistochemistry (IHQ). Serum anti-PLA2R was negative. Four months earlier she was started on cyclosporine, but stopped it due to mouth ulcers. She had nephrotic range proteinuria, no edema, when the painful blisters spread out on the trunk, back, limbs, scalp as well as ulcers in the oral cavity and oesophagus. The diagnosis of PV was confirmed by skin and oesophagus biopsy and IHQ showed the presence of IgG4 subclass antibody in the epithelial tissue. She received pulse and oral steroids along with azathioprine for the PV. The skin lesions were slowly healing and no more new blisters have appeared.

Discussion: The humoral auto-immune response in pemphigus produces anti-desmoglein 1 and 3, both IgG4. Desmogleins are responsible for adhesion in stratified squamous epithelia, when damaged produces to the blistering eruptions. There is a genetic predisposition between PV and MN, with HLA-DQA1, HLA-DRB1 and the thrombospondin gene (*THSD7A*). Environmental factors such as smoking and air pollution could act as a second trigger for the development of auto-immune diseases. PLA2R can be expressed in the bronchiolar tissue and in macrophages of the lung, however there is no evidence of histological damage in the pulmonary tissue. Although we found no description on the expression of PLA2R in the skin, in an attempt to find a common antigen for both diseases, we did search for anti-PLA2R in the skin, but it was negative. In conclusion, this is the first described case of association of pemphigus vulgaris and PLA2R-associated MN, both IgG4-related conditions that involve the production of different autoantibodies directed to skin and kidney antigens.

PO1501

A Case of an Elderly Woman with Membranous-Like Glomerulopathy with Masked Monoclonal IgG Deposits Whose Renal Biopsy Revealed Renal Cell Carcinoma

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Introduction: Membranous-like glomerulopathy with masked monoclonal IgG deposits (MGMID) is a recently described form of glomerulopathy with a unique histopathology reported by Larsen et.al. The pattern is characterized by subepithelial and/or mesangial immune deposits that are “masked”, to immunoglobulin staining by routine immunofluorescence but strongly stained for IgG and kappa light chain after protease digestion. Patients with MGMID are commonly young females and have a vague history of autoimmune diseases such as low titer antinuclear antibodies.

Case Description: A 65-year-old woman was referred to our hospital with urinary protein (0.80 g/gCr) and microscopic hematuria. Serum antinuclear antibody, rheumatoid factor, and M-protein were negative and serum C3 and C4 were normal. Plain CT showed no neoplastic lesions in the kidney, and a renal biopsy was performed. Part of kidney biopsy tissue contained clear cell renal carcinoma (RCC). Light microscopy revealed increased mesangial matrix and partial thickening and double contour of the basement membrane. Immunofluorescence examination of the frozen sections was negative for IgG and C3. Electron microscopy revealed electron dense deposits in both the subepithelium and mesangium (Churg classification stage II). After proteinase digestion, paraffin-embedded sections were stained again, and IgG and kappa light chain were strongly positive in granular pattern along the basement membrane (IgG subclass: IgG1>IgG4). Staining for anti-PLA2r/THSD7A antibody was negative, and staining for anti-serum amyloid P antibody was positive. Based on the above, this patient was diagnosed as MGMID. Subsequently, she underwent a partial nephrectomy for RCC, and her urinary protein decreased significantly.

Discussion: Although most patients with MGMID are young women (<40 years), this patient was an elderly woman with RCC. IgA nephropathy and membranous nephropathy have been reported as glomerular lesions associated with RCC. In this case, the proteinuria decreased after RCC resection, suggesting that RCC may be related to the development of MGMID in elderly patients, although the details are unknown. This is the first case of MGMID in Japan.

PO1502

Granulomatous Interstitial Nephritis: A Rare Cause of AKI

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Introduction: Granulomatous interstitial nephritis is a rare finding identified in < 1 % of native kidney biopsies. The most frequent etiology is drug related followed by systemic granulomatous conditions.

Case Description: 54-year-old African American male with diabetes, obesity, CKD stage 3 with a baseline Creatinine of 1.4 mg/dL and history of remote sarcoidosis was admitted with epididymo-orchitis treated with multiple antibiotic regimens including beta lactams; complicated with MRSA bacteremia and AKI with a creatinine peak of 3 mg/dL. Laboratory studies showed: Normal complement levels, serum calcium of 8.4 mg/dL with normal ACE level and urinalysis with no protein 9 WBC/HPF and 10 RBC/HPF. CXR showed prominent bilatral hila and patchy infiltrates. Renal Biopsy was done and revealed granulomatous interstitial nephritis, focal glomerulonephritis (GN) consistent with infectious related GN with focal acute tubular injury and atrophy with interstitial fibrosis. Image 1 shows giant cells on PAS. Patient was started on prednisone 40 mg daily for 2 weeks and subsequent taper. Was referred to the sarcoidosis clinic due to his remote history and found to have multisystemic granulomatous disease affecting the pulmonary, hepatic and ymphatic systems.

Discussion: Granulomatous interstitial nephritis (GIN) is an uncommon histologic diagnosis. It is known to be associated with antibiotic use and granulomatous disorders like sarcoidosis. The incidence of renal sarcoidosis ranges from 7-17 % manifesting as GIN or with renal damage due to altered calcium homeostasis. Corticosteroids are considered the mainstay of therapy.

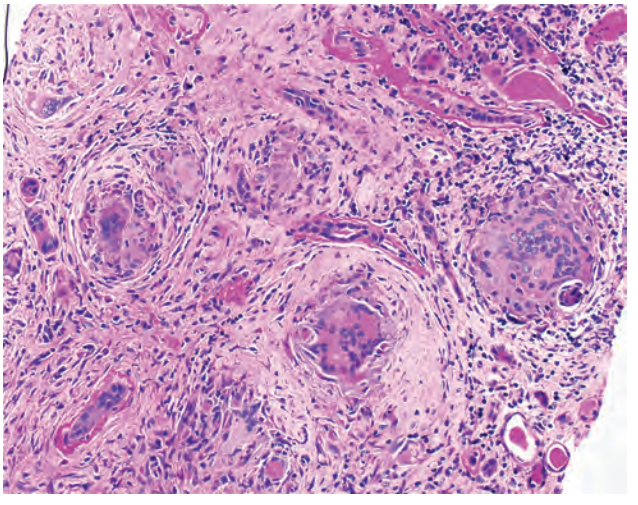

Image 1. PAS Staining

PO1503

Monoclonal Gammopathy in a Patient with Lupus Nephritis: A Case Report

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) has known associations with many disorders, including inflammatory and connective tissue disorders. Systemic lupus erythematosus (SLE) is not traditionally considered to have an association with MGUS. However, a few studies and case reports have emerged that have suggested an association between MGUS and SLE. We describe herein a case of a patient who was newly diagnosed with lupus nephritis but also was found to MGUS.

Case Description: A 53-year-old gentleman with a history of hypertension presented to the hospital with blurry vision and bilateral lower extremity rash. He was found to have acute kidney injury (creatinine 1.67 mg/dl), microscopic hematuria (21-50 RBCs/HPF), proteinuria (24 hour urine protein 1,148 mg/day), and low complements (C3 50 mg/dl, C4 7 mg/dl, and CH50 13 U/ml). Kidney biopsy confirmed focal proliferative glomerulonephritis with full-house immunofluorescence staining and three cellular crescents, consistent with class III lupus nephritis. Interestingly his ANA and double-stranded DNA serologies were negative. Serum immunofixation was positive for an IgM lambda type monoclonal gammopathy. Bone marrow biopsy showed 2.1% plasma cells. Hematology/oncology was consulted and diagnosed him with MGUS. Incidentally, he was found to have type I cryoglobulinemia as well, with cryoglobulin immunofixation positive for IgM kappa type. The patient was given high-dose steroids, transitioned to prednisone, and started on mycophenolate mofetil. A t two months of treatment creatinine was 1.1 mg/d, proteinuria improved to 300 mg/gm creatinine.

Discussion: The pathophysiologic mechanism that has been suggested for the development of MGUS in patients with lupus is dysregulation in B cell populations and immunoglobulin production. Lupus is known to produce hyperactivity in B cells and a

polyclonal increase in gamma globulins. It is likely that in some patients with lupus, B cell regulation becomes impaired in a way that allows a clonal, but not necessarily neoplastic, an expansion that results in increased production of paraproteins, leading to MGUS. This case adds to the literature showing that there indeed may be an association between MGUS and lupus.

PO1504

Bartonella Henselae Infective Endocarditis (BHIE): A Rare Cause of Pauci-Immune Necrotizing GN (PINGN)

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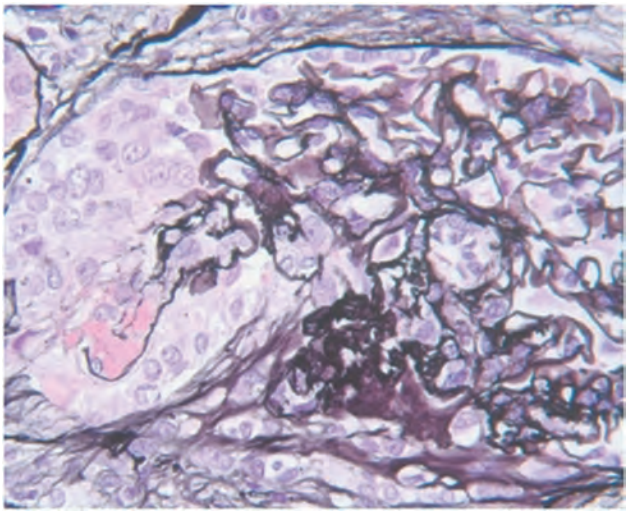
Introduction: Bartonella is the commonest cause of culture negative endocarditis. While, Infection Related GN (IRGN) can mimic pauci-immune vasculitis, the majority of cases of BHIE have been immune complex (IC) mediated. We present a rare case of BHIE related PINGN. Timely recognition of this atypical presentation led to appropriate medical therapy.

Case Description: A 33 yo M with HIV on HAART and recent tooth extraction was admitted with a severe headache due to a sub arachnoid hemorrhage from a ruptured right anterior cerebral artery mycotic aneurysm. TEE showed a vegetation on the aortic valve (AV). Blood cultures were negative. Initial SCr was 3.3 mg/dl and urinalysis had 2+ protein, 3+ blood with 29 RBC/hpf and a UPro/Cr ratio was 1.7 g/g. The C4 was low (10.2 mg/dL) and PR3-ANCA elevated-4.0 (NL <3.5 U/mL). The Bartonella henselae IgG titer was elevated-1:2,560 (NL <1:320). Renal biopsy revealed pauci-immune necrotizing GN (Figure) with no evidence of IC deposition. BHIE associated PINGN was diagnosed and treatment with doxycycline, ceftriaxone and gentamicin initiated. The AV was replaced and was positive for BH by PCR. After a prolonged course of antibiotics the SCr improved to 2.5 mg/dl.

Discussion: B henselae associated GN is a rare cause of PR3-ANCA positive GN with only 6 cases previously reported. By immunofluorescence, 4 cases were immune complex mediated with 2 cases having a pauci-immune necrotizing GN. We present only the 3rd case of B henselae associated PR3-ANCA and pauci immune necrotizing GN. The PR3-ANCA may be induced through B-cell activation after release of PR3 from neutrophils. Ruling out B henselae IE in cases of PINGN is critical in guiding management as this diagnosis leads to the initiation of antibiotics and avoids inappropriate treatment with immunosuppressive agents.



PO1505

Atypical Hemolytic Uremic Syndrome and Systemic Lupus Erythematosus-Dermatomyositis Overlap: A Challenging Scenario

Yelena R. Drexler, Juanly N. Rodriguez. *University of Miami School of Medicine, Miami, FL.*

Introduction: Overlap syndromes are rare disorders wherein at least two systemic autoimmune diseases meet diagnostic criteria. We present a case of atypical hemolytic uremic syndrome (aHUS) in a patient with systemic lupus erythematous (SLE) and anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5) dermatomyositis (DM) overlap.

Case Description: A 45-year-old woman with SLE diagnosed 8mo prior, treated with belimumab and prednisone, developed proximal muscle weakness, violaceous erythema of eyelids, neck, hands and feet with ulcers. Three weeks later, she presented with abdominal pain, shock and respiratory failure. Testing showed WBC 19,200/uL, lipase >600 and ionized calcium 0.47 mmol/L; acute kidney injury (BUN 64 mg/dL, SCr 2.4 mg/dL); anemia (Hb 7.1 g/dL); and thrombocytopenia (PLT 24,000). CT showed pancreatitis and omental nodularity. Given oliguria and hypocalcemia despite high-dose calcium infusion, she initiated renal replacement therapy. Further workup showed low C3 level 42, C4 level 7, elevated anti-dsDNA Ab 237 IU/ml and UPCR 2.2 g/g; haptoglobin <10, LDH 1,371 U/L, Positive direct Coombs, schistocytes on smear and ADAMTS13 activity 18%. Due to autoimmune vs microangiopathic hemolytic anemia, received pulse methylprednisolone and IVIG without improvement. She then started eculizumab. Within 7d, LDH decreased to 772, haptoglobin increased to 79 and platelets normalized. Further workup revealed elevated creatine kinase 1,271 U/L, aldolase 17 U/L, AST 566 U/L with normal ALT and positive anti-MDA5 and transcription intermediary factor 1-gamma (TIF-1γ) Abs, meeting criteria for DM. Patient continued eculizumab and prednisone. Eventually developed invasive aspergillosis and expired.

Discussion: We report a case of SLE–DM overlap with anti-MDA5 and TIF-1γ Abs complicated by aHUS and severe hypocalcemia in the setting of pancreatitis. The cutaneous manifestations are typical of MDA5-associated DM. Our patient did not develop interstitial lung disease, exemplifying range of variation from case to case. The presence of anti-TIF-1γ confers a 6-fold increased malignancy risk; finding of omental nodularity in this case would warrant further investigation. aHUS as a complication of SLE-DM overlap is rare, with mortality risk up to 52%. AKI, infection and low C3 are associated with highest mortality. Prompt diagnosis, high clinical suspicion and early initiation of eculizumab resulted in a rapid response.

PO1506

Anti-LRP2 Nephropathy in a Patient with Chronic Lymphocytic Leukemia

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Introduction: Anti-LRP2/anti-Brush Border nephropathy is a newly identified autoimmune tubulointerstitial nephritis triggered by circulating antibodies to low-density lipoprotein receptor-related lipoprotein 2 (LRP2). We present a case of anti-LRP2 nephropathy in a patient with chronic lymphocytic leukemia (CLL).

Case Description: A 74-year-old Caucasian male patient known to have CLL presented following a fall with a forearm laceration. At presentation, he had acute renal failure (sCr of 5.04 mg/dL) and severe thrombocytopenia (platelets of 11,000/u). Additional evaluation showed positive ANA and p-ANCA. The patient had proteinuria of 1754 mg/g of creatinine. The kidney biopsy showed moderate interstitial fibrosis and tubular atrophy involving 30-40% of the renal cortex. The tubular epithelium showed reactive-appearing nuclei as well as cytoplasmic thinning with loss of the proximal tubular brush border. Immunofluorescence showed IgG (3+) and C3 (3+) for the glomeruli capillary and the TBM. There was focal staining of the brush borders by IgG with positive LRP2 stain in the TBM. Electron microscopy revealed numerous subepithelial electron-dense deposits. The serum anti-LRP2 antibody titer was 1:100. The patient was started on dexamethasone and rituximab with improvement of the thrombocytopenia. Plasmapheresis was prescribed for 5 sessions, the creatinine continued to worsen (sCr of 7.73 mg/dL), and the anti-LRP2 titer did not improve. The patient is being transitioned to renal replacement therapy.

Discussion: The mechanism that links the ABBA disease with lymphoproliferative disease is still unknown. The current reported cases suggest an association between direct lymphoma renal infiltration, progression of the lymphoproliferative disease and the presence of the ABBA disease. However, in our reported case, the patient's underlying CLL was stable without evidence of renal infiltration. The poor response to treatment in this case is consistent with the poor outcomes of many anti-LRP2 reported cases. The renal biopsy on this patient also showed membranous glomerulonephritis. We presented a case with anti-LRP2 nephropathy/ABBA disease with concurrent CLL without evidence of kidney infiltration which responded poorly to immunosuppression therapy. The prognosis of ABBA associated paraneoplastic syndrome with underlying CLL warrants future investigation.

PO1507

Black Tar Heroin and AA Amyloidosis

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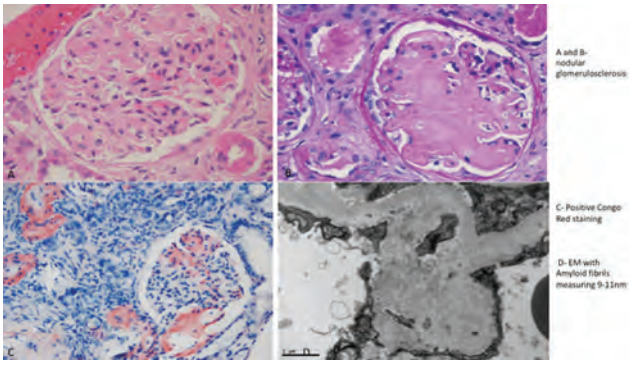
Introduction: AA amyloidosis due to deposition of serum amyloid A protein occurs as a secondary reaction to chronic inflammatory disease, chronic infections, and familial period fever syndromes. We present a case of AA amyloidosis secondary to chronic black tar Heroin use in the Intermountain West.

Case Description: A 61 yr. old Caucasian female with a history of Hepatitis C, IV Heroin use presented with bilateral leg pain, swelling, and abdominal distension. Examination was significant for ulceration in lower extremities with purulent blisters. Notable lab data include Hemoglobin of 8.2 g/dl, potassium of 6 meq/L, calcium of 10.6 mg/dl, BUN of 90 mg/dl, creatinine of 2.9 mg/dl, serum albumin of 2.1 g/dl, and ESR of 129 mm/hour. She had a urine protein to creatinine ratio of 12.3 g/g. Abdominal US revealed enlarged liver and normal renal echogenicity. The quantification of HCV RNA by polymerase chain reaction was negative, and her complement levels were within normal range. Cryoglobulin was also negative with a kappa/lambda light chain ratio of 1.33. Serum protein electrophoresis showed decreased albumin and immunofixation electrophoresis showed a faint band in IgG kappa suggestive of a specific immune response or an early monoclonal protein. Renal biopsy showed non-AL amyloid deposition involving glomeruli, and arteries. Mass spectrometry performed at Mayo Clinic Laboratories confirmed renal involvement by Amyloidosis, AA (serum amyloid A)-type.

Discussion: "Black tar heroin" has increasingly been identified as a risk factor for AA Amyloidosis. Impurities in heroin promote vascular sclerosis and lead to the use of injection into muscle and skin. The suppurative infections that follow stimulate

the production of serum amyloid A protein with subsequent deposition in the kidney leading to nephrotic syndrome and end stage kidney disease. Greater awareness of this complication may help prevention in areas with increased black tar heroin use.



Renal biopsy

PO1508

Guselkumab-Associated Severe AKI from Collapsing Glomerulopathy

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Introduction: Collapsing glomerulopathy (CG) has been commonly associated with viral infections, mainly HIV. Several medications have also been associated with CG. We present the first case of Guselkumab-associated rapidly progressive AKI from CG and acute tubular injury.

Case Description: 86-year-old African American female with history of HTN, RCC with left nephrectomy, CKD, CHF, and psoriasis (on Guselkemab treatment since 2018) presented to our hospital for worsening bilateral LE edema and AKI. On presentation, Scr was elevated at 3.75 and serum albumin was WNL (3.5). Three weeks prior to presentation, Scr was elevated but stable at 1.77 on outpatient labs. Of significance, pt. received Guselkemab injection one week prior to presentation. During hospital stay, UA was significant for proteinuria and hematuria. Spot urine total protein-to-creatinine ratio (TP/CR) was significantly elevated at 13.7. Of note, spot urine TP/CR was 1.6, four months prior to presentation. There was no right hydronephrosis or renal vein thrombosis seen on imaging. Serological tests including ANCAs, HBsAg, Hep C ab, HIV, RVP, COVID-19 PCR, Parvovirus B19 PCR, and CMV PCR were all negative. Patient initially received diuretic therapy for LE edema. Kidney biopsy performed during hospital stay showed CG and acute tubular injury. Electron microscopy examination of kidney biopsy specimen was significant for extensive effacement of podocyte foot processes and rare tubuloreticular inclusions in endothelial cell cytoplasm. Scr rapidly worsened to 7.98 and HD treatment was initiated. Our patient was also initiated on daily high dose oral corticosteroid therapy.

Discussion: Guselkumab, an IL-23 blocker is FDA approved for the treatment of plaque psoriasis and active psoriatic arthritis. A case of Ustekinumab (IL-23/IL-12 inhibitor) associated FSGS (after 2 years of treatment) has been reported in the literature. Our patient while on chronic Guselkumab treatment developed rapidly worsening AKI and CG, a week following the last dose of Guselkumab. We believe that in absence of any additional known risk factors, Guselkumab was responsible for AKI and CG in our patient. Our patient currently remains dialysis dependent. Clinicians should be aware of this very rare but potential association.

PO1509

Proteinuria and Hematuria, an Unfamiliar Side Effect of Statin Therapy

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Introduction: Statins are among the most commonly prescribed medications worldwide, and have a relatively mild side effect profile. We describe a rare manifestation of statin therapy, with proteinuria and microscopic hematuria.

Case Description: A 53-year old Hispanic lady with a history of proteinuria and hematuria for 1 year with negative Urologic workup was referred to nephrology for further evaluation. Patient complained of foamy urine. Her only medication was rosuvastatin 40 mg. Initial UA showed 2+ protein and 5-10 RBC/HPF. Lab work - BUN 16, creatinine 1.0 mg/dL, albumin 4.8 mg/dL, Urine Protein Creatinine Ratio 2.1 g/g creatinine. Serologies were negative and complement levels were normal. Patient was started on ARB and a low sodium diet for proteinuria. Proteinuria persisted and renal biopsy was recommended with suspicion of IgA nephropathy. Biopsy showed mild glomerular and tubular interstitial chronic injury likely secondary to arteriosclerosis. There was no immune complex deposition and no evidence of thin basement membrane disease. Genetic workup was negative for Alport's syndrome. Because of the rare association of Rosuvastatin with urinary abnormalities, we decided to hold patient's Rosuvastatin. Only three days later the patient reported that foamy urine had resolved. Repeat UPCR showed 99 mg protein/g creatinine. Hematuria also decreased to 0-2 RBC/HPF.

Discussion: Proteinuria is one of the lesser known side effects of statin therapy. It was initially found in the clinical development programme for Rosuvastatin, where it was found that the 80 mg dose caused proteinuria in 12% of patients. Furthermore, a comprehensive review of the renal effects of rosuvastatin, found that 1.2% of patients taking 40 mg of rosuvastatin developed 2+ proteinuria, and 0.3% developed 2+ proteinuria and 1+ hematuria. Our case highlights a rare manifestation of Rosuvastatin induced urinary abnormalities, which improve after stopping the drug. This should be kept in mind for patients on Rosuvastatin with negative workup for proteinuria and hematuria, before a renal biopsy is pursued.

PO1510

Rituximab for Membranous Nephropathy in a Patient with Sjögren Syndrome and Mixed-Connective Tissue Disease

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Introduction: Membranous nephropathy (MN), a cause of nephrotic syndrome, is characterized by the deposition of immune complexes in the glomerular basement membrane with resultant subepithelial "spikes" visualized under light microscopy. Although often a primary disease process, several secondary etiologies exist, including Sjögren's syndrome (SS) and mixed-connective tissue disease (MCTD). Treatment typically targets the underlying condition. Despite rituximab's demonstrated efficacy in MN, MCTD and SS, case reports for specific treatment of MN secondary to these conditions have primarily described regimens of systemic corticosteroids with or without cyclophosphamide.

Case Description: A 54-year-old-male was diagnosed with MN on renal biopsy in 2001. Despite features suggestive of a secondary etiology (tubulo-reticular structures, mild cellular increase by light microscopy, mesangial deposits, and irregular distribution of deposits by EM), both his initial presentation and subsequent relapse in 2010 responded to antiproteinuric therapy alone. Following treatment-resistent relapse, cyclophosphamide and prednisone were initiated in 2019 without improvement. A secondary evaluation was significant for strongly positive anti-ribonucleoprotein and anti-SSA antibodies with negative serologies for systemic lupus erythematosus. The patient reported only mild polyarthralgia and sicca symptoms. Following rheumatology consultation and salivary gland biopsy the patient was diagnosed with MCTD and SS. Rituximab 1000 mg on day 0 and 14 was administered, with partial remission noted 4 months following therapy. Complete remission was achieved 8 months following therapy and has been sustained for 13 months. His extrarenal symptoms of MCTD and SS have also resolved.

Discussion: Rituximab is a well-described treatment for primary MN, MCTD and SS. However, there is a paucity of literature evaluating its use in MN as the specific renal manifestation of MCTD and SS. This case illustrates the potential role for rituximab as an effective treatment for membranous nephropathy secondary to SS and MCTD when deciding on immunomodulatory therapy. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

PO1511

A Rare Case of Concurrent Glomerulonephritis and Autoimmunity

Janany J. Sabescumar, Rickinder Grewal, Hae Yoon Grace Choung. *University of Rochester, Rochester, NY.*

Introduction: We report a rare case of necrotizing and crescentic glomerulonephritis in the setting of Streptococcus mitis bacteremia.

Case Description: A sixty-one year old man with a history of hypertension, hyperlipidemia, and non-insulin-dependent diabetes presented to the emergency room with progressive lower extremity edema and dyspnea with tea-colored frothy urine. Initial workup revealed bilateral pulmonary edema and acute kidney injury with a serum creatinine of 1.84 mg/dL (0.8 mg/dL 6 months prior) with 9.18 grams proteinuria and an active urine sediment. He was initially diuresed for decompensated heart failure but further workup revealed hypocomplementemia and positive ANCA/proteinase-3 (PR3) antibody. A kidney biopsy revealed membranous glomerulonephritis (MGN) with focal endocapillary proliferative features and focal crescents with fibrinoid necrosis with positive PLA2R immunostaining and serum PLA2R IgG antibody testing revealing a titer of 1:2560. An echocardiogram revealed reduced left ventricular ejection fraction with a mobile aortic valve vegetation. Blood cultures obtained on admission ultimately grew Streptococcus mitis and he underwent aortic valve repair. Despite completion of a full antibiotic course, his creatinine remained impaired with nephrotic-range proteinuria and elevated serum PLA2R titers. Repeat renal biopsy revealed membranous glomerulonephritis and he was started on immunosuppression for treatment of PLA2R-associated MGN.

Discussion: Peri-infectious PLA2R-associated MGN and ANCA-associated glomerulonephritis appears to be a rare. While his proliferative ANCA-mediated glomerulonephritis was likely related to the infectious endocarditis, the relationship to the PLA2R-positive MGN remains unclear. We hypothesize that host immune response to infectious agents lead to an autoimmune process resulting in glomerulonephritis. It is possible that in addition to a genetic predisposition ("first hit"), a "second hit" which begins with activation of the innate immune response by an infectious agent leading to autoimmunity through various mechanisms including defective immune regulation, molecular mimicry, epitope spreading, and autoantigen complementarity.

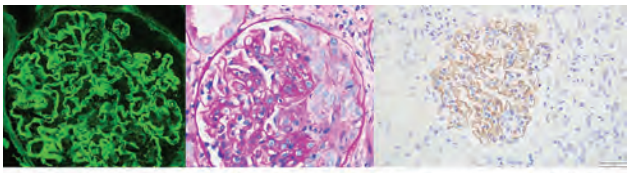

Figure (right to left) Immunofluorescence microscopy shows 3+ granular global glomerular capillary wall staining. Segmental cellular crescent (periodic acid-Schiff, original magnification x400), and Electron microscopy shows extensive stage I to 2 subepithelial electron dense deposits (original magnification x 10000)

PO1512

C2 Deficiency Associated with Severe Recurrent ANA-Negative Lupus and Microangiopathy

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Introduction: Deficiencies in the classical complement pathway have been associated with the development of systemic lupus erythematosus (SLE) and lupus-like disease in 10-20% of affected patients. In fact, SLE patients deficient in classical complement present at an earlier age, with severe manifestations and a worse prognosis. Several mechanisms have been described to explain these immune phenomena including impaired clearance of immune complexes, impaired handling of apoptotic cells, or changes in regulation of cytokines. Here, we present a case of a young female with ANA-negative lupus presenting with dyspnea and acute renal failure responsive to immunosuppressive therapy found to have C2 Complement deficiency.

Case Description: 44 year old female with sickle cell trait, ANA-negative SLE, ESRD due to biopsy-proven class IV lupus nephritis briefly requiring HD, pulmonary HTN, presented with signs of fluid overload, acute on chronic renal failure in the setting of malignant hypertension. Labs revealed thrombocytopenia of 52 with a creatinine of 2.66 (prior 1.61), hypocomplementemia and undetectable CH50 levels concerning for acute flare of SLE and an underlying functional complement deficiency. Low haptoglobin and peripheral smear with schistocytes raised concerns for microangiopathy. Hospital course was complicated by encephalopathy and possible CNS involvement of lupus. Renal biopsy confirmed chronic sclerosing immune complex glomerulonephritis with minimal activity. The patient responded well to high dose corticosteroids, plasma exchange and mycophenolate mofetil. Final serology confirmed persistent C2 complement deficiency.

Discussion: There is a well-studied link between immune-complex mediated disease and complement deficiency. Of these, C2 deficiency is the most common. In our case, a C2 deficiency was found in the setting of ANA-negative SLE with severe clinical manifestations. Our case raises the question of whether testing to exclude underlying complement deficiency is particularly indicated in patients with ANA-negative SLE. It also remains to be seen whether clinical manifestations of microangiopathy are prevalent in these patients, and whether therapeutics targeting complement may be effective in their treatment.

PO1513

De Novo IgA Vasculitis Following Exposure to SARS-CoV-2 Immunization

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Introduction: Immunizations have been previously described as potential triggering events for the development of certain glomerular diseases. However, there is paucity of reports of occurrence of glomerular diseases developing after exposure to a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.

Case Description: A 50-yearl-old man presented to a nephrology clinic for evaluation of persistent proteinuria. Six weeks prior to evaluation, the patient had reported developing a new rash approximately 2 weeks after receiving the first dose of a SARS-CoV-2 vaccine (Pfizer®). The rash was treated by his primary care provider with topical and oral corticosteroids, leading to partial improvement of the skin lesions. Three weeks after the first vaccine injection, the patient received his scheduled second vaccine injection. Within 2 days, the rash reappeared. This time, the lesions were more severe in nature, with a violaceous papular rash involving his lower legs and with some areas progressing to blisters. He also reported myalgias and arthralgias. A skin biopsy was performed and revealed IgA-dominant leukocytoclastic vasculitis. After completion of 2 weeks of oral corticosteroids, a urinalysis revealed proteinuria and a consultation to nephrology was requested. On examination, healing papules were noted on his legs but otherwise exam was normal. Serum creatinine was 0.9 mg/dL. Microscopic examination of the urinary sediment revealed acanthocytes. A urine protein-to-creatinine ratio (UPCR) was 1.1 g/g. Serum complements were normal and all pertinent serology was negative. A kidney biopsy was performed and light and immunofluorescence microscopy findings showed an IgA nephropathy. UPCR decreased to 0.7 g/g and rash completely subsided.

Discussion: The clinical presentation and pathological findings in this case strongly suggest that SARS-CoV-2 vaccine (Pfizer®) can trigger a clinical syndrome compatible with Henoch-Schönlein purpura. The recurrence of the rash following re-exposure to the vaccine injection (second dose) argues for a definite causal association by Naranjo criteria.

PO1514

Postinfectious Glomerulonephritis Complicated by Complement-Positive Coombs Autoimmune Hemolytic Anemia

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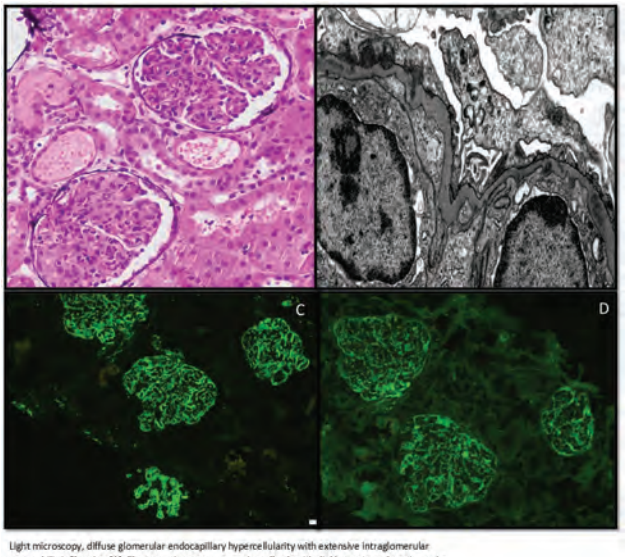
Introduction: Postinfectious glomerulonephritis (PIGN) is the most common cause of GN in children. Mild normocytic anemia is often noted during the acute illness and is usually thought to be secondary to hemodilution from fluid overload and/or depressed erythrocytes production. Here, we describe a case of PIGN and autoimmune hemolytic anemia in a pediatric patient.

Case Description: A 3-year-old girl presented with 5 days of gross hematuria, fatigue, and decreased urination. Laboratory evaluation revealed elevated potassium at 5.4 mmol/L (normal range 3.6-5.2 mmol/L), creatinine 3.04 mg/dL (0.19-0.49 mg/dL), and blood urea nitrogen 98 mg/dL (7-20 mg/dL), low hemoglobin (Hb) 8.4 g/dL (11.4-14.3 g/dL) and normal platelet count. Urinalysis showed numerous red blood cells (RBCs) and nephrotic range proteinuria. Bilirubin, lactic dehydrogenase, and haptoglobin were normal. Direct antiglobulin test (DAT) was positive for monospecific C3, and negative for IgG. Peripheral blood smear revealed mild RBC polychromasia and occasional helmet cells. Several hours after admission, her Hb dropped acutely to 6.3 g/dL requiring blood transfusion. Complement proteins C3 and C4 were low at <6 mg/dL (75-175 mg/dL) and 5 mg/dL (14-40 mg/dL), respectively. DNase-B Antibody was normal and dsDNA antibody was negative. A kidney biopsy revealed findings consistent with PIGN **(Image 1).** She received acute hemodialysis for the first 48 hours after admission for worsening hyperkalemia, uremia, anuria, and edema. Her Hb remained stable and did not require additional blood transfusions.

Discussion: Our case of concurrent PIGN and autoimmune hemolytic anemia is exceptionally rare. This unique association may explain the anemia that is often seen in PIGN. We suggest that PIGN cases with anemia should have a DAT performed.



Light microscopy, diffuse glomerular endocapillary hypercellularity with extensive intraglomerular neutrophilic infiltration **(A).** Electron microscopy, several small subepithelial hump type deposits and a few intramembranous deposits **(B).** Immunofluorescence, C3-dominant coarse granular glomerular basement membrane and mesangial positivity **(C)** with accompanying significant staining for IgG **(D).**

PO1515

Hydralazine-Induced ANCA Vasculitis and Lupus Nephritis

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Introduction: Hydralazine is a common antihypertensive drug, but drug induced glomerulonephritis (DI-GN) is observed in 5-10% of the population on hydralazine after three years of therapy. We present a case of rapidly progressive glomerulonephritis due to hydralazine.

Case Description: 65-year-old female with a history of hypertension, diabetes mellitus, and chronic kidney disease presented for altered mental status. Her serum creatinine (SCr) three months and two years prior were 2.3 mg/dl and 0.9mg/dl respectively. On presentation, her SCr was 12.7 mg/dL, and she was started on hemodialysis. During her hospitalization, she had persistent hemoptysis with worsening dyspnea, skin rash, and oral ulcers (Fig 1, 2). Work up revealed hematuria, low complement levels, positive histone antibody and ANCA titers, and negative double stranded DNA antibody (Table 1). Skin biopsy showed small and medium vessel vasculitis. Kidney biopsy revealed class 3 and 5 lupus nephritis with full house immunofluorescence staining and active cellular crescents (Fig 3). Review of her medications included hydralazine 25 mg three times a day for three years, and she was diagnosed with hydralazine induced glomerulonephritis and systemic vasculitis. She was given pulse steroids and cyclophosphamide with improvement in extrarenal manifestations, but no renal recovery.

Discussion: Hydralazine has been known to cause DI-GN since the 1950s, and it can manifest with features of pauci-immune glomerulonephritis and lupus nephritis. Drug induced vasculitis has a high incidence of renal involvement compared to drug induced systemic lupus erythematosus, however both entities have multiple auto-antibodies and ANCA positivity. The use of hydralazine has increased over the years due to trials demonstrating mortality benefit in heart failure. There is no consensus on the treatment, but discontinuing the offending agent, early diagnosis, and immunosuppressant therapy may result in favorable prognosis.

Table 1

Complement 3	76 mg/dL (90-180)
Complement 4	17 mg/dL (16-47)
Antinuclear antibody immunofluorescence and titer	Positive, titer of 1:320
Anti-histone antibody immunofluorescence	Positive (8.9 U)
dsDNA Antibody	Negative
ANCA immunofluorescence	Positive
MPO	Positive
PR3	Negative
pANCA titer	1:640

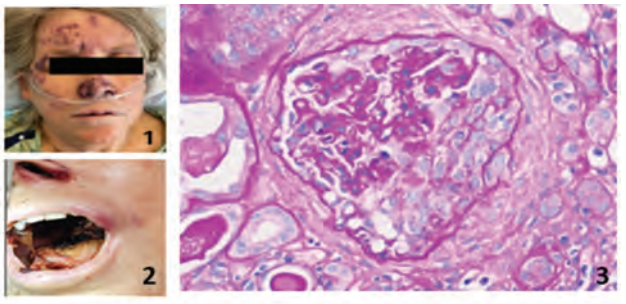

Figure 1 and 2: Skin and oral lesions; **Figure 3** Kidney Biopsy, PAS stain, immune complex deposits in glomerular capillary loops, and active cellular crescent

PO1516

Chicken or the Egg Causality Dilemma: Primary ANCA Vasculitis Complicated by Infective Endocarditis (IE) vs. IE Leading to ANCA Vasculitis

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Introduction: As the cases of infective endocarditis increase in the Unites States it is important to recognize the associated complications. Glomerulonephritis is a well-recognized but not fully understood consequence. Immune complex deposition is the most common etiology but ANCA-mediated kidney injury is increasingly described and even less understood.

Case Description: A 65 year old male presented with acute onset dysarthria, left facial droop, left sided weakness, and dizziness. 5 months prior he was diagnosed with PR3+ ANCA vasculitis after presenting with 18 lbs weight loss, purpura, anemia, hematuria and sub nephrotic proteinuria. He was treated with methotrexate and a steroid taper, which finished one week prior to the current presentation. Admission vitals were: 145/74 mmHg, heart rate of 90 bpm, afebrile, and 100% oxygen saturation on room air. Lab work revealed: hemoglobin of 10.7 K/uL, creatinine of 1.17 mg/dl (baseline 0.9), low C3: 81 mg/dL, positive PR3 (>8.0), positive c-ANCA (1:128), negative MPO and p-ANCA, and UA: 3+ blood, negative protein, and 11-20 WBC. MRIs of the brain and heart revealed numerous acute and subacute infarcts and severe mitral regurgitation respectively, concerning for small vessel vasculitis, and he was started on high dose steroids. Discovery of streptococcus mutans bacteremia was a surprise. Suspicion was raised that the ANCA vasculitis may have been a consequence of underlying sub-acute endocarditis rather than a primary disease hence a kidney biopsy was planned and he was discharged on steroids and IV antibiotics. Kidney biopsy confirmed the diagnosis of ANCA-mediated endocarditis-associated glomerulonephritis with the presence of glomerulosclerosis with fibrocellular/fibrous crescents, segmental fibrinoid necrosis but no obvious immune deposits on light microscopy. Granular deposits in the mesangial and capillary wall stained for C3, IgM, IgA, kappa and lambda. He underwent 6 weeks of ceftriaxone and mitral valve replacement. His renal function is mildly impaired; he is recovering neurologically.

Discussion: Endocarditis-associated GN typically requires treatment of the underlying infection without immunosuppression, but when the injury is primarily ANCA-mediated, this presents a unique challenge in that end-organ damage from vasculitis may not improve without immunosuppression.

PO1517

Crescentic Glomerulonephritis in Sjögren Syndrome

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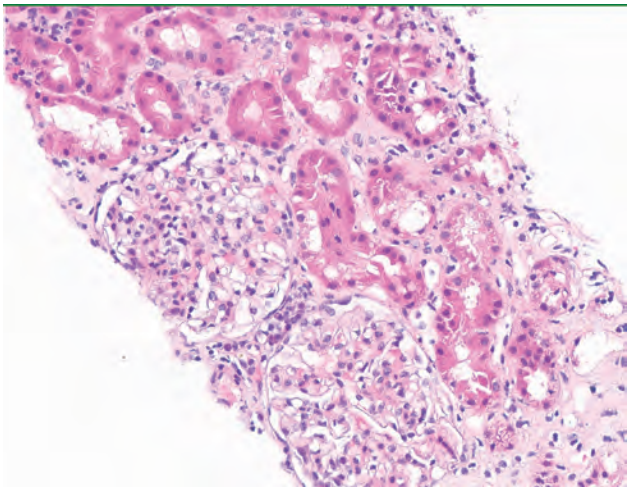
Introduction: Sjogren's syndrome (SS) is an infiltrative autoimmune disorder involving the parotid, lacrimal and salivary glands causing sicca syndrome. Kidney involvement is variable and most often results in tubulointerstitial nephritis. Glomerular disease is infrequent with MPGN and membranous nephropathy being most prevalent pathologically.

Case Description: Patient is a 21 year old female with SS, hypothyroidism and asthma who was being evaluated for fever and fatigue. Lab evaluation revealed acute kidney injury (AKI) with creatinine rising from 1.0 to 1.8 mg/dL over several weeks. Echocardiogram was concerning for mobile echodensity at the tricuspid valve, but transesophageal echo showed no abnormalities and evaluation for infection was negative. CT showed extensive prominent lymph nodes in the chest, abdomen, and pelvis but lymph node biopsy showed benign reactive hyperplasia without neoplasm. Renal ultrasound showed normal sized kidneys. Urinalysis was positive for trace proteinuria and sediment revealed dysmorphic RBCs. She was started on high dose prednisone and hydroxychloroquine for possible lupus nephritis but due to diagnostic uncertainty and unresolved AKI, kidney biopsy was performed.

Discussion: Kidney biopsy demonstrated plasma rich interstitial nephritis with severe tubulitis consistent with SS. Interestingly, the biopsy showed 3 active cellular crescents out of 21 glomeruli with focal crescentic GN. Tubulointerstitial nephritis is the most common renal pathology in primary SS leading to renal tubular acidosis, impaired concentrating ability and proximal tubule defects. GN in SS is rare but has been associated with membranoproliferative GN, membranous nephropathy and cryoglobulinemic GN. Crescentic GN was unexpected and the treatment plan was adapted to taper the prednisone, start on Mycophenolate Mofetil and trial on Rituximab.



Light microscopy for renal biopsy of Sjogren's case depicting interstitial nephritis and crescentic glomeruli

PO1518

Crescentic Glomerulonephritis and Membranous Nephropathy: A Case Report of a Rare Overlap

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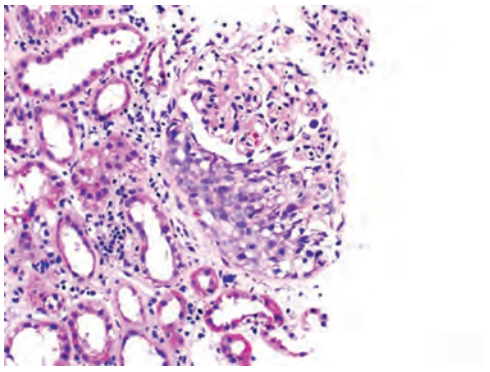
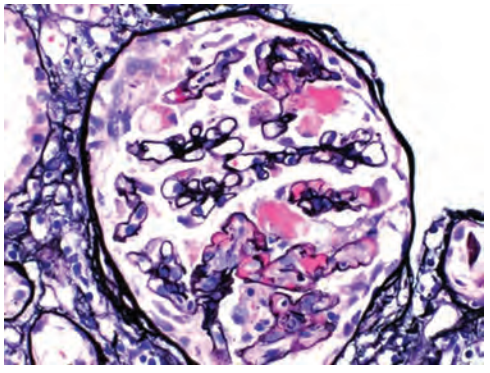
Introduction: Membranous nephropathy (MN) is a disease that affects the basement membrane of the glomeruli of the kidney resulting in proteinuria. The concurrent incidence of vasculitic glomerulonephritis and MN in the same patient is unusual. Herein, we report a case with this unusual combination.

Case Description: Our patient is a 53-year-old Hispanic male with a past medical history of tobacco use, type 2 diabetes mellitus, and hypertension who presented with hematuria and was found to have nephrotic range proteinuria and renal impairment. Blood workup revealed positive ANCA serology, which led to a renal biopsy that showed crescentic vasculitis in addition to membranous nephropathy. The patient was started on intermittent hemodialysis (HD) and treated initially with intravenous (IV) pulse steroids; subsequently, oral prednisolone and IV cyclophosphamide was initiated. The patient remained HD dependent at the time of discharge with the resolution of hematuria. A follow-up with an outpatient nephrology clinic was arranged.

Discussion: Membranous nephropathy complicated by crescentic glomerulonephritis has a more aggressive clinical course and decline in renal function compared to MN alone which can lead to initiating renal replacement therapy. However, immunosuppressive drugs can result in significant improvement of renal function if started early enough.



Light microscopy shows diffuse cellular crescent formation



Light microscopy shows a glomerulus with focal segmental fibrinoid necrosis

PO1519

Unmasking a Case of Membranous-Like Glomerulopathy with Masked IgG-κ Deposits

Alissa Ice, Darren W. Barefield. *Louisiana State University Health Sciences Center, Baton Rouge, LA.*

Introduction: Membranous-like glomerulopathy with masked IgG-κ deposits (MGMID) is a recently described, exceedingly uncommon entity of glomerular immune-complex deposition requiring antigen retrieval on formalin-fixed paraffin-embedded tissue. We report a rare case of MGMID in a young female with newly diagnosed APLA.

Case Description: An 18 year old female with no medical history presented with left leg swelling. Vital signs were normal and an enlarged, discolored left lower extremity was appreciated on exam. Initial laboratory results were remarkable for Cr 0.78 mg/dL, albumin 2.3 g/dL, platelets 128,000/μL, PTT 87.1 s, INR 1.02, and hematuria and proteinuria on UA. Imaging demonstrated an extensive acute DVT. Additional studies revealed positive APLA, unremarkable bone marrow and flow cytometry analyzes, and negative autoimmune panel. Hepatitis panel, ANCA, anti-PLA2R, serum free light chains, and serum and urine immunoelectrophoreses were normal. Furthermore, she was found to have 7.2 g of protein on 24 hour collection and biopsy results consistent with MGMID. She was discharged on a prednisone taper and losartan and later initiated on tacrolimus with stable renal function and improved proteinuria after six months.

Discussion: MGMID was first described in 2014 by Larsen et al found predominantly amongst young female patients with autoimmune phenomena with variable clinical progression regardless of the treatment. Similar to this case, subepithelial and mesangial deposits [A], predominant C3 on IF [B], SAP positivity [C], and IgG-κ deposits [D] appear to be characteristic [see figure]. Given these findings in the absence of the antigen-retrieval step, pathology misclassifcation as infection-associated glomerulonephrtis, membranous nephropathy, or C3 glomerulonehritis can significantly impact prognosis and treatment. Therefore, it is important to consider this additional step in pathology analysis in certain clinical presentations.

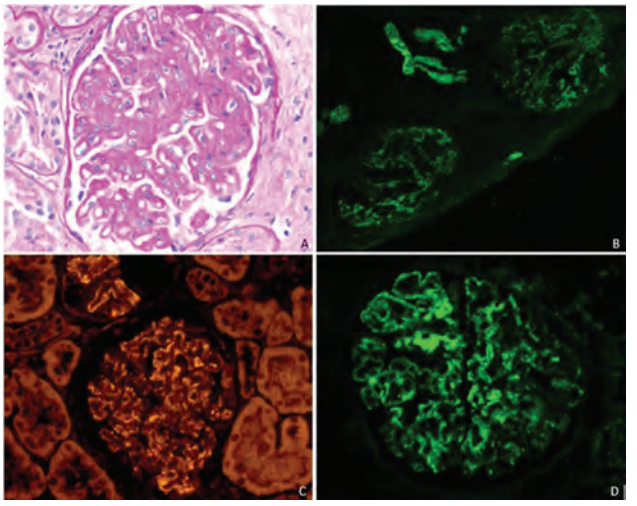


Figure 1: Pathology

PO1520

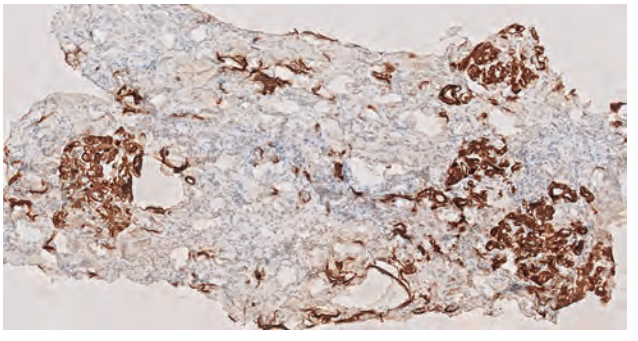
A Case of Secondary Renal Amyloidosis Associated with HIV

Dawn Maldonado, Ismail Omran, Carlos J. Gonzalez Gonzalez, Ayesha Mallick Imam, Arpita Joshi, Saeid Karandish, Majd Al Shaarani, Fadi E. Salem, Aaron S. Stern, Ishita Bansal, Maritza Brown. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Secondary amyloidosis is known to be associated with multiple chronic infections and inflammatory conditions including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and tuberculosis. HIV has not yet been established as a known association. We present a case of secondary amyloidosis associated with well-controlled HIV with no history of other potential etiologies.

Case Description: A 71-year-old man with hypertension and well-controlled HIV for 40 years (viral load undetectable and last CD4 917) was referred to the renal clinic for acute kidney injury and heavy proteinuria. He had complained of leg swelling and foamy urine. Spot urine protein:creatinine ratio was 10 and albumin was 1.6 mg/dL. The creatinine had slowly risen over several months from 0.9 mg/dL to a plateau of 1.8. Serologic work-up was unrevealing; PLA2r, complements, hepatitis serologies, ANA, ANCA, A1C, SPEP, immunofixation, and free light chains were all normal. Renal biopsy demonstrated amorphous deposits throughout the glomeruli which stained positive for serum amyloid A (SAA) (figure 1). We found no systemic causes to explain secondary amyloidosis. This case demonstrates a possible association of secondary amyloidosis with HIV.

Discussion: Only a few case reports have described an association of secondary amyloidosis with HIV. SAA renal amyloidosis has been described in a patient who acquired HIV via intravenous drug use. It was unclear if it was related to the HIV disease or to chronic inflammation from skin infections due to needle use. Renal amyloidosis has also been occasionally described in South African patients with HIV and in non-human primates with HIV-like disease. Elevated levels of amyloid A protein have been found in AIDS patients, suggesting a possible pathogenetic linkage. More studies are needed in this area to determine if there is a causal relationship between the two disorders and what is the best approach for management.



Positive SAA staining

PO1521

Renal Cell Carcinoma Presenting as Henoch-Schönlein Purpura with AKI and Leukocytoclastic Vasculitis in Adults

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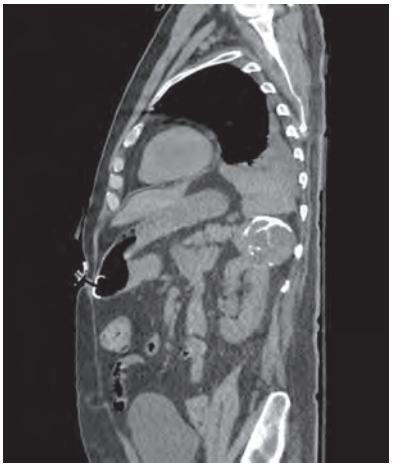
Introduction: Henoch-Schonlein purpura (HSP) is a small vessel vasculitis characterized by IgA tissue deposition. HSP presenting in adults is often the result of an underlying malignancy.

Case Description: A 60-year-old man with history of HTN, CVA, DMII, recent COVID-19 infection, presented for 2 week history of petechiae on bilateral upper and lower extremities. Skin biopsy findings were compatible with leukocytoclastic vasculitis (LCV). Patient on admission was also found to have AKI with creatinine 2.1 mg/dl, microscopic hematuria, and sub-nephrotic range proteinuria with urine protein/creatinine ratio of 2.66 g/g. Kidney biopsy findings were consistent with IgA dominant glomerulonephritis. Given multi-system involvement, patient was diagnosed with Henoch-Schonlein Purpura. Given unusual presentation with extreme of age, there was concern for malignancy. CT scan chest abdomen pelvis was performed which revealed a solid and septated 8.3 cm exophytic mass on the superior pole of left kidney. A partial left nephrectomy was performed with pathology report consistent with clear cell renal carcinoma. Patient's hematuria, proteinuria and skin rash resolved with surgical intervention. Creatinine remained stable in the 1.6-1.8 mg/dl range on discharge.

Discussion: Henoch-Schonlein purpura (HSP) is generally seen in the first decade of life. There have been a few cases of HSP presenting in adults due to underlying solid organ malignancies including renal cell carcinoma (RCC). Our case illustrates the importance of evaluating adults presenting with clinical findings of HSP for underlying malignancy. Treatment of underlying malignancy will improve vasculitis symptoms including renal parameters.



Exophytic and sepatated mass within superior pole of left kidney (Figure 1).

PO1522

A Case of Necrotizing Crescentic Glomerulonephritis due to ANCA Vasculitis and Fibrillary Glomerulonephritis

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Introduction: Fibrillary Glomerulonephritis is a rare disorder thought to be idiopathic in nature. Cases of fibrillary GN have been assoicated with malignancy, monoclonal gammopathy, autoimmune disease, or infection. We present a unique case of fibrillary GN with pauc-immune cresentic GN due to Myeloperoxidase antibody (MPO) vasculitis.

Case Description: A 77 year old lady with history of well controlled diabetes, hypertension, congenital deafness, presented with weakness, fatigue & weight loss for four weeks. She was noted to have severe anemia with Hemoglobin of 6.6 g/dl, and presumed acute kidney injury. Her labs on admission were remarkable for creatinine 2.5mg/dl (unclear baseline creatinine), eGFR 25ml/min, potassium 5.3, Bicarbonate 16, Sodium 128. Urinalysis showed large blood and 1+ protein. The serological workup was positive for P ANCA 1:640, C ANCA 1:640, MPO ab and negative for PR-3 ANA, SPEP, Free light chain ratio, HIV, Hepatitis panel. Endocscopy and Colonoscopy was negative for any obvious bleeding. Patient underwent renal biopsy which showed 7 out of 15 glomeruli with early fibrocellular crescents with fibrinoid necrosis, along with healing phase of necrotiizing arteritis. Immunoflourescence didn't show any preferrential staning for immunoglobulin, kappa or labmda. Electron microscopy showed messangial mild non branching randomly arrayed thick fibrils with no immune complex type deposits. EM findings were confirmed by positive DNAJB9 stain. Patient received treatment with pulse dose steriods, two doses of rituximab 1 gm 14 days apart and continued on prednisone for slow taper with good renal response. Due to the findings of Fibrillary GN addition workup for lymphoproliferative disorder was done Whole body CT scan was negative but flow cytometry testing still pending.

Discussion: We present a unique case of fibrillary GN and pauci-immune crescentic GN with positive MPO antibodies. The significance of fibirillary deposits in this setting is unclear and usually not seen with pauci-immune crescentic GN. Fibrillary GN is a very rare diagnosis mostly thought to be idiopathic in nature. This unique presentation of fibrillary GN with ANCA vasculitis questions the current pathogensis fibrillary GN and overall renal prognosis in association with glomerular pathologies like ANCA vasclitis

PO1523

An Unexpected Clue in the Urinary Space: The Overlap Between IgA Predominant Staphylococcus aureus-Associated Glomerulonephritis and IgA Nephropathy: A Case Report

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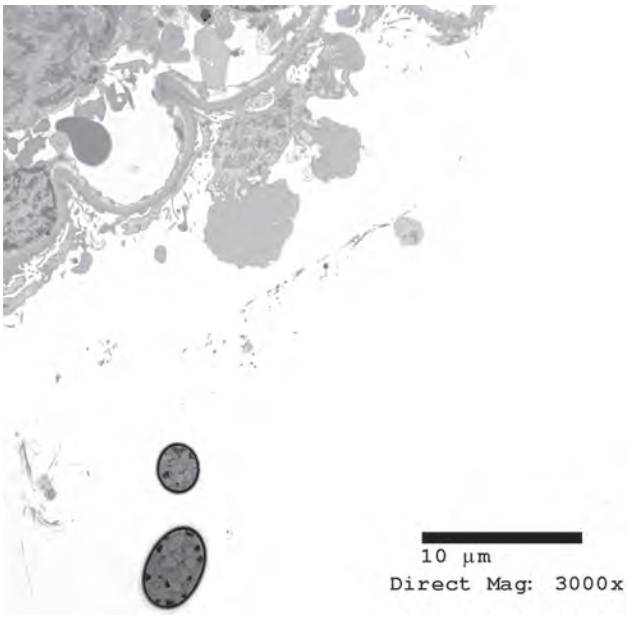
Introduction: There is significant histological overlap between IgA nephropathy (IgANP) and IgA predominant Staphylococcus-aureus associated glomerulonephritis (IgASAAGN). [1] [1] Satoskar et al., "Staphylococcus Infection-Associated Glomerulonephritis Mimicking IgA Nephropathy," November 2006.

Case Description: Kidney biopsy was performed in a 60 yo male for an unexpected decline in kidney function. IgASAAGN was diagnosed on histology and foreign particles that were consistent with staphylococci were noted in the urinary space on electron microscopy. The patient was found to have methicillin-sensitive staphylococcus aureus (MSSA) pneumonia. Two months later, after a second decline in kidney function, IgANP was diagnosed on repeat kidney biopsy.

Discussion: This patient is diagnosed with two distinct conditions on pathology samples that show very similar histological findings. The presence of SA in the urinary space is a previously unreported finding. SA infection is known as the initiating factor for the development of IgASAAGN. Recent studies have also suggested SA cell envelope antigens as a new candidate for the induction of IgANP and antigens have been colocalized with IgA deposits in the glomeruli of affected patients. [2] SA infection and IgA deposition seem to play an essential role in the pathogenesis of both conditions, and the consideration that they may be two extremes of a disease spectrum could be considered. If the role of SA in the development of IgA nephropathy is confirmed, it may be of interest to explore the role of anti-staphylococcal antibiotics in the treatment regimen of IgANP. [2] Koyama et al., "Staphylococcus Aureus Cell Envelope Antigen Is a New Candidate for the Induction of IgA Nephropathy."



Staphylococcus aureus in the urinary space

PO1524

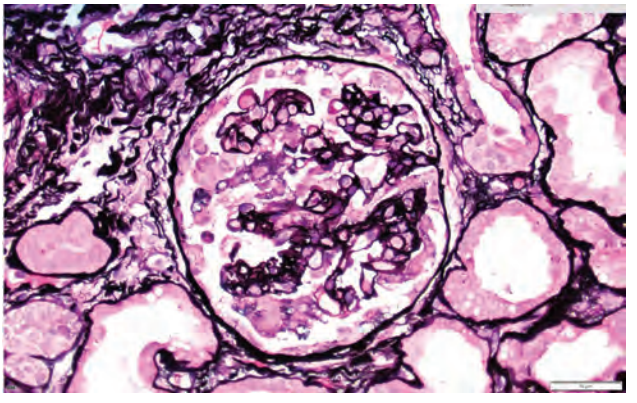
The Collapsing Variant of FSGS in a Patient with Hemophagocytic Lymphohistiocytosis due to an Aggressive T Cell Lymphoma

Manal Alotaibi, Akansha Agrawal, Carla L. Ellis. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Introduction: Collapsing FSGS is a histologic renal lesion, most often seen in patients with HIV infection. We report a rare case of collapsing FSGS in a patient with HLH due to T-cell lymphoma

Case Description: A 50 years old lady with a PMH of SLE who was admitted to the hospital with fatigue. She was diagnosed with hepatosplenic T-cell lymphoma and HLH. She received multiple coures of chemotherapy with a good response. During the course of hospitalization, she developed oliguric AKI with rising serum creatinine to 2 mg/dl from baseline 0.8 mg/dl with nephrotic range proteinuria of 9g/24hrs. Immunological workup was significant for high ANA titer 1:1280 but with normal complements C3 and C4, and negative anti-double strand DNA, anti-smith, anticardiolipin IgG, anti-GBM, and ANCA antibodies. Infectious workup was negative for HIV, syphilis, and hepatitis B and C. Kidney ultrasound showed normal-sized kidneys without hydronephrosis. She then underwent a renal biopsy, which revealed the collapsing variant of FSGS, characterized by glomerular collapse with overlying podocyte hypertrophy. The biopsy additionally showed the absence of tubuloreticular inclusions or electron dense deposits by electron microscopy. Immunofluorescence showed largely negative/baseline staining. Her renal function was improved by the time of discharge with serum Cr 0.9 mg/dl and improving in proteinuria.

Discussion: Collapsing FSGS can be associated with a variety of causes. It was seen frequently in patients with HIV infection. Other etiologies include non-HIV infections (e.g., CMV, parvovirus B19), drugs (e.g., pamidronate, interferon), lupus nephritis, diabetes mellitus, and genetic factors. Collapsing FSGS has been described with HLH in a few reported cases, which are mostly related to lymphoma. The renal involvement is believed to be caused by T cell activation and cytokine storm resulting in podocyte injury.



Jones Silver Stain at 40 x magnification: A glomerulus shows collapse of the glomerular tuft with overlying podocyte hypertrophy and hyperplasia.

PO1525

Diagnostic Dilemma: Glomerular Linear IgG Deposit with Negative Anti-GBM Antibody

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Introduction: Linear deposition of IgG along glomerular basement membrane (GBM) is hallmark of anti GBM glomerulonephritis. Subclass IgG 3 deposition is seen predominantly in these cases. Rare atypical anti-GBM cases have been described in literature as rare, indolent, no pulmonary involvement and undetectable antibodies. We describe a case of atypical anti GBM, four days after mRNA COVID vaccine.

Case Description: A 77-year-old male with history of hypertension presented with hypertensive emergency and acute kidney injury 4 days after first COVID vaccine (mRNA). Workup revealed sCr 2.6 mg/dl (1.5 mg/dl 1 month back), 3+ blood and 3+ protein by UA, normal C3, C4, ANA 1: 160, spot urine protein: creatinine- 2.2, serum albumin- 4g/dl. anti ds-DNA, ANCA and anti-GBM antibody was negative so was Hepatitis panel andHIV. Serum electrophoresis was negative for monoclonal protein. He did not have any pulmonary symptoms and CXR was negative for acute pathology. Renal biopsy was performed. LM: mild to moderate nodular mesangial expansion, mildly increased mesangial cellularity and focal segmental nodular mesangial sclerosis. IF showed positive linear global capillary loop staining with IgG (2+), with kappa (1+) and lambda (2+) co-staining. Trace mesangial IgM and granular C3 (trace1+) are also noted in the peripheral capillary loops. EM showed diffuse foot process effacement. Few subepithelial, intramembranous and mesangial electron dense deposits were seen. Additional IgG subclasses IF showed positive linear glomerular staining for IgG1 (3+), IgG2 (1+), IgG4 (1+), negative for IgG3.

Discussion: Although no definitive active glomerular crescents or necrotizing lesions were seen, positive linear IgG staining in the glomerular capillary loops was concerning for atypical anti-GBM disease in setting of negative antibody and negative IgG3A study looking at 20 atypical anti-GBM patients found that 1 year patient and renal survival was 93% and 85% respectively. A few patients in this study had biopsy findings of DFPE and sub-epithelial deposits like ours. There have been few reports of COVID vaccine unmasking glomerulonephritis. However, it needs further investigation.

PO1526

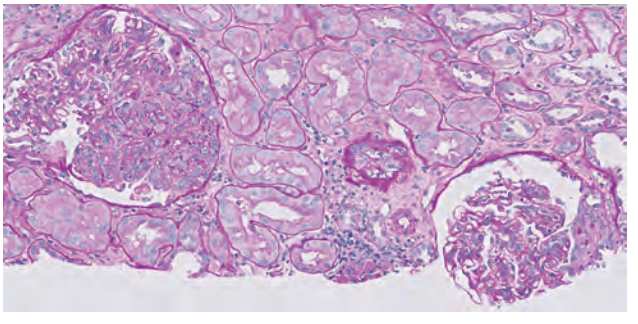
Rapidly Progressive Glomerulonephritis due to Crescentic IgA Nephropathy in the Setting of HIV

Fatima Cheema, Dawn Maldonado, Saeid Karandish, Carlos J. Gonzalez Gonzalez, Ismail Omran, Ayesha Mallick Imam, Temi-Ete I. Ediale, Majd Al Shaarani, Fadi E. Salem, Aaron S. Stern, Maritza Brown. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: In patients with HIV-related kidney diseases, the most widely recognized histological abnormality is focal segmental glomerulosclerosis (FSGS). Less commonly found is IgA nephropathy in HIV patients, which tends to have a chronic stable course. We report a case of crescentic IgA nephropathy and FSGS in a patient with rapidly progressive glomerulonephritis and newly diagnosed HIV.

Case Description: A 34-year-old transgender woman with a history of alcohol use disorder presented with a petechial rash and lower extremity edema for 1 week, and was found to have a new diagnosis of HIV with an elevated creatinine. CD4 count was 143 and viral load was 103,774, and she was started on renally-dosed dolutegravir, abacavir and emtricitabine. Creatinine on admission was 1.27 mg/dL (baseline 0.7), and increased over the next several days to 5.3. Urine microscopy revealed dysmorphic RBCs and granular casts, with spot urine protein:creatinine 2.3. Renal biopsy demonstrated crescentic IgA nephropathy (Oxford classification M1 E1 S1 T1 C2) with concomitant FSGS (NOS subtype). Cellular crescents were seen in 4/7 glomeruli (figure 1), mesangial and endocapillary hypercellularity in all non-sclerotic glomeruli, and FSGS in 2/7 glomeruli. Immunofluorescence showed strong granular segmental mesangial staining for IgA (3+) and C3 (3+), and was otherwise negative. She was started on pulse-dose steroids (methylprednisolone 500mg x 3 days followed by 1 mg/kg x 2 weeks), as well as plasmapheresis every other day for 5 sessions. Her renal function had not improved by the time of discharge.

Discussion: To our knowledge this is the first reported case of IgA-induced RPGN in the setting of newly diagnosed HIV. A few prior case reports describe stable IgA nephropathy in individuals with HIV, suggesting that there may be some unifying pathogenesis. This case highlights the need for investigation of this potential mechanism, which may help determine the optimal therapy for IgA nephropathy and IgA-induced RPGN in the setting of HIV.



PO1527

Features and Outcomes of Patients with C1q Nephropathy in the NEPTUNE and CureGN Cohorts: Comparisons to Minimal Change Disease and Focal Segmental Glomerulosclerosis

Scott E. Wenderfer,[1,2] Maria Larkina,[3] Mir Reza Bekheirnia,[1,2] Clarissa A. Cassol,[4] Carmen Avila-Casado,[5] Laura Barisoni,[6] William E. Smoyer,[7,8] Laura H. Mariani.[3] *[1]Baylor College of Medicine, Houston, TX; [2]Texas Children's Hospital, Houston, TX; [3]University of Michigan, Ann Arbor, MI; [4]Arkana Laboratories, Little Rock, AR; [5]University Health Network, Toronto, ON, Canada; [6]Duke University, Durham, NC; [7]Nationwide Children's Hospital, Columbus, OH; [8]The Ohio State University, Columbus, OH.*

Background: Predominant immunostaining for C1q distinguishes a subset of patients with primary glomerular disease. C1q nephropathy (C1qN) has been proposed but not universally accepted as a distinct glomerular disease. This study describes clinical characteristics and short-term outcomes of patients meeting the provisional CureGN definition of C1qN, including comparisons to patients with minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) without C1qN.

Methods: MCD and FSGS patients with C1qN were identified from the Cure Glomerulonephropathy Network (CureGN) and NEPTUNE cohorts. Comparisons were made to MCD and FSGS patients without C1qN, based on age, disease, and time since kidney biopsy, using 5-to-1 matching. We performed cross-sectional analyses of clinical and treatment data at enrollment and a longitudinal analysis of disease course.

Results: A total of 42 patients met the provisional CureGN definition for C1qN (16 adults >18yo, 11 teens 12-18yo, and 15 children <12yo), including 15 with MCD and 27 with FSGS. Those with C1qN were more commonly female (60 vs 49%, p=0.2) and black (34 vs 27%, p=0.4). At enrollment, those with and without C1qN had comparable kidney function (eGFR 90 vs 88 mL/min/1.73m^2, p=0.8). Individuals with C1qN were equally likely to have been treated with steroids or other immunosuppressive therapy (76 vs 81%, p=0.4) and to have ever achieved complete remission of proteinuria (defined as uPCR <0.3) (54 vs 65%, p=0.2). Median time to last follow-up was 3.1 yrs (IQR 1.9, 4.4) from enrollment and 4.8 yrs (IQR 3.3, 6.5) from biopsy date. While proportions with kidney failure were higher for FSGS compared to MCD (14 vs 1%, p=0.01), they were similar between patients with and without C1qN (7 vs 10%, p=0.6). There was a trend towards steeper GFR slope in C1qN patients (-4.8 vs -0.2 mL/min/yr, p=0.06).

Conclusions: FSGS and MCD patients with and without C1qN have comparable demographics and short-term outcomes in CureGN and NEPTUNE. Outcomes do not appear to be biased by differences in immunosuppressive therapies. Further interrogation of genetic and molecular profiles between patients with and without C1q immunostaining on biopsy may be more informative.

Funding: Private Foundation Support

PO1528

Morphologic Descriptors Most Predictive of Clinical Outcomes in Minimal Change Disease and FSGS

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Background: Previous studies applying the NEPTUNE Digital Pathology Scoring System (NDPSS) uncovered the value of kidney tissue features for clinically relevant patient subcategorization. This study aims to identify histologic and ultrastructural descriptors most predictive of clinical outcomes in NEPTUNE patients.

Methods: 39 glomerular, 9 tubulointerstitial, 2 vascular, and 20 ultrastructural descriptors were quantified using the NDPSS on 39 MCD, 61 MCD-like, and 124 FSGS NEPTUNE digital kidney biopsies. Outcomes included time from biopsy to disease progression (kidney failure or ≥ 40% eGFR decline with eGFR <90) and first complete remission (CR) of proteinuria (UPCR <0.3). Relative importance of descriptors for prediction of outcomes was obtained from random forest models, without adjusting for clinical features.

Results: The mean age, eGFR and UPCR at biopsy for the total 224 participants was 28.8, 85.2, and 5.4, respectively. Model performance was excellent (predictive discrimination= 0.902 for disease progression and 0.853 for CR). Most predictive descriptors included conventional (e.g., global sclerosis or segmental sclerosis, and interstitial fibrosis/tubular atrophy) and unconventional features [Fig]. Top 10 predictors included inflammation, podocyte abnormalities, and acute tubular injury for both outcomes; deflation, interstitial foam cells, and collapse for disease progression; and endothelial cell abnormalities, hyalinosis, and periglomerular fibrosis for CR.

Conclusions: Most predictive descriptors of proteinuric glomerulopathies reflected structural changes in various renal compartments. Reporting these descriptors should be standardized to guide the subcategorization of proteinuric glomerular diseases and improve targeted clinical care.

Funding: NIDDK Support, Other NIH Support - NCATS

	Disease Progression	Complete Remission
No/minimal changes #	2	3
Segmental sclerosis + tip lesions + other segmental lesions *	5	1
Inflammation *	4	5
Interstitial Fibrosis/Tubular Atrophy *	3	6
Global sclerosis/Obsolescent *	1	9
Visceral epithelial cell (podocyte) abnormalities *	7	8
Endothelial cell abnormalities *	14	2
Hyalinosis *	12	4
Any Deflation *	6	11
Periglomerular fibrosis	11	7
Acute tubular injury	9	10
Interstitial foam cells	8	13
Any Collapse *	10	16
Podocyte detachment	21	15
Arterial damage (presence vs. absence) *	15	21
Global mesangial sclerosis	19	19
Marginating leukocytes	20	18
Tubuloreticular inclusions	18	20
GBM abnormalities *	16	22
Interstitial edema	13	26
Microvillous transformation	27	12
Electron densities/hyaline material	25	14
Mesangiopathic changes *	24	17
Microcysts	17	25
Mesangial electron dense deposits	22	24
Loss of primary processes	26	23
Condensation of cytoskeleton	23	28
Foot process effacement	28	27

Note: Pathology descriptors were ordered by the averaged ranks across two outcomes. *These descriptors were obtained from grouping individual descriptors. # No/minimal changes descriptor is the reverse of all the other listed descriptors.

PO1529

Natural History of Focal Segmental Glomerulosclerosis (FSGS): The UK National RaDaR Idiopathic Nephrotic Syndrome Cohort

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Background: Idiopathic FSGS is an important cause of proteinuric renal disease leading to ESKD. Here we describe the natural history of FSGS using the UK National Registry of Rare Kidney Diseases Idiopathic Nephrotic Syndrome (RaDaR-INS) Cohort, including retrospective and prospective data from 3907 patients with nephrotic syndrome (NS) not attributable to glomerulonephritis or systemic disorders recruited from 107 adult and paediatric kidney units across the UK since 2010.

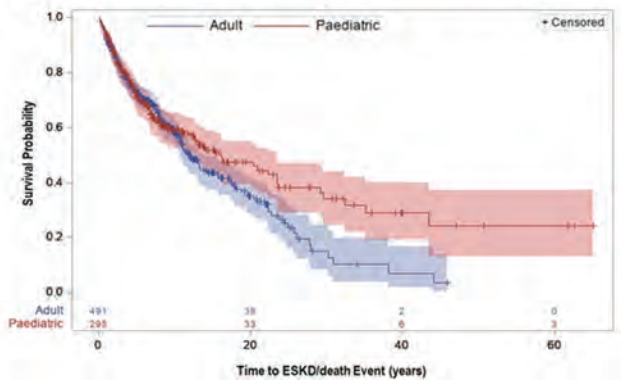
Methods: Participants included those with biopsy-proven or monogenic FSGS and ≥12 mo. observation from baseline. Patients with ESKD (CKD stage 5 or on renal replacement therapy) at or prior to baseline were excluded. Baseline date was defined as first database occurrence of renal biopsy, primary renal diagnosis, NS symptoms, PCR ≥1 g/g, or initiation of immunosuppression. Renal survival was defined as absence of ESKD or death with survival time calculated from baseline to last follow-up.

Results: Of 786 FSGS patients meeting eligibility, median baseline age was 28 yrs (IQR 9-49) with paediatric patients representing 38% of the study population. Median proteinuria at baseline was 5.9 g/g (IQR 3.3-11.0; n=140), while mean eGFR was 163 mL/min/1.73m^2 (SD 47; n=69) and 71 mL/min/1.73m^2 (SD 32; n=103) for children and adults, respectively. Median follow-up duration was 9.7 yrs (IQR 5.7-16.1) with ESKD/death events occurring in 46% of patients (1% death). Kaplan-Meier survival curves of children and adults show 50% renal survival probability of 16 years & 12 years, respectively (Figure 1).

Conclusions: The RaDaR-INS Cohort represents a large study population with lengthy follow-up data. These analyses indicate rapid progression and poor outcomes, highlighting a need for effective treatments for patients with FSGS.

Funding: Commercial Support - Travere Therapeutics

Figure 1: Kaplan-Meier survival curves (incl. 95% CI) of paediatric and adult FSGS patients



PO1530

Proteinuria End Points and Associations with Renal Survival in FSGS: Analysis of the UK National RaDaR Idiopathic Nephrotic Syndrome Cohort

Moin Saleem,[1,2] Jonathan Barratt,[9,10] Fiona E. Braddon,[3,12] Kevin Carroll,[11] Ulysses A. Diva,[6] Bruce M. Hendry,[6] Alex Mercer,[7] David Pitcher,[3,12] Retha D. Steenkamp,[3,12] A. Neil Turner,[8] Daniel P. Gale.[4,5] *[1]University of Bristol, Bristol, United Kingdom; [2]Bristol Royal Hospital for Children, Bristol, United Kingdom; [3]UK Renal Registry, Bristol, United Kingdom; [4]Royal Free Hospital, London, United Kingdom; [5]University College London, London, United Kingdom; [6]Travere Therapeutics Inc, San Diego, CA; [7]JAMCO Pharma Consulting, Stockholm, Sweden; [8]University of Edinburgh, Edinburgh, United Kingdom; [9]University of Leicester, Leicester, United Kingdom; [10]Leicester General Hospital, Leicester, United Kingdom; [11]KLC Statistics Ltd, Cheshire, United Kingdom; [12]The Renal Association, Bristol, United Kingdom.*

Background: In patients with FSGS, severity of proteinuria (PU) at onset and during follow up is associated with renal failure. In this study, we tested for associations between defined PU endpoints and renal survival in patients with FSGS from the UK National Registry of Rare Kidney Diseases Idiopathic Nephrotic Syndrome (RaDaR-INS) Cohort.

Methods: A total of 225 biopsy-proven or monogenic FSGS pts met study eligibility criteria, including a nephrotic PU value (≥3.5 g/g), a follow-up PU within 6-12 mo. and no ESKD (eGFR <15 mL/min/1.73m^2 or on renal replacement therapy) or death prior to first PU follow-up. Baseline pertains to first nephrotic PU value (T0 for survival analyses). Applied PU responder/non-responder definitions are described (Table 1). Time to ESKD/death was analysed using accelerated failure time modelling of the Weibull distribution.

Results: Within 6-12 mo. from baseline, 63% of patients achieved complete or partial remission (CR/PR), while 37% were non-responders (NR). Applying the FSGS partial remission of PU endpoint (FPRE) and including CR patients, 49% met this definition (CR/FPRE-R), while 51% were FPRE-NR. A higher probability for survival was observed among patients achieving remission definitions (Figure 1), extending median time to ESKD/death by ≈8 years for CR/PR vs NR, and ≈17 years for CR/ FPRE-R vs NR (Table 1) independent of initial PU level. Further analyses are ongoing.

Conclusions: Achieving partial or complete remission of PU is associated with clinically meaningful increases in time FSGS patients are alive and free from ESKD.

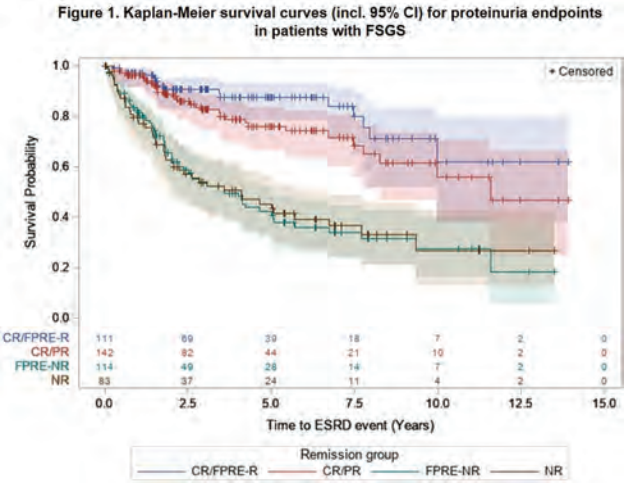
Funding: Commercial Support - Travere Therapeutics

Table 1: Proteinuria endpoints, events, and median time to ESKD/death by accelerated failure time modeling

	Proteinuria endpoints: PCR during follow-up (6-12 months from first nephrotic range PCR value)	Patients achieving proteinuria endpoint (n)	ESKD/death events (n)	Median time to ESKD/death Years (90% CI)*
Complete or Partial Remission (CR/PR)	PCR <3.5 g/g AND 50% decrease in PCR from first value ≥3.5 g/g	142	32	12.3 (8.6-17.6)
Non-Responder (NR)	Not achieving PCR <3.5 g/g AND 50% decrease in PCR from first value ≥3.5 g/g	83	45	4.2 (3.0-5.8)
CR or FPRE-Responder (CR/FPRE-R)	PCR <1.5 g/g AND 40% decrease in PCR from first value ≥3.5 g/g	111	16	20.8 (11.0-39.3)
FPRE non-responder (FPRE-NR)	Not achieving PCR <1.5 g/g AND 40% decrease in PCR from first value ≥3.5 g/g	114	61	4.1 (3.2-5.3)

*Accelerated failure time modeling

Figure 1. Kaplan-Meier survival curves (incl. 95% CI) for proteinuria endpoints in patients with FSGS



PO1531

Clinicopathological Characteristics of Adult Patients in the United States with Focal Segmental Glomerulosclerosis (FSGS)

Katherine R. Tuttle,[1] Clint Abner,[2] Kerime Ararat,[2] Patrick D. Walker,[2] Amin Yakubu,[3] Martin C. Bunke.[4] *[1]University of Washington, Spokane, WA; [2]Arkana Laboratories, Little Rock, AR; [3]Genesis Research, LLC, Hoboken, NJ; [4]Travere Therapeutics Inc, San Diego, CA.*

Background: Focal segmental glomerulosclerosis (FSGS) is a common histopathologic lesion of glomerular injury in patients with nephrotic syndrome. These analyses characterize clinical and histological features of FSGS in adults at time of kidney biopsy.

Methods: A retrospective study was performed using data from the Arkana Biopsy Database (January 1, 2016 to May 31, 2020) in patients that met study criteria, which included: ≥18 yrs, ≥1 FSGS positive kidney biopsy, and no prior kidney transplant, and available data on race/ethnicity. Outcomes included clinical and histologic characteristics. eGFR was calculated using CKD-EPI-creatinine equation without race modifier.

Results: Of 64,105 adult kidney biopsies performed during the study period, 2,065 (3.2%) FSGS positive cases were identified and 1,482 pts (71.8%) evaluated met study criteria. Demographic characteristics included: 56.2% male, 55.1% White, 32.1% African American (AA), 7.7% Hispanic and 3.4% Asian. Overall mean (SD) age at biopsy was 49.0 (17.2) with older ages in Whites (52.8 (17.3) yrs) and younger ages in Hispanics (39.4 (15.8) yrs). Mean urine protein to creatinine ratio was similar by race/ethnicity (range 5.1-6.0 g/g). Asians were more frequently biopsied at eGFR Stage 4 (32.7%) compared to other race/ethnicity groups: AAs (29.0%), Whites (23.1%), and Hispanics (18.7%). The highest rates of ≥50% global glomerular sclerosis (GS) were observed in AAs (31.1%) and lowest in Whites (14.6%). Whites (51.9%) and AAs (39.7%) exhibited the highest rates of severe foot process effacement (≥80%), while interstitial fibrosis and tubular atrophy ≥50% was more common in AAs (34.6%) compared to Hispanics (27.2%), Asians (17.7%) or Whites (14.7%). Of all FSGS types, "not otherwise specified" was most common across all race/ethnicity groups (range 64.2-75.4%). Among other FSGS types, tip lesion was most frequent in Whites (21.5%) and collapsing was most frequent in AA patients (12.4%).

Conclusions: Non-White patients are more frequently diagnosed with FSGS at later CKD stages with advanced GS. Strategies to improve earlier awareness and detection of FSGS are needed to allow effective intervention before severe kidney damage has occurred.

Funding: Commercial Support - Travere Therapeutics

PO1532

Long-Term Outcomes of Patients with Focal and Segmental Glomerulosclerosis Treated with Tacrolimus

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Background: Tacrolimus (TAC) is used to treat Focal and Segmental Glomerulosclerosis (FSGS). Prolonged treatment is often required and there is little data on long-term outcomes.

Methods: This is a retrospective study of 29 patients who received TAC as first line immunosuppression for nephrotic syndrome (NS) secondary to FSGS from December 2007- January 2020 at our institution.

Results: Mean follow up was 59.6 months (12– 144). The mean age at diagnosis was 42 years (range 18-85). 52% were Male. 59% were White, 10% Black, 21% Asian, 3% Chinese, 7% Other. Baseline mean eGFR was 64.4ml/min (18-90). 23/29 (79%) obtained complete (CR) or partial remission (PR) of NS, at a mean time of 5.09 months (range 1-31 months). 6/29 (21%) did not enter remission with TAC. 2/6 subsequently achieved

remission with CyP and prednisolone/rituximab. 7/23 (30%) patients who achieved remission with TAC had at least one relapse. 4/7 after stopping TAC, 1/7 during TAC wean and 2/7 with therapeutic TAC levels. 4/7 were treated by restarting or increasing TAC, 1/7 also had steroids added, 1/7 received rituximab (achieving remission) and 1/7 was not further treated with immunosuppression. 4/4 restarted with TAC monotherapy reachieved remission. 16/23 (70%) patients did not relapse and 7 of these remain off TAC and in remission (mean follow up of 92.6 months). At 1 year, the mean eGFR was 67.4 ml/minute (21-90). 1/29 patient developed end-stage kidney disease (ESKD) at 2 months. This patient had not responded to TAC. 16 patients have 5-year-follow up. The mean eGFR was 66.5 ml/minute (11-90). 1 further patient developed ESKD (this patient had not responded to TAC nor subsequent immunosuppression). 4 patients have 10-year follow-up. The mean eGFR was 80.8 ml/minute (67-90). 3 further patients developed ESKD. 1/3 had achieved PR, 1/3 had achieved CR but had multiple relapses despite re-treatment and 1/3 had CR but defaulted from follow up, presenting with ESKD 6 years later.

Conclusions: The long-term data from this study suggests tacrolimus can be effective in both achieving and maintaining remission of NS in FSGS. CR is associated with good long-term outcomes in most patients although relapse can occur and long term careful follow up is required. Non-responders have a worse outcome, although some patients do respond to alternative immunosuppression.

PO1533

Collapsing FSGS in a Patient with Acute Myeloid Leukemia and Prior COVID-19 Infection

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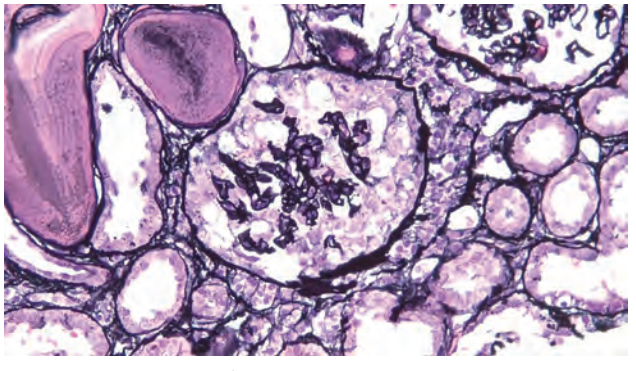
Introduction: Collapsing focal segmental glomerulosclerosis (c-FSGS) has been independently associated with COVID-19 infection, acute myeloid leukemia (AML), and apolipoprotein L1 (APOL1) risk variants. We describe a patient with homozygous APOL1 G1 risk allele and AML who developed renal failure due to c-FSGS and acute tubular injury.

Case Description: A 25-year-old male with a history of mild asthma and COVID-19 infection 1 month prior presented with a 3-week history of severe fatigue, weight loss, persistent dyspnea, and fevers. He was found to have leukopenia, thrombocytopenia, an acute kidney injury, and nephrotic range proteinuria. The patient was diagnosed with AML by bone marrow biopsy (BMBx). At presentation, his serum creatine was 2.8 mg/dL, which rapidly increased to 6.9 mg/dL over 2 weeks. Urine protein:creatinine ratio (UPCR) was 3.4g/g on admission. Renal biopsy demonstrated c-FSGS (Figure) and diffuse acute tubular injury. He was treated with standard remission induction therapy for AML with 7+3 therapy (7-day continuous infusion of cytarabine, daunorubicin on days 1-3, and high dose steroids). High dose steroids were continued for c-FSGS treatment with plan for a slow taper over several months. Within a few days of starting 7+3 treatment, his renal function began to improve. His 14-day BMBx demonstrated a hypocellular marrow consistent with complete remission. After 1 month, his creatine improved to 1 mg/dL, along with improvement in his serum albumin. Repeat UPCR is pending.

Discussion: COVID-19 is associated with immunologic alterations precipitating c-FSGS, especially in patients with APOL1 high risk alleles. Additionally, FSGS has been reported in AML, but the etiology behind glomerular pathologies in AML is unclear and likely multifactorial. Studies have indicated immunologic dysregulation related to leukemia, as well as viral-related etiologies. The trigger for c-FSGS in our patient is uncertain.



Light microscopy demonstrated focal and segmental glomerulosclerosis with global and segmental collapse.

PO1534

Role of LDL-Apheresis in Management of Glucocorticoid-Resistant Minimal Change Disease

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Introduction: Minimal Change Disease (MCD) is described as diffuse podocyte foot process effacement on kidney biopsy, resulting in nephrotic proteinuria, >3 grams/day. Glucocorticoids (GC) are the mainstay of therapy and most patients achieve complete remission in a few months. 7-12% patients, however, have GC-resistance and thus limited treatment options. Often, they are suspected of having focal segmental glomerulosclerosis (FSGS) due to biopsy sampling error. We present a challenging case of GC-resistant MCD, managed with immunosuppression, and ultimately lipid (LDL) apheresis.

Case Description: An otherwise healthy 20-year-old male presented for sudden onset lower extremity swelling and 10-pound weight gain. Work up including ANA, C3, C4, p-ANCA, c-ANCA, serum and urine immunofixation and renal ultrasound were unremarkable. Notably, LDL was 390 mg/dL, proteinuria of 9 grams/day and serum creatinine (Scr) of 0.96 mg/dL. Kidney biopsy revealed diffuse podocyte effacement, consistent with MCD. He was treated with oral prednisone 1 mg/kg/day and diuretics for several weeks with minimal symptomatic improvement and had worsening kidney function, Scr 1.5 mg/dL and proteinuria of 36 grams/day. Unfortunately, he also contracted COVID-19 disease prior to second kidney biopsy. Repeat kidney biopsy revealed acute tubular necrosis along with widespread podocyte effacement, without sclerotic lesions, ~10% interstitial fibrosis and tubular atrophy. He was empirically treated with tacrolimus for FSGS. However, proteinuria continued to worsen and peaked at 83 grams/day. Ultimately diagnosed as GC-resistant MCD, he was weaned off steroids, he was referred for LDL-apheresis therapy. He is maintained on tacrolimus and LDL apheresis with symptomatic improvement, still has significant proteinuria of 67 grams/day and advanced chronic kidney disease (CKD).

Discussion: The exact pathophysiology of nephrotic syndromes is unclear, mechanisms of T-cell dysfunction causing production of glomerular permeability factor and nephrotoxic hyperlipidemia have been described. In cases of GC-resistant diseases, immunosuppression has only been partially successful. LDL-apheresis has a role in the management of such nephrotic syndromes, thought to reduce circulating lipid induced disruption of podocyte integrity, and help prevent decline of kidney function and decrease proteinuria as seen in this patient.

PO1535

Infliximab-Associated Minimal Change Disease in an Adult with Ulcerative Colitis

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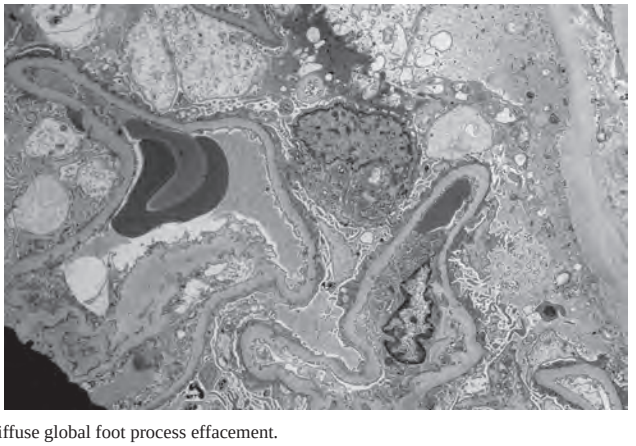
Introduction: Tumor necrosis factor-alpha (TNF-α) inhibitors are increasingly utilized for the treatment of several autoimmune conditions. They have been associated, in rare cases, with renal complications. We report a patient who developed minimal change disease (MCD) and interstitial nephritis while being treated with infliximab (IFX) for ulcerative colitis (UC).

Case Description: A 48-year-old male with a history of primary sclerosing cholangitis, liver transplant 8 years prior, psoriasis, and UC well-controlled on monthly IFX presented with a one-week history of lower extremity swelling, dyspnea, and weight gain. He was found to have rapidly progressive renal failure and nephrotic syndrome. Laboratory data showed a serum creatinine of 11mg/dL up from 1mg/dL 3-weeks prior and urine protein:creatinine ratio (UPC) of 11g/g. Renal biopsy demonstrated acute interstitial nephritis (AIN) on light microscopy. Electron microscopy revealed global podocyte activation and foot process effacement, consistent with MCD (Figure). He continued to become progressively oliguric despite escalating doses of diuretics and received two days of hemodialysis due to volume overload. After a total of 7 days of high dose steroids, his urine output increased and hemodialysis was stopped. IFX was discontinued due to the association of TNF-α inhibitors with MCD and AIN. After a month of prednisone, his creatine improved to 1.6 mg/dL and UPC improved to 0.3g/g.

Discussion: This is the first report of IFX associated MCD. Although IFX has been associated with IgA nephropathy, crescentic glomerulonephritis, renal artery occlusion, membranous glomerulopathy, and AIN in patients with spondyloarthritis spectrum diseases, no reports exist in the literature regarding MCD. However, several case reports of Etanercept, another TNF-α inhibitor, associated with MCD exist. TNF- α inhibitors are implicated in immunoregulatory effects in the kidney, which are not well understood.



Diffuse global foot process effacement.

PO1536

Anti-Phospholipase A2 Receptor Antibody Levels in Asian Patients with Primary Membranous Nephropathy: A Territory-Wide Study

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Background: Different cut-off values of anti-phospholipase A2 receptor (anti-PLA2R) antibody for differentiating between primary membranous nephropathy (PMN) and secondary membranous nephropathy have been reported. The optimal anti-PLA2R levels to reflect disease activity states in Asian patients with PMN remain undefined.

Methods: We conducted a territory-wide study in Hong Kong to investigate the serum anti-PLA2R levels in Chinese patients with PMN during 2017-2020. Anti-PLA2R levels were measured by commercial ELISA kits (EuroImmun, Germany) in serum samples collected from biopsy-confirmed PMN patients during active disease or remission, and their predictive values for active PMN were evaluated.

Results: Forty hundred and six serum samples from 320 PMN patients were analysed. 319 samples were obtained during active disease and 87 during disease remission. Anti-PLA2R titres during active disease were significantly higher than that during remission (95.1±235.0 RU/mL vs. 1.9±3.9 RU/ml respectively, p<0.001). Using 20 RU/ml as cut-off, the sensitivity (SN) and specificity (SP) for predicting active disease were 39% and 98% respectively [AUC 0.68, p<0.001; positive predictive value (PPV) and negative predictive value (NPV) were 98% and 30% respectively]. Using 10 RU/mL as cut-off, the SN and SP for diagnosing active PMN were 46% and 95% respectively [AUC=0.71, p<0.001; PPV and NPV were 97% and 32% respectively]. Anti-PLA2R titres correlated with urine protein-to-creatinine ratio and 24-hr urine protein levels (r= 0.32 and 0.37 respectively, p<0.001 and <0.001).

Conclusions: Anti-PLA2R showed good SP and PPV prediction for active PMN in Chinese patients, and correlated with severity of proteinuria. A lower threshold (≥10 RU/mL) may show improved SN for predicting active PMN in Asian patients.

PO1537

Qualitative and Quantitative Dosage of the Anti M-Type Phospholipase A2 Receptor Autoantibody: One-Year Experience in Quebec's Reference Center

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Background: Dosage of the M-type phospholipase A2 receptor antibodies (anti-PLA2R) is now an essential tool for diagnosis and management of primary membranous nephropathy (MN). Since October 2018, Hôpital Maisonneuve-Rosemont (HMR) has been designated as Quebec's reference center for serum anti-PLA2R antibody testing by the *Institut National d'Excellence en Santé et Services Sociaux* (INESSS), the regulatory body on drugs and tests usage in Quebec.

Methods: All patients who had a serum anti-PLA2R antibody testing performed at HMR from October 1st, 2018 to October 1st, 2019 were included in the study. Serum anti-PLA2R antibodies were screened by a qualitative test, followed by a quantitative test if the results were undetermined or positive. We calculated sensitivity, specificity, predictive value, and likelihood ratio for both tests, using kidney biopsy findings as the gold standard.

Results: In the province of Quebec, a total of 1690 tests were performed among 1025 patients during the study year. A small proportion of these patients (8%) were followed at HMR. Patients tested at HMR and in the rest of Quebec had similar characteristics. Test validity was only characterized for patients tested at HMR. Sensitivity and specificity were, respectively, 58% and 100% for the qualitative test, and 71% and 100% for the quantitative test. The combined net sensitivity was 42% and the net specificity, 100%. The net positive and negative predictive value were 100% and 84% respectively, whereas the net negative likelihood ratio was 0.58.

Conclusions: Serum anti-PLA2R antibody testing was widely used in Quebec during its first year of availability. In one of the biggest real life cohort described, the test performed as previously described in the literatur. Moreover, the two-step approach that was used at HMR, using a qualitative test before a quantitative test if needed, appears to be an efficient way to avoid quantitative testing in negative patients and to better characterize undetermined results on immunofluorescence.

Funding: Government Support - Non-U.S.

PO1538

Clinical Relevance of NELL1 Antibodies in Patients with Membranous Nephropathy

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Background: NELL1 was identified as a potential novel target antigen in membranous nephropathy (MN). Here, we studied the association of NELL1-antibody (ab) with treatment response and prognosis in a large cohort of MN patients.

Methods: Circulating NELL1-ab were detected by Western blot in a prospective cohort of 87 PLA_2R- and THSD7A-ab negative MN patients, 130 PLA_2R- or THSD7A-ab positive MN patients and 116 control patients with a biopsy-proven GN other than MN. Clinical follow-up included treatment, remission or relapse of proteinuria and development of kidney function.

Results: NELL1-ab were identified in 18 (21%) patients with PLA_2R- and THSD7A-ab negative MN but none of the control cohorts' patients. We identified NELL1-specific IgG1, IgG2, IgG3 and IgG4 subclasses in the serum of 12 (67%), 7 (39%), 11 (61%) and 15 (83%) NELL1-ab positive patients, respectively. NELL1-ab positive patients were significantly (p<0.05) older compared to PLA_2R-ab positive patients or MN patients without known target antigen (median age 70 vs 58 vs 58 years). Within 6 months of MN diagnosis, a malignant tumor was identified in 2 (11%) NELL1-ab positive, 7 (6%) PLA_2R-ab positive, 3 (50%) THSD7A-ab positive and 7 (10%) MN patients without known target antigen. 14 NELL1-ab positive patients were observed over a median follow-up of 75 months. One patient presented with eGFR < 30 ml/min due to severe hypertensive and diabetic kidney damage and developed ESKD after 69 months. All other 13 patients had a remission of proteinuria. 12 (92%) patients had a complete remission, although only 4 patients received an immunosuppressive therapy. Remarkably, of the 9 untreated patients with complete remission of proteinuria, 4 patients had persisting NELL1-ab in the circulation over the whole observation period and 2 patients reached complete remission of proteinuria before NELL1-ab disappeared. Renal function was stable in NELL1-ab positive patients but showed a more pronounced decline in NELL1-ab negative patients.

Conclusions: NELL1-ab positive MN patients had slightly more often a malignant tumor, but also were significantly older compared to PLA_2R-ab positive patients. Overall, NELL1-ab positive patients had a good prognosis. The presence of NELL1-ab in the serum did not show a close association with disease outcome.

Funding: Government Support - Non-U.S.

PO1539

Non-Pathogenetic THSD7A Antibodies in a Patient with No Membranous Nephropathy

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Background: PLA_2R- and THSD7A-antibodies (ab) are considered to be specific for the diagnosis of membranous nephropathy (MN). There is a controversial discussion whether the detection of circulating PLA_2R- or THSD7A-ab is sufficient to diagnose MN, without the need of a kidney biopsy.

Methods: Circulating THSD7A-ab were detected and their specificity evaluated by an indirect immunofluorescence test (IIFT), reducing, non-reducing and native Western blot techniques as well as a live cell assay. The kidney biopsy was investigated by immunohistochemistry and electron microscopy.

Results: A patient presented with high level proteinuria and was tested positive for THSD7A-ab using IIFT. Except for the diagnosis of diabetes mellitus, the medical history of the patient was unremarkable. Because of persistent proteinuria and a decline of kidney function, a kidney biopsy was performed, showing the diagnosis of diabetic nephropathy and excluding MN. A detailed biochemical characterization of the THSD7A-ab was performed to clarify these discrepancies between the serological and histomorphological findings. The circulating THSD7A-ab from the serum of the patient bound to recombinant THSD7A in the IIFT, co-localizing with THSD7A in co-immunofluorescence staining experiments and reacted with purified THSD7A in reducing WB analyses. However, these antibodies did not bind THSD7A derived from human glomerular tissue in any experimental condition (reducing, non-reducing, native). Moreover, the circulating THSD7A-ab did not recognize recombinant THSD7A under native conditions in the native Western blot or live cell assay. In contrast, THSD7A-ab from MN patients recognized native THSD7A in all experiments.

Conclusions: We show for the first time the existence of non-pathogenetic THSD7A-ab, which are not able to bind THSD7A *in vivo* and can hence not induce MN. Nevertheless, their presence can be detected by different assays, leading to false-positive results for pathogenic circulating THSD7A-ab. In cases of low THSD7A-ab positivity in IIFT, findings from different diagnostic tests such as kidney biopsy, Western blot analyses and live cell assays should be integrated in making a safe diagnosis of THSD7A-ab positive MN.

Funding: Commercial Support - Euroimmun AG, Lübeck, Germany, Government Support - Non-U.S.

PO1540

Urinary NPHS2-mRNA in Relation to Glomerular and Tubular Damage Markers in Patients with Membranous Nephropathy

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Background: Measurement of podocyte-specific mRNA in patients' urine samples has been proposed as a novel tool to monitor podocyte loss in glomerular disease, and may have prognostic value. In our hospital, we routinely measure timed urinary excretion of high- and low-molecular weight proteins as prognostic markers in patients with membranous nephropathy (MN). Here, we investigated the relationship between *NPHS2*-mRNA and high- and low-molecular weight proteins in patients with MN.

Methods: We included 35 patients with MN (80% male, median age 67, median eGFR 63). *NPHS2*-mRNA was measured in urinary pellets as described by Wickman *et al.* (JASN 2013). Normal values of urinary *NPHS2*-mRNA were obtained in spot urine samples of 19 healthy controls.

Results: Clinical characteristics and results of urinary measurement are shown in Table 1. Mean urinary *NPHS2*-mRNA/creatinine ratio (UPodCR) was 64 fold higher in patients with MN versus healthy controls. UPodCR showed weak but significant correlations with urinary IgG excretion and proteinuria selectivity index (Figure 1), but not with total proteinuria or eGFR (Table 1).

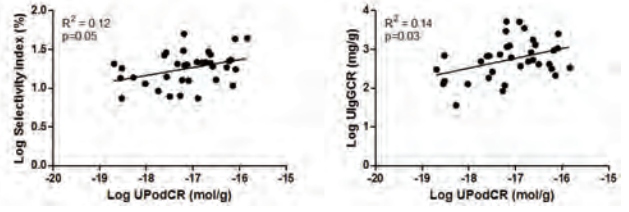
Conclusions: Urinary excretion of *NPHS2*-mRNA correlated significantly with protein markers of glomerular damage in patients with MN. However, correlations were weak. Prospective studies are needed to evaluate if urinary *NPHS2*-mRNA excretion holds independent prognostic value.

Table 1. Characteristics of patients with membranous nephropathy (N=35)

Characteristic		Correlations with UPod
Serum creatinine (µmol/L)	102 (82-124)	0.02 (0.37)
Selectivity index (%)	19.8 (12.7-23.2)	0.12 (0.05)
UAlb (g/g creat)	3.0 (2.2-5.1)	0.02 (0.47)
UIgG (mg/g creat)	143.2 (74.3-332.0)	0.14 (0.03)
Ualpha-1m (mg/g creat)	45.7 (25.3-67.6)	0.03 (0.32)
Ubeta-2m (mg/g creat)	1.6 (0.3-4.0)	0.07 (0.14)
UPod (ng/g creat)	4.4e-4 (1.6e-4-1.6e-3)	

Continuous variables are expressed as Median (interquartile range). Correlations are expressed in Spearman's R2 (p-value). UAlb = Urinary albumin, UPod = Urinary NPHS2 mRNA.

Figure 1. UPodCR correlations with protein markers of glomerular injury



PO1541

Urine Biomarkers Predict Treatment Response in the MENTOR Study

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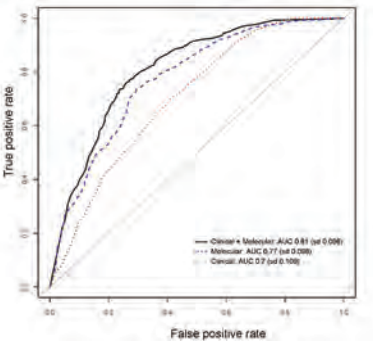
Background: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. The outcome of patients with MN is highly variable and clinical parameters do not reliably identify which patients will respond to immunosuppressive therapy (IS). In the MENTOR trial >40% of subjects did not achieve complete or partial remission (CR/PR) of proteinuria by 12 months despite IS with rituximab or cyclosporine, exposing them to unnecessary IS and portending potentially poor prognosis. We evaluated whether a panel of urinary molecular markers of kidney inflammation and fibrosis improves the ability to identify treatment responders in the MENTOR trial beyond clinical data alone.

Methods: We measured the abundance of 55 urinary cytokines, metalloproteases and their inhibitors at the time of randomization in 104 subjects using a Luminex-based multiplex assay. The primary outcome of interest was achievement of CR/PR at 12 months.

Results: Patients achieving CR/PR had significantly higher CrCl (94.25 ±31.42 vs 75.17 ± 28.52 mL/min/1.73m^2, p=0.002) and lower anti-PLA2R titre (168.5 IQR 20.5,341 vs 549 IQR 115.5,1345 U/mL, p= 0.0002) at baseline. Stepwise selection identified 3 clinical variables (CrCl, PLA2R, treatment) and 8 urinary proteins (IL9, IL10, GM-CSF, VEGF-A, TGFα, MMP2, MMP3, MMP10) associated with CR/PR. A model including the clinical and molecular variables improved discrimination of patients who are predicted to achieve CR/PR compared to a model containing clinical variables alone (ANOVA test p-value = 1.30x10^{-5}, AUC 0.81 ± 0.096 vs. 0.70 ± 0.109).

Conclusions: In summary, measurement of a panel urinary molecular markers improves the ability to predict remission at 12 months in patients with MN. Improved prediction of patients resistant to standard therapy using non-invasive markers has potential to offer more individualized treatment, to spare unnecessary treatment toxicity and to identify patients who may benefit from trials of novel therapeutic agents.

Figure: Receiver operating characteristic (ROC) curves for the prediction models selected by stepwise regression.



PO1542

Use of Urinary Proteins as Predictors of Response to Immunosuppressive Treatment in Membranous Nephropathy

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Background: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. Prognosis is defined by remission in proteinuria. Response to immunosuppression agents such as calcineurin inhibitors and rituximab vary. While the presence of anti-PLA2R antibodies may help to guide prognosis and treatment strategies, further identifying biomarkers that could refine treatment decision would be useful. Using data from the MENTOR trial (NEJM 2019), we evaluated whether 24-hour total urinary protein, urinary albumin, immunoglobulin M (uIgM), immunoglobulin G (uIgG), and urinary alpha 1 microglobulin (uα1m) at baseline could be used to predict response to immunosuppressive therapy at 12 months in patients with MN.

Methods: Logistic regression models were used to study the relationship between baseline urinary proteins with patients' treatment outcomes by treatment drug (rituximab or cyclosporine). The treatment outcome was defined as patients achieving either complete (CR; <0.3g/24 hours) or partial remission (PR; >0.3-<3.5g/24 hours) of proteinuria at 12 months.

Results: In both cyclosporine and rituximab arm, all urinary proteins exhibited a decline from baseline to 12 months post treatment. However, none of the baseline urinary proteins were found to be significantly associated with treatment response at 12 months (p>0.05 for all). Results were similar when restricted to patients with positive anti-PLA2R at baseline.

Conclusions: Baseline measures of the urinary albumin, uIgM, uIgG, and uα1m are not predictors of patients going into CR or PR at 12 months after treatment with rituximab or cyclosporine.

Table 1: Odds ratio of urinary protein predicting CR or PR at 12 months in patients treated with Rituximab or Cyclosporine (Fully Adjusted model)

Urinary Protein	Treatment Group	All Patients		Anti-PLA2R Antibody Positive Patients	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
α1M, per 10 mg / 24hr	Rituximab	1.018 (0.946, 1.096)	0.631	1.024 (0.939, 1.117)	0.591
	Cyclosporine	1.009 (0.950, 1.072)	0.767	1.006 (0.935, 1.082)	0.873
Albumin, per 100 mg / 24hr	Rituximab	0.996 (0.982, 1.011)	0.596	0.995 (0.978, 1.013)	0.577
	Cyclosporine	0.992 (0.978, 1.006)	0.270	0.990 (0.973, 1.007)	0.257
IgM, per 10 µg / 24hr	Rituximab	1.014 (0.984, 1.045)	0.369	1.015 (0.983, 1.047)	0.365
	Cyclosporine	1.012 (0.988, 1.036)	0.334	1.011 (0.986, 1.037)	0.388
IgG, per 100 mg / 24hr	Rituximab	0.988 (0.923, 1.057)	0.718	0.972 (0.901, 1.050)	0.472
	Cyclosporine	0.958 (0.909, 1.009)	0.101	0.941 (0.881, 1.004)	0.067

*Adjusted for adjust for age, sex, eGFR, and creatinine clearance

PO1543

APOL1 High-Risk Genotype Is Associated with Worse Renal Outcomes in Black Patients with Membranous Nephropathy

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Background: Black patients have a higher propensity for progression to end-stage kidney disease (ESKD) and this disparity persists in glomerular diseases studied thus far. Genetic variants in the Apolipoprotein L1 (*APOL1)* gene contribute to kidney disease burden in those with African ancestry. To date, there are no data on the role of *APOL1* risk alleles in outcomes among black patients with membranous nephropathy (MN).

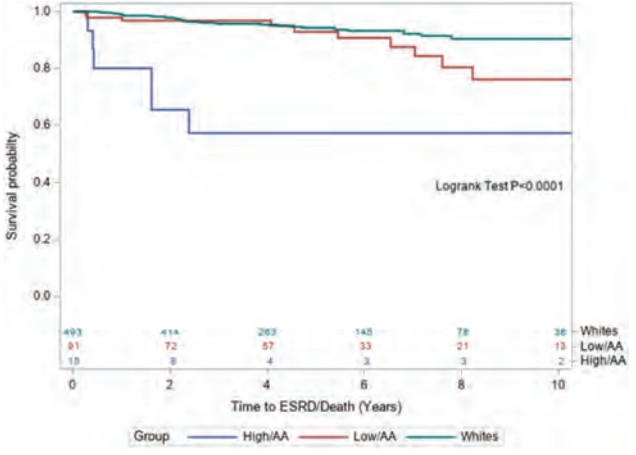
Methods: Sanger sequencing for *APOL1* risk allele genotyping was completed on patients of African-American ancestry (self or clinician reported) with diagnosis of MN enrolled in the Glomerular Disease Collaborative Network (GDCN) or Cure Glomerulonephropathy Network (CureGN) with DNA samples available were included.

White patients from CureGN were included for comparison. Data from CureGN or chart abstraction for GDCN patients were used to determine demographics, diagnosis, disease onset, and ESKD (dialysis initiation or transplantation). Fisher's exact, Wilcoxon rank, and Kaplan-Meier curves with log rank tests were used to evaluate differences between high risk (2 variants) and low risk (0/1 variant) and white population.

Results: There were 106 African American patients with diagnosis of MN in our study. Of these, 15 patients (14%) were high risk (two risk alleles of *APOL1*) and the remaining 91 patients (86%) were low risk (0/1 risk alleles of *APOL1*). Data were available for 493 white patients. Hazard ratio for composite outcome of ESKD/death was 4.21 (95% CI 1.54,11.51) among African Americans (high risk vs. low risk) and 6.37 (95% CI 2.74, 14.80) compared to white population. Time to endpoint was significantly faster in those with high risk *APOL1* genotype (Figure), p<0.0001.

Conclusions: High-risk *APOL1* genotype in African Americans is associated with faster time to ESKD/death compared to low-risk AA or white patients with MN.

Funding: NIDDK Support



PO1544

Treatment-Resistant Membranous Nephropathy in a Patient with NPHS2 Mutation

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Introduction: Membranous nephropathy (MN) is one of the most frequent causes of nephrotic syndrome (NS) in adults. NPHS2 gene encodes podocin, a protein of the slit diaphragm that is essential for recruitment of nephrin into the lipid rafts and for maintaining the glomerular filtration barrier. Recessively transmitted mutations in NPHS2 cause familial forms of steroid-resistant NS that progress to end-stage renal disease (ESRD).

Case Description: A 37-year-old male was referred to our clinic with NS and hypertension. Admission labs showed creatinine of 3 mg/dl, serum albumin of 3 g/dl, proteinuria of 20 g/d and microscopic hematuria (30 cells/µl). Immunological testing – ANA, ANCA, anti-C1q, anti-GBM – was negative, C3 and C4 were normal. Kidneys appeared normal on ultrasound examination. A renal biopsy was performed. Light microscopy revealed 19/23 glomeruli with global sclerosis and 4/23 glomeruli with thickening of GBM, podocyte hypertrophy and segmental sclerosis; there was also diffuse tubular atrophy, interstitial fibrosis and arteriolar hyalinosis. Electron microscopy showed subepithelial electron dense deposits with spike formation, with granular capillary loop staining for IgG4 in immunofluorescence. The histopathological diagnosis was stage II MN associated with diffuse glomerulosclerosis secondary to hypertension. In the meantime, the anti-PLA2R antibodies returned positive (titer 1/320). Therapy was started with Rituximab 1000 mg; a second dose was administered after 14 days. Despite treatment, NS persisted and kidney function worsened; hemodialysis was initiated 6 months after the diagnosis. One year later, the patient's 16-year-old son was diagnosed with NS, resistant to steroids. Genetic testing identified NPHS2 c.947C>T p.(Pro316Leu) heterozygous mutation in the family; the son was also heterozygous for c.3447dup, p.(Val1150Cysfs*39) in KANK1, inherited from the mother.

Discussion: Recent data suggest an important role of genes in the pathogenesis of MN; NPHS1 polymorphisms are associated with low remission rate after treatment and high disease progression. Our patient has a heterozygous mutation in NHPS2, resulting in abnormal signaling through the nephrin-podocin complex and podocyte disfunction. Therefore, it is very probable that in this case of primary MN genetics played a major role in treatment resistance and progression to ESRD.

PO1545

Primary Membranous Nephropathy Flare After COVID-19 Vaccination

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Introduction: Primary membranous nephropathy (MN) is most commonly due to phospholipase A2 receptor antibodies (PLA2R Ab). It is unclear whether the COVID-19 vaccine can trigger flares of glomerular diseases such as primary MN. We present a patient with MN and metastatic breast cancer who developed nephrotic syndrome after receiving her second mRNA-1273 COVID-19 vaccine with positive PLA2R Ab by ELISA suggesting MN flare.

Case Description: A 62 year old female with history of Stage IIIB T3N3M1 ER/PR positive HER-2 negative metastatic left breast invasive ductal carcinoma, hypertension, hyperlipidemia, and primary MN presented with bilateral leg edema, dyspnea, and proteinuria 2 weeks after COVID-19 vaccination. She had previous proteinuria of 7029 mg/24hr in August 2018 with PLA2R Ab 128 RU/mL in October 2018. She underwent modified radical mastectomy in September 2018 followed by adjuvant chemotherapy in November 2018, after which PLA2R Ab decreased to <2 RU/mL in February 2019 and urine protein/Cr ratio (UPCR) decreased to 1094 mg/g Cr in April 2019. She was diagnosed with metastatic breast cancer and started anastrazole transiently. She received mRNA-1273 COVID-19 vaccines in late January and February 2021. In March 2021, she presented with bilateral leg edema, dyspnea, and bilateral pleural effusions. Urinalysis had >1000 protein, 24hr urine protein 11.2 g, Cr 1.6 mg/dL, and PLA2R Ab 787 RU/mL. Renal biopsy showed immune complex-mediated glomerulopathy with positive PLA2R, consistent with primary MN stage II-III. Glomerular basement membrane deposits were strongly positive for IgG4. Electron microscopy showed numerous subepithelial and occasional intramembranous electron-dense immune-type deposits. She was treated with lisinopril and furosemide followed by rituximab in May 2021. Prior to rituximab PLA2R Ab was 342 RU/mL and UPCR was 8671 mg/g Cr.

Discussion: There is insufficient data on the risk of flare after COVID-19 vaccine in glomerular diseases. There have been a few case reports of primary MN and minimal change disease after COVID-19 vaccine as well as MN after influenza vaccine. Our case of primary MN flare after COVID-19 vaccine adds support to a potential association between SARS-CoV-2 antigens and loss of tolerance to the PLA2R antigen. Close follow-up of patients with primary MN and other glomerular diseases after COVID-19 vaccination is warranted.

PO1546

Primary Membranous Nephropathy Concurrent with ANCA-Positive Crescentic Glomerulopathy in a Hispanic Man

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Introduction: Primary membranous nephropathy (MN) is a common cause of glomerular disease in adults usually presenting with nephrotic syndrome. Crescents are an unusual finding in MN, its presence suggests a concomitant disease process, such as pauci-immune anti-neutrophil cytoplasmic antibody-related (ANCA) glomerulonephritis (GN).

Case Description: A 36-year-old Hispanic man presented with a 1-week history of worsening lethargy. Examination revealed an obese Hispanic man with rales on lung auscultation and lower-extremity edema. Laboratory results showed a serum creatinine (sCr) 8.8 mg/dL, BUN of 54 mg/dL. Urinalysis revealed 4+ protein, 25-50 red blood cells per hpf. Spot urine protein creatinine ratio (UPCR) was 19 g/g, p-ANCA titer 1:640. Urine toxicology screen was positive for cocaine. Other serologies and imaging were unremarkable. Renal biopsy showed MN with PLA2R positive staining as well as necrotizing and crescentic glomerulonephritis. Interstitial fibrosis and tubular atrophy were seen only in 10% of the sample. Management was initiated with a pulse of steroids followed by a taper, and renally dosed oral cyclophosphamide. The patient was initiated on hemodialysis due to uremic symptoms and volume overload. Three months after initiation of therapy, urine output significantly improved. Laboratory data showed: a 24 hours urine creatinine clearance of 31 ml/min, sCr 2.9 mg/dL, and UPCR 5.3 g/g. Patient was euvolemic. Hemodialysis was discontinued.

Discussion: MN and ANCA GN are distinct manifestations of renal injury with different clinical, laboratory, and pathology findings. Our case highlights an individual with both entities. We hypothesize that the patient's renal findings of p-ANCA and crescentic GN were likely associated with levamisole adulterated cocaine in the background of primary MN. The patient discontinued cocaine use after our discussions. We decided to treat the patient's MN with immunosuppressive therapy. Fortunately, the patient has responded favorably to our management with significant improvement in renal function.

PO1547

Clinical-Pathological Features of Podocyte Infolding Glomerulopathy

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Background: Podocyte infolding glomerulopathy (PIG) is characterized by presence of microstructural aggregates originated from cytoplasmic infoldings of podocytes in the glomerular basement membrane (GBM). Few PIG cases have been reported and the significance of this morphology is still unclear. This study aims to elucidate the incidence, clinical-pathological features and prognosis of PIG.

Methods: Renal biopsies with PIG features from January 2018 to December 2020 in Kingmed Diagnostic Laboratory were reviewed. Patients were divided into three groups according to their clinical and pathological findings.

Results: Among 87452 biopsies, 116 (1.37‰) cases were found to have features of PIG and 61 patients among them had complete clinical data and follow-up information. Most PIG cases were accompanied with other glomerular diseases, among which were 39 cases (63.9%) with lupus nephritis (Group PIG-LN), 14 cases (23%) with other glomerulonephritis such as membranous nephropathy, focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (Group PIG-GN). Only 8 cases (13.1%) presented with pure PIG with absence of immunoglobulins and complement deposits. In the PIG-LN group, most patients revealed presence of immunoglobulin deposits, with IgG in 84.6% of the patients, C3 in 74.4% and C1q in 69.2%. Similarly, electron dense deposits were seen in PIG-LN (61.5%) and PIG-GN (57.1%) in accordance with immunofluorescence. There is no significant difference in levels of proteinuria, hematuria and creatine among the three groups. Most patients in PIG-LN group showed increased ANA tier (100%) and decreased C3 level (84.6%). The patients in the pure PIG group showed more sensitivity to glucocorticoid therapy and got a significantly higher complete remission rate (75%) than those in group PIG-LN (53.8%) and group PIG-GN (14.3%).

Conclusions: PIG is a special type of podocyte injury, which is either a separate disease entity or concomitant with other GN, among which LN is the most frequent one. Patients with pure PIG tend to be more sensitive to glucocorticoid therapy compared with those coincide with other GN.

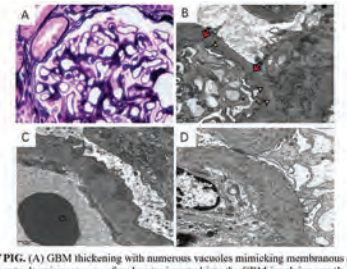

Figure 1. Different degree of PIG. (A) GBM thickening with numerous vacuoles mimicking membranous nephropathy; (PASM, ×600); (B) Mild PIG showing a few cytoplasmic processes of podocytes inverted into the GBM involving mostly the superficial area of GBM (C) Moderate PIG showing irregular GBM thickening with numerous podocytes cytoplasmic fragments extending into nearly half of the GBM; (D) Severely thickened GBM with a large number of cytoplasmic protrusions of podocytes involving the whole GBM layer.

Different degree of PIG.

PO1548

Baseline Characteristics of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits in the International Kidney Registry Consortium (K-REG)

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Background: Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) is a monoclonal gammopathy of renal significance-associated lesion unique for low rates of paraprotein and clone detection. Prognosis is poor with 30% of patients progressing to ESKD, but recent data suggest improved outcomes with clone-directed therapy regardless of clone-detection status. Here, we present the baseline kidney and hematologic characteristics of patients with PGNMID from the International Kidney Registry Consortium (K-REG).

Methods: PGNMID cases were identified retrospectively by K-REG sites. Baseline demographic, clinical, kidney biopsy, hematologic and treatment data were analyzed and stratified by presence or absence of clone detected, as well conservative vs. non-specific immunosuppression vs. clone-directed therapy prescribed.

Results: 134 patients from 15 sites in 3 countries with PGNMID were included, 13% of which had been included in previously published studies. The mean age was 57 (SD 17) years, 49 % of whom were female and 72% Caucasian. The median baseline eGFR was 35 (IQR 21-52) ml/min/1.73m^2 and median proteinuria 3.9 (IQR 1.5-7.2) g/day. IgG kappa was the most common involved paraprotein (61%). 30% of patients had a detectable circulating paraprotein by SPEP or sIFE and 11% by UPEP or uIFE. 75% of patients underwent a bone marrow biopsy. Overall, a clone was detected in 19% of patients. There were no significant differences in age, sex, race, baseline eGFR, or proteinuria based on clone or paraprotein-detection status. Clone-directed therapy was prescribed in 55% of patients, non-specific immunosuppression to 15% of patients and conservative therapy in 40% of patients. Clone-directed therapy was prescdribed in 82% of patients with a detectable clone vs. 52% of patients without a detectable clone(p=0.011).

Conclusions: In this large series of PGNMID, a minority of patients had detectable clone. Baseline demographic and clinical characteristics were not different based on clone-detection status but treatment varied significantly based on clone-detection status. Additional analyses of the K-REG cohort will provide insight into renal and hematologic responses.

PO1549

Kidney Outcomes in Biopsy-Proven Thrombotic Microangiopathy with Eculizumab Therapy

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Background: There are limited long-term data on kidney outcomes in eculizumab-treated patients with biopsy-proven thrombotic microangiopathy (TMA). We report our experience of using eculizumab in patients with primary (genetic/antibody mediated) TMA, secondary TMA syndromes associated with antiphospholipid syndrome (APS) or systemic lupus erythematosus (SLE), as well as TMA of undetermined etiology.

Methods: We reviewed adult patients with kidney biopsy-proven TMA treated with eculizumab between 2014-2019. Transplant recipients, pregnant patients and those with scleroderma, shiga-toxin related hemolytic uremic syndrome or thrombotic thrombocytopenic purpura were excluded. Kidney response to eculizumab at 26 weeks for patients not on kidney replacement therapy (KRT) and for those requiring KRT at the time of or within 1 week of initiation of eculizumab, was defined as an increase in eGFR of 15 ml/min/1.73m^2 and liberation from KRT respectively. Death within 26 weeks was considered lack of response.

Results: We collected data on 16 patients (primary TMA [n=3]; secondary TMA including SLE [n=3] and APS [n=4]; TMA of undetermined etiology [n=6]). The median time from biopsy diagnosis to treatment initiation was 3.0 days (IQR:-1.0,10.0) and the median duration of therapy was 303 days (IQR:160,604). 13 patients (81%) required KRT at the time of initiation of eculizumab. 4 patients died during follow up, 2 of whom died within 26 weeks. 6 (37.5%) patients exhibited kidney response to eculizumab, 5 of whom required KRT when therapy was started. 2 of 3 patients who did not need KRT initially eventually progressed to end-stage kidney disease after 1 and 5.5 years from treatment initiation. 3/6 patients (50%) and 3/8 patients (37.5%) with mild and moderate interstitial fibrosis and tubular atrophy (IFTA) on biopsy respectively responded to therapy, whilst those with severe IFTA (n=2) showed no response.

Conclusions: Although eculizumab use has been expanding rapidly for primary and secondary TMA syndromes, our data depicts a suboptimal kidney response, which appears independent of the need for KRT at treatment initiation. Severity of IFTA may be a predictor of kidney response to eculizumab. We suggest that more data is needed on long-term kidney outcomes with eculizumab across TMA syndromes before universally adopting this expensive therapeutic strategy.

PO1550

Recurrence of Atypical Hemolytic Uremic Syndrome After Kidney Transplantation: A Prospective Cohort Study

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Background: Since 2016, aHUS patients in the Netherlands are treated with a restrictive treatment protocol. Withdrawal of eculizumab is considered after a treatment period of three months. Furthermore, kidney transplantations in aHUS patients are performed without eculizumab prophylaxis, with initiation of eculizumab in case of post-transplant recurrence. This restrictive treatment protocol is monitored in the CUREiHUS study. Here, we present the CUREiHUS study results for kidney transplant patients.

Methods: All kidney transplant patients who received eculizumab therapy for a suspected aHUS recurrence, and who were included in the CUREiHUS study (after informed consent), were evaluated.

Results: In the period from January 2016 until October 2020 we included 15 (F 12, M 3; median age 42y, range 24-66) patients with suspected aHUS recurrence after kidney transplantation. Patients were classified as high (N=8) or moderate (N=7) recurrence risk. The time-interval to recurrence showed a bimodal distribution. Seven patients presented early after transplantation (median 3 m, range 0.3-8.8), with typical aHUS features: rapid eGFR loss and laboratory signs of TMA. Eight patients presented late (median 46m, range 18-69) after transplantation. Of these, 3 patients showed typical aHUS features, while in 5 patients no laboratory evidence of TMA was seen, and only a gradual eGFR loss. Treatment with eculizumab resulted in disappearance of TMA and improvement/stabilization of eGFR in 14 patients. Withdrawal of eculizumab was thus far proposed in 10 patients, and successful in only 5. Median follow-up after recurrence is 29 months (range 3-53 months). At last follow-up median eGFR was 32.0 ml/min/1.73m2 (range 7-80), considerably less than eGFR before recurrence (54.3 ml/min/1.73m2, range 22-103).

Conclusions: Patients with aHUS who develop recurrence after kidney transplantation do not fully recover kidney function. The major cause is treatment delay due to late recognition of disease recurrence in patients who present with a “creeping creatinine”. Discontinuation of eculizumab is often unsuccessful.

PO1551

A Case of Thrombotic Microangiopathy from an Intra-Abdominal Abscess

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Introduction: Infection mediated thrombotic microangiopathy (TMA) has a high mortality with many patients requiring kidney replacement therapy. Recognition of TMA can be difficult in the setting of sepsis as clinical abnormalities can overlap. We report a case of TMA from complicated diverticulitis and polymicrobial intra-abdominal abscess.

Case Description: A 25 year old non-vegetarian man presented with generalized abdominal pain, fatigue, chills and intermittent epistaxis. He was found to have severe acute renal failure with Coombs positive hemolytic anemia, thrombocytopenia, high fibrinogen, high PT/PTT, low ADAMTS13 activity (15%) and ADAMTS13 inhibitor. Further workup showed sigmoid diverticulitis with a large intra-abdominal and small intrahepatic abscess which was culture positive for *Streptococcus anginosus* (an oral microbe with proclivity to abscess formation) and *Escherichia coli*. Shiga toxin was not tested. Kidney biopsy revealed acute TMA. Drainage of the abscess and treatment with antibiotics resolved the systemic features of TMA. Renal recovery was protracted and the patient required dialysis for three months, with a last sCr of ~2mg/dl.

Discussion: Infection mediated TMA is an important third subgroup of thrombotic microangiopathy. The mechanism of injury is likely due to the concerted effort of both bacteria. *E.coli* produced shiga toxin causes direct damage to the endothelial cells, worsened by the incorporation of non-human sialic acid from dairy and meat, increasing toxin affinity to endothelial cells and injury. *S.anginosus* produces an exotoxin that can lyse erythrocytes and platelets allowing IgM binding to the exposed Tn antigen, leading to the coombs positivity observed. There is decreased hepatic synthesis of ADAMTS13 in sepsis, and ADAMTS13 autoantibodies are reported in *Ecoli* mediated TMA. Given high fatality rate, prompt recognition and treatment of the underlying infection is pivotal as ongoing infection propagates microangiopathy. Severe features of TMA can develop during the clinical course necessitating intensive treatments such as plasmapheresis. As infection can be a frequent trigger of TMA among patients with complement abnormalities, patients should undergo genetic testing of the regulatory genes involved in the complement system.

PO1552

Characteristics and Outcomes of Immune-Complex Membranoproliferative Glomerulonephritis and C3 Glomerulonephritis in Japan: A Retrospective Analysis of Data from the Japan Renal Biopsy Registry

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Background: The reclassification of membranoproliferative glomerulonephritis (MPGN) into immune-complex mediated MPGN (IC-MPGN) and C3 glomerulopathy (C3G) based on immunofluorescence findings in kidney biopsies has provided insights into two distinct diseases. C3G is further classified into dense deposit disease and C3 glomerulonephritis (C3GN) based on electron micrographic findings. Although these diseases have poor outcomes, limited Japanese literature confined to small, single-center cohorts exist on these diseases.

Methods: We retrospectively analyzed 81 patients with MPGN type I and III from 15 hospitals in the Japan Renal Biopsy Registry (J-RBR) to compare demographic, clinical characteristics and treatment outcomes of patients with IC-MPGN to those with C3GN.

Results: Of the 81 patients reviewed by immunofluorescence findings in kidney biopsies, 67 patients had IC-MPGN and 14 patients had C3GN. Age at diagnosis, systolic and diastolic pressures, proteinuria, impaired renal function, and hypoalbuminemia were significantly higher in patients with IC-MPGN than in those with C3GN. About 80% of the patients in both groups were treated with immunosuppressive therapy. At last follow-up (median 4.8 years), complete remission rate of proteinuria was significantly higher in patients with C3GN (64.3%) than in those with IC-MPGN (29.9%; P = 0.015). The renal survival rate was lower in patients with IC-MPGN when compared to C3GN (73.1% vs. 100%; log-rank, P = 0.031). Systolic blood pressure and renal function at baseline were independent predictors of progression to end-stage kidney disease.

Conclusions: The overall prognosis of patients with C3GN is more favorable than for patients with IC-MPGN.

Funding: Government Support - Non-U.S.

PO1553

Early Recurrence of C3 Glomerulopathy (C3G) in the Allograft

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Background: C3G encompasses both C3 glomerulonephritis (C3GN) and Dense Deposit Disease (DDD), a rare group of kidney diseases associated with alternative complement pathway dysregulation that commonly recurs in the allograft. How early recurrence occurs is underexplored.

Methods: We reviewed cases of recurrent C3G in the allograft at CUIMC. Protocol biopsies were encouraged for transplanted C3G patients (PTS) at 6 months if a for-cause biopsy (bx) had not already been performed. Median (range) reported.

Results: 13 PTS (9 C3GN, 4 DDD) were included (**Table 1).** 6 PTS (46%) had previous allografts fail due to C3G recurrence. Age at transplant was 32 years (18-71). Time from transplant to histologic recurrence was 54 days (5-472). 4 PTS (31%) had bland urine at first recurrence. 7 PTS (54%) had histologic recurrence at first allograft bx, 15 days (5-56) after transplant. After 2.3 years (0.33-10.1), 11 PTS (85%) remained with functioning allografts; 5 PTS (46%) had creatinine > 2 mg/dl. 2 DDD PTS had allograft failure. 6 PTS (43%) had acute T cell mediated rejection. 2 PTS received eculizumab-both were without clinical recurrence.

Conclusions: This series highlights earlier histologic recurrence of C3G in the allograft than previously reported, partly due to protocol bx. Many PTS were without urinary abnormalities. At last follow up, majority of PTS had significant transplant CKD and 2 lost their allografts. Future study is needed to better understand if early detection of recurrence, coupled with anti-complement therapies, improves outcomes.

Summary of Clinicopathologic Course After Histologic Recurrence

Patient ID	Transplant Type	Native Disease	Days to Histologic Recurrence	Protocol vs For Cause	Immunosuppression at Histologic Recurrence	Serum Creatinine (SCR) at Biopsy (mg/dl)	LM Findings at First Recurrence	Most Severe LM Findings on Follow Up	Most Severe Rejection on Follow Up	Allograft outcome	Eculizumab at last follow up	Follow Up Time OR Time to Allograft Failure (Years)
1	DDKT	DDD	24	For Cause	Tacrolimus, IVIG, Mycfortic	2.0	Mild Mesangial Proliferative	Mild Mesangial Proliferative	3A ACR	SCR 2.2, No hematuria, No proteinuria	Yes	3.2
2	LDKT	C3GN	12	For Cause	Tacrolimus, Mycfortic, Prednisone, Eculizumab	5.9	Mild Mesangial Proliferative	Mild Mesangial Proliferative	1B ACR	SCR 3.1, No hematuria, No proteinuria	Yes	3.4
3	LDKT	C3GN	5	Protocol	PLEX, Rituximab, IVIG (DSA+), Tacrolimus, Mycfortic, Prednisone	4.5	Mild Mesangial Proliferative	Diffuse Mesangial Proliferative with Mild Endocapillary Hypercellularity	1B ACR	SCR 2.9, Hematuria, Proteinuria	No	3.2
4	LDKT	DDD	472	Protocol	Tacrolimus, Mycfortic	1.5	LM negative, IF/EM+	LM negative, IF/EM+	None	SCR 1.4, No hematuria, No proteinuria	No	4
5	DDKT	C3GN	466	For Cause	Tacrolimus, Mycfortic	3.2	Mild Mesangial Proliferative	Mild Mesangial and Membranoproliferative, Severe Sclerosing	None	SCR 3.6, No hematuria, proteinuria	No	9.7
6	LDKT	C3GN	84	Protocol	Tacrolimus, MMF, Prednisone	1.5	LM negative, IF/EM+	Mild Mesangial Proliferative	None	SCR 1.5 No hematuria No proteinuria	No	2.3
7	LRKT	DDD	356	Protocol	Tacrolimus, MMF	1.9	Diffuse Mesangial Proliferative & Sclerosing	Mesangial and membranoproliferative proliferative, endocapillary proliferative, cellular crescents, severe sclerosing	2A ACR	Failed allograft, re-transplanted	No	10.1
8	DDKT	C3GN	54	For Cause	Belatacept, MMF	1.9	LM negative, IF/EM+	LM negative, IF/EM+	Chronic Active T Cell Mediated Rejection (borderline)	SCR 1.6, No hematuria, No proteinuria	No	2
9	DDKT	C3GN	21	For Cause	Tacrolimus, MMF	4.0	LM negative, IF/EM+	Mild Mesangial Proliferative	None	SCR 1.9, No hematuria, No proteinuria	No	2.3
10	LDKT	C3GN	8	For Cause	Tacrolimus, MMF	2.2	LM negative, IF/EM+	LM negative, IF/EM+	None	SCR 2.1	No	1.1
11	LDKT	C3GN	120	Protocol	N/A	2.0	LM negative, IF/EM+	Mild Mesangial Proliferative	Chronic Active T Cell Mediated Rejection (2A)	SCR 2.1	No	3
12	DDKT	DDD	80	For Cause	Tacrolimus, Mycfortic	2.1	LM negative, IF/EM+	Focal Sclerosing and Crescentic GN	None	Failed Allograft, on HD	No	0.33
13	LDKT	C3GN	15	For Cause	Tacrolimus, Mycfortic	1.6	LM negative, IF+	Mild Mesangial Proliferative	None	SCR 1.5, Hematuria, Proteinuria	No	3

PO1554

C3 Glomerulopathy in Children and Adolescents

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Background: C3 glomerulopathy (C3G) has been classified as a glomerular complement mediated disease with predominant C3 deposits almost a decade ago. Data regarding clinical course, treatment options and long term prognosis in children and adolescents is still scarce. The aim of the study was to retrospectively describe a single tertiary center's experience with C3G in the pediatric population, and correlate presentation, pathology, complement findings, response to treatment and disease prognosis.

Methods: A retrospective cohort study. Patients presented with C3G by the age of 18 years compromised the study group. All cases underwent kidney biopsy at presentation. Repeated kidney biopsy was performed on a need basis, in native or transplanted kidneys. Definition of C3G was based on the 2013 consensus guidelines. Patients underwent complement workup and genetic tests. Treatment regimen was not uniform.

Results: 17 patients were diagnosed with C3 glomerulopathy. Features of Dense deposit disease (DDD) were found in 8 patients, C3 glomerulonephritis in 6 patients. For 3 patients EM was not available. Mean age at diagnosis was 12.7 years (range 1.9 – 17.3). 6 girls and 11 boys. Median follow up 4.4 years (range 1.1-20.9). Treatment modalities ranged from ACE inhibitors and Angiotensin receptor blockers to corticosteroids, Mycophenolate Mofetil, Plasmapheresis, Rituximab and Eculizumab. Only 2 (12%) patients achieved complete remission. 4 (23%) patients reached end stage renal failure and had kidney transplantation. All of them had disease recurrence in the transplanted kidney. Complement workup was positive for C3Nef in 6 patients, C4Nef in 2 patients, C5Nef in 2 patients, factor H antibodies in 2 patients. Genetic testing was positive in one patient. Elevated creatinine at presentation, severe proteinuria, DDD in kidney biopsy– were correlated with worse prognosis.

Conclusions: Understanding the pathophysiology of C3G as a complement mediated disease has progressed during the past years. Still no guidelines exist regarding treatment and prognosis in the pediatric population. Our cohort presented a wide variability in disease course and presentation. Further understanding of the correlation between exact complement abnormality and C3G prognosis is warranted, especially now when new complement system blockers may become available.

PO1555

Utilizing Pharmacokinetic Studies to Optimize Therapy in a Child with C3 Glomerulonephritis and Nephrotic Syndrome: A Precision Medicine Approach

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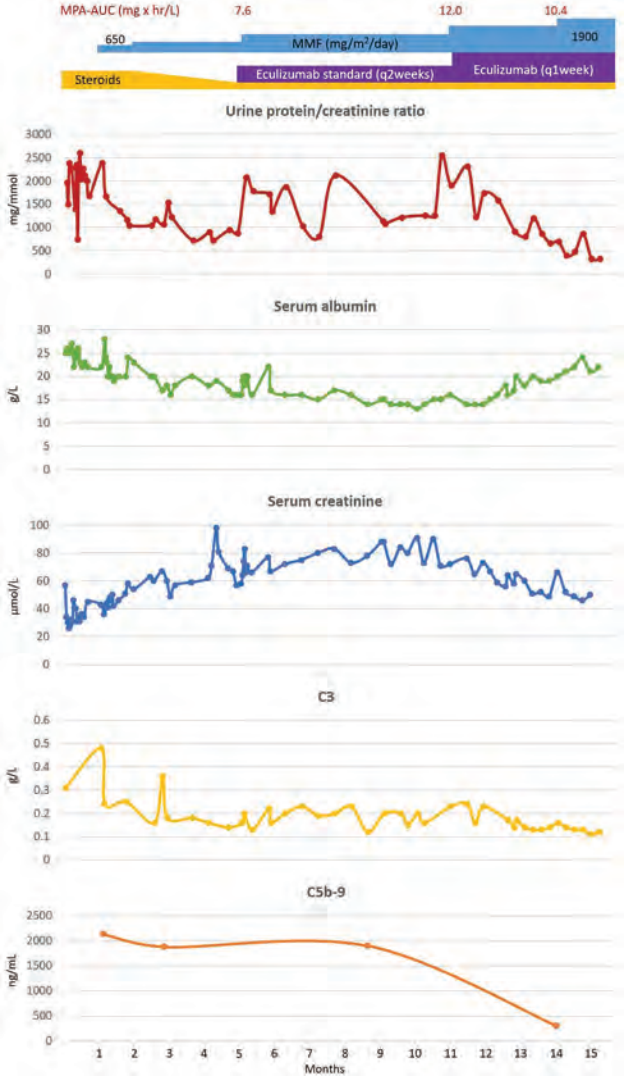
Introduction: C3 glomerulonephritis (C3GN) is caused by complement alternative pathway dysregulation, has no definitive treatment and is characterized by progression to ESRD. Terminal complement blockade has successfully been used especially in patients with elevated C5b-9 levels.

Case Description: We describe a 6 year old boy with C3GN, who presented with nephrotic syndrome, severe hypertension (4 anti-hypertensive medications) and acute kidney injury. Complement C3 level was 0.12 g/L (normal 0.8-1.5) with pos C3NeF and elevated C5b-9 levels (2135, normal <239ng/ml). Despite 6 months of treatment with steroid and MMF, he had ongoing nephrotic syndrome and worsening kidney function. He commenced on standard Eculizumab dosing. Despite 6 months of therapy, he had persistent severe hypertension, nephrotic syndrome requiring weekly albumin/furosemide infusions and worsening kidney function. Complement C3 levels remained low with elevated C5b-9 levels, suggesting sub-optimal terminal complement inhibition due to urinary loss. We confirmed sub-therapeutic plasma concentrations of eculizumab as free plasma eculizumab levels were low on day 7 (9, normal >99 ug/ml) and undetectable on days 10 and 14 post-infusion. Eculizumab frequency was subsequently increased to weekly with MPA-AUC guided adjustment of MMF dosing. Since then, his kidney function, C5b-9 levels (297ng/ml) and nephrotic syndrome improved significantly, leading to discontinuation of albumin/furosemide and anti-hypertensive medications.

Discussion: Use of pharmacokinetic studies can aid in individualized eculizumab treatment in C3GN patients with ongoing proteinuria and who failed to respond to standard dosing.



PO1556

Remission of C3 Glomerulonephritis with Rituximab

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Introduction: C3 glomerulonephritis (C3GN) is rare form of glomerulonephritis. It is diagnosed primarily by kidney biopsy with immunofluoroscence showing deposits of C3 along the basement membranes. It differs from dense deposit disease with absence of the pathognomonic deposits on electron microscopy (1). There are no radomized trials to guide therapeutic decisions. Spontaneous and treatment-associated complete remissions are rare.

Case Description: 69-year-old female with history of well controlled hypertension on amlodipine was sent to hospital with elevated creatinine of 2.52 (unknown baseline) with positive ANA - 1:320 titer. Patient was asymptomatic with negative family history of kidney disease. She denied taking NSAIDs. Serum creatinine on admission was 3.05 mg/dl. Urinalysis showed numerous RBCs with 2 g of proteinuria in the 24-hour urine collection. P- ANCA was positive. All other pertinent serologies were negative including complements, C- ANCA, MPO, PR3. Renal ultrasound revealed medical renal disease. Renal biopsy was performed and preliminary reports showed crescentic glomerulonephritis. Pulse dose steroids was started followed by oral prednisone. In addition, Rituximab was started weekly. Final biopsy confirmed C3GN. Patient did not require dialysis and renal function significantly improved after 4 doses of rituximab to serum creatinine of 1.5 mg/dl.

Discussion: In C3GN with rapidly progressive glomerulonephritis (crescents on biopsy), treatment is not well established. Most patients are treated with steroids in combination with either cyclophosphamide or Mycophenolate mofetil (2). Rituximab was used in some case reports (3). In our patient, since P-ANCA was positive and preliminary biopsy showed crescents, Rituximab was started immediately after pulse dose steroids. Patient did not require dialysis, due to good response and remission. Rituximab is a promising treatment option for C3GN. Reference Smith, R.J.H., et al C3 glomerulopathy — understanding a rare complement-driven renal disease. Nat Rev Nephrol 15**,** 129–143 (2019). Fernando Caravaca-Fontán et al. Mycophenolate Mofetil in C3 Glomerulopathy and Pathogenic Drivers of the Disease. Clin J Am Soc Nephrol. September 2020, 15 (9) 1287-1298. Giaime P et al. Remission of C3 glomerulopathy with rituximab as only immunosuppressive therapy. Clin Nephrol. 2015 Jan; 83(1):57-60.

PO1557

Myeloperoxidase Immunohistochemical Staining and Response to Eculizumab in a Pediatric Patient with Dense Deposit Disease

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Introduction: Previous studies have demonstrated residual complement mediated deposits in repeat renal biopsies of patients with C3 glomerulopathies (Dense deposit disease (DDD) and C3 glomerulonephritis) following eculizumab treatment despite clinical improvement. With the residual complement deposition, it is often difficult to determine whether there is a reduced complement mediated endothelial cell injury. Herein, we report the use of myeloperoxidase (MPO) immunohistochemical staining to show decreased glomerular endothelial cell injury in a pediatric patient with DDD on chronic eculizumab therapy.

Case Description: Our patient was diagnosed with DDD by renal biopsy when he was 5 years old after presenting with a serum creatinine of 5.2 mg/dL, a urine protein to creatinine ratio of 2.5, and a complement C3 level of 50 mg/dL. Functional complement testing showed the presence of C3 and C5 nephritic factors. He was treated with eculizumab (600 mg every 2 weeks) and azathioprine, and over the course of 6 months, his serum creatinine, proteinuria, and complement C3 levels returned to normal. After weaning the frequency of his eculizumab infusions, he experienced a flare of DDD 15 months after initial presentation with a serum creatinine of 3.6 mg/dL, urine protein to creatinine ratio of 7, and complement C3 level of 76 mg/dL. He was re-dosed with eculizumab (600 mg every 2 weeks) with a rapid response to treatment. He had normalization of his serum creatinine to pre-flare levels within 6 months. Since then he has been maintained on eculizumab infusions (600 mg every 4 weeks) along with mycophenolate mofetil. A second kidney biopsy was performed after 3 years of treatment with eculizmab to evaluate response to treatment. The biopsy showed some residual features of dense deposit disease including C3 complement deposition. To evaluate if eculizumab blocked complement mediated injury on glomerular endothelial cells, MPO staining of his initial and repeat biopsy was performed: his initial biopsy revealed diffuse endothelial staining for MPO along glomerular endothelium and the repeat biopsy showed either no MPO staining or weak MPO staining in the glomerular endothelium.

Discussion: In this case, we find that MPO immunohistochemical staining may be useful for monitoring the response to complement blockade in patients with DDD.

PO1558

Pregnancy-Associated Membranoproliferative Glomerulonephritis (MPGN)

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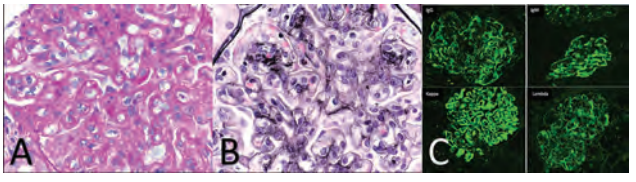
Introduction: Nephrotic syndrome (NS) in pregnancy is rarely due to MPGN. We present a case of MPGN in pregnancy for which no other cause was found.

Case Description: A 33-year-old G1P0 woman develops hypertension and proteinuria at 12 weeks gestation followed at 21 weeks by NS (7.5g/24h proteinuria, albumin 1.1 g/dL), AKI with creatinine (Cr) 1.1 mg/dL (up from 0.6), hematuria, and mildly elevated AST and ALT. C4 is low (5.9 mg/dL). SPEP and UPEP detect monoclonal IgG kappa with serum light chain ratio 5.1. ANA, anti-dsDNA, cryoglobulins, C3 nephritic factor, and serologies for hepatitis B and C, *T. pallidum*, and HIV are negative. Renal biopsy [figure] reveals MPGN. After counseling, she opts to end the pregnancy. Cr, AST, ALT, and hematuria rapidly normalize, but the proteinuria at first persists. Immunosuppression is offered, but she declines. The proteinuria slowly falls to <0.7 g/g Cr with supportive care and telmisartan over a year. Apart from low C4, an atypical hemolytic uremic syndrome (aHUS) panel is negative. Genetic testing for aHUS is also negative (heterozygous mutation in DGKE and heterozygous deletion in CFH R1-CFH R3). HLA analysis shows B35 and B51 alleles. C4d staining later performed on the biopsy is strongly positive.

Discussion: As in this case, NS in pregnancy is associated with an increased risk of complications such as superimposed preeclampsia. The etiology of this MPGN case is unknown, with no clear infectious or autoimmune cause. The C4d deposition and negative aHUS testing suggest a defect in the classic complement pathway. The paraprotein may or may not be involved as, though the immune complex deposition was polyclonal, monoclonal IgG-kappa has been rarely reported to activate complement in other autoimmune disorders. Regardless of mechanism, we speculate this MPGN case was triggered by pregnancy as it improved after the pregnancy with supportive care alone.



Biopsy yielded 20 glomeruli, with mesangial and endocapillary hypercellularity (A, PAS stain), mild tubular injury, and minimal fibrosis/glomerular sclerosis. Silver stain (B) showed diffusely thickened capillary walls with double contours. IF (C) was positive for IgG, IgM, kappa, and lambda.

PO1559

Comparing and Contrasting Glomerular Disease Patients: A Real-World Analysis Showing Demographic, Clinical, and Treatment Differences Across More Than 1,000 Patients

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Background: One-half of nephrologists selected glomerular diseases as their leading area of interest in nephrology in 2020. These rare and often-idiopathic disorders are seen as particularly challenging to manage, but an influx of promising pipeline drugs may offer new treatment options in the not-so-distant future.

Methods: 1,112 glomerular disease patient records were collected in collaboration with 290 US nephrologists via HIPAA-compliant, online chart review tool between December 20, 2020 – February 16, 2021.

Results: Chart audits reveal ~8% of nephrologists' patient populations have a glomerular disorder. Of that group, 26% have IgAN, 26% have FSGS, and 3% have Alport's Syndrome, among other conditions. IgAN patients are typically middle-aged, white males, in the middle-to-upper class and often present with hypertension, hyperlipidemia, and/or obesity. FSGS patients are mostly middle-aged, black males, in the lower-to-middle class and often present with hypertension, hyperlipidemia, obesity, and/or edema. Alport Syndrome patients tend to be younger (18-49), white males, in the lower-to-middle class and present with hypertension, hearing loss, and sometimes ocular abnormalities. Of the three conditions, FSGS patients are most heavily prescribed steroids and advanced therapeutics like MMFs, cyclophosphamide, and Acthar Gel and are least likely to be deemed "optimally managed" by their nephrologist. Alport patients are much less likely to receive steroids and are most likely to be seen as optimally managed. Interestingly, despite the value of ACEi/ARB therapy, 42% of IgAN patients were not on therapy at referral, with FSGS and Alport close behind. Nephrologists are trialing SGLT2is across conditions, with up to one-in-ten patients currently on the drug. A diagnosis for Alport Syndrome may take several months or even years after referral to determine (unlike IgAN and FSGS where it usually takes under four months). Alport is also the least likely of the three diseases to be diagnosed via kidney biopsy. Patient referrals are often deemed "late" by nephrologists, but particularly with the faster-progressing FSGS and IgAN.

Conclusions: Deeper understanding of key comparative differences among rare glomerular diseases may aid physicians in developing strategies for diagnosis and treatment.

PO1560

Glomerular Diseases in Flanders: Overview of the FCGG Biopsy Registry

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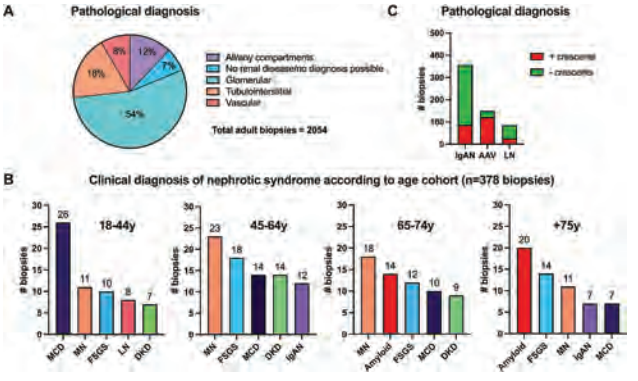
Background: High-quality population-based registries on glomerular diseases are required for epidemiological study and new trial design. The FCGG (Flemish Collaborative Glomerulonephritis Group) database is a population-based registry that has been including data on all native kidney biopsies performed in Flanders since 2017 (Northern part of Belgium) covering a population of approximately 6.5 million inhabitants.

Methods: Clinical data and nephrological diagnosis according to the ERA-EDTA Coding system for Primary Renal Disease are collected together with pathological data including primary and secondary pathological diagnoses according to the Mayo Clinic/Renal Pathology Society Consensus Guideline 2016. Here, we describe the main results of the first three years of the registry.

Results: From 2017 until 2019, 2178 biopsies were included, of which 5.7% were performed in the pediatric population. Median age (IQR) was 59 years (42-71). Biopsy incidence proportion was 130 biopsies p.m.p. per year in the adult population. Glomerular disease was present in 54% of the adult biopsies (Fig. 1A). IgA-nephropathy (IgAN) was the most frequently diagnosed disease in adults (17.3% of total, 30.2% of glomerular subcategory). The etiologies of the nephrotic syndrome differed across age categories, with membranous nephropathy (MN) being most frequently diagnosed in the total group of adult nephrotic patients (Fig. 1B). IgAN and pauci-immune glomerulonephritis (AAV) were the two most important causes of the nephritic syndrome in adults. A crescentic pattern of injury was most frequently diagnosed in adults with AAV, lupus nephritis (LN) and IgAN (Fig. 1C, crescents in 82%, 31% and 24% of biopsies, respectively).

Conclusions: The FCGG database is a valuable population-based registry that characterizes the epidemiology of glomerular disease in Flanders. These results are relevant to the clinician, will enable disease subgroup analyses and are useful to set up observational or interventional trials in patients with glomerular disease.



PO1561

CureGN Pediatric Glomerulopathy: Identifying Pathologic Molecular Signatures in Glomerulopathy with Quantitative Proteomics

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Background: Glomerular disease is a leading cause of end stage kidney disease with related treatment costs placing a significant burden on healthcare systems worldwide. Immunosuppressive glucocorticoids are a primary therapeutic approach yet can be ineffective in nearly 50% of patients. In this study we tested the hypothesis that the pediatric urinary proteome would contain unique protein signature that predict treatment response vs. resistance in glomerular diseases.

Methods: We performed proteomic analyses of serial clinically, histologically phenotyped and biopsy-confirmed pediatric urine samples from children with 3 glomerulopathies (MCD, FSGS and IgAN) to identify putative mechanistic differences between glomerular disease pathology and treatment responsiveness. 434 patient urine samples were analyzed by LC-MS/MS, and subsequently 1119 unique proteins were identified using MaxQuant and Scaffold-5 Q+ applying strict FDR (1%) with 2 peptide identification required. Protein lists were analyzed by clinical category (urine protein) using MetaboAnalyst 5.0 to perform univariate and multivariate statistical analysis, volcano plot, and heatmap visualization of protein clusters.

Results: Our analysis indicates specific and unique protein/molecular signatures separating MCD, FSGS and IgAN with respect to disease status and pathological diagnosis. Univariate analysis indicated that at least 62 proteins were significantly different in complete remission vs. proteinuric patients across all pathologies. Multivariate analysis showed significant contributions by several proteins to identify disease state and pathology. Heatmap analysis identified protein signatures that are differentially abundant across the 3 distinct glomerulopathies.

Conclusions: Pediatric glomerular disease and disease activity are associated with unique urine proteomes and if confirmed will lead to further identification of important biomarkers. We are currently performing validation of a subset of proteins as biomarkers to determine if they are diagnostic and predictive of treatment response.

Funding: NIDDK Support

PO1562

The Thromboembolism Among Hospitalized Patients with Different Types of Chronic Glomerulonephritis: A Retrospective Study Spanning 18 Years from a Single Tertiary Hospital

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Background: Chronic kidney disease is associated with hypercoagulability and platelet dysfunction. However, data on thromboembolism associating different types of chronic glomerulonephritis (CGN) are less.

Methods: We conducted a retrospective analysis using the database of hospitalization with CGN in Peking Union Medical College Hospital (PUMCH), China from 2000 through 2017. The tenth revision from the International Classification of Diseases (ICD-10) codes of discharge diagnosis was used to identify types of thromboembolism and 6 kinds of glomerulonephritis including lupus nephritis (LN), systemic vasculitis (AAV), Henoch-Schönlein purpura nephritis (HSPN), IgA nephritis (IgAN), idiopathic membrane nephropathy (IMN), minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Cochran-Armitage trend test and Logistic regression were used for analysis.

Results: Between 2000 and 2017, there were 15,714 hospitalizations with the aforementioned CGN. Their mean age was 51.7±19.8 years and 39.4% were males. The annual prevalence of overall thromboembolism increased steadily from 1.6% in 2000 to 6.6% in 2017 in a dose-response manner (p for trend <0.001). Among all thromboembolism cases, 49.8% had venous thromboembolism and 31.7% had a pulmonary embolism. The prevalence of thromboembolism in IgAN, FSGS, MCD, IMN, HSPN, LN, and AAV were 0.6%, 2.4%, 2.6%, 5.89%, 2.2%, 4.4%, and 5.3%, respectively. The patients with thromboembolism had a 2.30-fold increased risk of death (95%CI 1.53-3.46) after adjustment for age and gender. In multivariate analyses adjusted for multiple confounders such as gender, hypertension, diabetes, cardiovascular disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, infection, LN (OR 8.15; 95% CI 5.25-12.65), IMN (OR 6.93; 95% CI 4.39-10.92), AAV (OR 4.53; 95% CI 2.66-7.72), MCD (OR 4.42; 95% CI 2.56-7.61), HSPN (OR 4.05; 95% CI 2.33-7.03), and FSGS (OR 3.18; 95% CI 1.56-6.49) were significantly associated with the increased risk of thromboembolism compared with IgAN.

Conclusions: In the present study, chronic glomerulonephritis, particularly lupus nephritis, idiopathic membrane nephropathy, and systemic vasculitis were independently associated with an increased risk of thromboembolism.

PO1563

Identification and Validation of Infection-Related Acute Care Events in Patients with Glomerular Disease

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Background: Infections are an important contributor to morbidity and mortality in glomerular disease (GD). Accurate identification of infections using real world clinical data would support the conduct of observational studies examining infection risk, but standard approaches are labor-intensive. We sought to derive and test the validity of diagnosis-code based algorithms to identify infection-related acute care events (ACEs) within a large cohort of children and adults with GD.

Methods: CureGN is a prospective multi-center cohort study of patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, or IgA Nephropathy. We describe the sensitivity, specificity, and positive and negative predictive values (PPV/NPV) of four infection diagnosis code lists using manually curated infectious and non-infectious ACEs (hospitalization or emergency department visit) as the gold standard. We then validate the best performing code list within a more contemporary CureGN cohort, using multi-site adjudication of medical records.

Results: In the development phase, the optimal performing combination of diagnosis codes were those used by CureGN coordinators combined with those described by Sahli et al. (PPV 78%, 95% CI 73-83%) (Table 1). Using this code list, 265 infectious and 1231 non-infectious ACEs were identified among 2599 CureGN participants in the validation phase, of which 124 were randomly selected and adjudicated. The PPV and NPV for the final code set were 87% (95% CI: 75-99%) and 83% (95% CI: 72-93%) respectively.

Conclusions: Diagnosis codes can be used to accurately identify infection-related ACEs among patients with GD. Future studies should validate our findings in other GD cohorts and for specific infection types of high-severity or burden.

Funding: NIDDK Support

Table 1: Test characteristics of International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10) based code lists for infection

ICD10 Code List	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Development Phase				
CureGN[1]	87 (83-91)	96 (94-97)	85 (81-90)	96 (95-98)
Sahli[2]	71 (69-80)	95 (94-97)	81 (76-87)	92 (90-94)
Baker[3]	82 (77-87)	87 (85-90)	64 (58-69)	95 (93-96)
USRDS[4]	74 (69-80)	91 (89-93)	69 (63-76)	93 (91-94)
CureGN + Sahli	89 (85-93)	93 (91-95)	78 (73-83)	97 (96-98)
CureGN + USRDS	91 (87-95)	88 (86-90)	68 (63-74)	97 (96-98)
CureGN + Sahli + Baker	93 (90-96)	83 (80-85)	60 (55-65)	98 (97-99)
CureGN + Sahli + Baker + USRDS	94 (90-97)	79 (76-82)	56 (51-61)	98 (97-99)
Validation Phase				
CureGN + Sahli	75 (61-89)	91 (84-99)	87 (75-99)	83 (72-93)

[1]Glenn et al (2020), [2]Sahli et al (2016), [3]Baker et al (2012), [4]USRDS (2018)

PO1564

Patients with Glomerular Disease Are at Very High Risk of TB Infection Compared to the General Population

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Background: Advanced kidney disease is a known risk factor for active TB disease; however this risk has not been studied in patients with glomerular disease (GN). We sought to determine the incidence of TB disease in patients with GN and to explore the risk associated with immunosuppression (IS) treatment.

Methods: A population-level cohort was created using a centralized kidney biopsy registry (2000-2012) of all GN cases in British Columbia, Canada: IgA nephropathy (IgAN) n=857, focal segmental glomerulosclerosis (FSGS) n=564, ANCA-GN n=404, lupus nephritis (LN) n=360, membranous nephropathy (MN) n=398, minimal change disease (MCD) n=191, and other GN (n=305). TB disease was ascertained by linkage to administrative databases. High TB incidence was defined as >30/100,000 person years (PY) consistent with the definition used in first-world countries. Incidence rates were standardized to the general population to generate standardized incidence ratios (SIR, 95% CI). Hazard ratios were calculated using Cox proportional hazards regression.

Results: During a median follow-up 6.2 years, there were 41 cases of TB disease. TB incident rate was 197.4/100,000PY, and was higher in patients with LN vs. other types of GN (403.0/100,000PY, p<0.05). TB incidence in patients with GN was 23-fold higher than the general population (SIR 23.4, 16.8-31.7), and was high in both Canadian and foreign-born patients (range 124.1-579.6/100,000PY). TB incidence was higher during periods of IS use (282.4 vs. 147.9 per 100,000PY, p<0.05), and most cases (80.5%) had IS exposure prior to TB diagnosis. Time from IS to TB disease was highly variable, with median 3.9 years but 24% of TB cases occurred within 1 year. Reduced kidney function and higher proteinuria were also associated with increased TB risk (Table).

Conclusions: Patients with GN have a high risk of TB disease, irrespective of GN type or country of origin. TB disease can occur within months of starting IS, suggesting that all GN patients should be screened for latent TB early in their disease course.

	Univariable Hazard Ratio (95% CI)	p-value	Multivariable Hazard Ratio (95% CI)	p-value
GN type				
Non-LN	Ref	-	Ref	-
LN	2.47 (1.24, 4.93)	0.01	2.79 (1.37, 5.68)	<0.01
Country of origin		<0.01		
Canadian non-First Nations	Ref	-	Ref	-
Canadian First Nations	4.58 (1.55, 13.48)	<0.01	3.68 (1.21, 11.18)	0.02
Immigrant from low TB incidence country	2.04 (0.27, 15.24)	0.49	2.17 (0.29, 16.21)	0.45
Immigrant from medium TB incidence country	2.90 (1.27, 6.63)	0.01	3.10 (1.34, 7.16)	<0.01
	3.41 (1.55, 7.55)	<0.01	3.90 (1.75, 8.68)	<0.01
Proteinuria at biopsy (per g/day increase)				
≤11.1grams/day	1.11 (1.01, 1.23)	0.04	1.15 (1.04, 1.27)	<0.01
>11.grams/day	1.00 (0.90, 1.11)	0.96	0.99 (0.90, 1.10)	0.90
Kidney function at biopsy				
eGFR≥ 60	Ref	-	Ref	-
eGFR 15-10	1.35 (0.67, 2.70)	0.03	1.63 (0.80, 3.31)	0.18
Dialysis & eGFR <15	2.52 (1.10, 5.77)	0.40	2.81 (1.18, 6.69)	0.02
Exposure to Immunosuppression	2.13 (1.13, 4.03)	0.02	-	-

Risk Factors for TB in GN

PO1565

The Impact of Obesity on Glomerulonephritis: A Multicenter Cohort Study of Kidney Biopsy over 40 Years

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Background: Worldwide obesity has increased by almost three times between 1975 and 2020. Many studies reported that obesity related kidney disease was also increasing, and most of them were focal segmental glomerulosclerosis (FSGS). However, little was known about the prevalence and outcome of other type of glomerulonephritis (GN) in obese patients.

Methods: A total of 14,833 adult patients who underwent kidney biopsy and had body mass index (BMI) were identified in 18 tertiary hospitals during 1979-2018. Obesity was defined as BMI≥30 kg/m^2. We analyzed the prevalence of specific forms of glomerulonephritis in obese patients and effect of obesity on mortality and end stage kidney disease (ESKD).

Results: Obese patients in glomerular disease have increased about 12.8-fold over 40 years between 1979-1988 (0.6%) and 2009-2018 (7.7%). In GN patients with obesity, prevalence of IgA nephropathy (IgAN) is the most common (33.7%) followed by FSGS (13.3%), minimal change disease (MCD) (10.8%), membranous nephropathy (10.6%), diabetic nephropathy (DMN)(6.0%), lupus nephritis (LN) (2.7%), and hypertensive nephropathy (HT-N) (2.6%). The prevalence of FSGS (HR 1.60, 95%CI 1.24-2.06), DMN (HR 1.46, 95%CI 1.01-2.12) and HT-N (HR 2.14, 95% CI 1.29-3.54) were significant higher in obese patients compared than non-obese patients. Obesity had a 1.39-fold increased risk for ESKD progression during 93.8±0.8 months follow up in total patients (95%CI 1.11-1.73). Obesity had higher risks for progression of ESKD in MCD (HR 2.48, 95%CI 1.02-6.04) and LN (HR, 3.28, 95% CI 1.30-8.31). In patients with FSGS, DMN, and HT-N, obesity was not associated with ESKD. Obesity was not associated with mortality in GN patients although obesity was related to mortality only in MCD patients (HR 2.48, 95% CI 1.02-6.04).

Conclusions: Obesity rates are increasing in GN patients. The prevalence of FSGS, DMN, and HT-N are significantly higher in obese patients although IgAN is the most common form of GN. Obesity had significant risks for progression of ESKD in patients with GN, especially MCD and LN patients.

PO1566

Obesity at Time of Diagnosis Is Associated with Proteinuria in Glomerular Disease

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Background: Obesity is an established risk factor for chronic kidney disease (CKD). The relationship between obesity and glomerular disease outcomes is not well studied.

Methods: We evaluated a cohort of adult patients with biopsy-proven IgA nephropathy, focal segmental glomerulosclerosis (FSGS), ANCA-associated vasculitis (ANCA), or membranous nephropathy (MN) between January 2014 and June 2020, with follow up through April 2021. We categorized body mass index (BMI) at time of biopsy as <25 kg/m2, 25 kg/m2≥BMI<30 kg/m2 or ≥30 kg/m2. We used Fisher's exact and Kruskal-Wallis tests to compare baseline characteristics between groups and a proportional hazards model to evaluate factors associated with CKD progression to kidney replacement therapy (KRT). We used the sign rank test to compare Kaplan-Meier curves of KRT-free survival.

Results: The cohort included 153 patients: 77 (50%) male with median age 50 (IQR 38-65) years and median BMI 28 (IQR 24-34) kg/m2. Compared to patients with lower BMIs, patients with BMI >25 kg/m2 had higher median urine protein to creatinine ratios (uPCR) (p=0.02, Table 1). In univariate analyses, factors associated with progression to KRT were: blood pressure (p = 0.01), uPCR (p <0.01), and lower eGFR (p<0.001). BMI at biopsy was not associated with CKD progression, adjusted HRs (95% CIs): BMI 25≥BMI<30 kg/m2 - 1.09 (0.42-2.83); BMI ≥30 kg/m2- 1.54 (0.68-3.52). Logrank p-value for KM curves was 0.004, with paired uPCR values imparting the greatest distinction between curves (data not shown).

Conclusions: Among glomerular disease patients, BMI was associated with proteinuria, but not with progression to KRT.

Funding: NIDDK Support

Baseline Characteristics Across BMI Groups

Baseline characteristic: median [IQR] or n (%)	All (N = 153)	BMI < 25 (n = 43)	BMI 25-30 (n = 42)	BMI ≥ 30 (n = 68)	p
Age (years)	50 (38, 65)	50 (30, 72)	54 (42, 62)	49 (40, 62)	0.95
Male	77 (50)	18 (42)	27 (64)	32 (47)	0.10
Race (self-reported)	–	–	–	–	
Black	39(26)	6 (14)	10 (23)	23(34)	0.22
White	88(58)	29 (69)	25(59)	34 (50)	
Other	24(15)	7 (16)	7(16)	10 (14)	
	(N = 151)		(n = 41)	(n = 67)	
Primary disease	–	–	–	–	
ANCA	54(35)	21 (48)	14 (33)	19 (27)	0.10
FSGS	36(23)	7 (16)	11 (26)	18 (26)	
IgAN	42(27)	13 (30)	8 (19)	21 (30)	
Membranous	21(13)	2 (4)	9 (21)	10 (14)	
Systolic BP (mmHg)	134 (120, 145) (N = 152)	131 (118, 142)	130 (122, 145)	138 (127, 149) (n = 67)	0.14
Diastolic BP (mmHg)	76.00 (70, 84) (N = 132)	74.00 (68, 82)	75.00 (70, 82)	78.00 (72, 88) (n = 67)	0.35
eGFR (ml/min/1.73m2)	43 (19, 83)	46 (20, 82)	56 (21, 87)	38 (18, 75)	0.35
uPCR (g/g Cr)	2.33 (1.0, 5.6) (N = 151)	1.50 (0.6, 3.4) (n = 42)	2.90 (1.1, 5.7)	3.40 (1.3, 7.9) (n = 67)	0.02
uPCR (g/g Cr)	–	–	–	–	
<2	67 (44)	27 (65)	16 (38)	24(36)	0.01
>= 2	84 (56)	15 (35)	26 (62)	43(64)	
	(N = 151)	(n = 42)		(n = 67)	
KRT during follow up	42 (27)	11 (26)	11 (26)	20 (29)	0.92
Death during follow up	11 (7)	4 (9)	1 (2)	6 (9)	0.41

PO1567

When to Biopsy Type 2 Diabetes Mellitus (DM2)

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Background: DM2 patients may have diabetic (DN) or non-diabetic renal disease (NDRD) and a histological diagnosis is needed. There is no clear consensus on when to biopsy, but a predictive model was recently published(1).

Methods: Aim: Assess NDRD prevalence, histology and apply the predictive score in our cohort. **Methods**: Retrospective analysis of native kidney (NK) biopsies performed in our center from 2016 to 2020. Data collected included DM history, retinopathy, peripheral vascular disease (PVD), insulin prescription, proteinuria, BMI and hematuria >10 cells/HPF. A score >3 was highly suggestive of DN and would preclude renal biopsy (RB).

Results: 62 of 274 NK RB's had DM, 66.1% males with a mean age of 64±13.7 (range 23-83). Mean estimated glomerular filtration rate (MDRD4) was 41.4±26.5 ml/min/1.73m^2 (range 6-98) with mean BMI 27.9 (range 18-41). Mean proteinuria was 4453 mg/g (range 4-36249) and 51.6% had microhematuria. 51.6% had a DM history >10 and 28.3% < 5 years since diagnosis. 82.3% did not have retinopathy, 11.3% had neuropathy and 48.4% were on insulin. 27.4% had PVD, 6.5 % ischaemic cardiomyopathy (ICD) and 3 had a previous stroke. RB indications: 21 nephrotic syndrome, 2 nephritic syndrome, 6 proteinuria-hematuria, 18 non nephrotic proteinuria, 7 renal impairment and 8 AKI. Histology: 22 had DN (38.6%), 35 NDRD (61.4%) and insufficient in 5. NDRD included crescentic glomerulonephritis, membranous, FSGS, chronic tubulointertitial nephritis, ATN, IgA GN, minimal change, amyloid, hiperfiltration, glomerular sclerosis and chronic inespecific lesions. Longstanding DM (>10 y), retinopathy, neuropathy and PVD were independent predictors of DN (p value 0.02, 0.01, 0.001 and 0.001). Neither hematuria, nephrotic range proteinuria nor ICD were significant. Score: Patients with a score>3 had DN except 2 (oxalate crystals and cast nephropathy). 70.2% with a score<3 had NDRD and 84% of those with <1 did not have DN.

Conclusions: 61.4% do not have DN and NDRD is underdiagnosed. The score had excellent correlation with DN and could be efficient on RB decision making process in these patients. Validation in multicentric studies is desirable. 1.García-Martín F. et al. When to perform renal biopsy in patients with type 2 diabetes mellitus? Predictive model of non-diabetic renal disease. 10.1016/j.nefro.2019.07.005

PO1568

Year of Life Lost due to Premature Death from Glomerulonephritis in Thailand

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Background: The contribution of Glomerulonephritis (GN) on mortality is not fully known. The impact of each GN subtype on premature mortality can be measured by calculating the year of life lost (YLL), which takes into account the age at which deaths occur. Therefore, this study aimed to estimate premature mortality in GN using the average YLL.

Methods: In this retrospective study, we estimated the average YLL in each glomerular disease. The YLL is the difference between age at death and the standard life expectancy of an individual at the same age. To calculate YLL, we retrieved data from Ramathibodi Hospital Glomerular Registry during January 2011 to December 2020 and national data of standard life expectancy 2020. Individual deaths and date were obtained from the National Death Registry office. The average YLL is obtained by dividing total YLL by the total patients in each GN type. GN were categorized into primary GN (IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MGN) and minimal change disease (MCD)), and secondary GN (lupus nephritis(LN), ANCA-GN, infection related GN (iGN) or MPGN, and diabetic nephropathy (DN).

Results: A total of 1,022-kidney biopsies was performed. The median follow-up time was 67 (IQR 45, 92) months. Age for GN patients was 43.9 ± 16.7 years and 44.8 % males. The total and average YLL of all GN were 4741.9 years and 4.64 years, respectively. The average YLL for secondary GN (n = 391) was higher than primary GN (n = 469) being 7.31 vs 2.23 years ($p < 0.05$). DN (n= 97) had average YLL at 9.76 years followed by LN (n = 243) at 7.1 years. The average YLL (years) for primary GN were: FSGS (n=125), 2.52 years; MGN (n=106), 2.32; IgAN (n=164), 2.26; and MCD (n=74) 1.57.

Conclusions: GN causes premature mortality with secondary GN being associated with higher premature death than primary GN. DN and Lupus nephritis have the highest YLL. This study provides useful information on the impact of GN for prioritization of public health policies intervention.

PO1569

The Significance of Hematuria in Primary Proteinuric Glomerular Disease Outcomes

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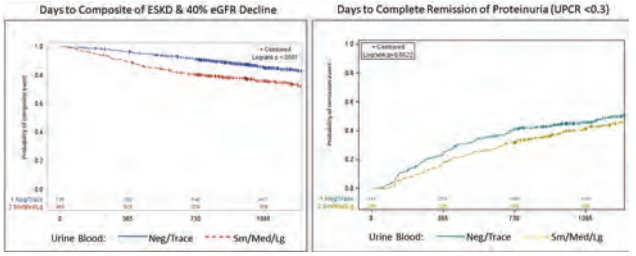
Background: Hematuria is associated with the incidence and progression of CKD. The study aims were to assess the prevalence of hematuria in a large cohort of proteinuric glomerular disease and assess the association between hematuria and kidney-related outcomes.

Methods: Hematuria was assessed at first reported study urinalysis in patients with MN, MCD, and FSGS in NEPTUNE and CureGN cohorts with >24 months of follow-up. Hematuria was defined as small, moderate, or large blood on urinary dipstick and no hematuria was negative or trace blood. Multivariable Cox proportional hazards models were fit for time to composite outcome (ESKD or 40% decline in GFR and eGFR <60) and proteinuria remission (UPCR <0.3 mg/mg).

Results: 1,108 adults and children were included. 412 (37%) patients had FSGS, 389 (36%) had MCD, and 307 (28%) had MN. 745 (67%) participants were positive for hematuria at first urinalysis. Those who had hematuria vs. those without at first urinalysis were more likely to have an underlying diagnosis of MN (37% vs 23%), be older (34 vs 25 years), have shorter time since biopsy (128 vs 315 days) and higher UPCR (3.6 vs 0.8). Patients with hematuria had higher rates of the composite outcome and lower rates of complete remission (Figure 1). After adjusting for diagnosis, age, sex, UPCR, eGFR, time since biopsy, and cohort, hematuria was associated with a higher hazard of reaching the composite outcome (HR 1.39 [1.05, 1.84], p-value 0.02) and lower hazard of reaching proteinuria remission (HR 0.71 [0.55-0.91], p-value 0.006).

Conclusions: Hematuria is prevalent among patients with podocytopathic disease not classically considered nephritic. There was an independent association between hematuria and worse kidney related outcomes. The underlying mechanisms warrants further investigation and include genetic predisposition, structural alterations in the glomerular basement membrane, and tubular toxicity from heme pigment.

Funding: NIDDK Support, Other NIH Support - NCATS



PO1570

Vacuolated Denatured Casts Are a Distinct Type of Urinary Casts Associated with Severe Nephrotic Glomerulopathy

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Background: Urinary casts identified through microscopic examination of the urinary sediment (MicrExUrSed) constitute clinically useful elements for the diagnosis of acute and chronic kidney pathologies. Granular, waxy and cellular casts are well characterized. However, a unique type of casts containing non-polarizable lipoid-like granules immersed within a lightly granular cast matrix is occasionally found. These casts have been labeled as vacuolated denatured casts (VDC). The clinical significance of VDC is not known. Herein, we present a case series of patients with specimens containing VDC.

Methods: We utilized an educational social media platform (Twitter) to probe for individual cases of VDC. We surveyed known educators who frequently post microphotographs of MicrExUrSed asking for filed cases of identification of VDC. Demographic and clinical characteristics were extracted and representative images were compiled for correct identification of VDC.

Results: Four urine microscopists (2 from South America, 1 from India, 1 from USA) contributed to the case series. A total of 12 cases were identified. Images were carefully reviewed to confirm identity of VDC. Median age 53 (27-78), 80% men, 50% had type 2 diabetes mellitus. Median serum creatinine at the time of MicrExUrSed was 3.6 (1.7-5.5) mg/dL. All (100%) patients had 3+ protein by urinary dipstick. Urine protein-to-creatinine ratio was in the nephrotic range in all 5 cases with available value [median 10.2 (3.3-11.8) g/g]. Concomitant findings included hematuria (58%), waxy casts (67%), granular casts (80%), fatty casts (42%) and renal tubular epithelial cells (58%). Histopathological diagnosis was available in 10 cases: 3 diabetic glomerulopathy, 3 focal segmental glomerulosclerosis, 2 transplant glomerulopathy, 1 membranous nephropathy and 1 advanced arterionephrosclerosis. Greater than 25% interstitial fibrosis was present in 6/10 (60%) cases.

Conclusions: VDC are a distinct type of casts that can be found in specimens of patients with advanced proteinuric glomerulopathy. The specific origin and composition of these casts remains unknown and requires further study.

PO1571

Detection of Urinary Acanthocytes for the Diagnosis of Glomerulonephritis

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Background: Acanthocyturia is a specific indicator of glomerulonephritis (GN). However, it is reported that the sensitivity of acanthocyturia for the diagnosis of GN is merely around 50%. Examiner expertise is expected to affect the ability to identify urinary acanthocytes. Thus, we hypothesized that in a well-equipped laboratory with proficient observers, the sensitivity of acanthocyturia for the diagnosis of GN can be improved.

Methods: In our institution, we have established a prospective data collection of individuals seen in nephrology consultation who had urine specimen subjected to microscopic examination (MicrExUrSed) as part of the clinical evaluation. Within this cohort, we identified cases in which a kidney biopsy was performed within 2 weeks of the MicrExUrSed. We assessed the performance of acanthocyturia in the diagnosis of biopsy-proven GN. Acanthocyturia reflects glomerular hematuria caused by forms of glomerular disease characterized by injury to the endothelium, mesangium, glomerular basement membrane or blood vessel, but not injury to the podocyte that classically presents with proteinuria. Therefore, podocytopathies were grouped with other diagnoses (tubular, interstitial, etc.) as non-GN

Results: Among 390 patients with MicrExUrSed, 70 underwent kidney biopsy and were included. Mean age was 55 years, 50% were women. White race accounted for 52% and self-identified black race for 39%. Mean serum creatinine was 4.2 mg/dL. Biopsy diagnosis was GN in 27 (39%) and non-GN in 43 (61%). The sensitivity of acanthocyturia for GN diagnosis was 74% (95% CI 53-89%), while the specificity was 86% (95% CI 72-95%). Five of 6 false positive cases had diabetic nephropathy. The positive predictive value of acanthocyturia for GN diagnosis was 77% (95% CI 61-88%) and the negative predictive value 84% (95% CI 73-91%). Acanthocyturia was predominantly detected in pauci-immune GN and IgA nephropathy, with both diagnoses accounting for 14 of the 19 (74%) cases. The hospital laboratory did not report acanthocyturia in any case and misreported it as "yeast" in 2 cases.

Conclusions: With optimal proficiency, the sensitivity of acanthocyturia can be significantly greater than previously reported. Because hospital laboratories do not report it, attempting identification of urinary acanthocytes by nephrologists should be encouraged.

PO1572

Feasibility and Acceptability of Home Urinalysis Monitoring Using a Smartphone Application

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Background: Monitoring proteinuria in patients with kidney disease is of crucial importance given its implications for long term disease progression and clinical management. As part of efforts to encourage test adherence, leveraging technology to provide a clinical grade urinalysis result from a home test can greatly enhance the clinical experience for patients, caregivers and providers.

Methods: Children and young adults (5-21 yrs old) at a single pediatric center participated. Caregivers or patients (>12yrs) completed a brief survey and then received a home urinalysis kit by mail. The Healthy.io smartphone app uses advanced computer vision to assess the urinalysis dipstick using the smartphone camera. Families downloaded the app through a text message link and performed a home urine test followed by a survey about their experience. Urine results immediately appeared in the app for patients and accessed by the study team through a secure portal. Patient satisfaction was compared between the new app and current practice (home albustix or a urine sample brought to clinic) using Wilcoxon rank test with a p value <0.05. Free text responses were analyzed to identify themes related to the app experience.

Results: 103 children, 63 (61%) male, median age 10.9 yrs. (IQR 7.8-14.2) were enrolled. Primary diagnosis included: 47 (46%) glomerular disease, 48 (47%) non-glomerular disease and 8 (8%) kidney transplant recipients. 101(98%) patients were satisfied with the smartphone app compared to 41(40%) patients who were satisfied with the current practice P<0.0001. (Table 1) Patients' free text comments were divided into themes in table 2.

Conclusions: The Healthy.io home urine testing app received very high rates of satisfaction among patients and caregivers compared to current practice and holds great potential to enhance patient-centered care.

Funding: Commercial Support - Healthy IO Company

Table 1: Patient satisfaction with current practice and Healthy.io home urinalysis smartphone app

Satisfaction Level	Current Practice	Healthy.IO app	Significance
Very Satisfied	15% (15)	81% (84)	P<0.0001.
Satisfied	25% (26)	17% (17)	
Neutral	55% (57)	2% (2)	
Dissatisfied	5% (5)	0% (0)	

Table 2: Written comments regarding App use, by themes

"Things I liked about the app"		"Things I would like to improve"	
Theme	**Number of responses**	**Theme**	**Number of responses**
Ease of use	68	Container shape	5
Immediate results	25	Results timed out	7
Accuracy	10	Packaging	6
Self-Explanatory	15	Lack of result interpretation	5
Convenience	35	Instructions- not able to pause/skip	2
Data capture	5		

PO1573

Proliferative Glomerulonephritis in a Patient with NK Cell Lymphocytosis

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Introduction: Monoclonal gammopathy of renal significance (MGRS) occurs in patients with non-malignant lymphoproliferative disorders who present with kidney injury secondary to monoclonal immunoglobulin deposition.[1] We present a rare case of proliferative glomerulonephritis (PGN) likely due to NK cell lymphocytosis.

Case Description: A 57-year-old male with NK lymphocytosis and HTN presented with progressively worsening oliguric renal failure (creatinine 1.1 to 6.2 mg/dL over 3 months) and elevated lambda free light chains (FLC) with a κ/λ ratio of 0.06 (κ=3.14, λ=52.58). Urine sediment showed numerous dysmorphic RBCs and granular casts. Renal biopsy (limited specimen) revealed PGN with polyclonal-IgG-dominant deposition and background of moderate interstitial fibrosis and tubular atrophy. Although obvious monoclonal lesions were absent and the PGN may have been coincidental, there was concern for a potential paraneoplastic GN induced by NK lymphocytosis or, less likely, MGRS. Thus, patient was treated with Cyclophosphamide-Bortezomib-Dexamethasone (CyBorD). However, due to worsening kidney function patient was started on hemodialysis, hoping for potential renal recovery. Despite significant hematologic response (plasma cell burden <1%), chemotherapy was discontinued after 7 months due to lack of renal improvement and worsening medication side effects.

Discussion: This case suggests a potential rare cause of PGN with polyclonal-IgG-dominant deposition due to NK cell lymphocytosis. This is the first case to describe a potential association between them. Additionally, while the patient did have a hematologic response to the CyBorD, there was no renal recovery. Although the PGN may have been coincidental, CyBorD therapy should have had some effect while treating PGN. This suggests a potentially aggressive form of the disease resulting in end-stage kidney disease within 3 months in our patient. It also brings up the question of whether it was the presence of NK cell lymphocytosis that worsened the renal prognosis. Such cases are extremely difficult to treat and likely have a poor prognosis. Reference: Leung, N., *et al.* The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol* **15,** 45–59 (2019). https://doi.org/10.1038/s41581-018-0077-4

PO1574

A Sporadic Case of Fibronectin Glomerulopathy in Which Mass Spectrometry Was Indispensable for the Diagnosis

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Introduction: Fibronectin glomerulopathy (FG) is an autosomal-dominant hereditary disease, which is caused by deposition of mutated fibronectin (FN). The immunostaining of FN is decisive for the diagnosis. We present a case of FG, in which FN was not detected with immunostaining and the detection of FN with mass spectrometry determined the diagnosis.

Case Description: A 60-year-old female with non-functional right kidney with calculi, 5-year history of proteinuria and 2-year history of hypertension presented with pretibial and palpebral edema. There was no family history of kidney diseases. Physical examination was significant for blood pressure of 176/98 mmHg and the edema. Laboratory test showed serum creatinine of 2.53 mg/dL, serum albumin of 2.3 g/L, urinary protein 5.8 g/day, and slight urinary glomerular RBCs. Anti-nuclear antibody, monoclonal protein, cryoglobulin, HCV, or hypocomplementemia was not detected. Open biopsy was performed. Light microscopy showed lobular glomeruli with mesangial expansion with PAS-positive material. Immunoglobulins, including κ and λ light chains, and complements were not deposited. Electron microscopy showed massive mesangial deposits with fibrillary structure. However, Congo red staining and immunostaining of DNAJB9 and fibronectin (IST-4 and IST-9) were all negative. Finally, the analysis of microdissected glomeruli with liquid chromatography/mass spectrometry (LC/MS) revealed abundance of FN, demonstrating the diagnosis of solitary FG.

Discussion: FG is caused by deposition of the soluble form of FN from serum, rather than the insoluble form produced by resident cells. Therefore, immunostaining with the monoclonal antibody IST-4, which can detect soluble FN, is usually positive in FG, while that with IST-9, which binds only to cellular FN, is negative. Although IST-4 staining was negative in the reported case, FN was detected with LC/MS. This might be due to a structural change of FN in the deposits, which hindered the binding of IST-4 antibody to FN. Furthermore, it was also confirmed that LC/MS is a powerful method to identify characteristics of unexplained glomerular deposits.

PO1575

To Treat or Not to Treat? Therapeutic Challenges in a Case of Advanced Renal Sarcoid

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Introduction: Use of potentially toxic therapy in patients with low chance of renal recovery is clinically challenging. Kidney biopsy with significant interstitial fibrosis and tubular atrophy (IFTA) and reduced estimated glomerular filtration rate (eGFR) suggests unlikely recovery. We describe a patient with advanced IFTA who recovered substantial kidney function with treatment.

Case Description: A 55-year-old man was diagnosed with pulmonary and renal sarcoidosis. Renal biopsy at diagnosis showed granulomatous interstitial nephritis with non-caseating granulomas and 20% IFTA. Prednisone was started but was discontinued by the patient for onerous side effects. Serum creatinine (SrCr) stabilized at 1.5-1.8 mg/dL. He returned two years later with SrCr 5.8 mg/dL (eGFR 12 ml/min/1.73m2). Urinalysis was bland. Serum calcium was 10 mg/dL, phosphorus 4.0 mg/dL and intact PTH 20 pg/mL. He lacked pulmonary or systemic symptoms to merit empiric treatment, and he was hesitant to receive steroids due to prior side effects. Given new concurrent diagnosis of a monoclonal gammopathy and sclerotic bone lesions, repeat renal biopsy was performed that showed granulomatous interstitial nephritis and 50% IFTA consistent with sarcoid. Despite concern for lack of recoverable kidney function due to high chronicity and reduced eGFR, treatment with high-dose prednisone was started based on the unknown time course of recurrence in a relatively young active patient. SrCr improved to 3.0-3.2 mg/dL (eGFR 23-25ml/min/1.73m2). He was compliant with steroid taper and his renal function remained stable. The gammopathy was not renally significant and sclerotic bone lesions were attributed to sarcoidosis.

Discussion: In this patient with active sarcoidosis, presenting with eGFR 12 ml/min/1.73m2 and 50% IFTA on biopsy, it would be reasonable to presume limited benefit and defer steroid treatment, especially given patient reluctance. However, there was significant recovery with treatment. This should prompt reconsideration of the prognostic value of renal pathology in sarcoidosis, especially in view of known heterogenous involvement. *The views expressed are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense, or the United States government.*

PO1576

Clinicopathological Characteristics of Adult IgA Nephropathy: A Retrospective Cohort Study

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Background: IgA nephropathy (IgAN) is the most common form of primary glomerular nephropathy and a leading cause of chronic kidney disease (CKD). These analyses characterize clinical and histological features of IgAN in adults at time of kidney biopsy.

Methods: A retrospective study of clinical and histologic characteristics was performed in patients (pts) ≥18 yrs of age with ≥1 IgAN positive kidney biopsy without prior kidney transplant reported from Arkana Laboratories (Jan 1, 2016-May 30, 2020). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-Epi equation without race modifier. All results are at the time of biopsy.

Results: Of 67,262 kidney biopsies performed during the study period, 4,384 (6.5%) IgAN positive cases met the study criteria and were included, of which, 62.7% were male, 49.6% White, 5.1% African American, 5.3% Hispanic, 5.6% Asian and 34.4% Unknown/ Other race/ethnicity. Mean (SD) age at biopsy was 47.7 (16.6) yrs. Urine protein to creatinine ratio/ 24-hour urine protein data were available for 52.4% of pts and the median (Q1-Q3) was 3.0 (1.0 – 5.0) g/g. Additionally, 65.2% of pts had hypertension, 63.1% had known hematuria, 25.7% had severe arteriosclerosis, 15.8% had severe arteriolosclerosis, and 27.2% and 20.9% of patients had CKD stage 3 and 4, respectively. The mean (SD) eGFR was 42.4 (32.1) mL/min/1.73m^2. Immunofluorescence, sclerosis, and fibrosis characteristics are presented in Table 1.

Conclusions: The large proportion of pts diagnosed at CKD stage ≥3 and high MEST-C scores for S and T suggest significant disease duration at the time of biopsy. Earlier intervention may be of value to prevent ESKD.

Funding: Commercial Support - Travere Therapeutics

Table 1. Immunofluorescence microscopy characteristics of adults with biopsy-confirmed IgA nephropathy

	n	%*
IgA		
Negative/Trace	9	0.2%
1+	53	1.2%
2+	1,376	31.4%
3+	2,945	67.2%
IgG		
Negative/Trace	3,746	85.5%
1+	359	8.2%
2+	218	5.0%
3+	60	1.4%
C3		
Negative/Trace	1,126	25.7%
1+	1,067	24.3%
2+	1,435	32.7%
3+	755	17.2%
Mesangial Hypercellularity		
No significant mesangial hypercellularity	2,310	52.7%
Mild to moderate mesangial hypercellularity	2,074	47.3%
Endocapillary Hypercellularity		
No endocapillary proliferation	3,640	83.0%
Minimal endocapillary hypercellularity	744	17.0%
Segmental Sclerosis		
Absence of segmental sclerosis and/or adhesion of tuft to Bowman capsule	1,539	35.1%
Presence of segmental sclerosis and/or adhesion of tuft to Bowman capsule	2,845	64.9%
Tubular Atrophy or Interstitial Fibrosis		
≤25%	1,838	41.9%
26–50%	1,292	29.5%
>50%	1,223	27.9%
Crescents		
C0 (No crescents)	3,575	81.6%
C1 (Present in ≥1 glomerulus)	662	15.1%
C2 (Present in >25% glomeruli)	147	3.4%

*May not equal 100% due to unknown values

PO1577

Natural History of IgA Nephropathy: Analysis of a UK National RaDaR IgA Nephropathy Cohort

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Background: Primary IgA nephropathy (IgAN) is the most common form of glomerulonephritis and a major cause of renal failure. Here we describe the natural history of IgAN using the UK National Registry of Rare Kidney Diseases (RaDaR). Since 2013, patients with biopsy-proven IgAN and eGFR <60 mL/min/1.73m^2 or proteinuria ≥1g/24h have been enrolled into RaDaR from 107 adult and paediatric kidney units across the UK, including retrospective and prospective data. Patients with systemic vasculitis or pre-existing liver disease were excluded.

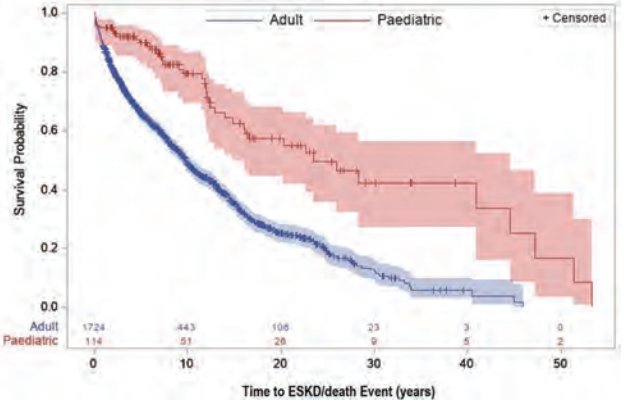
Methods: Baseline date was defined as first occurrence of renal biopsy, primary renal diagnosis or symptom presentation. Patients were grouped into those with ESKD (CKD stage 5 or renal replacement therapy) at or prior to baseline (ESKD group) and those without ESKD at baseline with ≥12 months follow-up (CKD group). For survival analyses, ESKD or death was applied with survival time calculated from baseline to last follow-up.

Results: In the ESKD group (n=326), median age at first dialysis (56% of patients) and kidney transplant (7%) was 38 yrs (IQR 29-50). In the CKD group (n=1838), median baseline age was 39 yrs (IQR 28-50) with paediatric onset of disease comprising 6%. Baseline median urine PCR was 1.5 g/g (IQR 0.6-3.2; n=356) and mean eGFR was 58 mL/min/1.73m^2 (SD 32; n=440). Median follow-up was 9.2 years (IQR 5.1-16.3) and ESKD/death occurred in 53% of patients (<1% death). Kaplan-Meier survival curves of paediatric and adult patients show 50% survival probability of 24 & 10 years, respectively (Figure 1).

Conclusions: RaDaR contains a large cohort with long follow up enabling detailed investigation of the natural history of IgAN. These results indicate associations between rapid disease progression and poor outcomes, highlighting a need for effective treatments for patients with IgAN with renal impairment or >1g/24h proteinuria.

Funding: Commercial Support - Travere Therapeutics

Figure 1: Kaplan-Meier survival curves (incl. 95% CI) of paediatric and adult IgAN patients with CKD at baseline



PO1578

Symptom Burden Among Immunoglobulin A Nephropathy (IgAN) Patients in a US Real-World Setting

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Background: Immunoglobulin A nephropathy (IgAN) is the most prevalent chronic glomerulonephritis and 15-40% of patients will progress to end stage kidney disease (ESKD) within 10-20 years of diagnosis. The symptom burden by eGFR and proteinuria levels has not been well described in IgAN and is presented here.

Methods: This is a descriptive, retrospective study of adult (≥ 18 years) patients in de-identified Optum® Electronic Health Records (2007-2019). Pre-processed physician notes were used to select patients with at least two IgAN records without any secondary or negative notion. Patients without a record of renal biopsy, valid eGFR and proteinuria

levels, or with a history of ESKD/kidney transplant were excluded. The demographic and clinical characteristics, including symptoms up to 12 months before and up to the 1st record of IgAN are presented here; these symptoms were stratified by eGFR and proteinuria levels.

Results: The final cohort consisted of 846 patients with a mean age of 48.5 years; 57.7% were male and 7.0% Asian. Proteinuria levels of ≥1 g/day were found in 35.7% of patients. The median eGFR was 39.0 ml/min/1.73m^2, median creatinine was 1.8 mg/dL, and 20.8% of patients had severe deterioration of kidney function (eGFR <15). Overall, more patients in higher chronic kidney disease (CKD) stages experienced any given symptom but this trend was not as consistent for higher proteinuria levels.

Conclusions: Our study found that a considerable proportion of patients experienced pain, fatigue and edema. Except in a few instances, all symptoms increased with lower eGFR levels but this trend was less apparent for proteinuria. Our overall findings suggest that a relatively large proportion of IgAN patients, even those with preserved kidney functions could be experiencing substantial symptomatic burden and this warrants further investigation.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Symptom*	CKD stage	eGFR#	Proteinuria				Total	
			< 1 g/day		≥ 1 g/day			
			n	%	n	%	N	%
Pain**	1, 2, 3a	>45	281	44.1	109	38.5	390	42.6
	3b, 4	44-15	167	50.3	113	46.0	280	48.6
Fatigue	1, 2, 3a	>45	281	16.4	109	12.8	390	15.4
	3b, 4	44-15	167	13.8	113	23.0	280	17.5
Edema	1, 2, 3a	>45	281	11.4	109	38.5	390	19.0
	3b, 4	44-15	167	21.0	113	28.3	280	23.9

*Captured via the International Classification of Diseases (ICD) code; #mL/min/1.73m^2; **multiple causes/locations

PO1579

Clinical Outcomes of Kidney Diseases Diagnosed in Active Duty Service Members

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Background: There are no studies that have reported glomerular disease prevalence and looked at the overall healthcare outcomes following renal biopsies in active duty soldiers. We aimed to determine the prevalence of renal diseases amongst the soldiers biopsied at out hospital and determine the outcomes for these individuals as a result of their diagnoses.

Methods: In this retrospective study, we evaluated the results of all native renal biopsies performed at Walter Reed National Military Medical Center from 2005 to 2020. We used this data to determine the prevalence of patients who progressed to have ESKD (End Stage Kidney Disease), renal transplantation, creatinine doubling, proteinuria greater than 3.5 grams/day, medical evaluation board (MEB), and death. The AHLTA and JLV EMR systems were used to collect data on the patients who met our inclusion criteria. After the data was collected, chi squared tests were performed and Kaplan Meier Curves were created for analysis.

Results: Among 169 patients (mean age =32 years old; 79% male; 48% white; 37% black; 7% Hispanic; 4% Asian; 3% pacific islander; 2% other), the most common indication for renal biopsy was for concomitant hematuria and proteinuria (31%) and the most common histologic diagnosis was IgA Nephropathy (23%). The mean time of follow up was 7.3 years. 11% progressed to ESKD, of whom 87% received a kidney transplant (10% overall). Approximately one third progressed to proteinuria greater than 3.5 grams per day and 5% died.

Conclusions: We identified IgA Nephropathy as the dominant histologic diagnosis in our patients undergoing renal biopsy between 2005 and 2020. Despite our patients being largely young and healthy individuals, renal biopsy identified severe disease with over 10% of patients progressing to ESKD and 5% mortality.

PO1580

Clinicopathological Features, Risk Factors, and Outcomes of Immunoglobulin A Nephropathy Associated with Hepatitis B Virus Infection

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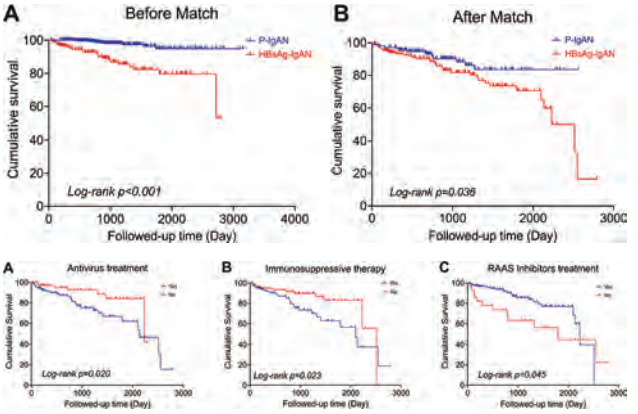
Background: Hepatitis B virus (HBV) infections are associated with an increased risk of kidney diseases. However, the effects of HBV infection on the prognosis of immunoglobulin A nephropathy (IgAN) are unclear.

Methods: A total of 838 patients with biopsy-confirmed IgAN were enrolled in this retrospective cohort study. The patients were categorized into either affected by IgAN and HBV infection (HBsAg-IgAN) or by primary IgAN with no sign of HBV infection (P-IgAN). A 1:1 propensity-score matching was performed between the two groups, followed by a Kaplan–Meier survival analysis, to compare the prognoses, and a Cox regression analysis, to identify factors influencing the HBsAg-IgAN outcomes.

Results: A total of 176 pairs of patients were successfully matched. A significant difference in the systolic blood pressure and urea, serum creatinine, uric acid, and 24-h urine protein levels was observed between the groups. A renal pathological analysis also revealed a significant difference in the mesangial hypercellularity between the groups. During a median follow-up period of 2.4 years, Kaplan–Meier analysis also revealed a significant difference in the renal survival between the groups. Furthermore, multivariate Cox analysis confirmed that HBV infection is an independent risk factor for IgAN progression (hazard ratio [HR] 2.096; 95% confidence interval [CI] 1.091–4.026). Finally, the HBsAg-IgAN patients who received treatment with renin–angiotensin–aldosterone system inhibitors had a better overall prognosis than those who received immunosuppressive therapy and antiviral treatment.

Conclusions: Our results indicate that the clinicopathological features and outcomes of patients with IgAN differ significantly between those with and without HBV infection, and that HBV is an independent risk factor for IgAN progression.

Funding: Government Support - Non-U.S.



PO1581

Factors Associated with ESKD in Mexican Patients with IgA Nephropathy: A Single-Centre Retrospective Cohort Study

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world among patients undergoing renal biopsy. To standardize the histological findings, the Oxford Classification (OC) has allowed clarifying kidney lesions that confer potential risk of progression. The aims are describe the factors associated with ESKD and treatment implemented in Mexican patients with IgAN.

Methods: We conducted a single-center, retrospective cohort study in a tertiary hospital in Mexico City, patients with biopsy-proven IgAN and followed up for at least 2 years and examined the relationship between clinical parameters and OC to predict the risk of ESKD after biopsy. We used age and sex adjusted Cox proportional hazards models to study the association of the predictor variables (MEST-C, global glomerulosclerosis and proteinuria > 1g/day) with the incidence of ESKD. The HRs were expressed with 95% confidence intervals (95% CI).

Results: 35 patients were included, mean age 37.2±15.2 years, 60% were female, mean eGFR and proteinuria at biopsy were 60.8± 34.6 ml/min/1.73m2 and 3.4± 4.0 g/day respectively. ESKD or eGFR decline by ≥50% as compared to baseline occurred in 10 patients (28.6%) in of follow-up of 2 years. The eGFR at 24 months post-biopsy 59.1± 39.6 ml/min/1.73m2. 18 patients received immunosuppressive treatment and 24 received prednisone. The distribution of MEST-C lesions were: M1-35(100%), E1-20(57.1%), S1-33(94.3%), T1-15(42.9%) and T2-5(7.5%), C1-11(31.4%) and podocytopathic features in 5 (14.3%). Of the MEST-C components, only T2 was significantly associated with ESKD (HR 4.66, 95% CI 0.8 to 27.1). After adjusting for confounding variables global glomerulosclerosis >50% (HR 1.92 [1.02-3.58], p=0.001) and new Oxford classification system (O-grade) grade III (HR 2.79 [0.89-8.58], p=<0.001) were independently associated with ESKD.

Conclusions: There are no reports in Mexico of clinical characteristics and outcomes of IgA nephropathy. This study demonstrates that IgA nephropathy was more common in young adults and women and that the progression to ESKD or the global glomerulosclerosis >50% is similar to the reported in the literature. IFTA >50%, and O-grade III were associated with the development of ESKD in Mexican population.

PO1582

External Validation of Two New IgA Risk-Prediction Tools in a Norwegian Cohort

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Background: Recently two prediction tools for IgA nephropathy (IgAN) have been developed combining clinical and histopathological parameters. Barbour and colleagues developed the *International IgAN Prediction Tool*, to predict the risk for 50 % decline in estimated glomerular filtration rate (eGFR) or end stage renal disease (ESRD) up to 80 months after diagnosis. Schena and colleagues developed the *IgA Nephropathy Clinical Decision Support System (CDSS)*, using artificial neural networks (ANN) to estimate the risk for ESRD. In the present study we aim to externally validate both prediction tools using a Norwegian cohort with long-term follow-up.

Methods: We included 306 patients with biopsy-proven primary IgAN. Histopathologic samples were retrieved from the Norwegian Kidney Biopsy Registry and reclassified according to the Oxford classification. The probability of the primary outcome, ESRD, was calculated by plotting the data from our cohort into the respectively online tools. The predicted outcome probabilities from the models were handled as a prognostic index in the validation analysis. We used principles for external validation of prognostic models: discrimination (concordance statistics), calibration (cox models and survival estimates), and model fit (akaike information criterion).

Results: Mean patient follow-up was 16.5 years, and a total of 61 (20%) patients reached ESRD. The cumulative dynamic time dependant receiving operating characteristics (tdROC) analysis showed no difference between the models with an area under curve (AUC) of 0.88 and 0.85 at 15 years for Barbour and Schena respectively. Integrated AUC (iAUC) at 20 years was 0.79 for Schena and 0.75 Barbour (p =0.2). Incident dynamic ROC-analysis at 5 and 20 years showed no significant difference in Scena's tool (AUC 0.80 and 0.74 respectively, p=0.08), but there was but there was a significant decrease in Barbour's tool (AUC 0.80 and 0.65 respectively, p<0.001). Concordance index was 0.85 for Barbour, and 0.82 for Schena (p=0.03).

Conclusions: Both prediction tools perform well and could become helpful tools for clinicians to identify patients at risk. Barbour's tool seem to loose prognostic discriminative value at a faster rate than Schena's over time.

PO1583

International IgA Nephropathy Network (IIgANN) Risk Prediction and Longitudinal Outcomes in the First South-Asian Prospective IgA Nephropathy Cohort (GRACE-IgANI)

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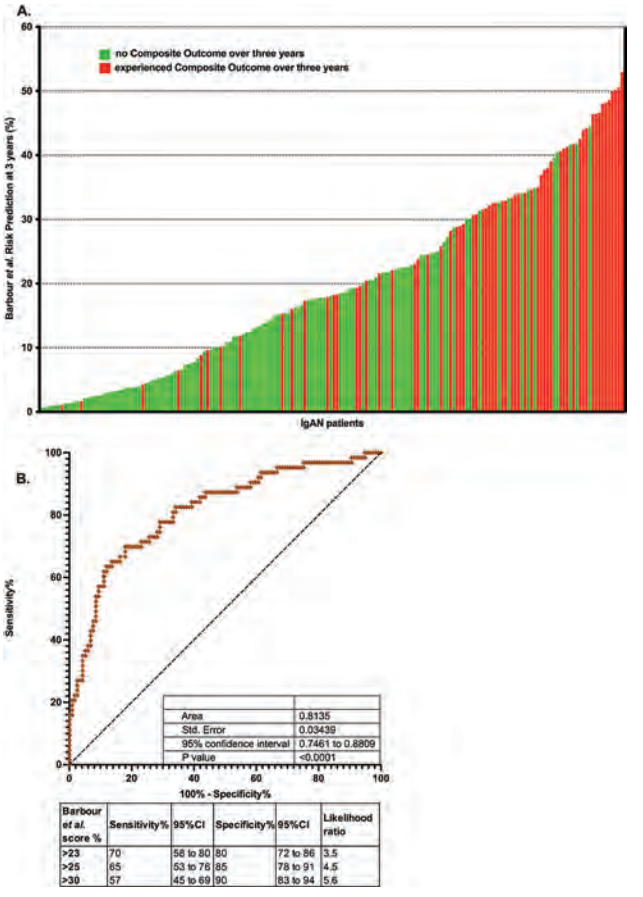
Background: The **G**lomerular **R**esearch **A**nd **C**linical **E**xperiments- **IgA N**ephropathy in **I**ndians is a prospective longitudinal cohort registered with WHO trial id: ISRCTN36834159. The performance of the IIgANN risk prediction score (Barbour *et al.*) has not been assessed in South Asian IgAN.

Methods: 201 consenting adult IgAN patients were consecutively recruited post kidney biopsy. 195 patients (97%) completed 3 year longitudinal follow-up. Of these, 180 patients had complete Oxford MEST-C score at baseline. Composite outcome (CO) was defined as ≥50% fall in eGFR from baseline and/or eGFR <15ml/min/1.73m2 or RRT/death.

Results: The median predicted 3-year risk of a 50% decline in eGFR or ESKD using the IIGANN risk prediction tool was 18.1% (IQR 7.4–31.2) at baseline. The minimum score was 0.64% and the maximum was 53%. Short course IS was used in 146/201 (73%) of patients. 72 patients (36.9%) experienced CO over 3 years. The median risk in patients with favourable outcome was 13.15% (IQR 4.2–21.7) and in those with CO was 32.2% (IQR 19.6–41), *P* <0.0001 (Figure A). The area under the ROC curve for detecting CO was 0.81 (95% C.I. 0.74 to 0.88, *P* <0.0001) (Figure B). The specificity for predicting CO for percentage risk score >23 was 80% (95% C.I. 72 to 86), and >30 was 90% (95% C.I. 83 to 94).

Conclusions: IIgANN predicted 3-year risk score >23% has good specificity for predicting CO over 3 years. Overall the score seems to be underestimating the actual CO over 3 years in the GRACE-IgANI cohort. This requires further validation.

Funding: Government Support - Non-U.S.



Barbour *et al.* 3 year prediction score and actual Composite Outcome over 3 years in GRACE-IgANI cohort.

PO1584

IgA Nephropathy Histopathology and Long-Term Renal Prognosis

Nora C. Maddy, Robert Nee, Sarah M. Gordon, Stephen W. Olson. *Walter Reed National Military Medical Center, Bethesda, MD.*

Background: The Oxford Classification established the mesangial hypercellularity (M), Endocapillary hypercellularity (E), segmental sclerosis (S), Tubulointerstitial fibrosis (T), and crescents (C) score as an important prognostic tool for IgA nephropathy (IgAN). However, these studies did not investigate the impact of complement 3 (C3) immunofluorescence (IF) staining or interstitial inflammation (iI) on long term renal outcomes, nor evaluate an ethnically diverse population which included African Americans.

Methods: We queried the military health system (MHS) by ICD-9/10 codes to identify potential IgA nephropathy cases. We then reviewed the electronic medical record to find those with biopsy-proven IgA nephropathy. Prespecified clinical data was collected to include MEST-C scores, iI, and C3 IF. Primary outcomes included >50% decline in estimated glomerular filtration rates (eGFR), chronic kidney disease (CKD) with eGFR <60ml/min/1.73m2, and end-stage kidney disease (ESKD).

Results: 172 patients were identified with a mean follow-up of 11 years. Mean age was 32 years; 77.9% male; 64.5% White, 9.9% Black, and 12.2% Asian/Pacific Islanders. C3 IF ≥2+ was significantly associated with ESKD (p=0.03) and >50% decline in eGFR (p=0.02). iI ≥ 15% was significant for ESKD (p=0.003), CKD (p=0.01), and >50% decline in GFR (p=0.01). T and C scores were significant for ESKD, CKD, and >50% decline in GFR (all p<0.001). S score was significant for ESKD (p=0.022) and CKD (p=0.009). E score was significant for CKD (p=0.003). M score was not significant for any of the primary outcomes.

Conclusions: We present histopathology associated long term renal outcome data for the most ethnically diverse IgAN cohort with the longest follow up to date in such a population. Our data suggests that degree of C3 staining on IF and amount of interstitial inflammation could augment the prognostic accuracy of the MEST-C score. In addition, it supports the theory that IgA immune complexes activate the alternative complement pathway which drives significant interstitial inflammation ultimately resulting in tubular atrophy and interstitial fibrosis. **Disclaimer**: The views expressed are those of the authors and do not reflect official policy of the Department of the Army/Navy/Air Force, Department of Defense, or United States government.

PO1585

Severity of Arterial and Arteriolar Sclerosis in IgA Nephropathy and Effects of Renin-Angiotensin System Inhibitors on Its Prognosis

Naoko Sugiura, Takahito Moriyama, Yoei Miyabe, Kenichi Akiyama, Kazunori Karasawa, Kosaku Nitta. *Tokyo Joshi Ika Daigaku, Shinjuku-ku, Japan.*

Background: IgA nephropathy (IgAN) patients often suffer from renal arterial intimal thickening (AIT) and arteriolar hyaline (AH) however, it is unclear whether these features are associated with a poor prognosis. This study aimed to analyse whether treatment with renin-angiotensin system inhibitors (RASI) improves those patient's survival.

Methods: This retrospective cohort analysis included total 871 patients with IgAN, grouped according to the absence or presence of AIT (Study 1; AIT0: n=415, AIT1: n=268) or AH (Study 2; AH0: n=405, AH1: n=354). The clinical, laboratory, and histological backgrounds of the patients were analyzed along with their 20-year renal prognosis. In the AIT1 and AH1 groups, the effect of renin-angiotensin system inhibitors (RASI) on renal prognosis after making adjustments for the background was analyzed and risk factors for progression were also analyzed.

Results: IgAN patients with AIT1 or AH1 had significantly higher age, blood pressure, body mass index, total cholesterol, uric acid levels, and proteinuria than patients with AIT0 or AH0. They also had more marked histologic findings, decreased renal function, and lower survival rates (AIT: 62.2% vs. 83.4%, p<0.0001; AH: 63.5% vs. 85.4%, p<0.0001). Multivariate Cox regression analysis considering with clinical and histological findings and treatments revealed AIT and AH as an independent factor for disease progression (AIT1: hazard ratio (HR), 1.98, p=0.017; AH1: HR, 2.12, p=0.014). The renal survival rate was significantly higher in IgAN patients with AIT1 or AH1who were treated with RASI than in those who were not treated with RASI after background adjustments (AIT1: 71.1% vs. 50.4%, p=0.023; AH1: 76.4% vs. 39.5%, p=0.006). RASI was found to be an independent factor in the prevention of progression, by multivariate Cox regression analyses (AIT1: HR, 0.40, p=0.014; AH1: HR, 0.42, p=0.007).

Conclusions: AIT and AH are associated with serious clinical, laboratory and histological findings and a poor prognosis. RASI was found to improve renal prognosis of those patients.

PO1586

Intensity of Glomerular Galactose-Deficient IgA1 Deposition Can Be a Marker of Disease Activity in IgA Nephropathy

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Background: Galactose-deficient IgA1 (Gd-IgA1) plays a crucial role in the development of IgA nephropathy (IgAN). Recently, it was reported that Gd-IgA1 specifically deposit on glomeruli of primary IgAN using Gd-IgA1-specific monoclonal antibody (KM55 mAb). However, the association between the intensity of Gd-IgA1 deposition and clinical parameters and histological severity are not clarified.

Methods: We performed immunostaining with KM55 mAb on paraffin sections of 141 patients diagnosed with IgAN at Juntendo University Hospital. We quantified the intensity of glomerular Gd-IgA1 by Image-J software, and analyzed its association with histological findings. We also analyzed the association of intensity of glomerular Gd-IgA1 deposition with creatinine, serum/urinary level of Gd-IgA1, and proteinuria.

Results: In all 141 patients with primary IgAN, glomerular Gd-IgA1 deposition was positive. We divided patients into tertiles according to the amount of Gd-IgA1 deposition by the Image-J software (low, middle, and high groups). The level of proteinuria in the high-intensity group was significantly higher than that in the other two groups (low vs high; $P<0.05$, middle vs high; $P<0.05$). Moreover, the level of urinary Gd-IgA1 was also higher in the high-intensity group (middle vs high; $P<0.05$). The percentage of acute lesions such as cellular crescents was significantly higher in the high-intensity group (low vs high; $P<0.05$).

Conclusions: Present study suggested that high intensity of glomerular Gd-IgA1 deposition is associated with histological severity, especially acute lesions. Thus, glomerular Gd-IgA1 staining can be considerable index for therapeutic intervention.

PO1587

Segmental Necrotizing/Crescentic Glomerulonephritis (SNGN) in IgA Nephropathy (IgAN): A Single-Center Experience

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Background: The presence of SNGN on renal biopsy generally portends a poor prognosis with rapidly progressive disease. We evaluate the presentation and outcomes of pts with IgAN to determine if the presence of SNGN portends a poorer prognosis in this pt population.

Methods: Biopsies done at Rush University Medical Center from 1992-2019, found IgAN in 73 pts in whom follow-up (FU) was available. SNGN was seen in 26 pts (36%). Clinical, laboratory, histologic features at biopsy, treatment and outcome data (doubling of SCr and ESKD) were collected retrospectively. Pts with and without SNGN were compared. Data is presented a mean±SD and a P value of <0.05 was significant.

Results: At biopsy there was no difference in age (42±16 vs 43±17 yrs), gender (54% vs 43% male), race or SCr (1.7±1.1 vs 1.6±1.1 mg/dl) in pts with compared to those without SNGN. Pt with SNGN had higher systolic BPs (140±14 vs 131±17 mmHg, P 0.02) and higher UPro/Cr ratio (2.8±2.7 vs 1.7± 1.7 g/g, P 0.04). All 15 SNGN pts tested were ANCA negative. The percent of glomeruli with global (GS)+segmental (SS) sclerosis (32±25 vs 38±28%) and interstitial fibrosis+tubular atrophy (IFTA) (22±20 vs 23±22%) was similar for those with vs without SNGN. In pts with SNGN, only 15% had lesions involving >25% of glomeruli. FU was similar on average (7±6 vs 8±7 yrs) in pts with and without SNGN and treatment with ACEi/ARBs was similar (88 vs 100%). A larger proportion of pts with SNGN were treated with immunosuppressive agents (69 vs 21%, P 0.003). At FU, doubling of SCr (25 vs 22%), ESKD (19 vs 21%) and renal survival at 10 yrs (80 vs 76%) were similar in pts with and without SNGN. In both groups, pts that progressed to ESKD had a higher proportion of glomeruli with GS+SS (SNGN: 63±16 vs 24±21%, P 0.002 and No SNGN: 64±27 vs 31±24%, P 0.002) and IFTA (SNGN: 47±19 vs 16±16%, P 0.006 and No SNGN: 41±27 vs 17±18%, P 0.01). In pts with SNGN, the proportion of glomeruli with SNGN was similar in those with and without ESKD (16±14 vs 18±17%).

Conclusions: In pts with IgAN, the presence of SNGN is frequently seen but does not alter prognosis. This may be the result of <25% involvement with SNGN lesions in the majority of our pts and more aggressive treatment in pts with SNGN. The presence of advanced GS+SS and IFTA at biopsy were most associated with progressive kidney disease rather than SNGN.

PO1588

Novel Scoring System Based on the Oxford Classification Indicating Steroid Therapy Use for IgA Nephropathy

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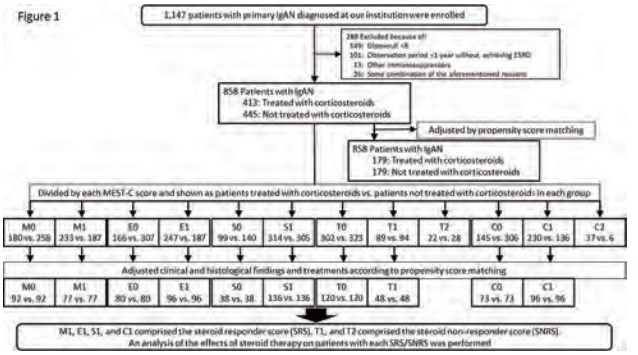
Background: The Oxford classification identifies predictors of the renal prognosis for IgA nephropathy (IgAN); however, it has been unclear about usefulness for deciding the management approach. We analyzed the clinical utility of this classification for indicating steroid therapy.

Methods: The effects of steroid therapy on the long-term prognosis for all 858 IgAN patients and patients divided with M0, M1, E0, E1, S0, S1, T0, T1, T2, C0, C1 and C2 scores according to the Oxford classification (M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental sclerosis; T, tubular atrophy/interstitial fibrosis; and C, crescents) were examined using Kaplan-Meier analysis and Cox regression analysis. The steroid responder score (SRS) and steroid non-responder score (SNRS) were determined using the obtained results. The effects of steroid therapy on renal prognosis according to the combination of the total SRS and SNRS for IgAN were analyzed using Cox regression analysis.

Results: Steroid therapy improved the 20-year renal survival rates in all IgAN patients (steroid (+): 75.5% vs. steroid (-): 61.7%, p=0.025) and patients with M1, E1, S1, C1, and T0 scores. We recognized the total score of M1, E1, S1, and C1 scores (0–4 points) as the SRS and that of T1 and T2 scores (0–2 points) as the SNRS. Multivariate Cox regression analysis revealed that steroid therapy improved the long-term renal prognosis in IgAN patients with higher SRS and lower SNRS (SRS4/SNRS0: hazard ratio [HR], 0.08 and p=0.008; SRS3/SNRS0: HR, 0.05 and p=0.025; SRS4/SNRS1: HR, 0.11 and p=0.007), but not in IgAN patients with lower SRS (0–3)/SNRS1 and any SRS/SNRS2.

Conclusions: Patients with M1, E1, S1, and C1 scores responded to steroid treatment; contrarily, those with T1 and T2 scores did not. A higher SRS was a useful indicator for steroid therapy. Nevertheless, prevention of progression in IgAN patients with SNRS was difficult with steroid therapy.



PO1589

Remission of Hematuria Is Associated with Favorable Prognosis in IgA Nephropathy

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Background: Recent studies have shown that remission of hematuria is associated with favorable clinical outcomes in patients with immunoglobulin A nephropathy (IgAN). The current study was conducted to compare the long-term clinical outcomes between patients with remission of hematuria and those with persistent hematuria using the stricter but intuitive definition of "remission of hematuria" than that used in previous studies.

Methods: This retrospective, multicenter, observational study was conducted using a cohort of patients diagnosed with IgAN through kidney biopsy at three tertiary hospitals. A total of 403 patients who had been followed up for more than 3 years and who underwent regular check-ups at intervals of at least 6 months were enrolled. Hematuria remission was defined as the presence of hematuria for at least 3 months after biopsy for diagnosis but with no RBC per high-power field observed in the urine under the microscope for at least 2 years thereafter.

Results: The mean annual rate of eGFR decline was lower in the remission of hematuria group than in the persistent hematuria group (-1.51 ± 2.86 vs. -2.60 ± 3.18 mL/min/1.73 m^2/year, p = 0.002). In the remission of hematuria group, the mean annual rate of eGFR decline decreased after hematuria disappearance (from -1.28 ± 7.06 to 0.09 ± 0.29 mL/min/1.73 m^2/year, p = 0.016). Multivariable analysis revealed remission of hematuria as an independent predictor of a 50% reduction in kidney function (hazard ratio, 0.55; 95% CI, 0.33 to 0.99). Renal survival, defined as a 50% reduction in kidney function, was better in the remission of hematuria group than in the persistent hematuria group (p = 0.030). However, free of ESRD was not significantly different between the two groups (p = 0.079).

Conclusions: In this study, which used a more rigorous but intuitive definition of hematuria remission than that used in previous studies, patients with remission of hematuria showed favorable kidney prognosis. This new definition for remission of hematuria could be used as a prognostic marker in actual clinical practice.

Comparison of renal outcomes between the two groups

Variable	Remission of hematuria (n=100)	Persistent hematuria (n=303)	p-value
Mean annual rate of eGFR decline (mL/min/1.73 m2/year)	-1.51 ± 2.86	-2.60 ± 3.18	0.002
50% Reduction in kidney function, no. (%)	17 (17.0)	62 (20.5)	0.45
ESRD, no. (%)	10 (10.0)	37 (12.2)	0.559

PO1590

Reduction of Urinary Levels of Lectin Pathway Complement Components in an IgA Vasculitis Patient After MASP-2 Inhibition with Narsoplimab

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Background: A young female suffering from IgA vasculitis was treated with 4 mg/kg weekly infusions of narsoplimab (a MASP-2 inhibitor) for 12 weeks. MASP-2 is considered the key activator of the lectin pathway (LP) by cleaving C4 and C2, after the binding of LP pattern recognition molecules to its ligands. Inhibition of MASP-2 is predicted to decrease complement activation in complement-mediated kidney diseases. In this exploratory study we measured the levels of different LP complement components to evaluate the influence of narsoplimab on complement activation.

Methods: Urine levels of complement activation markers (C4c, C3bc and soluble C5b-9) and serum and urine levels of ficolin-1, -2 and -3, MBL, CL-11, MASP-3, MAP-1 and PTX-3 were measured using sandwich-ELISAs. Urine samples were subjected to LC/MS-MS. Correlations between LC/MS-MS and sandwich-ELISA were conducted using simple linear regression and Spearman's rank correlation coefficient. Significance: *p* value < 0.05. Urine proteins were adjusted for creatinine excretion and expressed as specific protein/creatinine ratio.

Results: C4c/creatinine ratio, ficolin-3/creatinine ratio and C3bc/creatinine ratio levels were decreased 75%, 58% and 29%, respectively, from baseline to the end of the treatment; while levels of MBL and CL-11 remained stable during the treatment. C4c/creatinine ratio levels were significantly correlated to LC/MS-MS C4 data (R^2: 0.5059; Spearman r: -0.5824, *p*=0.0402). Circulating levels of complement components in serum were unaltered during treatment. Soluble C5b-9, ficolin-1, -2, MASP-3 and MAP-1 were undetectable in urine and PTX-3 was undetectable in both urine and serum.

Conclusions: This is the first report describing the effect of narsoplimab on urinary complement levels in a complement-mediated kidney disease. Our data suggest a decrease in local complement activation with narsoplimab treatment. Further studies are ongoing to evaluate the use of urine as a non-invasive, inexpensive and readily accessible resource to monitor responses to complement-directed treatments.

Funding: Commercial Support - Omeros Corporation

PO1591

Identification of Urinary Diagnostic Biomarker for IgA Nephropathy by Lectin Microarray

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Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis and the pathogenic roles of aberrantly glycosylated IgA1 have been reported. The glycan abnormalities are mediated by the alterations of glycan processing enzymes, such as decreased activity of β-1,3-galactosyltransferase (C1GALT1). However, it is unexplored whether the detection of urinary glycosylation changes contributes to the diagnosis of IgAN.

Methods: We measured the urinary glycan signals bound to 45 lectins on LecChip in the 493 patients with renal biopsy-proven kidney diseases at Okayama University Hospital from December 2010 to September 2017. To evaluate the diagnostic performance, we added the urinary glycan signals to the diagnosis model with the reference standard, *i.e.*, the presence of hematuria, 24 hr urinary protein excretion, and concentration of serum IgA.

Results: The inclusion of 6 lectins showed a significant improvement of the models; *Amaranthus Caudatus* (ACA) with the difference of AUC 0.038 [95%CI, 0.019 - 0.058, P < 0.001], *Agaricus Bisporus* (ABA) 0.035 [95%CI, 0.015 - 0.055, P < 0.001], *Maackia Amurensis* (MAH) 0.035 [95%CI, 0.015 - 0.054, P < 0.001], *Maackia Amurensis* (MAH) 0.035 [95%CI, 0.015 - 0.054, P < 0.001], *Maclura Pomifera* (MPA) 0.021 [95% Cl, 0.006 - 0.037, P = 0.006], *Jacalin* 0.019 [95%Cl, 0.004 - 0.034, P = 0.012], and *Lycopersicon Esculentum* (LEL) 0.016 [95%Cl, 0 - 0.032, P = 0.045]. All 6 lectins demonstrated reduced signals in IgAN patients and 3 lectins (ACA, ABA, MAH) showed false discovery rate (FDR) below 0.05. In 3 lectins, each signal plus reference standard showed good model fitting associated with the improvement of AIC. By decision curve analysis, there was a 3.45% net benefit by adding urinary glycan signals to ACA at the pre-defined threshold probability of 40%.

Conclusions: The reduction of Gal(β1-3)GalNAc (T-antigen), Sia(α2-3)Gal(β1-3) GalNAc (Sialyl T), and Sia(α2-3)Gal(β1-3)Sia(α2-6)GalNAc (disialyl-T) was suggested by binding specificities of 3 lectins. C1GALT1 and COSMC were responsible for the biosynthesis of these glycans, and they were known to be downregulated in IgAN. The urinary glycan profile may be useful for the identification of diagnostic marker for IgA nephropathy.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1592

Urinary Transferrin and IgG Are Significant and Early Markers of Tubulointerstitial Lesions in Patients with IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis and is a frequent cause of end-stage renal disease. There is a pressing need to identify suitable noninvasive biomarkers in IgAN, to aid with diagnosis, treatment decisions, prediction of the histological lesions and disease progression. Our aim was to assess diagnostic value of urinary transferrin and IgG excretions in prediction of morphological lesions in patients with IgAN.

Methods: 37 patients [19 female, age Me 33 (25; 48) years] with biopsy proven IgAN and without acute kidney injury, infectious diseases, severe heart failure, respiratory insufficiency, cancer were included in the study. 24-hour urinary excretions of transferrin (uTr), IgG (uIgG) were measured by immunoturbidimetric method. Tubulointerstitial fibrosis (TIF), tubular atrophy (TA) were assessed semi-quantitatively (0-lesions absent; 1-mild focal tubular and interstitial lesions; 2-moderate tubular and interstitial lesions; 3-diffuse tubular and interstitial lesions). All patients consistently were separated into two groups according to the degree of each morphological lesion (TIF or TA): "mild" (TIF or TA grade 0 or 1) and "severe" (TIF/TA grade 2-3).

Results: uTr, uIgG positively correlated (p<0,05) with TIF (r=0,38, r=0,43) and TA (r=0,38, r=0,45), respectively. We did not find correlations between uTr, uIgG and glomerulosclerosis. Using ROC-analysis all patients were separated in two groups using uTr or uIgG according to the degree of morphological lesions ("mild" or "severe") (Figure 1). We also found that all cut-off values of uTr, uIgG corresponded to the level of urinary protein excretion not more than 1,25 g/24hour.

Conclusions: Our data shows that uTr and uIgG can be used as markers of early tubulointerstitial lesions in patients with IgA nephropathy with mild protein excretion (<1,25 g/24hour).

Funding: Government Support - Non-U.S.

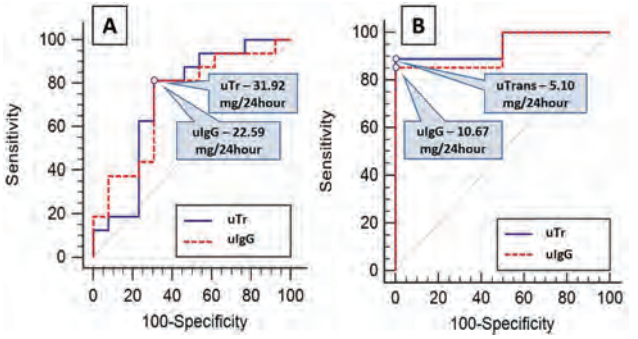

Figure 1. ROC curves of urinary transferrin and IgG excretions in prediction: A – TIF; B –TA.

PO1593

Precision Medicine Approach Identifies Patients with IgA Nephropathy at Risk for Progression Using Endothelin Activation Signatures

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis globally, with up to 40% of patients at risk of progressing to ESKD. Endothelin (ET) A receptor activation results in mesangial cell (MC) activation, proteinuria, inflammation, and fibrosis, all considered hallmarks of IgAN progression, suggesting the potential for therapeutic benefit of ETA antagonists. The aim of our study was to identify intra-renal transcriptional signatures of ET-activation to stratify patients at high risk of IgAN progression

Methods: We used two approaches to establish a transcriptional signature of ET-activation. First, using a targeted approach, an ET-activation network was generated using three publicly available datasets, produced a geneset of 60 transcripts to create an activity score which was assessed in kidney biopsy profiles in patients with IgAN (n= 25) from the European Renal cDNA Bank (ERCB). In addition, an ET-activation signature was also generated experimentally via RNAseq profiling of primary human MCs simulated with ET1 (4nM) +/- the selective ETA antagonist atrasentan (1nM, 25nM, n=3/group). Pairwise differential gene expression and gene set enrichment analysis (GSEA) was performed.

Results: The targeted analysis showed that the ET-activity score correlated with increased proteinuria (r=0.42, p=0.05) and decreased eGFR (r=-0.47, p=0.02) in patients with IgAN. The transcript network showed enrichment in endothelial and mesangial cell clusters in renal single cell RNASeq profiles. Differential expression analysis identified the ET gene network was reversed by atrasentan in MCs (25nM, n=780 genes, q£0.05). GSEA in MCs revealed up-regulation of cell proliferation, inflammatory and fibrotic networks, with ET1 treatment, which were blocked by atrasentan.

Conclusions: We generated an ET-activation score using a systems biology approach to stratify patients with IgAN. Intra-renal ET-activation signatures were associated with progression, providing additional support for the therapeutic potential of ETA receptor blockade in IgAN patients at high risk of progression. Ongoing work is focused on optimizing the signature, extending findings to additional cohorts and identifying mechanistic biomarkers

Funding: Other NIH Support - Federal grant, Commercial Support - Chinook Therapeutics

PO1594

NR3C1 Polymorphisms in Membranous and IgA Nephropathies

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Background: In other diseases (ex. asthma and pemphigus vulgaris) *NR3C1* single nucleotide polymorphisms (SNPs) were associated with glucocorticoid (GC) treatment outcomes. The aim of the study was evaluation of the frequency of *NR3C1* (SNPs) in adult membranous (MN) and IgA (IgAN) nephropathies biopsy proven patients.

Methods: We analyzed *NR3C1* SNPs: rs6198, rs41423247 and rs17209237 in 39 MN patients (mean age 42,9±14,22 y.; 14 ♀), 39 sex- and age-matched and 35-unmatched IgAN patients (mean age 33,5±12,3 y.; 34 ♀) and 39 sex- and age-matched and 136-unmatched healthy controls (mean age 48,7±17,9 years; 89 ♀) using RT-PCR and GWAS methods. The results were tested for Hardy-Weinberg equilibrium (control group; p>0,05) and compared between MN, IgAN and controls and within MN and IgAN between GC-resistant and -sensitive and GC-dependent and -independent groups using the χ^2 with Yate's correction test.

Results: The frequency of the minor C allele of rs6198 SNP was significantly increased in MN (p<0,05) and IgAN (p<0,05) compared to controls; and in GC-resistant MN (p<0,05), GC-resistant (p<0,05) and GC-dependent (p<0,05) IgAN. The rs6198 SNP genotypes were unequally distributed among GC-resistant MN (p<0,05), GC-resistant (p<0,05) and GC-dependent (p<0,05) IgAN. The frequency of the major A allele of rs17209237 was significantly increased in GC-sensitive (p<0,05) and -independent (p<0,05) IgAN. There was a disequilibrium in rs17209237 SNP distribution among GC-sensitive IgAN (p<0,05). The minor C allele was significantly more frequent among MN (p<0,05) and IgAN (p<0,05) relapse patients and there was rs6198 genotypes distribution inequality for these both groups (p<0,05; p<0,05).

Conclusions: Rs6198 and rs17209237 alleles and genotypes have different distribution between MN and IgAN and controls; and between patients differently responding to the GC treatment. Results indicate that they predict GC treatment outcomes and therefore should be further investigated for their potential prognostic value.

PO1595

A Rare Case of Paraneoplastic IgA Nephropathy in the Setting of Renal Cell Carcinoma

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Introduction: Paraneoplastic nephropathy can present in patients with malignancy. Renal cell carcinoma (RCC) is the most common urologic malignancy; there is a paucity of reported paraneoplastic nephropathies associated with this condition. As such, we present an intriguingly unique case of nephrotic range proteinuria in the setting of recurrent, metastatic renal cell carcinoma.

Case Description: An 81-year-old male with history of recurrent metastatic RCC, solitary kidney after a nephrectomy, with stage III chronic kidney disease (CKD) presents with newly worsening renal function. In a 3-month span, his creatinine (Cr) rose from 1.35 mg/dL up to 4.6 mg/dL, which prompted further evaluation. He had reported taking daily nonsteroidal anti-inflammatory drugs along with his ACE-inhibitor. Urinalysis showed microscopic hematuria with random urine protein/creatinine ratio resulted 16 g/g and renal ultrasound was unrevealing. Other serologic tests at the time were notable for C3 134 mg/dL, C4 32 mg/dL, negative ANA, negative C-ANCA. Of note, he had suffered an E. coli and MRSA UTI, clostridium difficile infection, and was treated for pneumonia with anti-microbials. A renal biopsy was obtained with pathology significant for IgA-dominant mesangial and capillary wall immune complex deposition with only segmental and weak C3 (Oxford score was reported as M1, E1, S1, T0, C0). Because of the weak C3, in spite of the patient's history of recent infections, a secondary para-neoplastic IgA nephropathy was favored. He was treated with Nivolumab plus Ipilimumab with improvement in serum Cr improved to 2.23 mg/dL in the following 3 months after starting immunotherapy and remained stable in one-year follow up.

Discussion: Acutely worsening renal function and nephrotic range proteinuria in the setting of malignancy prompts investigation into a paraneoplastic nephropathy. As in this case, secondary IgA mesangial nephropathy can rarely present with RCC. This association is scarce and furthermore there is a lack of understanding of the development of this glomerulopathy. Treatment of the underlying malignancy has shown to improve and preserve renal function. Further investigation into the immune-pathophysiology can help drive the development of further treatment strategies.

PO1596

Circulating and Depositing Glomerular Antibodies: A Concurrence or Coexistence

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Introduction: Anti-GBM disease is a systemic autoimmune disorder characterized by circulating IgG antibodies (rarely IgA and IgM), may coexist with pauci-immune antineutrophil cytoplasmic autoantibody-positive glomerulonephritis and membranous glomerulopathy. The concurrent or sequential presentation of anti-GBM disease with IgA nephropathy has been rarely described.

Case Description: We herein report a case of 31-year-old female who had presented with sudden onset of breathlessness, pedal oedema for 15 days and oliguria for 5 days with 1 episode of haematuria. There were no arthralgias, oral ulcers, alopecia, skin rash, sore throat and diarrhoea. Her marital life was of five years with no history of conception or abortions. On examination she had mild pedal edema and her BP was 180/130mm Hg. Blood investigations revealed haemoglobin 9.5g/dl, urea 209 mg/dl, serum creatinine of 17mg/dl. Urine microscopy showed 3+protein and plenty of RBC and protein creatinine ratio 4.3g/g. Serologic test results were strongly positive for IgG anti-GBM antibody (73.97 units) by ELISA; serum C3 and C4 levels were normal. Other serologic tests for ANA, Anti ds DNA antibody, rheumatoid factor, cryoglobulinemia, hepatitis B and C, and ANCA were negative. Kidney biopsy showed 6 glomeruli of which 2 were sclerosed, 2 with cellular crescents, one with fibrocellular crescent and the other fibrous crescent. Interstitium filled with infiltrate of lymphocytes and tubules showed red cell casts. Vessels were unremarkable. IF showed mesangial granular staining with IgA (3-4+), C3c (2+); and kappa (3+) and lambda (3+) light chains. The patient was initiated on hemodialysis and treated with three pulses of IV methylprednisolone followed by pulse cyclophosphamide. Plasmapheresis was done as there were cellular crescents in the biopsy. Patient progressed to ESRD and continuing on hemodialysis.

Discussion: Presentation of IgAN along with anti GBM without linear deposition on renal biopsy but with positive anti GBM titers makes this case interesting. The association of anti-GBM disease with IgA nephropathy could be a coexistence as IgAN is most common glomerular disease or these IgA mesangial deposits might have role in the pathogenesis of triggering GBM antigens and formation of antibodies in this case.

PO1597

Early Predictors for Stable Kidney Function in Lupus Nephritis

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Background: Early prediction of outcomes in LN is essential to adjust LN treatment. The aim of this study was to evaluate the early course of laboratory parameters and their association with long-term stability of kidney function.

Methods: We studied 433 patients from our local LN cohort recruited between 2008 and 2017. All patients had >36 months follow-up and complete evaluation at LN flare, 3-, 6-, and 12-months of follow up with hemoglobin, creatinine, 24h-proteinuria, albumin, anti-dsDNA-Ab, complement C3 and C4 fragments. The main outcome was stable kidney function defined as eGFR within 25% of the best eGFR attained in the first 12 months of treatment. Each variable was evaluated individually by ROC curves and in association with other variables. The change in area under the curve (AUC) was analyzed with De Long's test.

Results: Median follow up was 73 months (IQR 51-101). Kidney survival was 90% and 81% at 3- and 5-years, respectively. Stability of kidney function was 77% and 65% at 3- and 5-years, respectively. The predictive performance of each parameter varied with the timepoint where evaluated (Table). Serum albumin and hemoglobin AUCs improved from baseline to the 3- and 6-month timepoint. Proteinuria and eGFR AUCs improved at each timepoint up to the 12-month timepoint. C3, C4, and anti-dsDNA-Ab level did not improve at any timepoint vs. baseline. The best predictor of 36-month eGFR stability was proteinuria <1.0g/g by 12 months. The sum of proteinuria plus eGFR provided the best combined AUC at each timepoint (Figure 1).

Conclusions: Early course of albumin, hemoglobin, and serological parameters does not improve prediction for stable kidney function in LN. The predictive performance of each biomarker improves over time. The combination of proteinuria and eGFR remains the best predictor of kidney outcomes.

	eGFR	Proteinuria	Hematuria	Hemoglobin	Albumin	dsDNA-Ab	C3	C4
At flare	0.694	0.599	0.504	0.549	0.520	0.524	0.558	0.539
3 months	0.742	0.673	0.529	0.659	0.605	0.552	0.531	0.510
6 months	0.768	0.750	0.515	0.683	0.633	0.599	0.548	0.511
12 months	0.799	0.834	0.581	0.702	0.677	0.601	0.620	0.503

Table 1. Area under the curve (AUC) of the evaluated parameters to predict stable kidney function by 36 months.

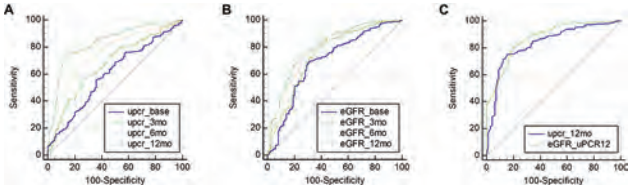

Figure 1. ROC curves of proteinuria (A), eGFR (B), and the sum of proteinuria plus eGFR (C) to predict stable kidney function by 36 months.

PO1598

Long-Term Outcomes of Lupus Nephritis in a Single Tertiary Care Center in South India

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Background: Lupus nephritis (LN) is a frequent and severe manifestation of SLE, a risk factor for chronic kidney injury and end-stage renal disease in SLE we evaluated the clinical presentation and outcome with various treatment regimens in patients with lupus nephritis

Methods: A retrospective study in 50 patients with biopsy proven LN [class III (12), class IV(11), class V(4), class III+IV(10), class III+V(7), class IV+V(6)] treated with IVMP for 3 days followed by monthly CYC for 6 months and oral corticosteroids 0.5-1mg/kg with tapering to 10mg/day at the end of 6th month as induction protocol. AZA or MMF as maintenance regimen based on clinician discretion. Clinical presentation, histopathological (LM+IF) features, treatment regimen, treatment response and renal relapse and out comes were evaluated.

Results: Patients had a mean follow up of 3.6 years, clinical presentation nephrotic N.S (36%), nephritic Nes (24%), RPGN (16%), nephritic-nephrotic NS-NeS (12%), AKI (12%).patients who had RPGN and AKI presentation had crescentic GN and high chronicity index.46% attained complete remission(C.R), 28% attained partial remission, 26% did not respond to treatment(N.R) at the end of induction.15 and 8 patients out of 23 who attained complete remission were initiated on MMF and AZA as maintenance regimen respectively, 13/15 in MMF group and 7/8 in azathioprine.patients continued to be in C.R at the end of 2 years, In patients who attained partial remission 5 on MMF, 5 on AZA, 4 on quarterly pulse doses of cyclophosphamide, 3/5 patients on MMF had C.R, 2/5 on AZA had C.R, 2/4 on quarterly pulse doses of CYC had C.R. 6 out of 13 non responders were not given maintenance regimen as patients progressed to CKD at the end of 6 months. 4/7 patients who did not respond to CYC as induction were treated with MMF, 2 patient were treated with rituximab and one with triple immunosuppression(tacrolimus+MMF+corticosteroids) ,1 patient who treated with MMF and 1 patient who treated with rituximab attained partial remission, no patient attained complete remission at the end of 2 years

Conclusions: Induction regimen with cyclophosphamide is non inferior when compared to various other induction regimen in LN. Quartely pulse dose of CYC has no better out comes when compared to AZA and MMF as maintenance. Non responders at the end of 6 months of induction does not have better outcomes at the end of 2 years

PO1599

The Relationship Between Renal Flares and Continuity of Medical Care in Patients with Lupus Nephritis

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Background: African American and Hispanic patients with lupus nephritis (LN) are known to have worse clinical outcomes compared to those of white patients, with higher prevalence of severe inflammatory nephritis, higher rates of doubling creatinine, End Stage Kidney Disease (ESKD) and death. In this study, we characterized the frequency and severity of renal flares of patients treated in our lupus nephritis clinic.

Methods: Patient demographics are presented as mean ±SD; student t-tests were used when appropriate; Chi-square tests were used to determine differences in the number of renal flares and the number of missed appointments (dichotomized into 0 vs. >=1).

Results: Between 2005–2019, a total of 116 patients with Lupus Nephritis treated at the multidisciplinary lupus clinic in a safety net hospital in Boston, MA were enrolled in our study. 23.3% of patients (n=27) self-identified as white or Asian and non-Hispanic (group 1); 76.7% of patients (n=89) self-identified as Black, African American and/or Hispanic (group 2). Patients' demographics and disease characteristics were similar between the two groups. Over the duration of the study, 59.5% of patients (n=69) did not experience any flare, and 40.5% of patients (n=47) experienced ≥1 flares. Of the patients that experienced ≥1 flares, 89% (n=42) missed one or more appointments over the course of the study. The rate of missed appointments in group 2 was significantly higher than the one observed in group 1 (85.4% vs. 48.1% respectively, p≤0.001).

Conclusions: This study represents one of the largest cohorts of patients with lupus nephritis with consistent, longitudinal, long term follow up. We found that in our black, African American and/or Hispanic patient population, there was a significant association between renal flares and missed appointments. In our safety net hospital setting, missed appointments frequently represents patients' inability to access care due to various challenges including lack of sick days at work, transportation challenges, access to certain technologies and language barriers. When looking to reduce racial and ethnical health care disparities, we should design interventions that are aimed at removing key barrier to health care access.

PO1600

Collapsing Glomerulopathy Can Worsen Prognosis in Lupus Nephritis

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Background: Collapsing glomerulopathy (CG) conveys a poor renal prognosis and is characterized by podocytopathy with segmental or global collapse of the capillary walls. While it can be idiopathic, it is often seen in association with other viral, drug, and autoimmune conditions including lupus nephritis (LN). This retrospective study describes features and clinical outcomes of 16 patients with SLE and biopsy proven CG.

Methods: Using our Glomerular Disease Collaborative Network registry, we performed retrospective chart review on patients with systemic lupus erythematosus and CG on kidney biopsy with or without an LN lesion from 2000 - 2021. For patients with multiple biopsies, the first biopsy with GC was identified as the incident biopsy. We defined poor renal outcome as reaching a renal endpoint of serum creatinine doubling, chronic dialysis initiation, or renal transplantation. Patients were characterized by baseline demographics, laboratory results, serologies, interstitial fibrosis, and medications.

Results: We identified 16 patients with mean age of 33 years at incident biopsy. Most were female (87.5%) and black (87.5%). Mean serum creatinine (Sr Cr) was 3.1mg/dL and mean proteinuria by 24-hour urine collection or spot urine protein:creatinine ratio was 7.12g. Excluding 2 patients with limited follow-up, 11 of 14 (78.6%) patients had poor renal outcomes. These patients were similar in age (mean 33 years) and were also majority female (90.1%) and black (90.1%). In this group, mean Sr Cr was 3.53mg/dL and proteinuria was 3.69g. This group had significant interstitial fibrosis and tubular atrophy (IFTA) with 71.4% moderate and 28.6% severe IFTA. They reached renal endpoint in 4.5 years (average). Of 3 patients who did not have a renal end point, mean Sr Cr was 1.83 mg/dL with less IFTA noted on biopsy. Treatment options varied with most receiving mycophenolate or cyclophosphamide.

Conclusions: This descriptive project confirmed that CG was associated with poor renal prognosis in LN; the majority of the patients required dialysis, proceeded to transplantation, or had doubling of serum creatinine during follow up. Despite treatment with standard of care agents, outcomes remained poor. Patients who had worse Sr Cr at presentation or severe IFTA had worse outcomes.

PO1601

Serological Activity in Pure Membranous Lupus Nephritis in a Predominantly Black Population

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Background: Clinically significant kidney disease is estimated to occur in nearly 60% of patients with systemic lupus erythematosus (SLE). A majority of these patients develop proliferative disease, however 10-15% develop a non-proliferative form of disease known as membranous lupus nephritis (LN) (Class V lupus nephritis). These patients typically present with significant proteinuria. Austin et al. reported 7% of patients with low complements levels and 21% with elevated anti-dsDNA levels. In this study we assess serological activity (C3, C4, anti-dsDNA) of pure membranous LN in a predominantly black patient population

Methods: Kidney biopsy log from 2010 – 2017, and a retrospective chart review was completed. We excluded any patients with proliferative disease (active or chronic). We analyzed serological activity (C3 level, C4 level & anti-dsDNA) at time of renal biopsy and again at 24 weeks.

Results: Of the total 101 patients with pure membranous LN, we had 54 patients with sufficient follow-up data. 52 of the 54 patients were female with an average age of 35.5; 92.5% (50 of 54) were black. At time of kidney biopsy, low C3 and low C4 was found in 54% and 41% of patients respectively. Whereas an elevated anti-dsDNA was identified in 39% with 20% having the classic triad of low C3, low C4 and elevated anti-dsDNA. When compared to 24 weeks (roughly end of induction therapy) low C3 and low C4 was found in 37% and 24% of patients respectively. Whereas an elevated anti-dsDNA was identified in 31% with 13% have the combination of low C3, low C4 and elevated anti-dsDNA

Conclusions: In this predominantly black population of pure membranous LN the majority of patients did not have the classic triad of low complements and elevated dsDNA (20% at time of diagnosis/biopsy). Compared to others looking at pure membranous we did find higher rates of low complements and elevated anti-dsDNA at time of diagnosis (54% with low C3 initially). Possibly due to our unique urban patient population which is >90 percent black; i.e. more severe SLE. Despite the majority of patients not having the classic triad of low C3, low C4, and elevated anti-dsDNA, clinical providers must be diligent in assessing the need for kidney biopsy in SLE and non-SLE patients as serological activity does not correlate with biopsy findings. Earlier treatment correlates with improved prognosis.

PO1602

Role of Kidney Biopsies in Systemic Lupus Erythematosus Patients: Clinicopathologic Correlation

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Background: Lupus nephritis (LN) affects >50% of the patients with systemic lupus erythematosus (SLE) and is a major cause for morbidity and mortality. The diagnosis of LN as well as the extent and severity of renal involvement are assessed via kidney biopsy. However, appropriate clinical indications for a kidney biopsy are not well defined in adults, nor is the predictability of the clinical presentation. Therefore, a clinicopathologic correlation of patients with SLE and presumed SLE who underwent a kidney biopsy is conducted.

Methods: We evaluated a total of 134 biopsy samples from 123 patients with either SLE or presumed SLE at the time of biopsy that were obtained during a 10-year period at a large medical center in New York City. 11 patients underwent a biopsy twice during that period. Laboratory, and clinical data were also collected retrospectively via chart review.

Results: 86% of the patients were female, 31% African American, 21% White, and 11% Asian. The mean age at the time of the biopsy was 36.2±12.6 years, the mean serum-creatinine 1.45±1.28 mg/dl, and the mean urinary protein excretion 3.86±3.43 g/d. 97% of the biopsy samples had evidence of LN, with the majority showing either Class IV+V (29%) or Class V (33%). About 13% had findings other than LN, such as TMA, focal collapsing features of the glomeruli, diabetic nephropathy, or possible ANCA vasculitis, with or without evidence of LN. Additionally, in patients of 65% of the biopsy samples, eGFR was ≥60 ml/min/1.73 m^2, and 29% (38/132) had a negative urine dipstick for blood. Complement levels were low in 88/128 instances, and anti-dsDNA was positive in 57% of the instances (n=127). When comparing all proliferative forms of LN (n=74) with Class V alone (n=44), patients with a proliferative form were younger, had a higher creatinine, higher proportion of hematuria, anti-dsDNA positivity, low complements, as well as a proteinuria level ≥1 g/d.

Conclusions: We conclude that normal serum-creatinine values may not preclude significant kidney pathology in SLE patients and those with proliferative forms of LN may have a negative urine dipstick for blood (16%), normal complement levels (14%), and/or a negative anti-dsDNA test (29%) around the time of the biopsy. Furthermore, patients with SLE may have other morphologic findings correlating with clinical renal presentation, instead of LN.

PO1603

Rituximab for Severe Recurrent Proliferative Lupus Nephritis After Kidney Transplantation: Pondering a Rare Case

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Introduction: Severe histologic recurrence of lupus nephritis (LN) post-kidney transplant(KTX) is extremely rare on standard transplant immunosuppression. Severe recurrence shortens allograft survival, yet treatment guidelines post-KTX are lacking.

Case Description: A 52-year-old African American (AA) man with ESRD secondary to LN underwent a second KTX from a deceased donor. He had a prior living-unrelated KTX with graft failure due to mixed rejection without LN recurrence. For the second KTX, he received Thymoglobulin induction and maintenance immunosuppressive regimen: Enteric-coated mycophenolate sodium (EC-MPS), Tacrolimus, Prednisone, with immediate graft function (nadir creatinine 1.4mg/dL). He developed leukopenia requiring a reduction of EC-MPS to 360mg twice daily. He developed nephrotic range proteinuria 6 months post-KTX but had stable allograft function, bland urine sediment, normal complements, and negative anti-dsDNA antibodies. Despite inactive serologies, allograft biopsy revealed diffuse proliferative sclerosing and crescentic LN (ISN/RPS class IV). Due to persistent leukopenia, Rituximab was chosen over commonly-used Cyclophosphamide (CYC) for therapy. He received intravenous Methylprednisolone (3000 mg) and Rituximab 800mg (375 mg/m2) for 4 doses. Complete B-cell depletion was maintained for 3 months. His proteinuria decreased from 6.9 g/g to 1.2 g/g, and renal allograft function remained stable.

Discussion: Severe recurrent LN post-kidney transplant is rare and can present atypically. Negative serologic markers, bland urine sediment and lack of LN recurrence on the first KTX did not rule out LN recurrence on the second kidney allograft. In our case, only the presence of persistent progressive proteinuria warranted allograft biopsy. AA ethnicity and reduction of EC-MPS were risk factors, which highlights the significance of full transplant maintenance therapy to prevent recurrent LN. B cell plays a pivotal role in LN pathogenesis. Rituximab targets CD20+ B cells and has been successfully utilized for refractory LN. It has a more favorable toxicity profile compared to CYC which has been the conventional treatment for clinically significant LN post-KTX. We propose Rituximab as a better treatment option for severe recurrence of LN post-KTX.

PO1604

Influenza Vaccination in Systemic Lupus Erythematosus (SLE): Effectiveness, Efficacy, Safety, Utilization, and Barriers

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Background: Influenza infections increase morbidity and mortality among immunocompromised individuals with SLE and lupus nephritis. Yet, they are highly preventable through vaccination. We aimed to describe the effectiveness, efficacy, safety, utilization and barriers to influenza vaccination in SLE so that targeted strategies can be implemented to improve vaccination rates.

Methods: We conducted a systematic review and meta-analysis of all published and unpublished studies up to 19 May 2021 via PubMed, Embase, Cochrane, WHO Clinical Trials, and ClinicalTrials.gov, which reported on our desired outcomes relating to influenza vaccination in SLE and lupus nephritis.

Results: Of 726 articles screened, 44 studies (14779 patients) were included. 9 studies reported on effectiveness, 20 studies on efficacy, 24 studies on safety, 12 studies on utilization, and 4 studies on barriers to influenza vaccination. Renal involvement or lupus nephritis was present in 20.9%. The majority were female (90.8%). The mean age was 41.3 years (95% CI 36.8-45.7), mean disease duration was 10.91 years (95% CI 7.10-14.72), and mean SLEDAI score was 4.15 (95% CI 3.18-5.12). Individuals who received influenza vaccination were less likely to develop pneumonia (relative risk, RR 0.38, 95% CI 0.08-1.86, p=0.23), acute bronchitis (RR 0.21, 95% CI 0.09-0.48, p=0.0002), and viral respiratory infections (RR 0.36, 95% CI 0.21-0.64, p=0.0005). Pooled seroconversion and seroprotection rates were 56.6% and 68.2% for H1N1, 56.7% and 73.7% for H3N2, and 46.8% and 69.9% for B influenza strains. Mean SLEDAI scores did not change significantly after vaccination. Flares occurred in 20.3%, while local and systemic adverse events occurred in 20.5% and 26.6%, respectively. Only 39.1% of SLE patients were currently vaccinated against influenza. Meta-regression showed that vaccination rates were significantly associated with increasing GDP of the country (p=0.002) and increasing mean years of disease duration (p=0.02). The most common barriers to vaccination were concerns over the safety or efficacy of the vaccine (37.2%), lack of doctor recommendation (23%), and having experienced side effects of other vaccines previously (13%).

Conclusions: Influenza vaccination is effective and safe in SLE and lupus nephritis. Targeted strategies are required to overcome barriers to improve influenza vaccination uptake.

PO1605

Lupus Nephritis in a Patient with Autoimmune Hepatitis: A Case Report

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Introduction: Overlapping of autoimmune hepatitis (AIH) and lupus nephritis (LN) is a rare entity, only occurring in 1-2.6% of AIH cases, and is difficult to diagnose due to the overlap of autoimmune features. Only a few case reports have been reported in the literature.

Case Description: 61-year-old male with established remote diagnosis of AIH well controlled on azathioprine on routine urinalysis had new-onset proteinuria (5 g/day) and hematuria. Renal biopsy showed membranoproliferative glomerulonephritis (MPGN) pattern on light microscopy with "full house" on immunofluorescence consistent with class IV renal-limited LN. He was treated with steroids and mycophenolate mofetil with remission of proteinuria and improvement in renal function.

Discussion: Our patient met systemic lupus erythematosus (SLE) criteria via 2019 ACR guidelines with positive ANA (1:320 with dual speckled and nuclear pattern) and renal biopsy results. He did not have any other systemic or constitutional findings. Although he had hypocomplementemia and thrombocytopenia, these were not scored due to his liver disease. He had indeterminate anti-dsDNA levels but later became consistently negative with therapy. Our patient's rather unique disease course and mixed autoimmune features show the challenges in diagnosis of overlapping AIH and LN. In patients like ours who do not exhibit other systemic signs of SLE, renal biopsy might be the only way to establish diagnosis. Hence, prompt clinical suspicion by the clinician is important in diagnosis and subsequent delivery of treatment. Further case reports will be beneficial in raising awareness of the overlapping of AIH and LN.

PO1606

Delayed Clinical Manifestation of Biopsy-Proven Thrombotic Microangiopathy in a Patient with Lupus Nephritis: A Case Report

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Introduction: Complement-mediated thrombotic microangiopathy (c-TMA) involves unregulated complement activation due to inherited or acquired mutations in complement regulatory proteins. Immune complex formation, an important component of lupus nephritis (LN) pathogenesis, can over activate the complement system leading to c-TMA in the kidneys. Findings of c-TMA in LN patients have been associated with end-stage kidney disease (ESKD) or death in up to 50% of patients.

Case Description: 32-year-old female, with a history of lupus and ISN/RPS class III LN since 2017 and recent stroke, was evaluated at our lupus clinic for LN flare with worsening kidney function, increased proteinuria and low complements. A repeat kidney biopsy showed focal proliferative and membranous LN (ISN/RPS class III and V) and a component of TMA. She received standard of care treatment for LN with methylprednisolone and cyclophosphamide, due to past mycophenolate therapy failure. Kidney function and proteinuria improved and complement levels normalized. Three weeks later, she was admitted with hemorrhagic shock secondary to renal subcapsular hematoma, stabilized with PRBC transfusions. After one week, she again developed worsening anemia, worsening thrombocytopenia and oliguric acute kidney injury with diuretic resistant anasarca prompting intubation and initiation of hemodialysis. Hemolysis panel revealed a low haptoglobin, high LDH and schistocytes on peripheral smear. Serum complements were low. Due to high suspicion of c-TMA, she received weekly eculizumab followed by eculizumab every 2 weeks. Three weeks later, her hemoglobin and platelets improved and LDH decreased. Her urine output improved and she was able to come off of hemodialysis. She remained with stage 3b CKD.

Discussion: In patients with LN, severe renally-limited TMA can present without systemic manifestations. In our patient, hematologic signs of TMA appeared only 4 weeks after her initial biopsy-proven TMA, and after clinical improvement of her LN. This highlights the importance of monitoring LN patients with asymptomatic renally-limited TMA closely, and treating them promptly once they develop clinical features of active TMA. Anti-complement therapy with eculizumab is shown to be effective in these patients.

PO1607

Clinical Course of Crescentic Glomerulonephritis in Singapore

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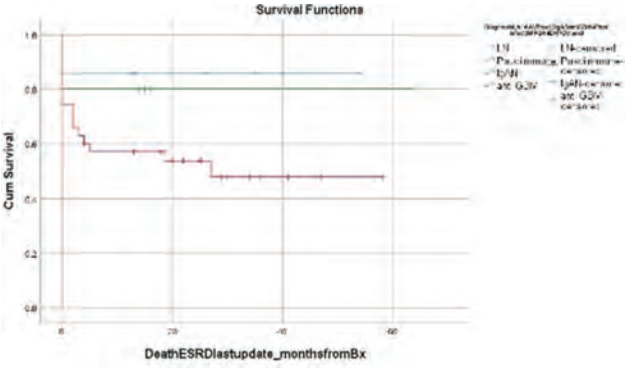
Background: Crescentic Glomerulonephritis (GN) is histologically representative of severe glomerular damage, and commonly manifests as rapidly progressive glomerulonephritis (RPGN). We report our center's experience with Crescentic GN over a 5 year period.

Methods: Retrospective cohort study of biopsy-proven glomerulonephritis with ≥10% crescents diagnosed between November 2015 and January 2021 in an academic medical center nephrology unit. Primary outcome was time to death or end stage renal failure (ESRF).

Results: We evaluated 50 patients (36% male), median age 64.7 years (IQR 51.2, 72.4) with crescents in 37.5% (17.4, 54.3) of the glomeruli sampled. At presentation, 70% had acute kidney injury with median serum creatinine 278 (118, 537) μmol/L and 26% required dialysis. The most frequent diagnoses were pauci-immune GN including ANCA-associated vasculitis (70%), lupus nephritis (14%), IgA nephropathy (10%) and anti-GBM disease (4%). At 6 months, the majority (94%) had received immunosuppressants including methylprednisolone (66%), prednisolone (88%), cyclophosphamide (70%), rituximab (12%), mycophenolate mofetil (36%) and plasma exchange (30%). Remission was achieved in 44%. Median follow up was 29.5 (19.8, 48.2) months. End Stage Renal Failure (ESRF) occurred in 32% at 0 (0, 2) months and death occurred in 18% at 5 (1, 23) months. ESRF and/or death occurred in 22 patients (44%). Survival was best for lupus nephritis (log rank p = 0.03) among the most common diagnoses (Figure 1). Multi-variable analysis (stepwise) found that pre-biopsy serum creatinine was independently associated with the primary outcome (HR 1.02, 95% CI 1.01–1.03 per 10 μmol/L increase) after adjusting for age, diabetes, crescents and histological diagnosis.

Conclusions: Despite the majority of patients receiving treatment, a significant proportion (44%) still reached the primary outcome of death and ESRF. Novel and efficacious treatment options are therefore needed to improve the outcomes and prognosis of patients with such a debilitative condition.



PO1608

Clinical Characteristics and Outcomes of Severe ANCA-Associated Renal Disease in a Multiethnic Urban Population

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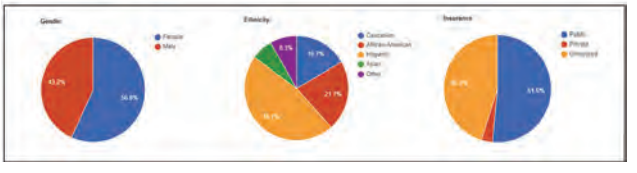
Background: To study the clinical characteristics, treatment and outcomes of ANCA vasculitides patients in an inner-city county hospital.

Methods: Retrospective study of 60 patients with biopsy-proven ANCA glomerulonephritis and a minimum follow-up of 6 months (median, IQR 23, 29 months) were included. Demographic and clinical information including pathology data, treatment and outcomes were collected. Multivariate regression analyses were done to study predictors of outcomes of estimated Glomerular Filtration Rate (eGFR) at 6 months and End Stage kidney Disease (ESKD).

Results: Patients represented an ethnically diverse population (Figure 1) with baseline characteristics as shown in Table 1. Mean age (SD) at diagnosis was 57.4 (13.7). Almost all patients (59/60, 98.3%) presented with hematuria and 17/60 (28.3%) had nephrotic-range proteinuria. Extra renal involvement most commonly pulmonary was seen in 35/60 (58.3%) patients. 44/60 (73.0%) had crescents and nearly all had interstitial fibrosis and tubular atrophy (IFTA) (median, IQR 30%, 56%). Most patients were induced with cyclophosphamide (49/60, 81.7%) and 16/60 (26.7%) received plasma exchange. eGFR (mean±SD) at baseline and 6 months follow up were 20.8±19.4 and 43.5±23.0 respectively. 15/60 (25%) patients progressed to ESKD. On multivariate linear regression analysis, age (B -0.5), IFTA (B -27.7) and baseline eGFR (B 0.3) predicted eGFR at 6 months and IFTA (OR, 95% CI, 111.5, 1.1-11907.7) and eGFR at 6 months (OR 0.9, 95% CI 0.8-1.0) were associated with ESKD (P <0.05) on multivariate logistic regression analysis. Ethnicity, ANCA type or titer, crescents on biopsy and treatment received did not predict eGFR at 6 months or ESKD.

Conclusions: In this cohort of patients with severe ANCA glomerulonephritis IFTA and baseline eGFR were the most significant predictors of eGFR at 6 months follow up which in turn was associated with progression to ESKD.

Figure 1: Patient Demographics



Patient Demographics

Serology	MPO n (%)	41/60 (70.7%)
	PR3 n (5)	15/60 (25.9%)
	Mean ANCA titer (95% CI)	69.46 (38.14-100.78)
Renal function	Baseline mean creatinine (95%CI)	4.93 (3.65-6.22)
	Baseline mean eGFR (95% CI)	20.80 (15.79-25.80)

Table 1: Baseline Characteristics

PO1609

Long-Term Outcome in Patients with ANCA-Associated Vasculitis (AAV): The Monocentric Experience of Brescia

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Background: Renal involvement in AAV is common, ranging between 80 and 90%; of note, up to 40% of patients (pts) with renal involvement will develop End-Stage Renal Disease (ESRD). We explored prognostic factors of renal and overall long-term survival in AAV pts with renal involvement.

Methods: Monocentric, retrospective study, including all pts with clinical or histological diagnosis of AAV with renal involvement followed at our Unit from 1990 to 2019, with follow-up (f-u) ≥12 months.

Results: We identified 281 patients. Median f-u was 75 months (IQR 33-141). Most pts were classified as MPA (71%), followed by GPA (26%) and eosinophilic granulomatosis with polyangiitis (3%). ANCA were positive in 97% (anti-MPO in 66%, anti-PR3 in 31%). At onset, median creatinine was 3.5 mg/dl (IQR 1.9-6.7) and proteinuria 1.1 g/24h (IQR 0.5-2); 20% of pts required haemodialysis (HD), with subsequent recovery of renal function in 55% of them. Induction therapy consisted of oral corticosteroids for all pts, with iv pulses >1g in 38% of cases; plasma-exchange in 27%; cyclophosphamide in 57% and rituximab in 33% of pts. Relapses were experienced in 31% of pts, with renal flares in 20%. Renal survival was 87%, 79% and 73% at 1,5 and 10 years, respectively. At multivariate Cox regression analysis, clinical diagnosis of MPA (HR 5.116, CI 3.437-7.408, p<0.0001) and HD requirement at onset (HR 13.469, CI 9.050-19.504, p<0.0001) were predictors of ESRD. Overall survival was 90%, 77% and 56% at 1, 5 and 10 years, respectively. Most deaths were due to infections (33%), followed by cardiovascular (CV) diseases (20%) and malignancies (13%). At multivariate Cox regression analysis, age (HR 5.724, CI 3.846-8.288, p<0.0001) and HD requirement at onset (HR 2.902, CI 1.949-4.202, p<0.0001) were predictors of mortality.

Conclusions: Despite several therapeutic advances, AAV with renal involvement are still characterised by poor prognosis, especially in pts requiring HD at onset and of older age; infection, CV diseases and malignancies were the main causes of death.

PO1610

Predicting Outcomes in ANCA-Associated Vasculitis Using a Complete National Cohort

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Background: Outcomes in ANCA vasculitis remain difficult to predict & therapeutic decision-making can be challenging. We aimed to establish if a renal risk score (RRS) could predict outcomes.

Methods: The Scottish Renal Biopsy Registry is a complete national dataset of all biopsies performed in Scotland. Those who had a first renal biopsy between 2014 & 2017 with evidence of ANCA vasculitis were included. Demographic data & outcomes were recorded. RRS was calculated. Each patient was categorised according to % of normal glomeruli, % of tubular atrophy/interstitial fibrosis & eGFR (CKD-EPI) at time of biopsy. Individual scores were summated & patients defined as low, medium or high risk. Cox proportional hazard models were created for survival to ESKD, relapse & death, stratified by risk group.

Results: Two-hundred & forty-six patients with biopsy proven ANCA vasculitis were identified. Fifty percent (n=123), 46% (n=112) & 5% (n=11) were stratified as low, medium & high risk respectively. Fifty-two percent (n=129) were male & mean age at biopsy was 66.7±12.2 years. Mean eGFR was lower in the high-risk category (8.6±6.1 'v' Low risk 45.7±26.0 ml/min/1.73m^2, p<0.001) & proteinuria was higher (405 (IQR 170-767) 'v' Low risk 81 (IQR 41-155) mg/mmol, p<0.001). Thirty-seven percent (n=91) were PR3 antigen positive. Eighteen (n=7%) patients experienced pulmonary haemorrhage; representation similar across all risk categories. Those categorised as medium or high risk were more likely to receive plasma exchange & or haemodialysis at presentation (p<0.001) compared with the low risk category. Overall, 16% (n=40) of patients relapsed with a trend to higher risk of relapse in the low risk group (27% of these patients, p=0.05). Thirty seven (15%) patients developed ESKD. Cox proportional hazard model for development of ESKD shows that those in high risk category were more likely to reach ESKD (adj HR 78.4, 95% CI 14-438.4, p<0.001).

Conclusions: A simple RRS, using routinely reported data, in patients with renal biopsy proven ANCA vasculitis can help to predict development of ESKD. It may also be predictive of future relapse in those with a lower RRS. The RRS could inform monitoring & treatment decisions. A unique strength of this data is that it is based on a complete national dataset making it less susceptible to bias from regional variations in practice.

PO1611

ANCA-Associated Crescentic Glomerulonephritis (AAV-GN) in Patients with Chronic Lymphocytic Leukemia (CLL): A Case Series

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Background: Previous case reports have identified an association between CLL and AAV-GN. However, information on the clinical and pathologic characteristics and long-term outcomes of AAV in the setting of CLL have not been well described.

Methods: We queried medical records and research databases of CLL and AAV subjects seen at our institution to identify patients with diagnoses of CLL and AAV-GN from 1990-2020. We analyzed patient demographics, AAV-GN, CLL specific characteristics, treatments, and outcomes. Kidney biopsies were also reviewed.

Results: We identified 12 patients with AAV-GN and CLL. The mean age at diagnosis was 65 years (48, 80) for CLL and 68 years (57, 80) for AAV-GN. 5 patients were diagnosed with CLL prior to AAV-GN, 4 the same month, and 2 developed CLL >3 years after AAV-GN. At the time of AAV-GN diagnosis, all had acute kidney injury, with a median serum creatinine (SCr) of 1.9mg/dL (SD 3.2). Other organs involved included lungs (n=3), skin (n=1), and eyes/ encephalitis (n=1). 9 patients p-ANCA-MPO and 2 had c-ANCA-PR3 and one with an indeterminate ANCA but had PR3. On light microscopy, all had crescents, no vasculitis of the arteries, but 9 patients had focal lymphoid infiltrates without a formal diagnosis of CLL in the kidneys. On immunofluorescence 6/12 had trace to 1+ of IgA, 5/12 with IgG and 4/12 with C3. 5/12 of the biopsies had mesangial deposits and majority (1 with diffuse and 7 with mild–moderate) had foot process effacement. All patients received treatment for AAV (9 with rituximab, and 3 with cytotoxic drugs). Renal outcomes were favorable with 11 patients showing an improvement or stabilization in SCr. One patient (p-ANCA MPO antibodies) developed end stage kidney disease, and 3 patients died, two from CLL and the other from heart failure.

Conclusions: In this case series of patients with CLL and AAV GN, the vast majority had had p-ANCA MPO, suggesting that the two conditions have either a common underlying lymphocyte dysfunction or that CLL is a predisposing factor to the development of AAV. Anti-CD20 monoclonal antibody therapy was most commonly used, and it led to remission of AAV-GN.

PO1612

Kidney Biopsy Chronicity Grading in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background: Kidney biopsy is valuable for prognostic assessment of renal outcomes in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) with glomerulonephritis (AAV-GN) but the impact of chronic changes is not determined.

Methods: A retrospective cohort study of MPO- or PR3-ANCA positive patients with AAV and active renal disease. We applied the Mayo Clinic Chronicity Score (MCCS), validated and evaluated its implications on outcome prediction in AAV-GN.

Results: We analyzed 329 patients with kidney biopsies available to score. The extent of chronicity was graded by MCCS as (i) minimal – 102 (31.0%), (ii) mild – 106 (32.2%), (iii) moderate – 86 (26.1%), and (iv) severe – 35 (10.6%). The MCCS grades correlated with the degree of renal function impairment at presentation (mean eGFR: 48.3 vs. 29.2 vs. 23.7 vs. 18.5 mL/min/1.73 m^2, p<0.0001). Higher degrees of the individual components of the MCCS (glomerulosclerosis, interstitial fibrosis, tubular atrophy and arteriosclerosis) were associated with lower median eGFR (p<0.0001) and decreased event free (kidney failure (KF) and death) survival (p=0.002, p<0.0001, p<0.0001 and p=0.017, respectively). Patients with lower MCCS grades recovered renal function more frequently (p<0.0001). Increasing MCCS grades were associated with decreased renal recovery (p=0.001), more frequent events and shorter time to KF (p<0.0001), KF and death (p<0.0001), and death (p=0.042), independently of remission-induction treatment used (CYC or RTX). The MCCS stratified renal outcomes for each MCCS grade and can be used in clinical practice as a cut-off for KF prediction (MCCS≥4).

Conclusions: Chronic changes on kidney histology independently predict renal function, outcomes and response to treatment in AAV-GN.

PO1613

The Effect of Cumulative UVB Dose on ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) has a relapsing-remitting course but the precise triggers of onset and relapse are unknown. The potential effect of ultraviolet B (UVB) radiation on disease phenotype and activity, mediated by vitamin D (vitD), has been proposed, given the marked incidence variation of AAV phenotypes and serotypes with latitude. Using a well-validated vitD proxy (cumulative-weighted

UVB dose (CW-D-UVB) at wavelengths that induce vitD synthesis) we hypothesized that prolonged periods of low ambient UVB are associated with an increased risk of GPA phenotype and AAV relapse in this subgroup.

Methods: The UKIVAS (n=1994) and Irish Rare Kidney Disease (RKD) (n=439) registries were used (total n=2433). Inclusion criteria: i). definite AAV diagnosis, ii). positive proteinase-3 (PR3) or myeloperoxidase (MPO) serology and/or positive histopathology. Logistic regression was used to investigate the relationship between latitude, CW-D-UVB and AAV phenotype/serotype in the entire cohort. A multi-level model was then applied to examine their effect on AAV relapse risk in the RKD subgroup.

Results: CW-D-UVB varied across seasons and latitudes. There was no relationship between latitude/CW-D-UVB at disease onset and AAV phenotype/serotype. MPA, MPO-ANCA, older age and rituximab maintenance were protective against relapse. There was no association between CW-D-UVB and relapse risk, even when examining phenotype specific risk (table 1).

Conclusions: We found no association between cumulative UVB, a validated vitD proxy, and AAV phenotype, ANCA serotype nor AAV disease activity in a genetically homogeneous cohort. These findings cast doubt on the role of vitD in AAV disease activity.

Random effects:	Variance (SD)
Patient ID	0.75 (0.86
Fixed effects:	**OR (95% CI, p)**
CW-D-UVB (kJ/m2)	1.20 (0.87 - 1.66, 0.28)
Not MPA (Ref: MPA)	1.69 (0.95 - 2.98, 0.07)
Age at diagnosis (years)	0.72 (0.58 - 0.90, 0.003)
Gender (male)	0.89 (0.58 - 1.37, 0.60)
Not MPO-ANCA (Ref: MPO-ANCA)	1.10 (0.63 - 1.92, 0.73)
Treatment: (Ref: AZA/MMF/MTX/Other)	
Rituximab	0.41 (0.16 - 1.03, 0.06)
Cyclophosphamide	0.58 (1.25 - 2.66, 0.50)
Glucocorticoid monotherapy	1.85 (1.02 - 3.35, 0.04)
Off treatment	2.69 (1.65 - 4.40, <0.001)
CW-D-UVB: Not MPA (Ref: MPA)	0.83 (0.56 - 1.24, 0.36)

N = 439, 2080 observations. The OR refers to the probability of having an AAV relapse (relative to remission). Cumulative-weighted UVB dose (CW-D-UVB), Standard deviation (SD), Microscopic polyangiitis (MPA), Myeloperoxidase (MPO), Odds ratio (OR), 95% Confidence interval (95% CI), Azathioprine (AZA), Mycophenolate mofetil (MMF), Methotrexate (MTX)

Multi-level model investigating the association between CW-D-UVB and AAV relapse

PO1614

A Severe Presentation of Systemic Lupus Erythematosus (SLE) and ANCA-Associated Vasculitis (AAV) Overlap Syndrome

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Introduction: An increasingly recognized overlap syndrome (OS) of lupus nephritis and ANCA positive crescentic glomerulonephritis is rare and presents treatment challenges. It's not clear whether to treat as LN or ANCA vasculitis. Here we describe a severe presentation of OS, the subsequent management and positive outcome.

Case Description: A 42 y.o. woman with no PMH presented with 3 weeks of cough, dyspnea, fever, malaise, AKI and hypoxia. Her hgb was 6.3 g/dL and creatinine 17.4 mg/dl (normal 1.5 years prior). UA showed large hgb and >182 RBCs and UPCR 5.72 g/g. Serologies were significant for elevated DsDNA, RNP ab, Smith ab and positive ANA with low complement levels. MPO ab was elevated to >8.0 (<=0.9) and anti GBM negative. Cardiolipin ab was elevated but beta 2 glycoprotein ab and lupus anticoagulant ab were negative. Chest CT showed multifocal opacities. She was urgently started on hemodialysis and solumedrol 1g for 3 days then prednisone 60mg daily. On day 2 of admission she underwent renal biopsy. Her course was complicated by hemoptysis and bronchoalveolar lavage showed diffuse alveolar hemorrhage (DAH). She was initiated on plasmapheresis. Biopsy demonstrated necrotizing crescentic GN with immunofluorescence showing full house pattern and complex deposits with strong ANA staining of nuclei. Given the biopsy results and serologies the patient was diagnosed with LN/AAV overlap. The patient was started on Cytoxan 750mg monthly administration. She completed 7 daily sessions of plasmapheresis and renal function recovered sufficiently to stop dialysis. Two months after discharge, her renal function continued to improve with her most recent creatinine down to 2 mg/dl.

Discussion: LN and AAV overlap is rare and there are no guidelines regarding management of these patients. This case stresses the importance of having a high suspicion of LN/AAV when a young, female patient presents with new onset renal failure and DAH. The patient benefited from early, aggressive treatment targeting both disease processes including early initiation of high dose steroids. Secondly, plasma exchange should be initiated emergently with severe presentation, including DAH. Plasmapheresis did not reduce incidence of ESKD in PEXIVAS trial, however, we suspect in this case it contributed to the good outcome. Lastly, little is known about outcomes in these patients, but this is an example of a severe presentation with a positive outcome.

PO1615

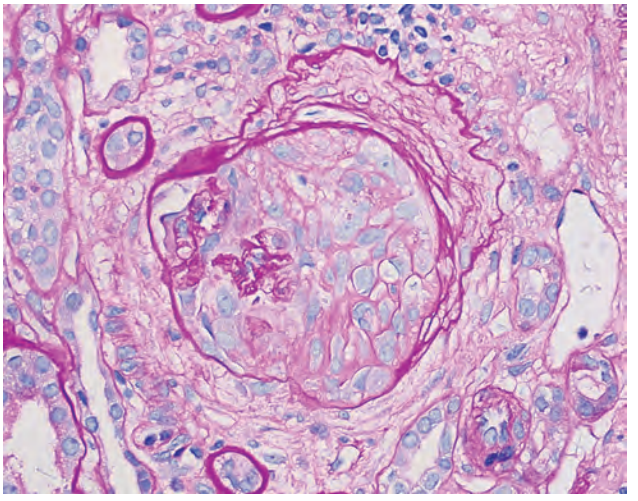
Pauci-Immune Crescentic Glomerulonephritis Associated with Pulmonary Coccidioidomycosis

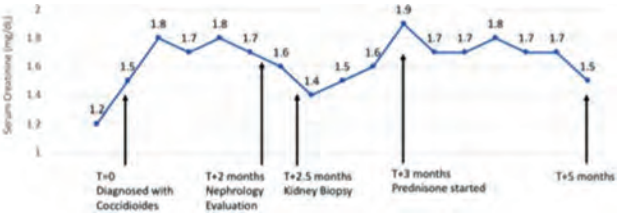
Elvira González, Erika R. Bracamonte, Amy Yau. *Banner University Medical Center Tuscon, Tucson, AZ.*

Introduction: Coccidioidomycosis is an endemic fungal infection in the southwestern United States There are around 150,000-300,000 cases annually, of which 60% occur in the state of Arizona. Most patients are asymptomatic. 40% have primary pulmonary involvement and present with dyspnea and fatigue. A minority (around 1%) have extrapulmonary dissemination with unknown incidence of renal involvement.

Case Description: We report a 70-year-old immunocompetent patient with CKD (baseline creatinine of 1.2 mg/dL) recent diagnosis of pulmonary coccidioidomycosis presenting with AKI due to ANCA negative pauci-immune crescentic GN. Our patient was referred to nephrology for worsened renal function, creatinine of 1.7 mg/dL. He was diagnosed with pulmonary coccidioidomycosis 3 months prior and started on fluconazole 400 mg daily. Due to concern for disseminated coccidioidomycosis, underwent a renal biopsy showing minimally active pauci-immune crescentic GN (Fig 1). Complement levels were normal, ANCA immunofixation, anti-MPO and anti-PR3 titers were negative. He was initiated on prednisone 60 mg daily with appropriate supportive therapy and gradually tapered over the following three months with partial improvement to his creatinine to 1.5 mg/dL from a peak of 1.9 mg/dL (Fig 2).

Discussion: This is the third known reported case of pauci-immune crescentic GN associated with coccidioidomycosis, and one of a handful of case reports describing pauci-immune crescentic GN in patients with chronic fungal infections. Our case highlights the importance in understanding the pathogenesis and prognosis of chronic fungal infections and GN.





PO1616

Infective Endocarditis Associated Pauci-Immune GN: Look Before You Leap

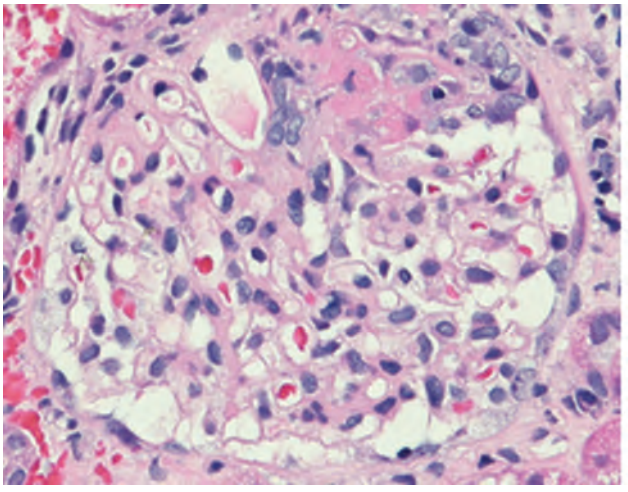
Stephanie S. Pavlovich, William C. Bennett, George Terinte-Balcan, Gerald A. Hladik, Koyal Jain. *University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC.*

Introduction: Small vessel vasculitis has a broad array of potential etiologies. A patient with known cryoglobulinemia due to hepatitis C (HCV) presenting with fever, glomerular hematuria and leukocytoclastic vasculitis because of endocarditis illustrates the importance of a judicious diagnostic evaluation.

Case Description: 41-year-old male with a history of HCV and intravenous drug use presented with confusion, migratory arthralgias and receptive aphasia over 3 months. 1 month prior to admission he was diagnosed with HCV-related type III cryoglobulinemia and started on therapy with glecaprevir/pibrentasvir. On exam he had a temperature of 38.4°C, petechial rash, receptive aphasia and systolic murmur. Laboratory data showed creatinine 1.23mg/dL, CRP 45.1mg/L, rheumatoid factor 15.9 IU/mL, type III cryoglobulins, PR3-ANCA 49.6U/mL and normal complement levels. Skin biopsy showed leukocytoclastic vasculitis. MRI of the brain showed foci of hemosiderin deposition consistent with vasculitic lesions. Blood cultures grew *E. faecalis* and echocardiogram showed a mitral valve vegetation. Kidney biopsy showed pauci-immune necrotizing GN

and diffuse ATN. As creatinine worsened (peak 2.66mg/dL), mycophenolate (MMF) was added after resolution of bacteremia following iv antibiotics. 1 week after stopping antibiotics, he was readmitted with AKI, nephritic syndrome, and recurrent *E. fecalis* bacteremia. MMF was stopped and antibiotics restarted with improvement in creatinine (1.40mg/dL) and urine sediment.

Discussion: This is a rare case of PR3-ANCA vasculitis due to *E. faecalis* endocarditis. A kidney biopsy and high index of suspicion is crucial in diagnosing pauci-immune GN in patients with preexisting vasculitis. Absence of hypocomplementemia raised suspicion for a superimposed process. This case highlights the importance of a careful evaluation in patients presenting with vasculitis despite appropriate treatment of a preexisting vasculitic syndrome.



PO1617

A Rare Case of Crescentic Glomerulonephritis, Diffuse Proliferative Class IV Lupus Nephritis, and Collapsing Glomerulopathy in a COVID, P-ANCA, and Myeloperoxidase-Positive Patient

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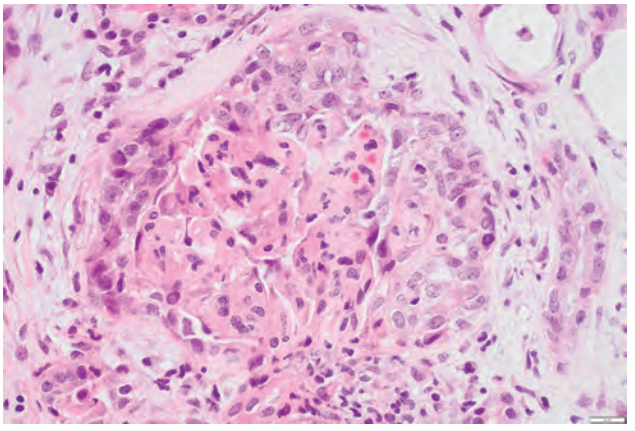
Introduction: An unusual case of Diffuse Class 4 Lupus Nephritis, along with Collapsing Glomerulopathy from asymptomatic COVID infection

Case Description: 42 year old Asian female presented with painless hematuria, anasarca, reduced hearing, and eye redness over a month. She had empiric antibiotics and steroids prior to admission. On admission, she was hypertensive with anasarca. Labs revealed AKI creatinine of 2.5 mg/dl, proteinuria of 11 grams, and serum albumin 1.9 gm/dL. Urine analysis showed dysmorphic RBCs, RBC casts. Ultrasound showed 12 cm kidneys bilaterally. She had normal complements and DS DNA, anticardiolipin and lupus anticoagulant negative. ANA, anticentromere antibody, COVID, PANCA, MPO all positive. Kidney biopsy showed crescentic glomerulonephritis, diffuse proliferative glomerulonephritis Class IV, collapsing glomerulopathy, full house pattern on IF. EM showed sub endothelial, mesangial, and para mesangial deposits, diffuse podocyte foot process effacement, corona virions in endothelial cells. The patient did not have any COVID symptoms and was treated with pulse steroids, MMF induction, hydroxychloroquine, and ACE I. Serum creatinine improved to 1.33 mg/dl, proteinuria improved to 5.6 grams. Her eye redness and hearing impairment resolved.

Discussion: This is a rare case of diffuse class IV lupus nephritis with normal complements, DS DNA, and full house pattern on IF. She tested positive for COVID, was asymptomatic, and was able to start treatment. Corona virions and podocytopathy was noted on EM. Improvement in proteinuria, serum creatinine, albumin, and resolution of anasarca were used to monitor response to treatments. Complements and DS DNA could not monitor disease activity. Thus, clinicians should not rely purely on serologies for diagnosis but should pursue kidney biopsy for definitive diagnosis and treatment. Patients may have atypical presentations.



PO1618

Schistosomiasis in a Patient on Rituximab for ANCA-Associated Glomerulonephritis

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Introduction: Rituximab and glucocorticoids induce remission in ANCA associated vasculitis with renal involvement. Rituximab induces B-cell depletion and influences T-cell immunity, which predispose patients to serious infectious complications. We present a case of schistosomiasis in a patient on rituximab for Pauci Immune Glomerulonephritis (GN) associated with ANCA vasculitis.

Case Description: A 39 years old female from Honduras with history of sero-negative arthritis, acute kidney injury with pauci immune, focal necrotizing and diffuse crescentic GN on kidney biopsy and P-ANCA positive, was treated on rituximab and glucocorticoids. Ten months later, while in remission she presented with nausea, vomiting, obstipation and abdominal pain. Her labs showed, Hgb: 10.4g/dl, WBC: 6780/mcl, Eosinophils 25%, Cr: 0.7mg/dl, H. Pylori: Positive. Guaic negative. Stool negative for ova/parasites. Endoscopy showed non-bleeding erosive gastropathy with scattered punctate ulcerations in the duodenum. On biopsy diffuse acute and chronic inflammation, focal cryptitis, erosion of mucosa, Schistosoma Mansoni ova in glands of stomach, duodenum and jejunum were noted. CT brain negative for cysticercosis. CT chest showed calcified granulomas in right middle lobe and right lower lobe. On reevaluation she admitted to consuming snails. Rituximab maintenance therapy was not continued because of schistosomiasis. She was admitted for a multidisciplinary approach. Renal function remained stable protein/creatinine ratio 0.8, Myeloperoxidase negative . Patient was started on Praziquantel 1.2 g tid and prednisone 60 mg for 5 days which was followed by another cycle after 4 weeks to treat any remaining adult schistosomes. Repeat EGD and colonoscopy with multiple biopsies to ensure eradication of schistosomiasis before resuming rituximab is planned.

Discussion: Our case emphasizes the need to consider parasitic infections when starting patients from endemic areas on immunosuppressive therapy. Schistosomiasis can involve multi-organ systems and can lead to potentially debilitating and fatal complications such as liver fibrosis, portal hypertension, hypersplenism, esophageal variceal bleeding, GN and nephrotic syndrome. Detailed history for dietary habits and lifestyle is important. Serology, antigen detection or other diagnostic tools can be used when the suspicion is high.

PO1619

Porcine Desiccated Thyroid Extract Associated Dual Positive ANCA Vasculitis

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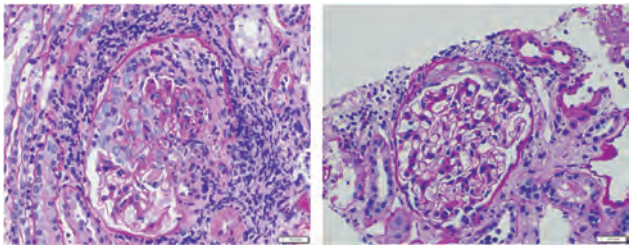
Introduction: Among medications used for thyroid disorders associated with small vessel vasculitis, the most well-known is propylthiouracil. However, there have been no reported cases of ANCA-associated vasculitis (AAV) with desiccated thyroid replacement hormones. We report the first case of drug-induced ANCA vasculitis presumed to be associated with porcine desiccated thyroid supplementation (Armour Thyroid).

Case Description: A 43-year-old Caucasian woman with Hashimoto's thyroiditis and bipolar disorder presenting with 1 month of generalized fatigue, subjective fevers, and foamy urine was found to have acute kidney injury with creatinine (Cr) peaking at 3.80 mg/dL from baseline 1.0 mg/dL. She recently started desiccated thyroid supplementation prior to the onset of symptoms. Urinalysis revealed active sediment with hematuria and subnephrotic proteinuria with 24-hour urine protein 1.1 gm/day. Serologic testing was notable for MPO Ab IgG positive >8.0 AI and PR3 Ab IgG positive > 6.4 AI. Further serologic workup, including anti-histone Ab, was negative. Kidney biopsy revealed features consistent with pauci-immune glomerulonephritis with cellular and fibrocellular crescents, mild interstitial inflammation and tubulitis, and mild arteriosclerosis and hyaline arteriosclerosis. She was not taking any other known medications associated with drug-induced vasculitis. She received pulse dose steroids with taper per the PEXIVAS trial

protocol and Rituximab therapy per the RAVE trial protocol. Cr improved (1.6 mg/dL) after induction therapy with persistent mild proteinuria at <500 mg/g at 6 months. Dual MPO and PR3 positivity persisted until Rituximab completion, after which only MPO positivity continued.

Discussion: It is well known that anti-thyroid medications can cause drug-induced AAV. However, this renal limited AAV case with desiccated thyroid supplementation suggests clinicians should also be aware of AAV as a possible adverse consequence of thyroid supplementation. Management should include discontinuation of the offending agent and consideration of immunosuppression with standard induction regimens based on disease severity.



PO1620

Renal Survival in Anti-Glomerular Basement Membrane Disease

Lauren Floyd,[1] Anna S. Li,[2,3] Nina Brown,[4] Helen Alderson,[4] Silke R. Brix,[2,3] Ajay P. Dhaygude.[1] *[1]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; [2]The University of Manchester Faculty of Biology Medicine and Health, Manchester, United Kingdom; [3]Manchester University NHS Foundation Trust, Manchester, United Kingdom; [4]Salford Royal NHS Foundation Trust, Salford, United Kingdom.*

Background: Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated kidney disease. Presentation with severe kidney dysfunction in need of renal replacement therapy (RRT) often results in end stage kidney disease (ESKD). Reliable predictors of kidney survival are needed.

Methods: Retrospective analysis of patients with anti-GBM disease from the North West of England.

Results: Seventy patients with GBM nephritis were identified, 20 patients presented double positive for anti-neutrophil cytoplasmic (ANCA) and GBM antibodies (28.57%). Median age was 64 years (Interquartile range 43 – 76 years). 39 patients were female (55.7%). Median kidney function at presentation was an estimated glomerular filtration rate of 593 ml/min (eGFR, IQR 419.75 – 835.75 ml/min). Sixty patients required RRT at presentation, and twelve of these patients recovered sufficient kidney function to withdraw RRT (25.5%). Median follow up was 41 months (IQR 11 - 77.5), and during follow up two additional patients developed ESKD (n = 50). The median presenting eGFR was numerically higher but not significantly different in patients that required dialysis initially and recovered residual function compared to patients that remained dialysis dependent, and no cut-off was detected (p=0.25). Patients with presenting eGFR as low as 2 – 3 ml/min recovered function.

Conclusions: Timely aggressive therapy to salvage kidney function is crucial. Better predictors of outcome are needed to optimise management in GBM vasculitis.

PO1621

Validation of the Renal Risk Score in Anti-GBM Disease

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Background: Anti-glomerular basement membrane (GBM) disease is a rare immune mediated kidney lesion of an aggressive nature often resulting in end stage kidney disease (ESKD). Clinical and histological variables predicting outcome are needed to individualise therapy and improve outcome.

Methods: We performed a retrospective multicentre analysis and investigated the Renal Risk Score (RRS) proposed in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis for its prognostic value in anti-GBM disease. We used the published cut-offs for percentage of normal glomeruli (N0 > 25%, N1 10 - 25%, N2 < 10%), estimated glomerular filtration rate (eGFR, G0 > 15 ml/min/1.73 m2, G1 ≤ 15 ml/min/1.73 m2) and a simplified cut off for tubular atrophy and interstitial fibrosis (T0 ≤ mild to moderate, T1 ≥ moderate). We assigned points to each parameter (N1 = 4, N2 = 6, G1 = 3, T1 = 2 points) and patients to risk groups, low (0), intermediate (2 - 7), and high risk (8 - 11 points).

Results: Seventy patients with GBM nephritis were identified, 20 patients presented double positive for ANCA and GBM antibodies (28.57%). Median age was 64 years (Interquartile range, IQR 43 – 76 years). 39 patients were female (55.7%). Median eGFR at presentation was 593 ml/min (IQR 419.75 – 835.75 ml/min). Median follow up was 41 months (IQR 11 - 77.5 months), and fifty patients developed ESKD (71.42%). Forty-seven biopsies were available for scoring. Four patients were low risk, and none developed ESKD (0%). Eight patients belonged in the medium risk group, and five of these developed permanent kidney-failure (62.5%). Of 35 patients in the high-risk group, 30 patients developed ESKD (85.7%). Three patients had the highest score of 11 points, and none remained dialysis independent (100%). The risk groups differed in renal survival (p<0.001).

Conclusions: Low percentage of normal glomeruli, higher grade of tubulointerstitial damage and severe kidney failure are associated with poor outcome in anti-GBM disease. Combining these variables, the Renal Risk Score accurately predicted kidney survival in anti-GBM disease.

PO1622

Anti-Glomerular Basement Membrane Disease in Pregnancy

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Introduction: Anti-glomerular basement membrane (GBM) vasculitis is a rare immune mediated inflammation resulting in organ- and life-threatening disease. Presentation during pregnancy presents an additional challenge to preserve organ function and life of the unborn child.

Case Description: We report the case of a 23-year-old woman, 18 weeks pregnant, presenting with haemoptysis and acute kidney injury. Her chest X Ray demonstrated multilobar consolidation with perihilar prominence consistent with pulmonary haemorrhage. Her blood tests detected an anaemia (Hb 51 g/L) and kidney failure (eGFR 17 ml/min). Her GBM antibody was 30.3 AI. She received daily plasma exchange (PLEX) for 7 days until her GBM antibody normalised. Additionally, she was commenced on 1gram of cyclophosphamide, and following her plasma exchange sessions she received 1gram of rituximab. Her acute kidney injury progressed (eGFR 13 ml/min), and renal replacement therapy was initiated to manage fluid overload and for foetal health. She remained 8 days in the high dependency unit on high flow oxygen therapy due to respiratory failure due to her diffuse alveolar haemorrhage needing daily transfusions to maintain her haemoglobin. Daily gynaecology reviews were performed. Post rituximab, PLEX was recommenced after 72 hours and continued daily for another week with 13 sessions in total. The patient stabilised, renal replacement therapy was discontinued, and she was discharged after a hospital stay of 27 days. Her baby was delivered via caesarean section due to the development of preeclampsia at week 28 gestation. Twelve months later, patient and baby are healthy with normal development per percentile, and patient's kidney function has recovered with a current eGFR of 86 ml/min.

Discussion: Timely and aggressive therapy is crucial to salvage kidney function in anti-GBM disease. Here, we present a case of a pregnant patient highlighting that a certain amount of cyclophosphamide is acceptable in life-threatening maternal conditions. Additionally, we demonstrate the possibility to significantly reduce cyclophosphamide in anti-GBM disease by adding in rituximab.

PO1623

Itolizumab, a Novel Anti-CD6 Therapy, in Systemic Lupus Erythematosus Patients: Interim Safety Results from the Phase 1b EQUALISE Dose-Escalation Study

Chaim Putterman,[1] Richard Furie,[2] Jai Radhakrishnan,[3] Vandana S. Mathur,[5] Krishna R. Polu,[5] Stephen Connelly,[5] Joel M. Rothman,[5] Cherie T. Ng,[5] Leslie Chinn,[5] Maple M. Fung,[5] Dolca Thomas,[5] Kenneth Kalunian.[4] *[1]Yeshiva University Department of Medicine, Bronx, NY; [2]Northwell Health, New Hyde Park, NY; [3]Columbia University, New York, NY; [4]University of California San Diego, La Jolla, CA; [5]Equillium, Inc, La Jolla, CA.*

Background: CD6 is a co-stimulatory receptor predominantly expressed on T cells. The CD6 ligand, ALCAM, is expressed on antigen presenting cells, epithelial and endothelial cells. Itolizumab (ITO) is a humanized IgG1 monoclonal antibody that binds CD6 and blocks ALCAM interaction to inhibit T cell activation and trafficking.

Methods: EQUALISE is an open-label Phase 1b 2-part study evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of subcutaneous doses (SC) of ITO (0.4 to 3.2 mg/kg). Part A enrolled adults with active or inactive SLE who received ≥1 SLE treatment. Treated subjects received ITO SC Q2 weeks x 2. Part B, which evaluates ITO in subjects with active proliferative Class III/IV LN for 24 weeks, is currently enrolling (NCT04128579).

Results: Part A enrolled 34 subjects: 0.4 mg/kg (n=6), 0.8 mg/kg (n=7), 1.6 mg/kg (n=7), 2.4 mg/kg (n=6), and 3.2 mg/kg (n=8). Similar baseline characteristics were noted across cohorts. The mean age was 51, with 94% female, 74% white and ~11 years since SLE diagnosis. C3 and C4 were within normal ranges. Mean eGFR was 98 ml/min/1.73m2 and the median UPCR was 91 mg/g (range 48-1505). SC dosing of 0.4 mg/kg to 2.4 mg/kg (n=26) was well tolerated, with 38% reporting an AE, predominantly mild injection site reactions, with no SAEs reported. >85% of 3.2 mg/kg subjects reported an AE, the most common was injection site reactions, with 2 non-treatment related SAEs reported in 1 subject (hypotension, syncope). 4 3.2 mg/kg subjects (50%) discontinued treatment after 1 dose voluntarily. In all cohorts, there were no notable changes in vital signs or labs, except for transient declines in lymphocyte counts without clinical sequelae. PK and PD results show dose-proportional increases in ITO exposure and rapid and dose-dependent decreases in CD4 cell surface expression of CD6.

Conclusions: 2 SC doses of ITO up to 2.4 mg/kg SC in SLE subjects were well tolerated; with less tolerability to the 3.2 mg/kg dose, as 50% discontinued after 1 dose. The data support continued evaluation of ITO in SLE/LN. The ongoing EQUALISE Part B assesses ITO safety and efficacy in Class III/IV LN patients.

Funding: Commercial Support - Equillium, Inc

PO1624

Itolizumab, a Novel Anti-CD6 Antibody, in Systemic Lupus Patients with Proteinuria: An Interim Subgroup Analysis from EQUALISE, a Phase 1b Study

Chaim Putterman,[1] Richard Furie,[2] Jai Radhakrishnan,[3] Vandana S. Mathur,[5] Krishna R. Polu,[5] Stephen Connelly,[5] Joel M. Rothman,[5] Leslie Chinn,[5] Nuwan Nanayakkara,[5] Maple M. Fung,[5] Cherie T. Ng,[5] Dolca Thomas,[5] Kenneth Kalunian.[4] *[1]Yeshiva University Department of Medicine, Bronx, NY; [2]Northwell Health, New Hyde Park, NY; [3]Columbia University, New York, NY; [4]University of California San Diego Health Sciences, La Jolla, CA; [5]Equillium Inc, La Jolla, CA.*

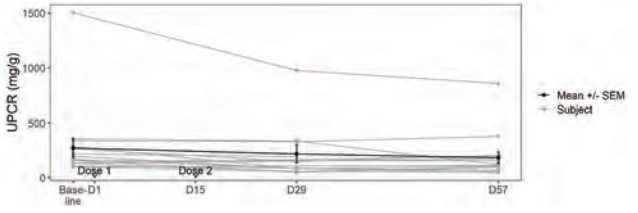
Background: CD6 is a co-stimulatory receptor that is expressed on T cells. The CD6 ligand, ALCAM, is found on antigen presenting cells, as well as epithelial and endothelial cells. Itolizumab (ITO), a humanized IgG1 monoclonal antibody that binds CD6 and inhibits the interaction of CD6 and ALCAM, inhibits T cell activity and trafficking. ITO is being evaluated as a treatment for systemic lupus erythematosus (SLE) and lupus nephritis (LN).

Methods: EQUALISE (NCT04128579) is a Phase 1b US study of ITO in SLE patients with and without active proliferative LN. Part A enrolled SLE patients (N = 34) who had received ≥ 1 SLE treatment but did not have active proliferative LN. Patients received 2 open-label doses of 0.4 to 3.2 mg/kg each SC on Day 1 and Day 15 with follow up through Day 57.

Results: A subgroup analysis of 16 subjects with Baseline (mean of screening and Day 1) urine protein/creatinine ratio (UPCR) > 100 mg/g was performed. Mean age was 55, 94% were female; 81% white and the mean years since SLE diagnosis was approximately 11. Mean baseline eGFR was 95 ml/min/1.73m2 and UPCR was 272 mg/g (range 100-1505). On Day 29, a geometric mean decrease in UPCR of ~45% was observed in these 16 subjects with greater decline seen for subjects with higher Baseline UPCR values. By Day 57, 6 weeks post treatment the decrease was ~34% from Baseline (Figure). Notable is one subject (1.6 mg/kg dose) who had significant Baseline UPCR of 1505 mg/g, by Day 29 the UPCR had declined to 974 mg/g, and at Day 57 declined to 857 mg/g. SC treatment was well tolerated. Of the 6 subjects who had a total of 12 treatment-emergent adverse events (AEs), 4 were from the 3.2 mg/kg cohort. All AEs were mild or moderate in severity.

Conclusions: Patients with SLE and mild baseline proteinuria tolerated ITO treatment well. EQUALISE Part B will further explore the safety and efficacy of ITO in LN patients.

Funding: Commercial Support - Equillium, Inc



Urine protein: creatinine ratio over time (mean±SEM) and individual subjects

PO1625

Adding Low-Dose CYC to RTX Combined with a Tailored RTX Maintenance Regimen Seems to Favor Stable Remission in Severe ANCA Vasculitis

Renee Ysermans, Matthias H. Busch, Joop Aendekerk, Pieter van Paassen. *Maastricht University Medical Center, Department of Internal Medicine, Maastricht, Netherlands.*

Background: Rituximab (RTX) and cyclophosphamide (CYC) are effective remission-induction therapies in ANCA-associated vasculitis (AAV). High dose CYC is however considered toxic, whereas RTX monotherapy may increase the risk of relapse, depending on the choice of maintenance therapy and baseline disease severity. Particularly with renal involvement, stable remission will favor prognosis. In this respect, adding low dose CYC to RTX could be superior to RTX alone. We checked this premise by retrospectively analyzing our data derived from a pragmatic, clinical approach in patients with severe AAV.

Methods: Between 2007 and January 2019, 246 patients with severe active AAV, needing remission-induction therapy, were screened and 62 patients were included. Remission-induction consisted of either RTX (1000mg two times) or RTX-CYC (1000mg RTX and 15mg/kg CYC intravenously, two times). Corticosteroid tapering was identical in both groups. RTX during the maintenance phase was tailored according to either CD19+ B cell repopulation (≥5 cells/ µl) and/or a rise in ANCA level, combined with clinical symptoms, without signs of a major relapse. Primary outcome variables were major relapse rate and adverse events at 2 and 5 years, compared with the log-rank test.

Results: 28 patients received RTX only and 34 patients received RTX-CYC. Disease presentation, severity of disease (BVAS), and laboratory parameters (serum creatinine, CRP, and total IgG) at baseline were similar. Renal involvement was more prevalent in the RTX-CYC patients (85.3%) as compared to RTX only (60.7%) ($P = 0.028$). Relapse rates within 2 years were significantly higher in the RTX only group (n=7 in RTX only, n=1 in RTX-CYC, $P = 0.015$), whereas the number of patients receiving RTX maintenance and the number of infusions did not differ. After 5 years, however, relapse rates did not differ (n=9 in RTX only, n=7 in RTX-CYC). The rate of infections, hypogammaglobulinemia, end stage renal disease, malignancies, and mortality did not differ after 2 and 5 years.

Conclusions: Adding low dose CYC to RTX is safe and may favor the prevention of major relapses in patients with severe AAV, predominantly with renal involvement. Future prospective studies are needed to examine the role of reconstituted B cells and ANCA features to better define tailor-made treatment decisions.

PO1626

Preferences Regarding Treatment with Plasma Exchange for ANCA-Associated Vasculitis: An International Patient Survey

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Background: Patient preferences regarding plasma exchange (PLEX) for ANCA-associated vasculitis (AAV) are uncertain. We sought to elicit patient preferences regarding the use of PLEX in AAV.

Methods: An online survey was circulated via national vasculitis and kidney patient networks. Respondent characteristics were collected and information regarding PLEX in AAV was provided including its minimal effect on mortality. One year risks of end stage kidney disease (ESKD) and serious infections with and without PLEX in AAV were presented across 5 serum creatinine categories: 150, 250, 350, 450 and 600µmol/L. For each scenario, participants were asked: "If they were a patient with a new diagnosis or relapse of AAV, would they choose treatment with PLEX (yes or no) given its absolute risk reduction in ESKD, but absolute risk increase in serious infections?" Multilevel multivariable logistic regression was performed to identify independent predictors of choosing treatment with PLEX.

Results: There were 549 responses. The mean age of respondents was 57.4 (SD 14.5) years, 72.3% were female, and respondents were from the United States (58.1%), United Kingdom (23.7%), Canada (14.0%), and other countries (4.2%). The majority had AAV (86.7%). 190/549 (34.6%) would always choose PLEX and 87/549 (15.8%) would always decline PLEX across the baseline risks of ESKD or serious infections presented. Independent predictors for choosing PLEX included age (OR 0.98, 95% CI 0.96-0.99 per 1 year increase), country (United Kingdom OR 2.73, 95% CI 1.20-6.21), diagnosis (individuals with vasculitis other than AAV were more likely), previous dialysis (OR 3.34, 95% CI 1.37-8.16), previous PLEX (OR 5.13, 95% CI 2.50-10.49), and increased baseline risk of ESKD (Cr 350 and 450µmol/L only).

Conclusions: One third of participants would always choose treatment with PLEX across the 5 scenarios presented. The decision to choose PLEX is influenced by age, country, previous dialysis, and the baseline risk of ESKD and serious infections. Patient values and preferences are needed to inform shared decision-making regarding PLEX in AAV.

PO1627

Maintenance of Remission and Risk for Relapse in Myeloperoxidase Positive Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Kidney Involvement

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Background: Optimal time of remission-maintenance therapy in patients with MPO-ANCA associated vasculitis (MPO-AAV) is not established. Defining clinical and laboratory parameters to guide safe withdrawal of maintenance immunosuppression is required in order to mitigate the risk of relapse.

Methods: A retrospective cohort study of all patients followed at the Mayo Clinic with MPO-AAV (MPA and GPA) and kidney involvement. Relapse rate, correlation with MPO-ANCA status and remission-maintenance strategy were characterized.

Results: We analyzed 159 MPO-ANCA positive patients with active kidney involvement. A total of 66 (41.5%) patients had at least 1 relapse. MPO-ANCA patients who became and remained seronegative did not relapse (HR 0.032, [95%CI, 0.001-0.970], p=0.048). MPO-ANCA reappearance after seronegative conversion was associated with increased relapse risk at 24 months (HR 3.651, [95%CI, 1.114-11.966], p=0.012). Immunosuppression was withdrawn in 80 (50.3%) and this was predicted by persistent MPO-ANCA seronegative conversion (OR 3.028, [95%CI, 1.262 – 7.268], p=0.013). In patients who withdrew remission-maintenance therapy, 32 (40.0%) relapsed (in comparison with 34 relapses [43.0%] in those who maintained immunosuppression, p=0.697). ENT involvement (OR 6.095 [95%CI, 1.280 – 29.010], p=0.023) and MPO-ANCA reappearance (OR 9.248, [95%CI, 3.126 – 27.361], p<0.0001), were independent predictive factors for relapse after withdrawal.

Conclusions: Our results suggest that patients who seroconverted and remain MPO-ANCA negative are at lower risk of relapse: remission-maintenance treatment might be withdrawn without an additional risk of relapse. MPO-ANCA reappearance after seronegative conversion is a risk factor for relapse at 24 months. Serial MPO-ANCA determinations are useful to guide clinical decisions on remission-maintenance treatment strategies.

PO1628

Renal Histological Biomarkers and Response to Different Induction Regimens in ANCA-Associated Glomerulonephritis: The REASSESS Study

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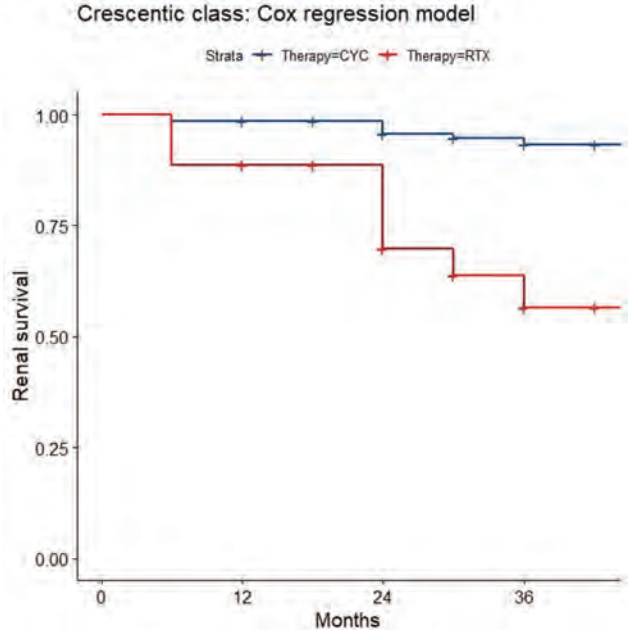
Background: The role of kidney biopsy on ANCA-associated vasculitis (AAV) is still debated: despite its significant prognostic value, whether it has an impact on the induction regimen choice has not been explored yet.

Methods: 323 AAV patients with biopsy-proven renal involvement were collected retrospectively from eleven centers and stratified according to the histopathological characteristics at the kidney biopsy and the induction regimen employed.

Results: The median follow-up time was 36 months; the eGFR was 19 ml/min/1,73m^2; 53% were MPO-ANCA and 41% PR3-ANCA. 58% were treated with Cyclophosphamide (CYC), 18% with Rituximab (RTX) and 24% with RTX-CYC. According to the *Berden* classification, 24% biopsies were classified as Focal, 31% as Crescentic, 33% as Mixed and 12% as Sclerotic. Renal remission rate at 6 months and relapse-free survival were comparable in the different groups. In the unadjusted survival analysis with the K-M curve, patients in the Crescentic group treated with RTX had a shorter ESRD-free survival compared to the CYC group (p=0.033) and the RTX-CYC one (p=0.044). This was confirmed with a Cox regression analysis adjusted for sex, age, ANCA type, AAV diagnosis, creatinine and proteinuria when comparing the RTX group with the CYC one (HR 8.30 [95% CI 1.64-42.01], p=0.011).

Conclusions: Response rates and relapse risk were comparable in the overall cohort and in each histopathological subgroup. The ESRD-free survival in the Crescentic class was shorter in the RTX group compared to the CYC one.



PO1629

ANCA Vasculitis Induction Management in the COVID-19 Pandemic: Results of an International Retrospective Cohort Study

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Background: Induction therapy for severe ANCA-associated vasculitis (AAV) combines glucocorticoids (GC) with either rituximab (RTX) or cyclophosphamide (CYC). The coronavirus 2019 disease (COVID-19) pandemic has increased concern around using aggressive immunosuppression; whether this concern has impacted AAV management is unknown. Here, we report treatment regimens and outcomes of patients with active AAV receiving induction immunosuppression during the first wave of the pandemic.

Methods: We retrospectively studied AAV patients with new or relapsing disease receiving remission induction therapy during the first wave of the COVID-19 pandemic across sites in the US, UK and Europe. Primary outcome was achievement of complete remission at 6 months.

Results: Of 191 patients with a mean age of 65 years old, 52% were female and a majority (89%) were Caucasian. Standard induction was deployed across all sites. Out of the US, UK, and European patient populations, the US used higher GC pulses leading to a higher average cumulative GC dose for remission induction (4153 mg, 2174 mg, 3408 mg, respectively, p<0.001) and had the highest proportion of patients given RTX induction therapy (64%; p=0.005). Complete remission was achieved in 90% of patients. Improvement in kidney function at 6 months was similar with all treatment regimens (6 ml/min^2 increase, p=0.68). Sixteen patients were diagnosed with COVID-19 and had similar exposures to CYC and RTX. There were no differences in remission rates, ESKD or death when stratified by induction therapy type.

Conclusions: Induction immunotherapy practices differ across the world, but specialists continued their standard management during the COVID-19 pandemic. AAV outcomes or rates of COVID-19 infection were not influenced by different induction regimens.

Treatment differences and 6M remission among different cohorts

Treatment variables	Entire cohort	United States	United Kingdom	Europe	P-value
Use of pulse GCs, n (%)	117 (61); n=191	35 (80); n=44	44 (53); n=83	38 (59); n=64	0.013
Mean (SD) cumulative dose of IV pulse methylprednisolone in mg	930 (981); n=175	1658 (1243); n=43	730 (755); n=74	647 (733); n=58	<0.001
Mean (SD) cumulative GC for remission induction in mg	2962 (1841); n=171	4153 (2427); n=35	2174 (1229); n=83	3408 (1642); n=53	<0.001
RTX use only, n (%)	84 (44); n=191	28 (64); n=44	28 (34); n=83	28 (44); n=64	0.005
CYC use only, n (%)	49 (26); n=191	5 (11); n=44	23 (28); n=83	21 (33); n=64	0.037
RTX and CYC, n (%)	49 (26); n=191	10 (23); n=44	28 (34); n=83	11 (17); n=64	0.066
Remission at 6 months, n (%)	160 (90); n=178	37 (90); n=41	64 (85); n=75	59 (95); n=62	0.164

PO1630

Non-Sucrose Containing IV Immunoglobulin in ANCA Vasculitis Has No Adverse Effects on Renal Function

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Background: Intravenous immunoglobulin (IVIG) has proven to be effective as an immunomodulator in several autoimmune and inflammatory diseases, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Moreover, in the era of B cell-depleting therapies, secondary immunodeficiencies are common, urging suppletion by IVIG. Reported adverse effects are generally mild in nature. However, concerns have been raised about the safety profile of IVIG in relation to renal function. IVIG associated kidney injury is proposed to be mainly related to sucrose stabilized products. Non-sucrose containing alternatives are available and increasingly used. We therefore aimed to analyze the safety of non-sucrose containing IVIG with regard to renal function in patients with AAV.

Methods: AAV patients of the Maastricht University Medical Center were retrospectively analyzed for dynamics of serum creatinine levels before and after IVIG using the Wilcoxon signed rank-test. Subanalyses were performed with regard to the presence of ANCA-associated renal disease and IVIG indication. In addition, correlation analysis was conducted to evaluate the relation between serum creatinine change and cumulative IVIG dose during a 1year follow-up.

Results: 36 with 49 courses of IVIG were included in the short-term and 54 patients with 70 courses of IVIG were included in the long-term analysis. No significant differences were found between serum creatinine levels before and after IVIG in the short-term (median [IQR], 132 [88-159] and 125 [86-173] mmol/L, P = 0.380), with a median follow-up of 16 days after the initial IVIG infusion, and the long-term (median [IQR], 104 [86-147] and 110 [90-152] mmol/L, P = 0.077), after 1 year. One patient with active AAV and renal involvement had a reversible serum creatinine increase >30% 6 days after IVIG. Subanalyses showed no significant changes in serum creatinine levels with regard to renal involvement and IVIG indication. There was no association between serum creatinine change and cumulative IVIG dose 1 year after the initial IVIG infusion (P = 0.667).

Conclusions: This study shows no short-term and long-term deleterious effects on renal function in response to treatment with non-sucrose containing IVIG in patients with AAV.

PO1631

Efficacy and Safety of a Combination Treatment of Mycophenolate Mofetil and Corticosteroid in Advanced IgA Nephropathy: A Multi-center, Prospective Study

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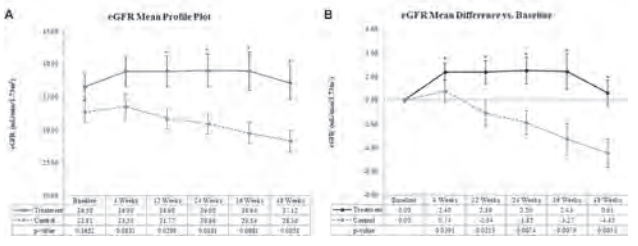
Background: It remains unclear whether immunosuppressive agents are effective in patients with IgA nephropathy (IgAN). We sought to determine the efficacy of mycophenolate mofetil (MMF) and corticosteroid combination therapy in patients with advanced IgAN.

Methods: We conducted a multicenter, randomized, placebo-controlled, parallel group study of a 48-week administration of MMF and corticosteroids in biopsy-proven advanced IgAN patients with an estimated glomerular filtration rate (eGFR) between 20-50 mL/min/1.73m^2 and a urine protein-to-creatinine ratio (UPCR) greater than 0.75g/day. The primary outcome was complete (UPCR<0.3g/day) or partial remission (reduction of UPCR >50% compared to baseline) at 48 weeks.

Results: Of the 48 randomized patients, complete and partial remission rates were higher in the MMF and corticosteroid combination therapy group (29.1% vs. 5.0%, *P*=0.05). In contrast to the combination therapy group, eGFR in the control group significantly decreased from 36 weeks onwards, resulting in a final adjusted mean change of -4.39 ± 1.22 mL/min/1.73m^2 (*P*=0.002). The adjusted mean changes at 48 weeks were 0.62 ± 1.30 and -5.11 ± 1.30 mL/min/1.73m^2 (*P*=0.005) in the treatment and control groups, respectively. The amount of UPCR was also significantly different between the two groups, where the adjusted mean difference was -0.47 ± 0.17 mg/mgCr in the treatment group and 0.07 ± 0.17 mg/mgCr in the control group (*P*=0.04). Overall adverse events did not differ between the groups.

Conclusions: In patients with advanced IgAN with a high risk for disease progression, combination therapy of MMF and corticosteroid appears to be beneficial in reducing proteinuria and preserving renal function.

Fig. 2



PO1632

Pharmacodynamic and Clinical Responses to BION-1301 in Patients with IgA Nephropathy: Initial Results of a Ph1/2 Trial

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis globally, with up to 45% of patients at risk of progressing to ESKD. The initiating step in IgAN pathogenesis is the excess production of galactose-deficient IgA1 (Gd-IgA1), resulting in the formation of immune complexes that cause kidney inflammation and damage. A Proliferation-Inducing Ligand (APRIL) is elevated in IgAN patients and correlated with higher levels of Gd-IgA1 and proteinuria, and lower eGFR. BION-1301 is a novel monoclonal antibody targeting APRIL. Here we present interim results from Part 3 of a Phase 1/2 study that characterizes the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary activity of BION-1301 delivered by IV administration in patients with IgAN.

Methods: Part 3 of this Phase 1/2 study (NCT03945318) is an ongoing multicenter, multicohort, open-label study in up to 40 IgAN patients. In Cohort 1, BION-1301 is dosed at 450mg IV every 2 weeks for up to 12 months. Key objectives of the study include safety and the characterization of PK, PD, immunogenicity and changes in proteinuria. Key eligibility criteria include: (1) urine protein ≥0.5 g/24h or baseline UPCR ≥0.5 g/g, (2) stable/optimized dose of ACE-I/ARB or ACE-I/ARB intolerant and (3) biopsy-verified diagnosis of IgAN within the past 10 years.

Results: Preliminary results from the first 5 patients show BION-1301 is well tolerated with no serious adverse events and no adverse events leading to discontinuation to date. BION-1301 drives durable reductions in serum free APRIL, Gd-IgA1, IgA and IgM, with a lesser reduction in IgG. A clinically meaningful reduction in 24-hour UPCR was observed within 3 months. Updated data in all IV treated patients, along with mechanistic response kinetics, will be presented at the meeting.

Conclusions: BION-1301 is a novel anti-APRIL monoclonal antibody being developed as a potential treatment for patients with IgAN. BION-1301 offers disease modifying potential by directly targeting the pathogenesis of IgAN. Promising early biomarker and clinical activity support the continued development of BION-1301 in IgAN.

Funding: Commercial Support - Chinook Therapeutics

PO1633

Atrasentan Exhibits a Consistent, Predictable Pharmacokinetic Profile Among Healthy Asian Adults

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Background: Atrasentan, a potent and selective endothelin-A receptor antagonist, is under investigation for reducing proteinuria and preserving kidney function in IgA nephropathy and other glomerular diseases. Two phase 1 studies evaluated the pharmacokinetics (PK) and safety of atrasentan in healthy adults of Chinese (Study M11-521) and Japanese (Study M11-522) parentage.

Methods: Study M11-521 was an open-label, randomized (for single-dose regimens), single-center study of single and multiple doses of atrasentan in 36 healthy Chinese adults. Single doses of atrasentan tablets (0.5, 1, or 1.5 mg) were administered in Part I, and multiple once-daily doses of atrasentan 1.5 mg were administered in Part II. Study M11-522 was a double-blind, randomized, placebo-controlled, single-center study of single doses of atrasentan (0.5, 0.75, or 1.25 mg) in 36 healthy Japanese adults. Blood samples were collected for analysis of plasma PK parameters, including the area under the plasma concentration-time curve (AUC) and the maximum observed plasma concentration (C_{max}).

Results: In Study M11-521, atrasentan AUC increased proportionally with dose in the 0.5 mg to 1.5 mg dose range, and C_{max} increased proportionally with dose in the 1 mg to 1.5 mg dose range. No statistically significant differences were observed in either the dose-normalized AUC_∞ for the comparison of the 1.5 mg and 0.5 mg dose groups ($P \geq 0.260$) or the dose-normalized C_{max} for the comparison of the 1.5 mg and the 1 mg dose groups ($P = 0.279$). In Study M11-522, a linear increase in atrasentan mean AUC_∞ was observed across the 0.5 to 1.25 mg dose range; dose-normalized mean AUC_∞ did not show any statistically significant difference across the doses ($P = 0.735$). Atrasentan was generally well tolerated. No clinically significant vital signs, electrocardiogram activity, or laboratory measurements were observed, and no apparent significant differences among the dose regimens were found with respect to safety.

Conclusions: Dose-proportional increases in AUC were observed across the studied range, which includes the 0.75 mg dose being studied in ongoing clinical trials. These data support the safety and tolerability of atrasentan and suggest a consistent and predictable PK profile among patients of Asian descent.

Funding: Commercial Support - Abbvie, Chinook

PO1634

Randomized Clinical Study to Evaluate the Effect of Personalized Therapy on Patients with Immunoglobulin A Nephropathy (IgAN)

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Background: IgAN is the most common biopsy-proven glomerulonephritis in the world. Approximately 40% of IgAN patients reach end-stage kidney disease (ESKD) 20 years after their kidney biopsy. The high prevalence of ESKD shows that IgAN has a high economic impact in the countries because renal replacement therapy is costly. Moreover, the disease's onset in the second and third decades of life represents a social challenge because young adult patients are very active and highly productive in the workplace. This challenge is one more reason to move from a generalized therapy for all patients to a personalized therapy. Many randomized controlled trials (RCTs) have been conducted, stratifying IgAN patients based on the laboratory findings (serum creatinine, estimated glomerular filtration rate (eGFR) and daily proteinuria). In contrast, data from the kidney biopsy has been used only for clinical diagnosis. **Aim**. We have designed a RCT to study personalized therapy in biopsy-proven IgAN patients with active and chronic renal lesions.

Methods: Our clinical study of IgAN (CLIgAN) is a multicentre, prospective, controlled and open-label randomized clinical trial based on patient's stratification at the time of their kidney biopsy. The trial has been registered in ClinicalTrials.gov (NCT 04662723). We will consider, first, the type of renal lesions followed by serum creatinine values, eGFR and proteinuria. Primary and secondary end points have been established. Second, we will determine whether personalized therapy can slow the decline of the renal function and delay the ESKD.

Results: We will enroll 132 IgAN patients with active renal lesions (66 patients per arm) in the first RCT (ACIgAN). They will receive corticosteroids combined with renin-angiotensin system blocker (RASB) or RASB alone. Two hundred ninety-four IgAN patients with chronic renal lesions at high or very high risk of chronic kidney disease (147 patients per arm) will be enrolled in the second RCT (CHRONIgAN) in which they will receive sodium-glucose cotransporter -2 inhibitor (SGLT2-i) combined with RASB or RASB alone.

Conclusions: Using this approach we hypothesize that patients could receive personalized therapy based on renal lesions to ensure that the right drug gets to the right patient at the right time.

Funding: Private Foundation Support

PO1635

Enhanced Efficacy of Corticosteroid Therapy by Tonsillectomy in IgA Nephropathy

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Background: Efficacy of corticosteroid therapy in IgA nephropathy may vary among countries or races. Nowadays, the strategy to enhance efficacy of corticosteroid therapy is desired. In 2014, our randomized controlled trial demonstrated that corticosteroid therapy combined with tonsillectomy had superior anti-proteinuric effect than that of corticosteroid therapy alone (Nephrol Dial Transplant. 2014). However, the benefit of combining corticosteroid therapy with tonsillectomy for long-term renal survival was uncertain. Therefore, in a Japanese nationwide prospective cohort dataset, we aimed to evaluate whether the benefit of corticosteroid therapy may increase when it was combined with tonsillectomy, or not.

Methods: Patients were registered between April 1, 2005 and August 31, 2015 at 44 facilities throughout Japan. The primary outcome was a 50% increase in serum creatinine from baseline or dialysis induction. Two interventions were focused in the present study: corticosteroid with or without tonsillectomy. Survival analysis was adjusted with baseline clinicopathological parameters including eGFR, proteinuria, hematuria, RAS inhibitor use and MEST-C score in Oxford classification.

Results: Enrolled 991 patients showed 75.4 ml/min as mean eGFR and 0.58 g/day as median level of proteinuria. Among them, 634 (64.0%) and 425 (42.9%) patients received corticosteroid therapy and tonsillectomy, respectively. During the median follow up of 5.5 years, 87 patients (8.8%) reached primary outcome. Adjusted hazard ratio (HR) of corticosteroid therapy for primary outcome in patients with tonsillectomy was 3-fold favorable than that in those without tonsillectomy (HR 0.18, 95% confidence interval [CI] 0.06-0.65, versus HR 0.59, 95%CI 0.34-1.01; P value for interaction between corticosteroid therapy and tonsillectomy 0.060).

Conclusions: Enhanced efficacy of corticosteroid therapy by tonsillectomy in IgA nephropathy was confirmed in a Japanese nationwide prospective cohort.

Funding: Government Support - Non-U.S.

PO1636

The Potential Role of Monthly Corticosteroid Pulse in IgA Nephropathy

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Background: The risk of corticosteroid therapy may be underestimated in IgA nephropathy (IgAN). Previous studies provided that a fifth part of patients was older than 60 years and the rate of diabetes mellitus (DM) was increased in IgAN. The novel corticosteroid therapies with not losing benefit and reduced risk of corticosteroid are desired. Here, we aimed to determine whether monthly corticosteroid pulse is non-inferior in proteinuria remission and superior in blood glucose control to standard corticosteroid therapy or not.

Methods: Design: Retrospective, non-inferiority study. Participants: Adult patients with IgAN received intervention described below between 2013 and 2020. Intervention: Monthly corticosteroid pulse alone for 6 months versus standard corticosteroid therapy having oral corticosteroid for 6 months and three times of pulse corticosteroid in the same 6 months (Lancet 1999). Outcomes: The primary outcome was proteinuria remission (<0.3g/day) at 1 year and we prespecified 0.67 in odds ratio (OR) as non-inferiority margin. The secondary outcome was safety of blood glucose care, which was defined by less than 0.3 in change of hemoglobin A1c% between baseline and 6 months.

Results: The enrolled 83 patients (22 patients >60 years old and 11 patients with DM) showed median proteinuria 0.93g/day and mean eGFR 60.5ml/min at baseline. There was no significant difference in proteinuria remission between the two groups but including the non-inferiority margin (16/21[76.2%] versus 38/62[61.3%], adjusted OR 4.10, 95%CI 0.47 to 36.1). The safety of blood glucose care in monthly corticosteroid pulse group was significantly superior to that in standard group (19/21[90.5%] versus 35/62[56.5%], adjusted OR 14.2, 95%CI 2.02 to 98.9).

Conclusions: Compared to standard corticosteroid therapy, the current study showed that monthly corticosteroid pulse did not reach the statistical requirements for a proven non-inferiority on proteinuria remission, but significantly exhibited safety outcome in the control of blood glucose. Prospective larger studies are needed to determine the role of monthly corticosteroid pulse in IgAN.

PO1637

The Beneficial Effects of Renin-Angiotensin System Inhibitors on IgA Nephropathy with Global Sclerosis

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Background: In IgA nephropathy (IgAN), global sclerosis has been recognized as one of the risk factors for progression, because it induces glomerular hypertension and hyperfiltration in the remained glomeruli. The reno-protective effects of renin-angiotensin system inhibitors (RASI) are considered to decrease glomerular hypertension and hyperfiltration, but their effectiveness in IgAN with global sclerosis has been unknown.

Methods: Of the 871 IgAN patients diagnosed at our institution, we classified them into three grades by the ratio of global sclerosis (G) against whole glomeruli [G0 (n=225): none, G1 (n=455): at least one but <25%, G2 (n=191): ≧25%]. We compared each clinical background and 20-year prognosis. Then, we examined the effect of RASI initiated during follow-up period on the long-term prognosis in patients with G1+G2 and in patients with G2 by Kaplan-Meier analysis and Cox regression analysis. To adjust the background characteristics between patients treated with or without RASI, propensity matching score was performed.

Results: The age, blood pressure, proteinuria, renal function, and histological findings were significantly severer with increasing grade in G0, G1, and G2, and 20-year renal survival rate was 83.5%, 75.0% and 54.4% in patients with G0, G1, and G2, respectively (p<0.001). After propensity matching between patients treated with or without RASI, 366 patients in G1+G2 and 90 patients in G2 were eligible for the evaluation. The 20-year renal survival rate was significantly higher in the patients with RASI than in the patients without RASI (G1+G2: 84.5% vs. 50.9%, p<0.001, G2: 63.8% vs. 33.5%, p=0.037). In multivariate Cox regression analysis considering clinical and histological findings and treatment, RASI was an independent factor to prevent progression in patients with G1+G2 and G2 (G1+G2, hazard ratio: 0.39, 95% confidence interval: 0.25-0.62, p<0.001; G2, hazard ratio: 0.35, 95% confidence interval: 0.19-0.66, p=0.001).

Conclusions: In this study, global sclerosis was associated with severer clinical and histological findings, and poor prognosis. However, RASI initiated during follow up period was found to improve renal prognosis in IgAN with at least one global sclerosis.

PO1638

Atacicept Reduces Serum Gd-IgA1 by Quartiles in IgAN Patients

Jonathan Barratt,[1] James A. Tumlin,[2] Celia J. Lin,[3] Yusuke Suzuki,[4] Marshall W. Fordyce,[3] Gerald B. Appel.[5] *[1]University of Leicester, Leicester, United Kingdom; [2]Emory University, Atlanta, GA; [3]Vera Therapeutics, Inc., South San Francisco, CA; [4]Juntendo Daigaku, Bunkyo-ku, Japan; [5]Columbia University Irving Medical Center, New York, NY.*

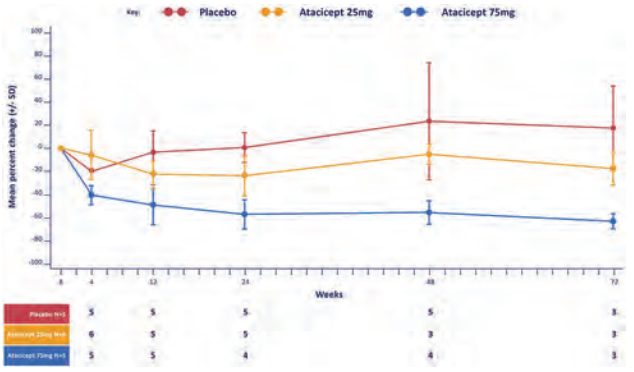
Background: Gd-IgA1 plays a central role in IgAN pathogenesis. Higher Gd-IgA1levels are independently associated with a greater risk of renal function deterioration that differ per Gd-IgA1 quartile. The Ph2a JANUS trial was the first to show substantial Gd-IgA1 reduction with atacicept in IgAN patients (pts). This analysis investigated whether atacicept could reduce Gd-IgA1 level by quartile and therefore potentially mitigate the poor prognosis of IgAN based on Gd-IgA1.

Methods: The JANUS study enrolled 16 IgAN pts with persistent proteinuria. Pts were randomized to atacicept 25mg, 75mg, or placebo (PBO). Gd-IgA1 was assessed at baseline (BL), wks 4, 12, 24, 48, and 72. At BL, pts were divided into 4 equal groups according to the quartiles of Gd-IgA1 distribution and assessed at each timepoint. A separate cohort of ~150 IgAN pts from the Univ of Leicester was used as a reference population for quartile determination.

Results: In IgAN pts, dose-dependent reductions in Gd-IgA1 were observed for up to 72 wks with atacicept (Fig 1). For pts in the highest quartile all 3 of 3 in the PBO group had no significant change over 48-72 wks, while all 4 of 4 in the atacicept highest quartile group had significant reductions. PBO pts transiently increased or decreased Gd-IgA1 levels by 1 quartile, atacicept 25 mg stably reduced Gd-IgA1 levels by 1 quartile in 2/6 (33%) pts and atacicept 75 mg stably reduced Gd-IgA1 levels by at least 1 quartile in 4/5 (80%) pts and by 2 quartiles in 3/5 (60%) pts. These results were generally consistent when using quartiles determined by the larger reference Univ of Leicester population.

Conclusions: In IgAN pts atacicept demonstrated a durable and substantial reduction in Gd-IgA1 in a dose dependent manner up to 72 wks. A stable 2 quartile decrease in Gd-IgA1 levels was observed in the atacicept 75 mg arm. The ongoing Ph2b ORIGIN trial evaluating up to atacicept 150 mg in IgAN pts will help determine how reduction of Gd-IgA1 translate to renal function.

Funding: Commercial Support - Vera Therapeutics, Inc.



Mean percent change in Gd-IgA1 over time

PO1639

Remission of IgA Nephropathy with Hydroxychloroquine

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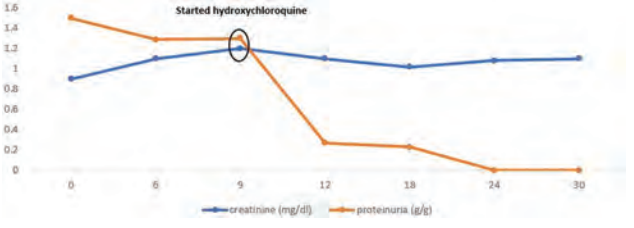
Introduction: IgA nephropathy is the most common form of glomerulonephritis in the world. Treatment options include blockade of renin-angiotensin-system (RAS) as the first line of therapy. Steroids may be beneficial in refractory cases, however, can result in several adverse effects. Data regarding use of immunosuppression is inconclusive. Combination of RAS inhibition and hydroxychloroquine has shown to reduce proteinuria in recent studies, though, complete remission with long term use has not been described. We report the case of a 46-year-old Asian female with IgA nephropathy, who was treated with maximally tolerated RAS inhibition and hydroxychloroquine for about 24- months resulting in complete remission of proteinuria and hematuria.

Case Description: The patient was referred to nephrology for evaluation of hematuria and proteinuria (1.5g/g, Serum creatinine 0.9mg/dl). Serological work-up was negative. She was initiated on angiotensin receptor blocker (ARB) and underwent kidney biopsy which confirmed IgA Nephropathy. There were 8 glomeruli with 20-25% sclerosis, mild to moderate chronic tubulointerstitial nephritis and fibrosis, no crescents, mild mesangial proliferation and hypercellularity with IgA staining 3+. She did not have any significant improvement in proteinuria despite maximally tolerated ARB (losartan 100 mg daily) therapy for three months. Her kidney function also declined, creatinine 1.2mg/dl. Hydroxychloroquine 200mg daily was then initiated along with regular eye exams and hepatic function tests. Repeat workup in three months showed improvement in proteinuria to 0.2g/g and creatinine 1.1mg/dl. She was continued on the same regimen for about 24-months, with recent work-up showing complete resolution of proteinuria and hematuria.

Discussion: As per our literature review, this is the first reported case of IgA nephropathy treated with RAS inhibition and hydroxychloroquine over a span of almost two years resulting in complete remission. Hydroxychloroquine can be considered, in select cases, as an alternative to steroid therapy in refractory proteinuria.



Trend of serum creatinine and spot proteinuria measurement

PO1640

Long-Term Follow-Up Study of Immunosuppressive Therapy in IgAN Patients with CKD Stage 3 and 4

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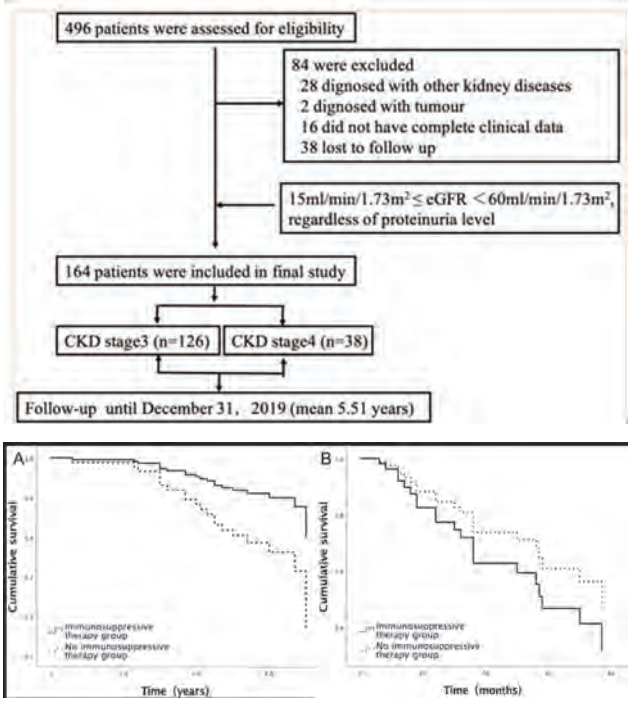
Background: The benefits of immunosuppressive therapy in patients with IgAN remain controversial, especially for those with more severe renal pathology and reduced renal function.

Methods: A total of 496 primary IgAN patients were screened between 2012 to 2014. Patients were divided to 4 groups according to CKD stage and the treatment. The primary endpoints were doubling of creatinine, progression to ESRD or death. The secondary endpoint was decrease in eGFR. Subgroup analysisof CKD3 immunosuppressive treatment group was conducted to explore the factors affecting the prognosis after treatment.

Results: 164 patients were enrolled and mean follow-up time was 5.5 years. There were 126 patients in CKD3 stage and 38 patients in CKD4 stage. Immunosuppressive therapy significantly improved prognosis in patients with CKD stage3 (HR 0.435[95% CI 0.200-0.944];p=0.035), but no difference for CKD stage4(p=0.364). Subgroup analysis showed baseline eGFR(OR 0.909[95%CI 0.834-0.991];p=0.031), serum IgG level(OR 0.809 [95%CI 0.658-0.995];p=0.045) were associated with primary outcome and loop necrosis (OR 0.189[95% CI 0.050-0.709], p=0.014), proportion of crescents (OR 0.200[95% CI 0.100-0.521], p=0.003), interstitial fibrosis>50%(OR 5.490[95% CI 1.323-22.727]) were associated with secondary outcome. Remission within 1 year could be an indicator of good long-term prognosis (HR 0.555[95%CI 0.296-0.759; p=0.035]).

Conclusions: For IgAN patients with CKD stage3, immunosuppressive therapy should be actively applied under the general treatment, but for patients with CKD stage4, it should be carefully. Patients with good renal function, more acute lesions of renal pathology would have a better prognosis after immunosuppressive therapy. Patients who achieved remission within 1 year would have better long-term prognosis.



PO1641

An International Delphi Survey on IgA Nephropathy: Results from the DEFINE Physicians Study

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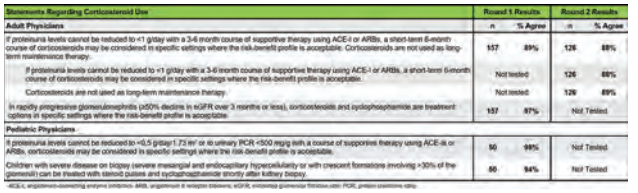
Background: It is unclear whether treatment guidelines for patients with IgA nephropathy (IgAN) are uniformly applied in clinical practice. The DEFINE: Physicians initiative sought to describe the opinions of nephrologists about the pathophysiology, diagnosis, and optimal management of adult and pediatric patients with IgAN.

Methods: A 2-round Delphi survey was distributed to nephrologists in Canada, France, Germany, Italy, Spain, the UK, and the US. A 1-9 Likert scale (9=strongly agree) was used to score statements. Consensus was defined as median and mean score ≥7, and ≥75% of participants scoring agreement (ie, score 7-9). Feedback collected in Round 1 was used to revise statements not achieving high consensus (≥90% agreement) for retesting in Round 2. Moderate consensus was defined as 75-89% agreement.

Results: In Round 1, 207 participants with a median clinical experience of 18 years (range, 5-49) rated 19 statements about IgAN. Half (50%) of participants worked in nonacademic settings. All statements met criteria for moderate or high consensus after the second round. Notably, a statement on corticosteroid therapy in adult patients reached moderate consensus after Round 1 and was divided into 2 parts in Round 2 (Figure 1). Both revised statements reached levels of agreement similar to the original statement. In contrast, a statement on corticosteroid and cyclophosphamide use in adults with rapidly progressive glomerulonephritis and 2 statements on corticosteroid therapy in pediatric patients reached high consensus in Round 1 (Figure 1).

Conclusions: High consensus regarding clinical decisions and the importance of controlling proteinuria in IgAN was observed in this Delphi survey. Although the level of consensus related to corticosteroid use was lower for adult patients vs pediatric patients, the level of consensus was relatively high for both groups.

Funding: Commercial Support - Travere Therapeutics, Inc.



Statements Regarding Corticosteroid Use	Round 1 Results		Round 2 Results	
Adult Physicians	n	% Agree	n	% Agree
If proteinuria levels cannot be reduced to <1 g/day with a 3-6 month course of supportive therapy using ACE-I or ARBs, a short-term 6-month course of corticosteroids may be considered in specific settings where the risk-benefit profile is acceptable. Corticosteroids are not used as long-term maintenance therapy.	157	89%	126	88%
If proteinuria levels cannot be reduced to <1 g/day with a 3-6 month course of supportive therapy using ACE-I or ARBs, a short-term 6-month course of corticosteroids may be considered in specific settings where the risk-benefit profile is acceptable.	Not tested		126	88%
Corticosteroids are not used as long-term maintenance therapy.	Not tested		126	89%
In rapidly progressive glomerulonephritis (≥50% decline in eGFR over 3 months or less), corticosteroids and cyclophosphamide are treatment options in specific settings where the risk-benefit profile is acceptable.	157	87%	Not Tested	
Pediatric Physicians				
If proteinuria levels cannot be reduced to <0.5 g/day/1.73 m² or to urinary PCR <500 mg/g with a course of supportive therapy using ACE-is or ARBs, corticosteroids may be considered in specific settings where the risk-benefit profile is acceptable.	50	98%	Not Tested	
Children with severe disease on biopsy (severe mesangial and endocapillary hypercellularity or with crescent formations involving >30% of the glomeruli) can be treated with steroid pulses and cyclophosphamide shortly after kidney biopsy.	50	94%	Not Tested	

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; PCR, protein:creatinine ratio

Figure 1

PO1642

Long-Term Effectiveness of Low-Dose Prednisone Treatment in Relapses of Steroid-Sensitive Minimal Change Disease

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Background: Treatment of relapses of steroid-sensitive minimal change disease (SMCD) involves administration of high doses of prednisone for several weeks, implying significant pharmacological toxicity. In a previous pilot study, the efficacy of treatment with low doses of prednisone for the treatment of relapses in these patients was demonstrated.

Methods: Retrospective analysis of SMCD relapses treated with low doses of prednisone in two centers, was performed, and the response to treatment, the time to reach remission and the free-time of relapse was studied, comparing it with previous relapses of the same patients treated with standard doses of steroids.

Results: 85 relapses in 21 patients with SMCD were analyzed. The median age of patients was 35 years (IQR 18-53), with 62% being male. The mean proteinuria at relapse debut was 5.37 ± 4.11 g/g, serum albumin 2.47 ± 0.94 gr/dL and creatinine 0.86 ± 0.35 mg/dL. Thirty-six relapses (42.3%) were treated with low doses of prednisone (LDP) and compared with 49 previous relapses (57.6%) of the same patients, treated with high doses of prednisone (HDP). The mean initial prednisone dose in relapses treated with LDP and HDP was 0.45 ± 0.1 mg/kg and 1.00 ± 0.3 mg/kg, respectively (p=0.001). The mean cumulative dose of prednisone in relapses treated with LDP and HDP was 1771 ± 1303 mg and 3894 ± 2134 mg respectively ($p < 0.001$). There were no differences in treatment duration between relapses treated with low and high corticosteroids doses (124 days vs 153 respectively; p=0.2). All patients achieved complete remission after steroid treatment. Mean time to remission was 18.4 days for relapses with LDP and 17.1 days for HDP ($p = 0.6$). The mean free time to relapse after treatment with low doses was 12.6 months vs 10.9 months for those treated with high doses ($p = 0.6$).

Conclusions: Among SMCD patients, treatment of relapses with low doses of prednisone (0.5 mg/kg) is effective and safe, allowing to minimize cumulative steroid doses and derived toxicity.

PO1643

DEFINE Physicians: An International Delphi Survey to Identify Consensus in the Care of Patients with FSGS or Idiopathic Nephrotic Syndrome

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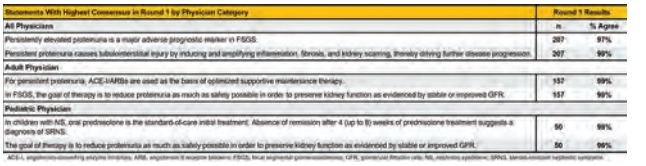
Background: The extent to which real-world practice aligns with guidelines for management of focal segmental glomerulosclerosis (FSGS) and pediatric idiopathic nephrotic syndrome (INS) is unknown. The DEFINE: Physicians project sought to describe physicians' opinions on the pathophysiology and optimal management of FSGS/INS in real-world settings.

Methods: DEFINE: Physicians was a 2-round Delphi survey that recruited nephrologists from North America and Europe. A total of 22 FSGS/INS statements were scored using a 1-9 Likert scale (9=strongly agree). Consensus was defined as median and mean score ≥7, and ≥75% of participants scoring agreement (ie, score 7-9). Statements not achieving high consensus (≥90% agreement) in Round 1 were revised and retested in Round 2.

Results: This study involved 207 adult and pediatric nephrologists. Median clinical experience was 18 (range 5-49) years; 103 participants (50%) worked in nonacademic settings. In Round 1, 21 statements met consensus criteria and 7 statements not achieving high consensus were revised or divided into multiple parts, creating 11 revised statements for testing in Round 2. In Round 2, 9 of 11 statements met at least moderate consensus. Round 1 statements with high consensus described prognostic significance of proteinuria and disease management (Figure 1). Controversial statements retested in Round 2 pertained to distinction between primary and secondary FSGS in adults, and to management of frequently relapsing INS in children (Figure 2).

Conclusions: The level of consensus in this Delphi survey was high for statements on treatment decisions and the importance of proteinuria control. The main area where high consensus was not reached pertained to differentiation between primary and secondary FSGS and managing frequently relapsing INS in children, suggesting that these areas require further research.

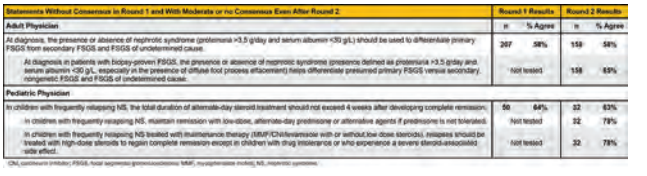
Funding: Commercial Support - Travere Therapeutics, Inc.



Statements With Highest Consensus in Round 1 by Physician Category	Round 1 Results	
All Physicians	n	% Agree
Persistently elevated proteinuria is a major adverse prognostic marker in FSGS.	207	97%
Persistent proteinuria causes tubulointerstitial injury by inducing and amplifying inflammation, fibrosis, and kidney scarring, thereby driving further disease progression.	207	99%
Adult Physician		
For persistent proteinuria, ACE-I/ARBs are used as the basis of optimized supportive maintenance therapy.	157	99%
In FSGS, the goal of therapy is to reduce proteinuria as much as safely possible in order to preserve kidney function as evidenced by stable or improved GFR.	157	99%
Pediatric Physician		
In children with NS, oral prednisolone is the standard-of-care initial treatment. Absence of remission after 4 (up to 8) weeks of prednisolone treatment suggests a diagnosis of SRNS.	50	99%
The goal of therapy is to reduce proteinuria as much as safely possible in order to preserve kidney function as evidenced by stable or improved GFR.	50	96%

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome

Figure 1



Statements Without Consensus in Round 1 and With Moderate or no Consensus Even After Round 2	Round 1 Results		Round 2 Results	
Adult Physician	n	% Agree	n	% Agree
At diagnosis, the presence or absence of nephrotic syndrome (proteinuria >3.5 g/day and serum albumin <30 g/L) should be used to differentiate primary FSGS from secondary FSGS and FSGS of undetermined cause.	207	58%	159	58%
At diagnosis in patients with biopsy-proven FSGS, the presence or absence of nephrotic syndrome (presence defined as proteinuria >3.5 g/day and serum albumin <30 g/L, especially in the presence of diffuse foot process effacement) helps differentiate presumed primary FSGS versus secondary, nongenetic FSGS and FSGS of undetermined cause.	Not tested		159	63%
Pediatric Physician				
In children with frequently relapsing NS, the total duration of alternate-day steroid treatment should not exceed 4 weeks after developing complete remission.	50	64%	32	63%
In children with frequently relapsing NS, maintain remission with low-dose, alternate-day prednisone or alternative agents if prednisone is not tolerated.	Not tested		32	78%
In children with frequently relapsing NS treated with maintenance therapy (MMF/CNI/levamisole with or without low dose steroids), relapses should be treated with high-dose steroids to regain complete remission except in children with drug intolerance or who experience a severe steroid-associated side effect.	Not tested		32	78%

CNI, calcineurin inhibitor; FSGS, focal segmental glomerulosclerosis; MMF, mycophenolate mofetil; NS, nephrotic syndrome

Figure 2

PO1644

Safety and Efficacy of ANG-3070 in Patients with Primary Proteinuric Kidney Disease: A Phase 2 Study Design

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Background: Primary proteinuric kidney diseases (PPKDs) are among the leading causes of End-Stage Kidney Disease (ESKD). Receptor tyrosine kinases like PDGFR, DDR1, DDR2 are thought to play a role in the progression of PPKDs to ESKD. ANG-3070, a selective oral tyrosine kinase inhibitor, has demonstrated beneficial effects in chronic kidney disease animal models. **Objective**: Describe the design of a proof-of-concept study of ANG-3070 in the treatment of PPKD patients with persistent proteinuria while on standard of care (SOC).

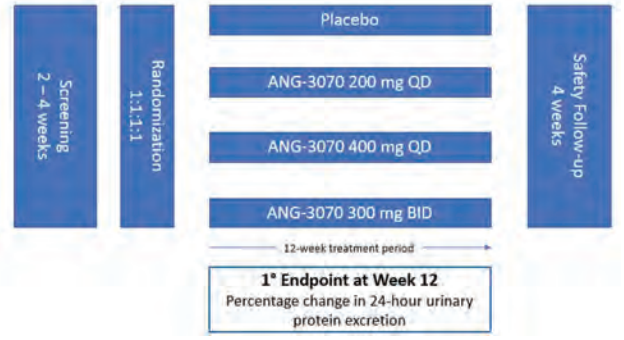
Methods: A 12-week, randomized, double-blind, placebo-controlled study enrolling 100 patients with biopsy-proven PPKD and persistent proteinuria, ≥ 1 g/day, while on the SOC including maximum tolerated RAAS inhibitors. Patients will be randomized 1:1:1:1 to 200 mg or 400 mg once-daily or 300 mg twice-daily of ANG-3070 or placebo (Fig.1).

Results: The primary endpoint is the percentage change in 24-hr urinary protein at Week 12. Key secondary endpoints evaluated at week 12 include percentage change in 24-hr urinary albumin, number of patients with complete remission in proteinuria (24-hr urinary protein < 300 mg), number of patients with partial remissions in proteinuria (24-hr urinary protein reduction of ≥ 50% from the baseline and a 24-hr urinary protein < 3.5 g/day if the baseline 24-hr urinary protein > 3.5 g), number of patients with ≥ 50% reduction in 24-hr urinary protein from the baseline, and number of patients with ≥ 50% reduction in 24-hr urinary albumin from baseline. An independent data monitoring committee will review safety throughout the study.

Conclusions: This Phase 2 study will provide data about the safety and efficacy of ANG-3070 in PPKD patients that will inform the design of a Phase 3 study.

Funding: Commercial Support - Angion Biomedica, Inc.

Figure 1.



PO1645

Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) for the Treatment of Pediatric Nephrotic Syndrome (NS)

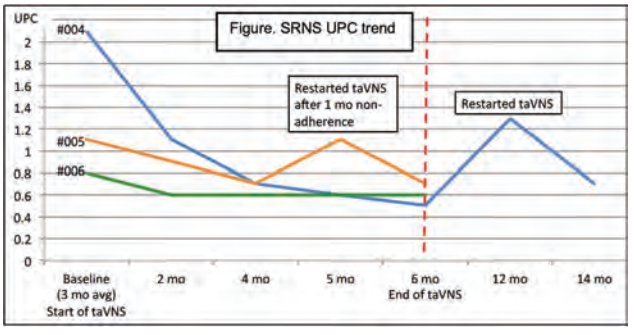
Christine B. Sethna,[1,2] Kumail Merchant,[1] Stavros Zanos,[2] Timir Datta-Chaudhuri,[2] Pamela Singer,[1] Laura J. Castellanos,[1] Rachel Frank.[1] *[1]Steven and Alexandra Cohen Children's Medical Center, New Hyde Park, NY; [2]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY.*

Background: Children with NS, especially those with frequent relapses (FRNS) or steroid resistance (SRNS), are exposed to prolonged courses of immunosuppressant medications with side effects and variable efficacy. There is an urgent need to identify novel and safe therapies to treat pediatric NS. taVNS modulates the immune system via the cholinergic anti-inflammatory pathway and has become a therapy of interest for treating immune-mediated illnesses. The objective was to conduct an open-label early feasibility study of taVNS therapy for pediatric NS.

Methods: Children with FRNS (≥2 relapses in previous 6 months) or SRNS (no remission after 4 weeks of steroids) were enrolled. Participants with FRNS were in remission and off immunosuppression (off steroids >14 days and other immunosuppression >3 months). SRNS patients were on a stable regimen of medications for 6 months prior to enrollment. Participants performed taVNS therapy 5 minutes daily for 6 months with a TENS 7000 unit. taVNS was delivered to the auricular branch of the vagus nerve via the left cymba concha. Cytokine levels were compared using the Wilcoxon test.

Results: Seven participants (3 FRNS, 3 SRNS, 1 genetic congenital nephrotic syndrome [CNS]) had a median age of 7 years (range 3-17) and 63% were male. FRNS participants remained relapse-free during the study period (two continued taVNS at 9 and 13 months and remained in remission). SRNS participants had a 25-76% reduction in urine protein to creatinine ratio (upc) compared to baseline (Figure). Upc decreased (13.7%) in the participant with CNS but remained in nephrotic range. All but one participant (non-compliant) had a reduction in TNF-α (7.33pg/mL vs. 5.46pg/mL, p=0.03). No adverse effects were reported.

Conclusions: taVNS prevented NS relapses in FRNS, reduced proteinuria in SRNS, and reduced TNF-α levels without any adverse effects, suggesting taVNS as a promising therapy for pediatric NS. A larger, randomized clinical trial is needed to confirm these findings.



PO1646

A Study Comparing Rituximab and Modified Ponticelli (MP) Regimen in Primary Membranous Nephropathy(PMN)

Abhishek Kumar, Arpita Ray Chaudhury, Saugat D. Gupta, Sriranjan Mukherjee, Moumita Sengupta. IPGMER Nephrology *Institute of Postgraduate Medical Education and Research, Kolkata, India.*

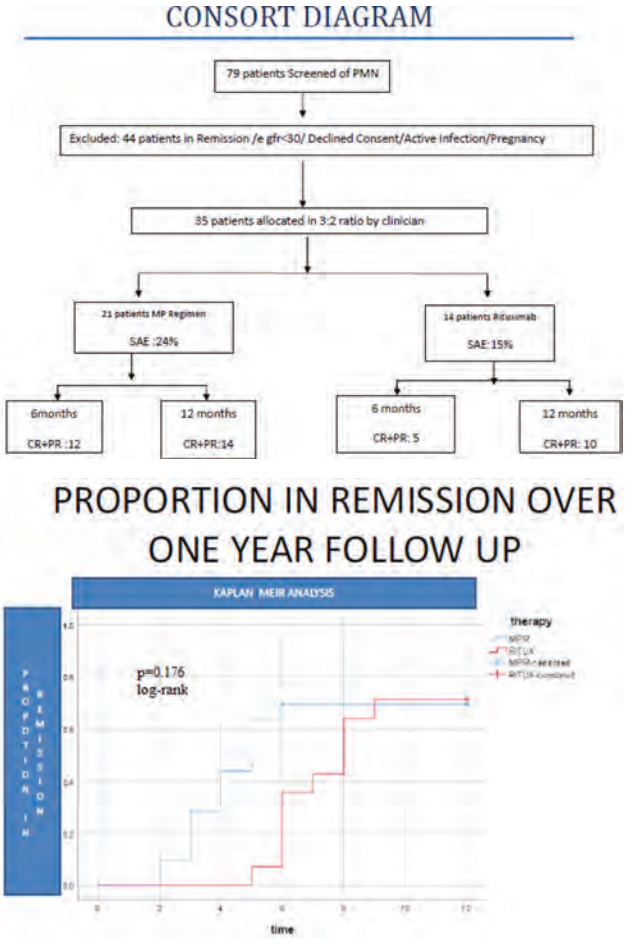
Background: The study was designed in December 2018 when the Gemritux trial had established Rituximab as an alternative to MP regimen in the treatment of PMN. So we designed a study comparing Rituximab and MP Regimen.

Methods: We allocated 35 adults with PMN and proteinuria >3.5 gm/day in a 3:2 ratio to MPregimen or Rituximab 375mg/m^2 on days 1,8,15 and 22.The primary outcome was complete or partial remission(CR+PR)at 6 and 12 months in the 2 groups. The other findings included trends of 24 hr urine protein, albumin, creatine and seriousadverse events at 6 and 12 months in both groups.

Results: At 6 months, 12 of 21 patients (57.14%) allocated to MP Regimen and 5 of 14 patients (35.71%) allocated to Rituximab experienced remission(CR+PR) (odds ratio [OR], 2.4; 95% CI, 0.596 -9.670, p value 0.10). At 12 months, 14 of 21 patients (66.66%) allocated to MP Regimen and 10 of 14 patients (71.43%) allocated to Rituximab experienced remission(CR+PR) (odds ratio [OR], 0.8; 95%CI, 0.184-3.487, p value 0.383). Serious adverse events occurred in 15% of patients receiving Rituximab and in 24% receiving the MP Regimen.

Conclusions: We found No Statistically Significant difference betweenRituximab and the Modified Ponticelli Regimen in the treatment of membranous nephropathy. A head-to-head, longer follow up study comparing MP Regimen versus Rituximab is required in terms of duration of remission and side effect profile between the two treatment groups.

Funding: Government Support - Non-U.S.



Time To Remission Analysis

PO1647

Felzartamab in Patients with Anti-Phospholipase A2 Receptor Autoantibody Positive (Anti-PLA2R+) Membranous Nephropathy (MN): Interim Results from the M-PLACE Study

Brad H. Rovin,[1] Sharon G. Adler,[2] Elion Hoxha,[3] Ben Sprangers,[4] Rolf A. Stahl,[3] Jack F. Wetzels,[5] Bettina Schwamb,[6] Rainer Boxhammer,[6] Quynh Nguyen,[6] Stefan Haertle,[6] Pierre M. Ronco.[7,8] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]The Lundquist Institute, Torrance, CA; [3]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]University Hospitals Leuven, Leuven, Belgium; [5]Radboud Universiteit, Nijmegen, Netherlands; [6]MorphoSys AG, Martinsried, Germany; [7]Sorbonne Universite, Paris, France; [8]INSERM UMRS 1155, Paris, France.*

Background: Primary MN is a rare autoimmune kidney disease. In ~70% of cases, autoantibodies to PLA2R on podocytes form immune complexes that damage the glomerular filtration barrier and typically lead to nephrotic syndrome. Current MN therapies fail to directly target CD20–/CD38+ plasma cells that are the main source of autoantibodies. Depleting plasma cells by targeting CD38 may be an effective strategy for MN, particularly in patients (pts) with high anti-PLA2R Ab titers. Here we report proof-of-mechanism data for felzartamab (MOR202), a fully human anti-CD38 monoclonal antibody (Ab).

Methods: M-PLACE (NCT04145440) is an open-label, multi-national Phase Ib/IIa study of adults with anti-PLA2R+ MN requiring immunosuppressive therapy (IST). Cohort 1 includes de novo and IST-relapsed pts (n=20) and Cohort 2 IST-refractory pts (n=10). Participants receive nine felzartamab infusions (16 mg/kg) over six 28-day cycles (weekly in Cycle 1; monthly thereafter), followed by a 28-week observational follow-up. Concomitant IST use is prohibited. The primary endpoint is the incidence and severity of treatment-emergent adverse events. The key secondary endpoint is the immunologic response rate, as determined by anti-PLA2R Ab reductions. Exploratory endpoints include evaluations of proteinuria and kidney function.

Results: As of April 2021, 12/30 planned pts were enrolled (Cohort 1, n=8; Cohort 2, n=4). Median age was 62.5 years (range 43 to 77 years), 83% were male, and median baseline anti-PLA2R Ab titer was 178 U/mL (18 to 1027 U/mL). Seven pts had received ≥4 weeks of felzartamab therapy. At Week 4, 5/7 pts had a >50% reduction from baseline in anti-PLA2R Ab (Cohort 1, n=3; Cohort 2, n=2); the other 2/7 pts had reductions from baseline of –16.8% and –5.0% (both Cohort 1). Mean % decline in anti-PLA2R Ab from baseline to Week 4 was –53.0% (–92.0% to –5.0%). B-cell counts were not markedly changed from baseline. Felzartamab was well tolerated.

Conclusions: The M-PLACE proof-of-concept study has so far shown that felzartamab rapidly and substantially reduces anti-PLA2R Ab titers in pts with anti-PLA2R+ MN. Longer follow-up is required to assess felzartamab safety and efficacy in this population.

Funding: Commercial Support - MorphoSys AG

PO1648

Evaluating the Efficacy of Rituximab in Primary Membranous Nephropathy: An Observational Study from Southern India

Megha Saigal, Swarnalatha Guditi. *Nizam's Institute of Medical Sciences, Hyderabad, India*.

Background: Membranous nephropathy, is an immunological disease. It can occur secondary to infection, malignancy, or SLE. In 70% of patients M-type phospholipase A2 receptor (PLA2R) was positive, and these patients are considered to suffer from primaryMN. In primary MN immunosuppressive therapy is started in patients with progressive disease activity. There have been several studies comparing the efficacy of different immunosuppressive regimens, however the role of rituximab as a primary/ secondary immunosupressive agent in primary MN has not been evaluated among Indian population

Methods: Single centre observational pilot study 20 subjects with histological/ serum Pla2r positive progressive primary membranous nephropathy were recruited. They were then either started on conventional immunosupressve therapy (modified ponticelli regimen) and if no or partial response were initiated on rituximab as a second line agent or in some cases as a primary immunosupressive agent. Rituximab was started as375mg/ m^2 a 4weekly doses. Data regarding urine protein creatinine ratio, serum albumin, serum creatinine, CD 19 count, time to achieve to remission and side-effects were noted.

Results: In our study, males were 65% (13), females contribute to 35% (7). After rituximab therapy 75% (15/20) achieved remission, significant changes were seen in the form of decrease in proteinurea and increase in serum protein and serum albumin levels **p value <0.05**. Time to achieve remission & median no. of doses required was 1.66 ± 0.81 months and 3 respectively. 85% sustained remission attained, with mean duration of followup being 10.16 + 5.96 months.

Conclusions: Therapy with rituximab as a primary/ secondary immunosupressive agent was effective in inducing and maintaining remission in a significant proportion of patients with primary MN.

Baseline parameters N=20	Pre-rituximab	Post-rituximab	P value
Age at onset (yrs) Mean (SD)	22.9 (17.75)		
Age at Rituximab therapy (yrs) Mean (SD)	26 (17.07)		
Male : female	13:7		
Duration Of illness (months) Mean (SD)	35.3 (37.77)		
Syst.HTN (N) (%)	6 (33.3)		
Creatinine (mg/dl) Mean (SD)	0.71 (0.45)	0.873 (0.693)	0.08
eGFR (ml/min) Mean (SD)	133.74 (49.14)	134 (59.1)	0.25
Haemoglobin (gm/dl) Mean (SD)	12.59 (1.41)	12.79 (1.37)	0.59
S. Protein(gm/dl) Mean (SD)	5.53 ± 1.13	6.38 ± 1.10	**0.001**
Albumin (gm/dl) Mean (SD)	2.80 ± 1.03	3.68 ± .96	**0.002**
Proteinuria (gm/day) Mean (SD)	3.15 ± 2.75	1.07± 1.71	**0.001**
T. Cholesterol (mg/dl) Mean (SD)	258.16 (12.7)	252.8 (72.3)	0.96
HDL(mg/dl) Mean (SD)	59.5 (12.8)	60.4 (15.9)	0.96
LDL(mg/dl) Mean (SD)	166 (75.1)	146.8 (65.8)	0.64
TG (mg/dl) Mean (SD)	147.1 (44.07)	127.9 (30.4)	0.4
CD19	354.13 ± 198.73	2.53 ± 4.918	**0.00**
Remission (Complete + Partial)	15(75%)		
Complete remission	5 (25%)		
Partial remission	10 (50%)		
No remission/ others	5 (25%)		

Results

PO1649

Intravenous Cyclophosphamide vs. Calcineurin Inhibitors as Treatment in High-Risk Idiopathic Membranous Nephropathy: The Benefit in MAKE Is Preserved in the Presentation IV?

Angela M. Cordoba Hurtado,[1] L. M. Perez-Navarro,[1] Jesus D. Lima-Lucero,[1] Virgilia Soto,[2] Rafael Valdez-Ortiz.[1] [1]*Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico;* [2]*Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico*.

Background: The use of intravenous cyclophosphamide (IV CYC) in high-risk idiopathic membranous nephropathy (IMN) has not been fully evaluated in the MAKE primary endpoints (serum Cr doubling, ERSD, mortality). In our center, the treatment of high-risk IMN is performed with IV CYC or with calcineurin inhibitors (CNI) according to criteria of accessibility and availability of the drug. Our aim was to compare the immunosuppressive treatment scheme with IV CYC vs CNI in primary MAKE events in patients with high-risk IMN.

Methods: Retrospective cohort study. Patients with a diagnosis of IMN diagnosed between January 2012 and January 2020 were included. The patients were treated with IV CYC or CNI. With a minimum follow-up of 12 months and MAKE primary events were recorded in addition to complete, partial, composite response and adverse events at the end of the study.

Results: Thirty-seven patients of which 14 (37.8%) were treated with IV CYC and 23 (62.2%) with CNI. The mean age was 46 ± 15.3 years, 54% male, and 27% hypertensive. Average PrU / CrU 10.43 ± 4.4 gr/gr; mean serum albumin 1.8 ± 0.68 gr/dL; and GFR by CKD EPI of 75ml/min/1.73m^2. With a follow-up of 45.91 ± 23.9 months, no baseline differences were observed between the groups. Table 1

Conclusions: The comparison between IV CYC *vs* CNI for high-risk IMN shows similar outcomes focused on MAKE. However, the comparison in composite and partial response shows a result in favor of the use of CNI. This perspective provides clinical evidence about the use of IV CYC, which is why it is suggested that there are possible differences between our findings and those reported so far with oral CYC. Prospective clinical trials are required to have conclusive results.

Table 1. Outcomes by treatment IV CYN *vs* ICN

	IV CYC n=14 (%)	ICN n= 23 (%)	*P (95% CI)*
Complete response	28.5	56.5	0.103
Partial response	7.12	30.4	0,001
Compund response	35.7	85.9	0,001
Relapses	20.8	25	0,082
MAKE	15.5	18	0,8

PO1650

An 8-Week Course of Cyclophosphamide and Steroids Is Effective Therapy in Patients with Membranous Nephropathy (MN) and Low PLA2Rab Levels

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Background: We introduced individualized therapy in patients with MN and positive anti PLA2R antibodies (aPLA2R) by IIFT test. Treatment (cyclophosphamide combined with steroids) was stopped when the IIFT test (measured at 8, 16, or 24 weeks) became negative. After 8 weeks, 71% of patients were in immunological remission. Unfortunately, 30% of these latter patients needed renewed therapy within 12 months because of immunological and/or clinical relapse. We questioned if quantitative aPLA2R measurement would predict response.

Methods: Available, stored serum samples were retrieved, and aPLA2R levels were measured by ELISA (EUROIMMUN Lübeck, Germany). Good outcome was defined as immunological remission at 8 weeks, followed by clinical remission without clinical relapse nor the need for additional immunosuppressive therapy within 12 months.

Results: Serum samples of 60 patients were available for analysis. Patients were grouped according tertiles of aPLA2R (Table). Higher aPLA2R levels were associated with more severe proteinuria. Patients in the lowest tertile were more likely to develop immunological remission at 8 weeks (95% vs 65% and 50% in the middle and highest tertiles). Moreover, in the subgroup of patients who were treated for 8 weeks only, fewer patients in the lowest tertile of aPLA2R needed renewed immunosuppressive therapy, although not statistically significant (16% vs 43%, p 0.054).

Conclusions: Individualized treatment of MN patients with cyclophosphamide and steroids has been recently introduced. In this study we show that baseline aPLA2R levels predict immunological remission at 8 weeks. Furthermore, patients with low aPLA2R levels at baseline seem to be more likely to have a good overall outcome.

Funding: Commercial Support - EUROIMMUN research lab, Lübeck, Germany

Baseline clinical characteristics and immunological remission at week 8

	Lowest tertile <98 RU/ml	Middle tertile 98-210 RU/ml	Highest tertile >210 RU/ml	P-value*
N	20	20	20	
Age (yrs) Gender M/F	62 ± 13 17 / 3	60±12 13 / 7	62±13 14 / 6	NS NS
S creatinin (umol/L) S albumin (g/L) UPCR (g/10mmol)	148 [113-160] 21 [18-28] 6.7 [4.2-8.1]	119 [95-170] 23 [16-26] 9.3 [5.9-13.6]	142 [103-166] 18 [14-26] 9.4 [6-13.1]	NS NS 0.022
aPLA2Rab negative at 8 weeks (N (%))	19 (95)	13 (65)	10 (50)	0.005

Data shown as mean±SD or median[IQR]. *By kruskall-wallis test of Fishers' exact test, as applicable

PO1651

Prospective Cohort Study of Antibody-Guided Therapy in Patients with Membranous Nephropathy

Anne-Els van de Logt, Coralien Vink- van Setten, Jack F. Wetzels. *Radboud Universiteit, Nijmegen, Netherlands.*

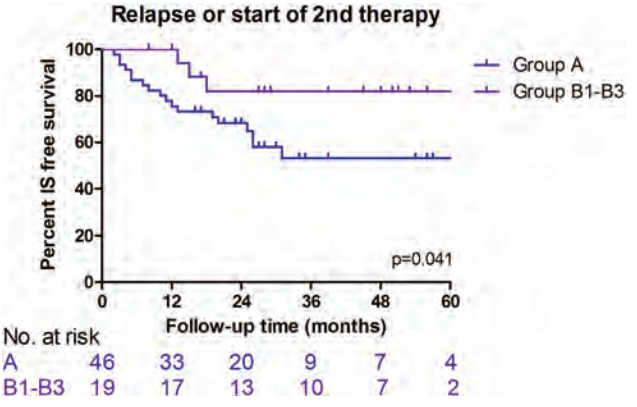
Background: Guidelines advise a standard course of 6 months of cyclophosphamide (CP) and steroids in patients with membranous nephropathy (MN). We hypothesized that monitoring of aPLA2R- antibodies (aPLA2R) may enable individualized (and shorter duration of) therapy.

Methods: Patients with MN, with positive aPLA2R and high risk of progression were included. Treatment consisted of CP (1.5 mg/kg/day combined with steroids). aPLA2R were monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If the IFT test was negative, CP was stopped and prednisone tapered. If the IFT test remained positive at 24 weeks, CP was switched to MMF and therapy continued.

Results: Sixty-five patients (48 males) were included; mean age 61 ± 12 yrs, median serum creatinine 136 [IQR 100-161] µmol/l, serum albumin 21 [IQR 16-26] g/l and UPCR 7.7 [IQR 5.4-11.1] g/10 mmol. Follow-up was 37 [IQR 27-58] months. aPLA2R test was negative in 46 patients after 8 weeks (group A), in 10 patients after 16 weeks (group B1), in 1 patient after 24 weeks (group B2) and in 8 patients aPLA2R remained positive after more than 24 weeks (group B3). In group A no clinical remission (PCR >3.0 g/10 mmol) was observed in 26 % (12 patients) compared to 21 % (4 patients) in group B1-B3 (Log rank p=0.579). Overall 22 patients (34 %) received additional immunosuppressive (IS) therapy because of persistent proteinuria (after aPLA2R disappearance) or clinical relapse. IS free survival was lower in group A compared to group B1-B3. (Figure 1).

Conclusions: Approximately 50% of patients developed long-term clinical remission after 8 weeks of therapy. Our data support aPLA2R-guided therapy. However, in approximately 25% of patients immunological remission was not followed by clinical remission, underlining the need for better biomarkers.

Funding: Other NIH Support - Dutch Kidney Foundation



Relapse or start of second immunosuppressive therapy

PO1652

Economic Evaluation of the MENTOR Trial Comparing Rituximab and Cyclosporine for the Treatment of Membranous Nephropathy (MN)

Matthew J. Kadatz,[1,2] Scott Klarenbach,[3] Helen So,[3] Fernando C. Fervenza,[4] Daniel C. Cattran,[5] Sean Barbour.[1] On behalf of the MENTOR trial investigators *[1]The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; [2]Vancouver Coastal Health Research Institute, Vancouver, BC, Canada; [3]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [4]Mayo Clinic Minnesota, Rochester, MN; [5]University of Toronto, Toronto, ON, Canada.*

Background: The MENTOR trial (MEmbranous Nephropathy Trial Of Rituximab) showed that rituximab (RTX) was noninferior to cyclosporine (CSA) in inducing complete or partial remission of proteinuria and was superior in maintaining proteinuria remission. However, the cost of RTX is high and it's cost-effectiveness has not been determined.

Methods: A Markov model (Fig 1) was used to determine the incremental cost-effectiveness ratio (ICER) of RTX compared with CSA for the treatment MN from the perspective of a health care payer with a life-time time horizon ($2020 USD). The model outcomes were informed by data from the MENTOR trial and previously published literature. Cost and utility inputs were obtained from the literature.

Results: Based on 1,000 simulations, the mean additional cost of RTX therapy for MN compared with CSA was $168,064 with an improvement in utility of 6.70 QALYs (Fig 2). RTX was cost-effective (assuming a willingness-to-pay threshold of $50,000 / QALY) compared with cyclosporine, with an ICER of $25,071 per additional quality adjusted life year (QALY) over a lifetime time horizon (45 years).

Conclusions: While the initial cost of RTX is high, RTX is a cost-effective option (assuming willingness to pay thresholds of $50,000 or greater) for the treatment of MN when compared with the alternative of CSA. The cost-effectiveness will be further improved with the use of less expensive biosimilars.

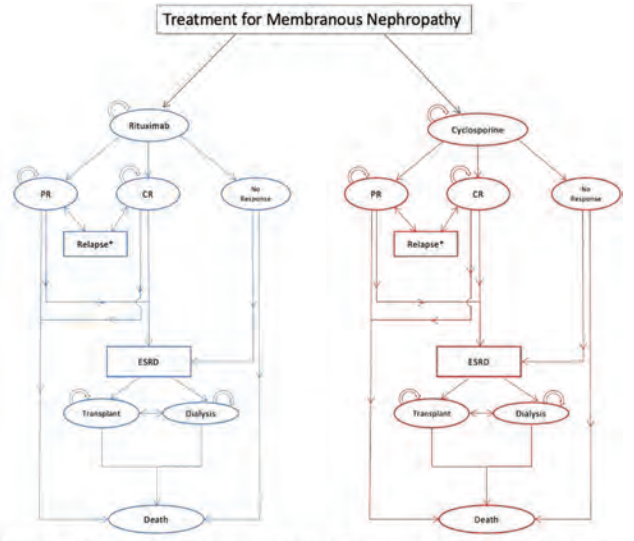


Figure 1: Diagram of health states and possible transitions in the Markov model.

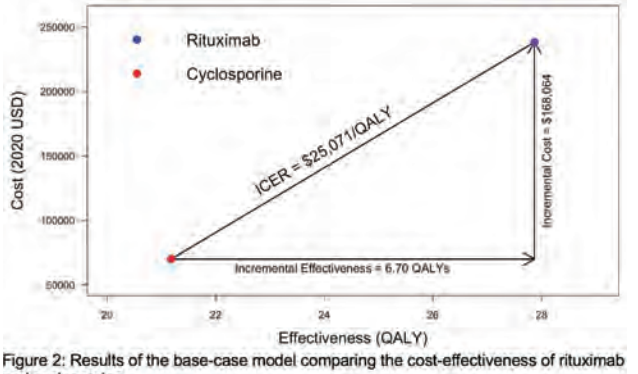


Figure 2: Results of the base-case model comparing the cost-effectiveness of rituximab and cyclosporine.

PO1653

A Multicenter, Prospective, Open-Labeled Study of Acthar Gel Alone or with Tacrolimus to Reduce Urinary Proteinuria in Patients with Idiopathic DNA-JB9-Positive Fibrillary Glomerulopathy

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Background: Fibrillary Glomerulopathy (FGN) is a rare primary glomerular disease characterized by glomerular accumulation of nonbranching, randomly arranged 10-30 nm in diameter fibrils. The resulting podocyte dysfunction and progressive proteinuria leads to ESRD rates of 50% within 4 years. Herein we present data on 15 patients treated with ACTH or ACTH + Tacrolimus completing 12 months of therapy.

Methods: **Study Design:** Randomized prospective open labeled study of 12 months of SQ ACTH alone or with Tacrolimus in 15 patients with biopsy proven, DNA-B9 + Fibrillary glomerulopathy. **Study Drug Dosing:** ACTH 80 units SQ 2X/ week, Tacrolimus-1.0 mg PO BID. **Primary Endpoint:** Change in UP/Cr ratio (mg/gm) in patients after 12 months of ACTHar gel alone or in combination with Tracrolimus **Definitions:** Responders-Complete-Partial-Clinical response defined at **≤ 300 mg/gm** or ≥ **50% reduction** or ≥ **30% reduction** in UP/Cr from baseline at 12 months.

Results: Of the 15 patients completing 12 months of treatment, **14.3%** acheived complete remission (UP/Cr ratio < 300 mg/gm); **26.0%** acheived a ≥ 75% reduction from baseline, while **60.7%** acheived a ≥ 50% reduction in UP/Cr at 12 months. A total

of **86.6%** acheived a minimum 30% reduction in UP/Cr. The addition of Tacrolimus to ACTH tended to further lower UP/Cr at 12 months (1654.7±317 vs.4449.5±1665) respectively, but did not reach statistical significance

Conclusions: In summary, depo-repository ACTH induced a complete or partial remission in 75% of patients with DNA-JB9 + Fibrillary GN. The addition of Tacrolimus in this population tended to improve complete-partial response rates.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals, Clinical Revenue Support

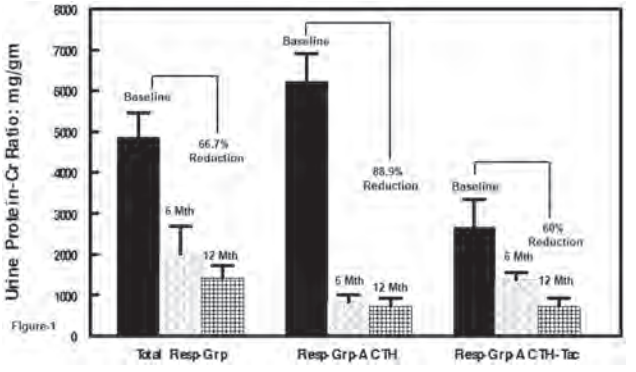


Figure-1

Responder Group

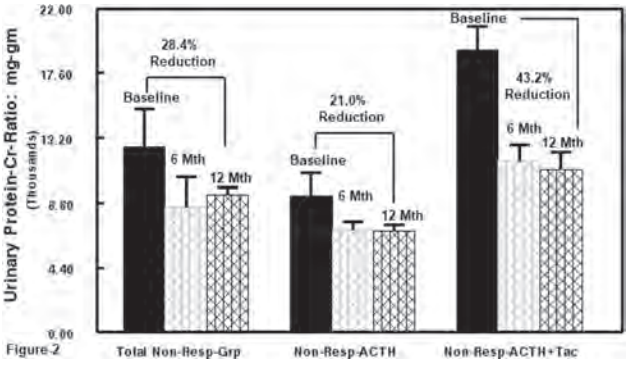


Figure-2

Non-Responder Group

PO1654

BCX9930, an Oral Factor D Inhibitor in Development for Treatment of Complement-Mediated Diseases, Inhibits Complement Alternative Pathway (AP) Activity in Healthy Subjects

Xilin Chen,[1] Fugang Zhu,[1] Cynthia D. Parker,[1] Melanie Cornpropst,[2] William P. Sheridan,[2] Matthew Davidson,[2] Yarlagadda S. Babu.[1] *[1]BioCryst Pharmaceuticals Inc, Birmingham, AL; [2]Biocryst Pharmaceuticals Inc, Durham, NC.*

Background: Factor D, the rate-limiting enzyme of the AP, is required for the formation of C3 convertase as well as amplification of complement activities initiated by the lectin pathway (LP) and classical pathway (CP). AP amplification is responsible for up to 80% of the LP and CP complement responses (Harboe et al, Clin Exp Immunol 2004). BCX9930 is an orally administered, potent and selective inhibitor of factor D, and has potential for the treatment of complement mediated glomerular diseases including, C3 glomerulopathy, IgA nephropathy, primary membranous nephropathy, and lupus nephritis. This study assessed the effects of oral dosing of BCX9930 on the AP activities in *ex vivo* activated serum in healthy subjects.

Methods: Serum samples from the BCX9930-101 study (NCT04330534) of multiple ascending doses ranging from 50 to 500mg every 12hrs (Q12h) were used to evaluate complement activities with AP-specific Wieslab C5b-9 (AP Wieslab) assay. Levels of complement split products Bb, C3a, C5a and soluble C5b-9 (sC5b-9) in the supernatants from the AP Wieslab assay were further analyzed by multiplex assays.

Results: Oral dosing of BCX9930 resulted in rapid (within ≤1hr) and maximal suppression (median >98% relative to pre-dose levels) of AP Wieslab at all dose levels. The duration of suppression was dose-dependent. At steady state for doses ≥200mg Q12h, maximal suppression persisted for at least 2 dosing intervals (24hrs) following the last dose. Doses of 200, 400 and 500mg Q12h reduced Bb, C5a and C5b-9 levels by >95% through 12hrs post-dose at steady state in the supernatants from AP Wieslab assays. At the highest dose level analyzed, 500mg Q12h, mean inhibition of Bb, C5a, and C5b-9 increased to >98%, and mean inhibition of C3a was 95%.

Conclusions: Oral BCX9930 potently suppressed AP activity in healthy subjects. Suppression ≥95% was achieved through at least 12hrs post-dose across all described assays for the selected clinical dose of 500mg twice daily. As the AP amplification loop also enhances the signal of the CP and LP, BCX9930 has potential to treat diseases mediated by any of the 3 complement pathways. These results support further development of oral BCX9930 for the treatment of complement mediated glomerular diseases.

PO1655

Early Eculizumab Withdrawal in Atypical Hemolytic Uremic Syndrome Is Safe and Cost-Effective

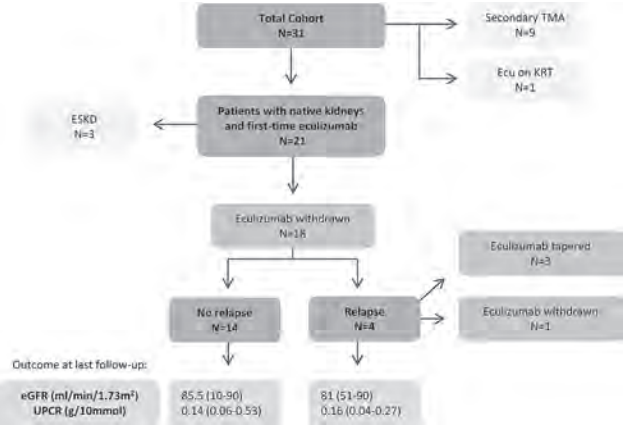
Romy N. Bouwmeester, Caroline Duineveld, Kioa L. Wijnsma, L.P.W.J. Van Den Heuvel, Jack F. Wetzels, Nicole Van De Kar. on behalf of the CUREiHUS study group *Radboudumc, Nijmegen, Netherlands.*

Background: The introduction of eculizumab has improved outcome in patients with atypical hemolytic uremic syndrome (aHUS). The optimal treatment strategy is debated. It is unknown if unbiased withdrawal of eculizumab is a safe strategy. Here we report the results of the CUREiHUS study, a national observational study monitoring eculizumab discontinuation in Dutch aHUS patients after three months of therapy.

Methods: All pediatric and adult aHUS patients with native kidneys and first-time eculizumab treatment (n=21) were evaluated. At last, an extensive cost-effective analysis was conducted.

Results: In the period from January 2016 till October 2020 we included 21 patients. All patients showed full recovery of hematological thrombotic microangiopathy (TMA) parameters after start of eculizumab. A renal response was noted in 18 patients. After a treatment duration of 13.6 weeks (range 2.1-43.9), eculizumab was withdrawn in all patients (Figure 1). During follow-up (80.7 weeks (0.0-236.9)), a relapse occurred in four patients (19.0%). Median time to first relapse was 14.3 weeks (7.1-62.0). Eculizumab was re-initiated within 24 hours in all relapsing patients. At last follow-up, there were no chronic sequelae, i.e. no clinically relevant increase in serum creatinine, proteinuria and/or hypertension, in the relapsing patients. No clinically relevant predictors of relapse (including the presence of a pathogenic mutation) could be determined. The total medical expenses, including costs of among others hospital admission and disease recurrence, of our population were only 33% of the fictive expenses made when patients would have received eculizumab every fortnight.

Conclusions: It is safe and (cost-)effective to discontinue eculizumab after three months of therapy in patients with aHUS in native kidneys. Larger data registries are needed to determine factors to predict relapse(s) and short- and long-term outcomes.



Outcomes of CUREiHUS patients

PO1656

Outcome of Kidney Transplantation in Atypical Hemolytic Uremic Syndrome Without Eculizumab Prophylaxis: A Single-Center Experience

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Background: A high risk of aHUS recurrence (60-80%) is reported after kidney transplantation. Therefore, it is suggested to perform kidney transplantation in aHUS patients with eculizumab prophylaxis. In 2017 we reported a favorable outcome after kidney transplantation in aHUS patients without eculizumab prophylaxis, using kidneys from living donors and a transplantation protocol aimed at reduction of endothelial injury. (1) Here, we present the results of our treatment protocol with prolonged follow-up.

Methods: All patients with a previous history of aHUS who received a living or deceased donor kidney transplantation in the Radboud University medical center between 2011 and 2020 were evaluated.

Results: We included 26 aHUS patients (M 9; F 17, median age at transplantation 47y, range 22-69). In 22 patients (85%) 24 genetic variants were found: C3 (N=14), CFH (N=8), CFB (N=2). Recurrence risk was considered high in 18 patients and moderate in 8 patients. Nineteen patients received a graft from a living donor (LD) and 7 patients a graft from a brain-death deceased donor (DBD). All patients were treated with low-dose tacrolimus. Six patients (23%) developed aHUS recurrence (4/19 LD, 2/7 DBD) and were treated with eculizumab. Of note, recurrence occurred >12 months after transplantation in two patients. No patient lost the graft due to aHUS recurrence. One patient lost the graft due to rejection and BK nephropathy, one patient died with a functioning graft due to infections. After a median follow-up of 63.6 months (range 12-116) median eGFR was 53.5 ml/min/1.73m2, and proteinuria was negligible (median urine protein-creatinine ratio 0.12 g/10mmol, range 0.04-0.4).

Conclusions: Kidney transplantation without eculizumab prophylaxis is feasible and safe with a relatively low recurrence rate. Atypical HUS recurrence may present late after kidney transplantation and may not be prevented by short course eculizumab prophylaxis.
References: (1) Duineveld, C., et al., Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series. Am J Kidney Dis, 2017. 70(6): p. 770-777.

PO1657

Podocytes Soften in Proteinuric CKD: A Potential New Mechanism for Proteinuria?

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Background: Proteinuria is one of the most common manifestations of glomerular injury, and an important predictor of disease progression. Podocytes are a critical component of the glomerular filtration barrier, and as such podocyte injury is a major cause of proteinuria. Historically, investigators have focused on biochemical changes in podocytes that occur following podocyte injury. In contrast, little is known about the changes in the biophysical properties of these highly specialized epithelial cells.

Methods: 3 different models of proteinuric glomerular disease were studied: (1) Akita$^{+/-}$ Ren$^{+/-}$ mice (a murine model of diabetes and renin-mediated hypertension that we have recently shown develops progressive glomerulosclerosis that mimics human diabetic kidney disease, n = 7), (2) Myo1e$^{-/-}$ mice (a mouse model of genetic FSGS characterized by deficiency of a non-muscle myosin involved in actomyosin contraction, n = 6), and (3) Col4a5$^{-/-}$ mice, a mouse model of Alport's syndrome (n = 12). The stiffness of glomeruli, glomerular basement membrane (GBM), and podocytes was measured using atomic force microscopy (AFM) and associated histology (picrosirius red, silver, and WT1 staining). Similar stiffness measurements were performed in human FSGS and healthy kidney donor biopsies.

Results: AFM measurements revealed that glomerular stiffness increased in Akita$^{+/-}$ Ren$^{+/-}$ and Col4a5$^{-/-}$ mice, a finding that correlated with the degree of glomerulosclerosis. Glomerular stiffness was not increased in Myo1e$^{-/-}$ mice. GBM stiffness was increased in Akita$^{+/-}$ Ren$^{+/-}$ and Myo1e$^{-/-}$ mice, but not in Col4a5$^{-/-}$ Alport's mice. In all 3 mouse models, as well as in human FSGS biopsies, podocytes were softer than in healthy control kidneys.

Conclusions: Taken together, these are the first data demonstrating that podocytes soften in proteinuric glomerular disease. Given the major rearrangements in the actomyosin network that occur in podocytes of proteinuric kidneys, our data suggest that podocyte softening may be a common manifestation of podocyte injury. Further work is ongoing to understand whether this softening is solely a consequence of podocyte injury, or if it also contributes to ongoing podocyte damage.

PO1658

Novel Small Molecule Compounds Protect Podocytes from Injury In Vitro and In Vivo

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Background: Podocyte dysfunction and loss is a key determinant of proteinuria and glomerular injury. Thus, maintaining healthy podocytes is a therapeutic strategy against kidney disease. We previously developed a high-content imaging-based assay and used it to identify a number of small molecule compounds that show protection of podocytes from injury, suggesting it to be a viable strategy for the discovery and development of novel podocyte-protective agents.

Methods: Differentiated mouse podocytes were seeded on collagen-I coated multi-well plates as previously described (Lee et al. JASN, 2015). Cells were exposed to puromycin aminonucleoside (PAN, podocyte injury inducing agent), with compounds from the screening libraries, or DMSO as control, for 48 hours. Cells were fixed and stained which allowed detection using the Opera High-Content Screening (HCS) System. Columbus software was used to quantify morphology properties such as roundness, as well as the overall F-actin signal. Drosophila based screening assays were used to determine efficacy of selected hits in vivo.

Results: PAN damage resulted in quantitative reduction in F-actin fiber numbers and intensity, and increased roundness in podocytes in the ultra-miniaturized assay system. Screening of a library of chemical compounds identified >28 hits that dose-dependently reduced podocyte damage. A set of 9 compounds showed significant protection in a drosophila model of kidney injury, supporting the findings from the high-throughput screening assay.

Conclusions: Our 1536-well plate-based assay system identified a number of small molecule compounds that dose dependently protected podocytes from damage in vitro. A drosophila model of kidney injury validated most of the in vitro data from the podocyte screening assay. Current in vitro and in vivo mechanistic studies are underway to elucidate new insights into podocyte pathways that are therapeutically targeted by the selected hits. These agents hold promise as novel therapeutics for kidney disease patients with podocyte pathologies.

Funding: NIDDK Support

PO1659

Characterization of the Direct Effect of Mycophenolic Acid on Murine Podocytes

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Background: Mycophenolic Acid (MPA) is the active component of Mycophenolate Mofetil, a selective, noncompetitive inhibitor of the inosine monophosphate dehydrogenase. Blockade of the de novo purine synthesis depletes the pool of deoxyguanosine triphosphate, leading to a specific suppression of proliferation of B- and T-Lymphocytes. MMF has an established role as a therapeutic agent in childhood nephrotic syndrome, where it currently serves as a second line option for frequent relapsing and steroid dependent cases. Although its immunological functions are well studied, direct effects of MPA on podocytes remain largely unknown. With first preliminary results showing a protective effect in vivo, the present study aims to examine the direct effect of MPA on murine podocytes and its abilities to alter albumin-induced podocyte injury.

Methods: Cultured murine podocytes were exposed to albumin for 48 hours, with one group receiving treatment with MPA for the second 24 hours. Cells were stained with a Synaptopodin antibody and additional markers to visualize components of the cytoskeleton. Currently, we are analyzing apoptosis through a TUNEL assay as well as alterations in intracellular Calcium content with Fluo-4 and fura red. In addition, we study podocyte mobility under injury and with MPA intervention by migration assays. We will also study small GTPases content and activity through a pull-down assay for RhoA and Rac1. In an unbiased approach, podocytes were exposed to either 2 hours of 10 mg/l MPA or an additional 22 hours of 4 mg/l MPA. Total RNA was isolated and subjected to RNASeq anaylses.

Results: Synaptopodin immunofluorescence shows significant alterations of the actin cytoskeleton through albumin exposure. MPA treated cells reveal a restorative ability of the drug, with a recovery of stress fiber formation and a reduction of albumin-induced vacuoles. mRNA expression analyses are in progress.

Conclusions: First results show a promising effect of MPA on stress fiber formation. The additional functional assays will be finished by late summer this year and will give an important insight to MPAs ability to influence pathways, known to be affected during the development of proteinuric diseases. The RNAseq results will provide an objective and detailed picture of the direct effects of MPA on podocytes.

PO1660

Integration of Plasma Proteomics and Metabolomics Revealed Multiple Protein-Metabolite Networks in Steroid-Resistant Nephrotic Pediatric Patients

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Background: Nephrotic Syndrome (NS) is a common glomerular disease in children. Glucocorticoids (GC) are the mainstay of NS treatment, but steroid-resistant NS (SRNS) develops in 5-20% of children, dramatically increasing risk for progressive CKD vs. children with steroid sensitive NS (SSNS). There are no validated biomarkers able to predict which children will have SRNS. Here, we used previously published plasma proteomic and metabolomic profiles from children with SSNS and SRNS to test the hypothesis that integrating proteomic + metabolomic data could identify biomarkers and/or targets to define SRNS pathways that were not identified in the individual datasets.

Methods: Proteomic data from 15 paired NS plasma samples (n=7 SSNS; n=8 SRNS) and relative concentrations of metabolites estimated from plasma NMR metabolomics data from the same subjects underwent joint pathway analyses using MetaboAnalyst 5.0. software. Fold change (FC) was calculated as the ratio of pre-treatment to post-treatment for each protein and metabolite, and then log2 transformed. Proteins with $Log_2FC<-10$ or $Log_2FC>10$ and metabolites with $Log_2FC<-1$ or $Log_2FC>1$ were included in the analyses.

Results: Pathway analyses of proteomic data identified "ECM receptor interaction" and "focal adhesion" as the most significantly up- and down-regulated pathways in SRNS vs. SSNS, whereas "Valine, Leucine & Isoleucine biosynthesis", and "Glycosaminoglycan biosynthesis" were the most up- and down-regulated metabolic pathways in SRNS, respectively. Integrated proteomic + metabolomic pathway analyses identified 3 metabolic pathways that were perturbed in SRNS but not in SSNS: 1) "Nicotinate & Nicotinamide" pathway was perturbed in 50% of SRNS subjects (4 SRNS vs. 0 SSNS), 2) "Butanoate" was perturbed in 37.5% of SRNS subjects (3 vs. 0), and 3) "Glycine, Serine & Threonine" metabolism was perturbed in 25% of SRNS subjects (2 vs. 0).

Conclusions: Integrating proteomic + metabolomic data from children with SRNS vs. SSNS have identified multiple pathways and protein-metabolite linkages with potential to become future candidate biomarkers or drug targets of SRNS

PO1661

Spatially Resolved Analysis of Glomerular Structures in Alport Syndrome and FSGS

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Background: Many transcriptomics studies highlighted the molecular mechanism underlying glomerular diseases, but very little is known about interglomerular heterogeneity and how each glomerular is affected during progressive CKD. Using Spatial transcriptomics, which allows the characterization of the gene expression based on morphological context, we showed important differences between glomeruli of Alport Syndrome (AS) and FSGS patients and defined the interactive gene networks involved in glomerulus damage using healthy glomeruli as reference.

Methods: Using the Nanostring GeoMX Digital Spatial Profiling (DSP, Whole Transcriptomic Atlas) we generated spatial maps of gene expression of human AS (COL4A5 and COL4A$) and FSGS glomeruli (both males and females) and compared them to age-matched healthy controls. A total of 90 regions of interest were selected. After data QC and Q3 normalization, data were analyzed using different platforms and integrated with histopathology assessment.

Results: Data distinguished genes associated with podocyte, glomerular endothelial and mesangial cell phenotype. Unsupervised clustering and dimensionality reduction analysis showed clear differences between not only diseased and normal glomeruli (which presented homogeneous gene expression profile), but also between glomeruli of AS vs FSGS. Though glomeruli of AS and FSGS were histologically similar within each sample, they presented different transcriptomics profiles (for instance, while oxidative phosphorylation, focal adhesions were common to all gloms in AS, Apelin, PI3K-Akt, and Hippo signaling were unique to only a few glomeruli). Marked differences between males and females were observed in both AS and FSGS glomeruli (sheer stress and leukocyte transendothelial migration was more typical in AS male than female, while insulin signaling was only present in AS female. Similar heterogeneity patterns were observed in FSGS). In contrast to FSGS, AS were more enriched for genes associated with TCA cycle, protein processing in the ER, and neurotrophin signaling.

Conclusions: DSP revealed significant interglomerular heterogeneity in AS and FSGS regardless of age and gender leading to the discovery of pathways defining disease phenotypes at single glomerulus level. These preliminary data using DSP may allow the discovery of potential new therapeutic targets for CKD patients.

Funding: NIDDK Support

PO1662

EGR1 Is an Injury Marker in Podocytes

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Background: There is no good marker that depicts injured podocytes in human histology samples as well as desmin staining in rodent samples. EGR1 (Early Growth Response 1) is a transcriptional factor that regulates cell survival, proliferation, and cell death in response to growth factors, DNA damage, and ischemia. We have reported that injured podocytes express EGR1 protein in the early stages of damage in animal experiments and that EGR1 is expressed on podocytes in human glomeruli. This study aims to explore an association between EGR1 staining in podocytes and podocyte injury in human glomerular diseases.

Methods: Patients who underwent kidney biopsy at Jikei University Hospital, Tokyo, from June 2018 to March 2020 were recruited. Exclusion criteria included age < 20 years, glomeruli < 8, tubulointerstitial diseases, and kidney transplant patients. Blood and urine were collected during the kidney biopsy, and estimated glomerular filtration rate (eGFR), urinary protein to creatinine ratio (UPCR), urinary nephrin mRNA, and urinary podocin mRNA were measured. From the kidney biopsy specimen, the percentage of glomeruli with podocytes expressing EGR1 (%EGR1), the percentage of sclerotic glomeruli (%GS), and the glomerular podocin expression scores were measured. The %EGR1 was compared with these parameters using Spearman's rank correlation coefficient.

Results: Ninety-eight patients were included in this study (male, 58%; median age, 49 [interquartile range, 36–60] years; eGFR, 65 [44–79] mL/min/1.73m^2, UPCR, 0.90 [0.43–2.46] g/g; %EGR1, 26.1 [14.6–41.4]%; IgA nephropathy, n=35; hypertensive nephrosclerosis, n=10; membranous nephropathy, n=6; lupus nephropathy, n=5; minimal change disease (MCD), n=5; and focal segmental nephrosclerosis (FSGS), n=3). The %EGR1 was correlated with UPCR, urinary nephrin mRNA, urinary podocin mRNA, and glomerular podocin expression scores (rho=0.303, 0.378, 0.369, and -0.286; and P=0.0024, <0.001, <0.001, and 0.0043, respectively) but not with eGFR and %GS. In the subgroup with IgA nephropathy, %EGR1 was also correlated with UPCR and urinary podocin mRNA (rho=0.413 and 0.378; and P=0.014 and 0.025, respectively). Interestingly, the %EGR1 was low in MCD (8.33 [0.0–15.4]%), and high in FSGS (40.0 [36.8–46.3]%).

Conclusions: EGR1 expression in podocytes is associated with podocyte injury. EGR1 could be a podocyte injury marker in human glomeruli.

Funding: Government Support - Non-U.S.

PO1663

The CLVS1 H310Y Variant Associated with Steroid-Responsive Nephrotic Syndrome Affects Podocyte Function and Glomerular Filtration Barrier Integrity

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Background: We identified a rare homozygous variant, *p.H310Y*, in the gene encoding clavesin1 *(CLVS1*) as a novel cause of steroid sensitive nephrotic syndrome (SSNS). Knockdown of the orthologous *CLVS1* gene in zebrafish resulted in edema phenotypes that could be rescued with WT *CLVS1* mRNA but not the *H310Y* variant. *CLVS1* knockout in cultured human podocytes decreased endocytosis, increased reactive oxygen species (ROS) accumulation, and increased apoptosis. These aberrant phenotypes were rescued in the presence of glucocorticoids, mimicking the steroid responsive phenotype of *CLVS1 H310Y* patients. Treatment with ROS inhibitors also rescued the reduced viability phenotype in *CLVS1* KO podocytes.

Methods: To better understand the effects of the *CLVS1 H310Y* variant on podocyte homeostasis, we created human podocyte cell lines with CRISPR-Cas9 mediated heterozygous and homozygous *CLVS1 H310Y* knock-in (KI) mutations. We evaluated the KO and KI podocytes through automated live-cell imaging. Additionally, we further evaluated the effects of reduced *CLVS1* function on podocyte function *in vivo* in zebrafish.

Results: Clavesin1 is specifically required for clathrin mediated endocytosis in cultured human podocytes. Additionally, homozygous *H310Y* KI podocytes displayed similar corticosteroid responsive phenotypes to *CLVS1* KO lines, including increased apoptosis that could be rescued with ROS inhibition, while heterozygous KI lines were unaffected. Furthermore, we confirmed that the *H310Y* variant reduces binding to a critical antioxidant transporter, alpha tocopherol transfer protein (p=0.006), likely contributing to the ROS phenotypes. Electron microscopy analysis and quantification of excreted proteins revealed podocyte effacement and decreased glomerular filtration barrier integrity in zebrafish with knockdown of orthologous *CLVS1* when compared to controls (p<0.0001).

Conclusions: Our data further demonstrates the importance of clavesin1 in the maintenance of podocyte viability and GFB integrity. It also suggests that oxidative stress regulation may be compromised in patients carrying pathogenic *CLVS1* variants and highlights the potential for alternative therapies for NS patients that target ROS accumulation in podocytes.

Funding: Other NIH Support - NICHD, Commercial Support - Goldfinch Bio

PO1664

Rare Variants in RCAN1-3 Genes Are Enriched in Patients with CKD

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Background: We recently identified rare variants in the gene encoding Regulator of Calcineurin Type 1 (*RCAN1*) as a novel cause of FSGS/SRNS. Cells expressing mutant *RCAN1* and human podocytes with reduced *RCAN1* displayed increased CN activity that resulted in increased susceptibility to apoptosis compared to WT *RCAN1*. There are two additional proteins in the RCAN family, RCAN2 and RCAN3, both of which are capable of regulating CN activity. To further elucidate the role of pathogenic variants in RCAN genes in the etiology and pathogenesis of chronic kidney disease, we screened patients with CKD for rare variants in *RCAN1-3* genes. In addition, we performed kinase screening to identify compounds that can rescue the phenotype induced by defective RCAN1.

Methods: In collaboration with the Genome England Consortium, we examined associations between potentially pathogenic variants in *RCAN1-3* genes and kidney disease in the large multi-ethnic National Health Service database. We compared the percentage of patients with rare (MAF <0.01), functional *RCAN1-3* variants in patients with CKD (renal and urinary tract disorders) and patients with neurological disorders. We also used target kinase inhibition to examine additional potential RCAN1 regulatory kinases.

Results: Of the 4,153 patients in the UK National Health Service data set with CKD, 39 (0.94%) had rare functional *RCAN 1-3* variants compared to 87 (0.57%) of the 15,141 patients with neurological disorders, revealing a significant enrichment of rare pathogenic variants in *RCAN1-3* genes in patients with kidney disease compared to those without (p=0.0006). Pharmacological inhibition of additional RCAN regulatory kinases including DYRK1A (Harmine) or BMK1 (Ax15836 and XMD8-85) could rescue the elevated CN activity (p =0.4946. 0.3980 and 0.0912 respectively) and reduced viability (p>0.05) in disease causing mutant *RCAN1* expressing cells compared to WT controls.

Conclusions: This data suggests that not only are *RCAN1-3* likely single gene causes of NS/FSGS, but functional variants in the genes may also act as susceptibility or modifier genes that contribute to development of CKD. Our findings also highlight the therapeutic potential of targeting RCAN1 regulatory molecules in the treatment of FSGS.

Funding: Commercial Support - Goldfinch Bio

PO1665

Spatial Transcriptomic Profiling of Collapsing Glomerulopathy

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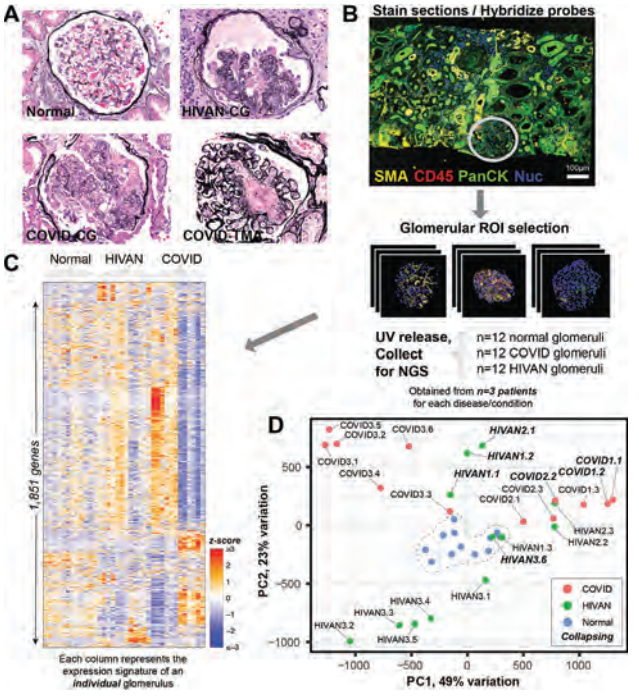
Background: Collapsing glomerulopathy is a histologically distinct variant of focal and segmental glomerulosclerosis that presents with heavy proteinuria and portends a poor prognosis. Collapsing glomerulopathy can be triggered by viral infections such as HIV and SARS-CoV-2. However, it is not known if distinct molecular mechanisms drive histologically indistinguishable lesions of collapsing glomerulopathy in different clinical contexts.

Methods: Transcriptional profiling of collapsing glomerulopathy lesions is difficult since only a few glomeruli may exhibit this histology within a kidney biopsy. Therefore, we used recently developed spatial transcriptional profiling to quantify 1,852 transcripts in individual glomeruli from HIV and SARS-CoV-2 infected patients with biopsy confirmed collapsing glomerulopathy.

Results: We compared transcriptional signatures on the basis of disease or histology and identified distinct pathways of injury in HIV and SARS-CoV-2 associated collapsing glomerulopathy and thrombotic microangiopathy (Figure). Focused validation using immunohistochemistry and RNA in situ hybridization showed good concordance with spatial transcriptional profiling results.

Conclusions: Spatial transcriptional profiling represents a powerful new method to dissect transcriptional programs of pathologically discernible kidney lesions.

Funding: Other NIH Support - NCATS 3 UG3/UH3TR002158-04S1



PO1666

Protein Kinase R Inhibition Ameliorates Mitochondrial Dysfunction in the Tg26 HIV-Associated Nephropathy Mouse Model

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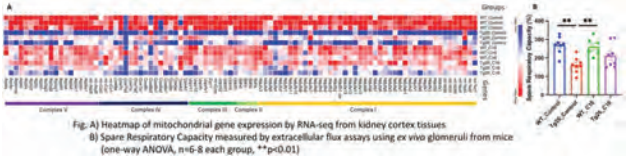
Background: Double-stranded RNA (dsRNA)-activated protein kinase (PKR) is a sensor for dsRNA in response to viral infections, including HIV-1. We previously reported that *APOL1* risk alleles damage podocytes through double-stranded RNA-activated protein kinase (PKR) activation (Okamato, Comm Biol, 2018). Here, we hypothesized that PKR activation could be a mechanistic pathway shared by HIV- and APOL1-mediated nephropathies. Hence, we investigated the effects of PKR inhibition on HIVAN in the well-characterized Tg26 mouse model, which expresses HIV regulatory and accessory genes.

Methods: We evaluated the kidney phenotype of Tg26 mice and wild-type mice treated with the PKR inhibitor (C16) from 6 to 12 weeks of age. We profiled kidney gene expression by RNA-seq and mitochondrial function by the extracellular flux assay using *ex vivo* glomerular tissues.

Results: Kidney disease manifestations, including albuminuria (mean [IQR]) (668 mg/g Cr [60, 1064] vs 2564 [1785, 5646], p=0.03) and global glomerulosclerosis (0.0% [0.0-0.0] vs 8.1 [2.3, 15.8], p=0.008), were reduced in the C16 treated group compared to the vehicle control group. C16 treatment increased mitochondrial gene expression (Fig.A), ameliorated mitochondrial dysfunction, and restored spare respiratory capacity as measured by extracellular flux assay (Fig.B).

Conclusions: PKR inhibition ameliorated mitochondrial dysfunction associated with the HIVAN phenotype observed in Tg26 mice, suggesting that PKR activation contributes to the development of mitochondrial dysfunction in HIVAN.

Funding: NIDDK Support



PO1667

Recurrent Nephrotic Plasma Activates Pro-Fibrotic Signalling Pathways Downstream of Protease-Activated Receptor 1

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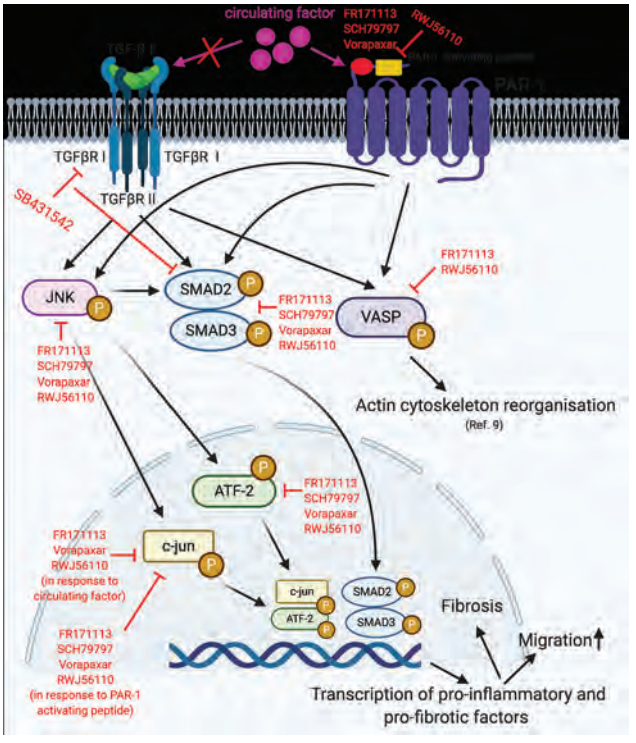
Background: Post-transplant recurrence of steroid-resistant nephrotic syndrome (SRNS) is thought to be due to an unknown "circulating factor", the identity of which has so far remained elusive. Our previous work suggests a signaling role for protease-activated receptor-1 (PAR-1), leading to impaired podocyte function. The signaling pathways downstream of PAR-1 in podocytes are unknown and could reveal novel mechanistic insights into the disease.

Methods: Conditionally immortalized human podocytes (ciPods), glomerular-like structure spheroids, and human kidney organoids were treated with PAR-1 agonist peptide or nephrotic plasma (NP), in the absence or presence of four different PAR-1 antagonists.

Results: PAR-1 agonist and patient relapse NP, but not paired remission plasma, induced the phosphorylation of VASP, JNK, and proteins involved in pro-fibrotic pathways. These changes were inhibited by PAR-1 inhibitors, but not by TGF-β1 inhibition. Four PAR-1 inhibitors demonstrated specific antagonistic properties. The phosphorylation of VASP and JNK in a 3D spheroid model and from stem-cell derived kidney organoids corroborated the finding from the 2D model. Functionally, relapse NP induced podocyte motility and podocyte loss from spheroids both of which were also selectively rescued by PAR-1 inhibitors. Treatment of kidney organoids with relapse NP induced the same VASP and pro-fibrotic phosphorylation in podocytes and the loss of podocyte-specific markers.

Conclusions: We propose that the circulating factor acts as a pro-fibrotic effector by activating PAR-1. A greater understanding of these signaling pathways will lead to the identification of novel therapeutic targets for this disease.

Funding: Government Support - Non-U.S.



Proposed mechanism of PAR-1 signaling induced by recurrent SRNS plasma

PO1668

Molecular and Functional Characterization of Human Urinary APOL1 G2/G2 High-Risk Genotype Podocyte

Oyindamola C. Adebayo,[1,2] Pepe M. Ekulu,[2,3] Jean-Paul Decuypere,[2] Mohamed A. Elmonem,[2,4] Agathe B. Nkoy,[2,3] Djalila Mekahli,[2] Benedetta Bussolati,[5] L.P.W.J. Van Den Heuvel,[2,6] Fanny O. Arcolino,[2] Elena N. Levtchenko.[2] *Laboratory of Pediatric Nephrology, Department of Development and Regeneration, Katholieke Universiteit Leuven, Leuven, Belgium [1]Center for Molecular and Vascular Biology, Department of Cardiovascular Sciences, Katholieke Universiteit Leuven, Leuven, Belgium; [2]Department of Development and Regeneration, Katholieke Universiteit Leuven, Leuven, Belgium; [3]Division of Nephrology, Department of Pediatrics, University Hospital of Kinshasa, Faculty of Medicine, University of Kinshasa, Kinshasa, Congo (the Democratic Republic of the); [4]Department of Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt; [5]Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy; [6]Department of Pediatric Nephrology, Radboud University Medical Center, Nijmegen, Netherlands.*

Background: Apolipoprotein L1 (*APOL1*) risk variants, G1 and G2, increase the risk of various non-diabetic kidney diseases in the African population. To date, the precise mechanisms by which *APOL1* risk variants induce injury on podocytes and other kidney cells remain unclear. Trying to unravel these mechanisms, most studies used animal or cell models created by gene editing.

Methods: Conditionally immortalized human podocyte cell lines from urine of a donor carrying *APOL1* high risk genotype, G2/G2 was developed. The *APOL1* G2/G2 cell lines were characterized for podocyte markers at both the mRNA and the protein levels, using real-time quantitative PCR, Western blot and immunofluorescence staining. Following induction of *APOL1* expression by 50 µg/mL polyinosinic-polycytidylic acid (poly(I:C)), we assessed the functional features of APOL1-induced podocyte dysfunction such as cell detachment, cell viability, cell death, autophagy, cytoskeleton organization and podocyte permeability. As control, *APOL1* wild type (G0/G0) podocytes previously generated from a Caucasian donor were used.

Results: We successfully generated human *APOL1* G2/G2 urinary podocyte cell lines. Upon exposure to poly(I:C), G2/G2 and G0/G0 podocytes upregulated *APOL1* expression resulting in podocytes detachment, decreased cells viability and increased apoptosis rate in a genotype-independent manner. G2/G2 podocyte cell lines exhibited altered features, including upregulation of CD2AP, alteration of cytoskeleton, reduction of autophagic flux and increased permeability in an *in vitro* model under continuous perfusion.

Conclusions: The human *APOL1* G2/G2 podocyte cell model is a useful tool for unraveling the mechanisms of APOL1-induced podocyte injury and the cellular functions of APOL1.

PO1669

Topology Mapping of Membrane-Inserted ApoL1

John C. Edwards, Jonathan M. Bruno. *Saint Louis University, Saint Louis, MO.*

Background: ApoL1 inserts into membranes at pH 6 where it has anion permease activity. Titration of the cis compartment to pH 7.5 suppresses the anion permease and activates a cation channel. How ApoL1 is arrayed in the membrane-inserted form at various pH values is unclear.

Methods: Cys was substituted for Ser or Thr at positions throughout ApoL1 and resulting mutants expressed in E. coli. Purified mutants were allowed to insert into phospholipid vesicles at pH 6.0, held at pH 6.0 or titrated to pH 7.5, and reacted with extravesicular membrane-impermeant fluorescent Cys modifying reagent, Alexafluor-568-maleimide. Unreacted reagent was quenched. Non-membrane-inserted protein was removed by chaotropic extraction and Sepharose 4B chromatography. Membrane-associated protein was separated on SDS-PAGE along with ApoL1 standards for quantification. Ratio of fluorescence intensity to mass of ApoL1 protein was normalized to that of protein modified after detergent denaturation to determine relative accessibility of each Cys to the modifying reagent.

Results: Cys substitutions were generated at amino acid positions 40, 80, 149, 173, 186, 200, 204, 226, 247, and 365. We found three patterns of reactivity after membrane insertion. Cys at positions 40, 149, and 365 showed reactivity that was roughly comparable to that in detergent solution with little difference between pH 6.0 and 7.5, consistent with exposure to the aqueous solution on the cis face of the membrane under all conditions. In contrast, Cys at positions 186, 226 and 247 showed decreased reactivity after membrane insertion that was similar at both pH 6.0 and pH 7.5; these positions are not fully accessible from the external solution. Finally, Cys at positions 80, 173, 200, and 204 had decreased reactivity at pH 6.0 with increase in reactivity at pH 7.5, suggesting these positions may be initially buried in the membrane upon insertion at low pH, but titration to neutral pH induces a structural transition that exposes them to the external solution.

Conclusions: Mapping accessibilty of individual amino acid positions in ApoL1 support a model in which a substantial structural transition accompanies the pH shift-induced activation of the cation channel.

Funding: NIDDK Support

Relative reactivity of membrane-inserted cysteine substitution mutants at pH 6.0 or 7.5

	S40C	S80C	S149C	T173C	S186C	S200C	T204C	T226C	S247C	S365C
pH 6.0	0.88	0.32	0.88	0.56	0.60	0.19	0.42	0.23	0.42	0.85
pH 7.5	0.88	2.34	1.18	2.49	0.67	0.74	1.25	0.24	0.37	0.63

PO1670

Deep Learning-Based Segmentation and Quantification of Podocyte Foot Process Morphology

Linus Butt,[1] David Unnersjö-Jess,[1] Martin Höhne,[1] German Sergei,[2] Annika Wernerson,[3] Anna Witasp,[3] Bernhard Schermer,[1] Kasia Bozek,[2] Thomas Benzing.[1,2] *[1]Uniklinik Koln, Koln, Germany; [2]University of Cologne Center for Molecular Medicine Cologne, Cologne, Germany; [3]Karolinska Institutet Enheten for medicinska njursjukdomar, Huddinge, Sweden.*

Background: The advent of super-resolution light microscopy enabled imaging of the nanoscale dimensions of podocyte foot processes and the slit diaphragm and subsequent quantification of morphological alterations upon glomerular injury. However, these morphological analyses require manual work, which is time-consuming and investigator-dependent.

Methods: We used novel sample preparation protocols and applied super-resolution STED microscopy and conventional confocal microscopy to image podocyte foot processes in murine and human kidney tissue. Deep learning-based segmentation was utilized to automatically segment both the slit diaphragm pattern as well as several thousands of individual foot processes per sample.

Results: Our algorithm, the **a**utomatic **m**orphological **a**nalysis of **p**odocytes (AMAP), segmented the FPs and the SD at high accuracy and more effectively as compared to a previously published semi-automatic dataset. The morphological quantifications show a high agreement with our previous analysis, thereby confirming the correlation of albuminuria with certain morphological alterations of podocytes. In addition, we applied AMAP to human patient tissue and found different patterns of effacement in different disease entities.

Conclusions: The combination of three-dimensional optical imaging and deep-learning segmentation can be used to perform extensive morphological analyses of podocyte in health and disease. It confirms our previous semi-automatically performed analyses in a mouse model of FSGS and can be applied to patient material in order to assess morphological alterations in glomerular disease while eliminating investigator-bias. We believe AMAP can in the future complement the diagnostic algorithms in research and clinical pathology.

Funding: Government Support - Non-U.S.

PO1671

Podometrics in Different Cortical Zones and Associations with the Number of Non-Sclerotic Glomeruli

Kotaro Haruhara,[1,2] Go Kanzaki,[2] Takaya Sasaki,[2] Saeko Hatanaka,[2] Yusuke Okabayashi,[2] Akira Shimizu,[3] Luise A. Cullen-McEwen,[1] Nobuo Tsuboi,[2] Takashi Yokoo,[2] John F. Bertram.[1] *[1]Monash University, Clayton, VIC, Australia; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [3]Nihon Ika Daigaku, Bunkyo-ku, Japan*.

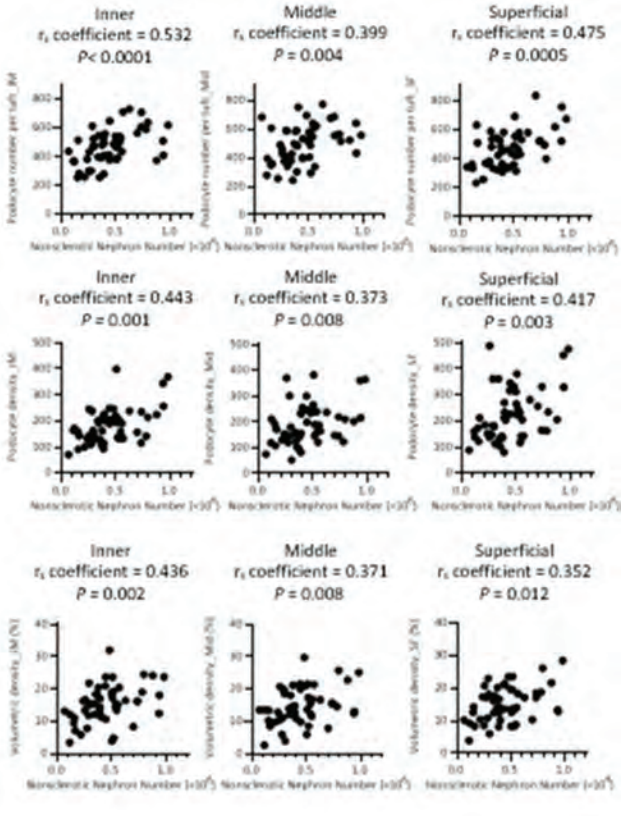
Background: Reduced nephron and podocyte number are common features in CKD. While it is well known that glomerular volume and glomerular density (glomerular number per cortical area) differ between cortical zones, zonal differences in podometrics and correlations with nephron number have not previously been explored.

Methods: Non-sclerotic glomerular number per kidney was estimated using the physical disector/fractionator combination. Podocyte density, podocyte number, podocyte volume and volumetric density of podocyte to glomerulus in each cortical zone were estimated using model-based stereology on a single histological section immunostained with two podocyte markers and imaged by confocal microscopy.

Results: Fifty autopsy kidneys were studied. The median age was 68 years ranging from 28 to 85 years. Median eGFR was 74 mL/min/1.73m^2. The median number of non-sclerotic glomeruli per kidney was 421,547 (IQR, 289,095–548,233). Non-sclerotic glomerular number was directly correlated with podocyte number per tuft, podocyte density and volumetric density of podocytes in each cortical zone (Fig). Glomeruli in the superficial cortex were smaller than glomeruli in other zones and had the highest podocyte density and smallest podocyte volume. Podocyte number and volumetric density of podocytes were similar across the cortical zones.

Conclusions: These results demonstrate for the first time that a higher number of non-sclerotic glomeruli is directly associated with three beneficial indices of podocyte and glomerular health. Podocyte number and volumetric density of podocytes were the more reliable indicators of non-sclerotic nephron number, independent of cortical zones.

Funding: Government Support - Non-U.S.



PO1672

Can Podocyte Number and Density Predict the Response to Therapy in Patients with Primary FSGS?

Natasha de Zoysa,[1] Jonathan E. Ling,[2] Kotaro Haruhara,[1,3] Peter G. Kerr,[2] David J. Nikolic-Paterson,[2] John F. Bertram,[1] Luise A. Cullen-McEwen.[1] *[1]Monash University Faculty of Medicine Nursing and Health Sciences, Clayton, VIC, Australia; [2]Monash Medical Centre Clayton, Clayton, VIC, Australia; [3]Tokyo Jikeikai Ika Daigaku Igakubu Igakuka, Minato-ku, Japan*.

Background: Podocyte loss is a key event in primary focal segmental glomerulosclerosis (FSGS). Common first-line therapy for patients with primary FSGS involves steroid therapy with or without blood pressure control; however 40-70% of patients achieve no remission. Animal studies have shown that treatment efficacy is achieved partly through preservation of podocyte number, as well as podocyte protective effects. Animal studies have also determined that podocyte number and density are predictive of FSGS severity. Therefore, this study **aimed** to determine if podocyte number and density can predict the response to therapy in patients with primary FSGS.

Methods: A retrospective cohort study of renal biopsies was conducted from 2009-2020 in Melbourne, Australia at a tertiary hospital (Monash Medical Centre). Patients diagnosed with primary FSGS were screened (n=84). Patients were excluded for lack of consent for samples to be used for research purposes (n=38), risks of other forms of FSGS (n=13), insufficient clinical data available (n=2), no biopsy tissue available (n=7) or <6 glomerular profiles available in the biopsy (n=5). Included patients were allocated into groups of treatment responders (n=11) or non-responders (n=8) based on urinary/serum data 6 months following initial diagnosis and commencement of treatment. Biopsies were immunofluorescently stained for podocyte-specific markers. Model-based stereology was used to estimate podometrics. Sections were re-stained with PAS to measure the glomerulosclerotic index (GSI).

Results: Podocyte number per glomerulus in responders (347 (215-606); median (IQR)) was 45% higher than in non-responders (190; 143-263) (P=0.03). Podocyte density in responders (76; 58-142 per $10^6\mu m^3$ of glomerular volume) was similar to non-responders (66; 44-88 per $10^6\mu m^3$ of glomerular volume) (P=0.38). GSI was significantly higher in non-responder patients (1.1; 0.6-2.3) than responders (0.6; 0.2-0.9) (P=0.04), and was significantly and negatively correlated with podocyte number (r = -0.64; P=0.003) and podocyte density (r = -0.48; P=0.04).

Conclusions: Podocyte number per glomerulus in diagnostic renal biopsies could be used as a predictor of treatment response for patients with primary FSGS.

Funding: Government Support - Non-U.S.

PO1673

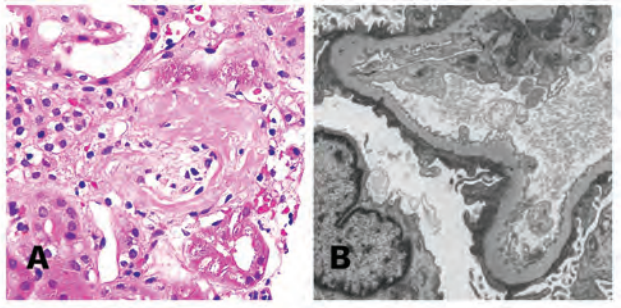
Nephrotic Syndrome in a Patient with Systemic Lupus Erythematous: Is it Lupus Podocytopathy?

Nora H. Hernandez Garcilazo,[1] Mohamed Hassanein,[2] Christopher C. Garces,[1] Si Yuan Khor,[1] Beenu Kaw.[3] *[1]Michigan State University, East Lansing, MI; [2]Cleveland Clinic, Cleveland, OH; [3]Sparrow Health System, Lansing, MI*.

Introduction: Lupus podocytopathy (LP) is a rare form of lupus nephritis (LN) that clinically mimics minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). We present a case of LP in a patient with systemic lupus erythematosus (SLE).

Case Description: A 73-year-old female with a history of SLE (on Hydroxychloroquine), and nephrolithiasis presented with left flank pain for 2 weeks. Physical exam was notable for peripheral edema and left costovertebral angle tenderness. Labs showed a creatinine 1.02 mg/dL (baseline 0.7), serum albumin 2.6 mg/dL, and urine microalbumin/creatinine (MA/Cr) ratio of 7.5 g/g. Further workup revealed a positive ANA, negative anti-dsDNA antibodies, and normal complements. Kidney biopsy showed FSGS, tip variant, and 100% podocyte foot process effacement (FPE). She was started on high-dose prednisone, simvastatin, ACE inhibitor, and furosemide with potassium supplementation for significant pedal edema. Two months later, her MA/Cr ratio improved to 3 g/g. Prednisone was slowly tapered off over a 7-month period during which symptoms were well-controlled and MA/Cr ratio continued to improve.

Discussion: Nephrotic syndrome in patients with SLE raises suspicion for LP, which represents 1% of LN biopsies. Biopsy findings include diffuse FPE (>70%) on electron microscopy, and absence of immune deposits on light, immunofluorescence, and electron microscopy. LP is divided into MCD or FSGS, with the latter having higher rates of hypertension, acute kidney injury on presentation, and overall worse outcomes. Treatment consists of a short course of high-dose glucocorticoids; however high rates of relapse are observed and tend to coincide with SLE activity.



A. H&E of a glomerulus showing focal segmental glomerulosclerosis, with segmental scars near the tip of the glomerular tuft. There is mild mesangial matrix expansion.

B. Electron microscopy showing diffuse podocyte foot process effacement with no mesangial or glomerular basement membrane immune-type electron-dense deposits identified.

PO1674

Minimal Change Disease as a Sequela of Psoriasis in an Adult

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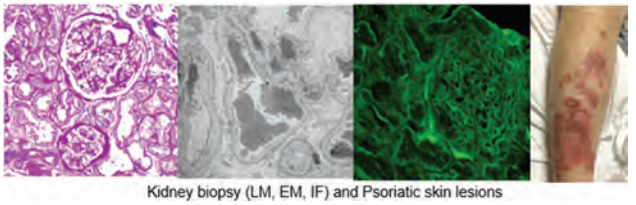
Introduction: Minimal change disease (MCD) is usually found in children but can be an uncommon presentation in adults. Relation to psoriasis has not been significantly established even though the latter has been associated with kidney disease such as IgA nephropathy, focal segmental glomerulosclerosis leading to kidney failure. This is an interesting case given that this is a young patient with psoriasis presenting with a flare in the setting of newly diagnosed MCD.

Case Description: A 34-year-old male with history of psoriasis presented with severe body edema after psoriatic flare two weeks prior admission. He was found to have exceptionally low serum albumin of 1.4g/dL, massive proteinuria with spot urine protein creatinine ratio of 7.6 and significant hyperlipidemia. Protein electrophoresis did not show glomerular pathology or spikes in proteins and extensive serological workup was normal. Kidney biopsy reported MCD. Patient improved quickly with steroids of 1mg/kg/day, IV furosemide and albumin infusion. Six months later, the patient was readmitted with new psoriasis flare and again nephrotic syndrome with 7.2g of proteinuria. His symptoms resolved quickly with same treatment used on the first admission. Follow up in clinic one-month post discharge showed normal renal function with proteinuria now at 100mg/day.

Discussion: While there has been evidence of link between psoriasis and kidney disease, finding of MCD is a unique development. The idea can be postulated that since psoriasis is a disease due to dysfunction of T-cells among other causes, a flare can be the initiating event leading to dysregulation of an otherwise stable immune system. This T-cell dysregulation has also been noted in MCD. The underlying cause of MCD is not clear. However, a lot of studies suggest that T-cell dysfunction is one of the implicated agents, known for cell destruction, causing damage to the glomerular membrane leading to the loss of proteins. The rarity of this case belies the complexity of the immunological process leading to the presentation and further research needs to be done to document and establish this as the pathologic process linking the two diseases.



Kidney biopsy (LM, EM, IF) and Psoriatic skin lesions

PO1675

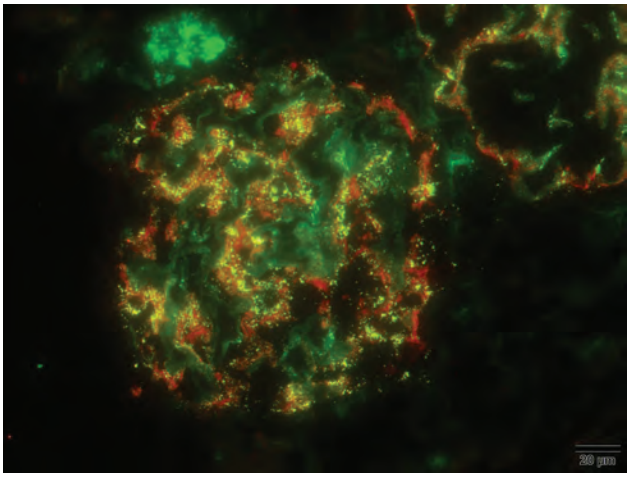
Collapsing FSGS from Acquired Nephrin Antibody

Hsiao L. Lai,[1] Abdullah Thayyil,[1] Astrid Weins,[2] Keith H. Keller.[2] *[1]East Carolina University, Greenville, NC; [2]Brigham and Women's Hospital, Boston, MA.*

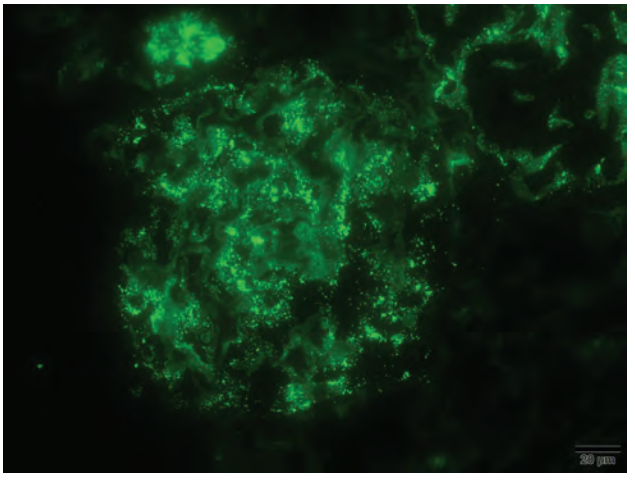
Introduction: Deficits in nephrin and other podocyte components are known to result in congenital nephrotic and familial FSGS syndromes. Weins *et. al.* recently described acquired anti-nephrin antibody localizing in glomerular podocytes of patients with minimal change disease.

Case Description: A 16 year old male referred for new onset nephrotic syndrome progressive over 2 weeks was found to have serum albumin 1.2 gm/dL, UPCR 3.1, and elevated lipids with BP 160/100 mm Hg. Hepatitis B/C, HIV, SLE screens were negative. Renal biopsy demonstrated focal collapsing lesions with diffuse podocyte effacement. Immunofluorescence showed punctate IgG, kappa and lambda light chain staining in podocytes, but no albumin. Anti-human IgG colocalized with nephrin in the granular staining. ParvoB19 and COVID-19 titers were negative. Creatinine rose from 0.65 to 1.65 and UPCR to 10.3 but improved rapidly with high dose prednisone and ACEi. Serology for circulating anti-nephrin 2 weeks into treatment was negative, consistent with previous finding that circulating antibody levels quickly drop to low or undetectable with partial clinical remission.

Discussion: This case strengthens evidence that anti-nephrin antibodies cause disruption of the slit pore diaphragm which appears to be readily responsive to immune therapy. Anti-nephrin mediated podocytopathy may present with a spectrum of glomerular histopathology, which on the background of other susceptibility factors, can lead to more severe presentations such as collapsing FSGS.



Yellow represents merge of IgG and anti-nephrin



Punctate IgG stain in podocytes

PO1676

Anti-Nephrin Autoimmunity in Early Primary FSGS

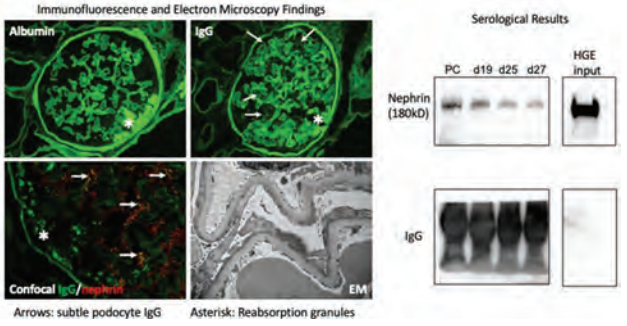
Astrid Weins,[1,2] Walter P. Mutter,[3,2] Keith H. Keller,[1,4] Sujal I. Shah,[1,2] Helmut G. Rennke.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Newton Wellesley Hospital, Newton, MA; [4]Broad Institute, Cambridge, MA.*

Introduction: Minimal change disease (MCD) and primary FSGS are important diagnoses in adults and children with acute nephrotic syndrome (NS). We have reported anti-nephrin-mediated autoimmunity in NS with MCD on kidney biopsy (KBx). Here, we describe a patient with KBx-proven diagnosis of early primary FSGS and persistent anti-nephrin IgG in glomeruli and serum.

Case Description: A 69yo Caucasian man with history of type 2 DM presents with acute kidney injury (sCr 3.49g/dl), anasarca, hyperlipidemia, sAlb1.8g/dl, UPCR 18g/gCr. Serologies including ANA, HIV, anti-PLA2r are negative; FLC ratio is 2.91. A kidney biopsy is ordered; the differential diagnosis includes MCD, membranous nephropathy, FSGS and paraprotein-related diseases. The biopsy contains 52 glomeruli with 12% global sclerosis, and 2 glomeruli with early segmental sclerosis with capillary collapse, epithelial hyperplasia and protein reabsorption granules (PRGs). Diabetic glomerular changes are not seen. Tubular atrophy and interstitial fibrosis are mild, and vascular sclerosis is moderate to severe. Immunofluorescence microscopy (IF) shows trace mesangial IgM and fine granular podocyte IgG with equal kappa/lambda. Electron microscopy reveals diffuse podocyte foot process effacement without deposits and loss of

slit diaphragms. Confocal imaging of IgG/nephrin IF confirms substantial overlap in the fine podocyte granules (arrows), but not in coarse PRGs (asterisks). A diagnosis of early primary FSGS is made. Sera collected on post-biopsy days 19, 25 and 27 are serologically positive for anti-nephrin. The patient was started on oral glucocorticoids, and on d27 was in partial remission (UPCR 2.6g/gCr, SAlb 2.8g/dl). Anti-B cell therapy is considered.

Discussion: Our findings reveal that autoimmune-mediated anti-nephrin podocytopathy can trigger irreversible podocyte injury leading to FSGS, likely in patients with additional predisposing factors. This enhances our understanding of diffuse progressive podocytopathies; accurate and early diagnosis identifies patients who benefit most from B-cell-targeted immunosuppressive therapy.



PO1677

Nephrotic Syndrome Secondary to Minimal Change Disease Following Moderna COVID-19 Vaccine

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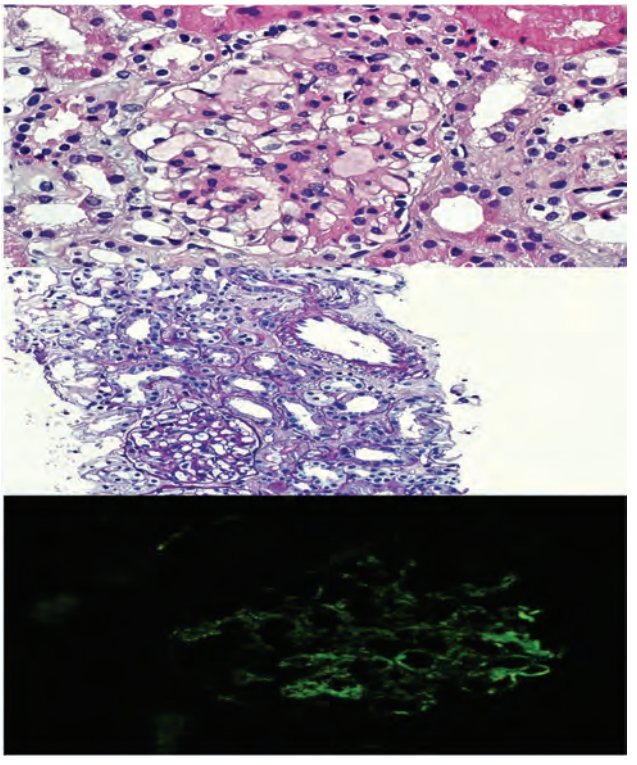
Introduction: Minimal Change Disease (MCD) has been reported following vaccines against hepatitis, pneumococcus, influenza and measles. In the COVID-19 era, 3 cases of new-onset MCD and one case of MCD relapse have been reported following the Pfizer-BioNTech COVID-19 vaccine. We herein report a case of MCD after receiving the first dose of Moderna COVID-19 vaccine.

Case Description: A 43-year-old Ethiopian man with no significant past medical history presented with progressive bilateral lower limb edema for two weeks. His symptoms started 7 days after receiving the first dose of COVID-19 vaccine. He then developed dyspnea and scrotal swelling over the following 10-14 days. On physical examination, his blood pressure was 150/92 mm Hg. There was decreased air entry at lung bases, significant bilateral lower limb pitting edema extending to above the knees and scrotal swelling. Lab investigations revelaed hypoalbuminemia, hyperlipidemia and proteinuria of 15 grams. There was no hematuria and his immunologic and serologic work up was negative. Renal biopsy showed minimal change disease with underlying IgA nephropathy. There was no global or segmental glomerulosclerosis, mesangial or endocapillary proliferation. Patient was started on oral prednisolone and furosemide. His edema resolved, serum albumin doubled and proteinuria decreased within the first week of treatment.

Discussion: Symptoms of MCD have been reported 4 days to 16 weeks after vaccination. Although the pathogenesis of MCD is not fully understood, studies suggest that T-cell dysfunction might play a role. More studies are needed to determine the incidence and pathophysiology of this adverse event post COVID-19 vaccine. It is not clear in this case if or when the second dose of the COVID-19 vaccine should be administered.



PO1678

Antiproteinuric and Podocytoprotective Effects of Direct Oral Anticoagulant Therapy in Glomerular Disease

Amanda P. Waller,[1] Katelyn Wolfgang,[1] Eman Abdelghani,[1] Bryce A. Kerlin.[1,2] *[1]Abigail Wexner Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University College of Medicine, Columbus, OH.*

Background: Podocyte injury is a key determinant of chronic kidney disease (CKD) progression toward end stage kidney disease. We and others have recently uncovered a putative podocytopathic role for intraglomerular thrombin during proteinuric glomerular disease. Direct oral anticoagulant (DOAC) therapies limit thrombin activity but their ability to improve podocyte health and potentially slow CKD progression remains unknown. Thus, the aim of this study is to determine if DOACs reduce thrombin-mediated podocytopathy during glomerular proteinuria. We hypothesized that DOACs would preserve podocyte health and function in a podocyte-specific model of proteinuric glomerular disease.

Methods: Diphtheria Toxin was used to induce proteinuria in transgenic rats expressing human diphtheria toxin receptor (DTR) in a podocyte-specific manner and was subsequently treated with 1) Dabigatran (20 mg/kg; Dabi), 2) Rivaroxaban (3 mg/kg; Riva), or 3) Sham (saline) and compared to healthy controls (n=7-9/group). Morning spot urine was collected on day 0 and 10 post-DT. Glomeruli were isolated from the kidney, dissociated into single-cell suspensions, and analyzed by flow cytometry after immunofluorescent synaptopodin antibody and TUNEL staining.

Results: Both Dabi and Riva significantly reduced proteinuria (**Fig A**) and terminal podocyte injury (TUNEL positive podocyte fraction; **Fig B**). In addition, there was a trend toward *in situ* podocyte preservation with both DOACs with a significant overall effect of DOAC therapy on podocyte survival **(Fig C)**.

Conclusions: Both Dabi (a direct thrombin inhibitor) and Riva (a direct factor Xa inhibitor) reduce proteinuria and enhance podocyte health in a podocyte-specific model of proteinuric glomerular disease. These data suggest that DOACs may be repurposed as a novel approach to slow or halt proteinuric glomerular disease progression. Because thrombotic disease is a life-threatening co-morbidity of both glomerular disease and CKD, this approach may enable simultaneous thromboprophylaxis and glomerular disease therapy.

Funding: NIDDK Support, Private Foundation Support

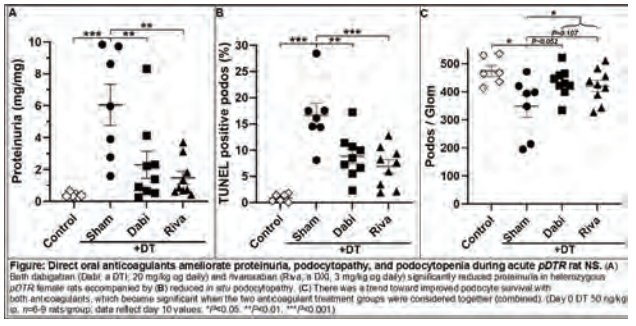


Figure: Direct oral anticoagulants ameliorate proteinuria, podocytopathy, and podocytopenia during acute *pDTR* rat NS. (A) Both dabigatran (Dabi; a DTI; 20 mg/kg qg daily) and rivaroxaban (Riva, a DXI, 3 mg/kg qg daily) significantly reduced proteinuria in heterozygous *pDTR* female rats accompanied by (B) reduced *in situ* podocytopathy. (C) There was a trend toward improved podocyte survival with both anticoagulants, which became significant when the two anticoagulant treatment groups were considered together (combined). (Day 0 DT 50 ng/kg ip, n=6-9 rats/group; data reflect day 10 values; *P<0.05, **P<0.01, ***P<0.001)

PO1679

A Highly Efficient and Reproducible Differentiation Protocol for Induced Pluripotent Stem Cell-Derived Podocytes

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Background: Podocyte processes intertwine to create a slit diaphragm, which, when compromised leads to filtration dysfunction, proteinuria, and eventually to renal failure. It is critical to be able to study the disease and test therapeutic interventions in patient-derived cells, and assess genetic and environmental aspects. Current protocols for differentiation of iPSCs into podocytes (iPodos) suffer from a lack of podocyte maturity or low reproducibility. Our goal was to test and optimize multiple protocols to establish a more translatable, physiologically relevant, and reproducible method.

Methods: We compared two distinct published protocols [Ciampi 2016; Musah 2018]. Additional conditions were tested, including varying the extracellular matrices, media, and length of differentiation. Podocyte signature was evaluated by IF, flow cytometry, and Nanostring analysis. For models of injury, we utilized protamine sulfate (PS) or puromycin aminonucleoside (PAN) treatment. A mouse podocyte cell line was used as a control.

Results: Both protocols generated iPodos with similar efficiency, as measured by synaptopodin, nephrin and podocin staining. iPodos generated from protocol-1 could be maintained in culture up to 14 days but remained relatively immature, based on the expression of collagen α1α2α1(IV) and lack of α3α4α5(IV). Response to PS and PAN treatment was variable compared to mouse podocytes. Altering the matrix from collagen to laminin did not improve reproducibility. iPodos from protocol-2 developed more filopodia and complex cell-cell junctions and appeared more homogeneous, with extended survival up to 4 weeks post-differentiation. PS treatment induced a significant and reproducible dose- and time-dependent decrease in synaptopodin expression, and a more robust accumulation of phalloidin aggregation. Both effects were effectively prevented by cyclosporin A, a calcineurin inhibitor, in a similar manner as in mouse podocytes. iPodos from protocol-2 also showed a more consistent dose-dependent response to PAN injury.

Conclusions: We achieved a more robust and translatable iPodos platform utilizing human iPSCs. Patient-derived iPodos will be an invaluable tool to enable a precision medicine-based approach to validate new therapeutic approaches for podocytopathy-driven kidney disease.

Funding: Commercial Support - Goldfinch Bio

PO1680

Novel Ex Vivo Culture System Reveals Mechanosensitive "Sarcomere-Like Structures" During Early Podocyte Spreading

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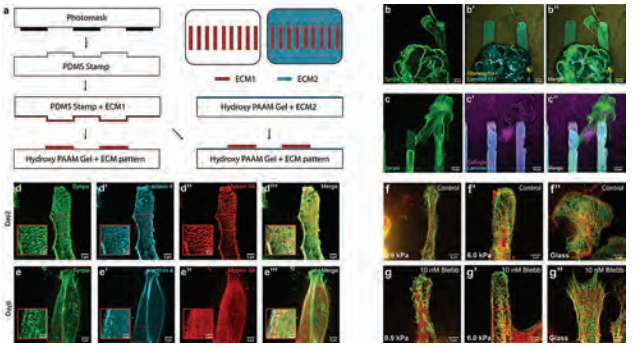
Background: Chronic kidney disease and ESKD are widespread health problems with no cure, in part because the biophysics underlying them are still not clear. A recently discovered feature of injured podocytes includes the de novo assembly of sarcomere-like stress fibers, identified by their alternating myosin and synaptopodin/a-actinin-4. It is not known whether these indicate a transient healing phenotype or are a feature of the cascade leading to foot process effacement.

Methods: To model the early events of podocyte injury, we developed a new in vitro system that enables the study of podocytes outside of their native microenvironment, but with in vivo-like mechanobiological and extracellular matrix (ECM) features. This system includes controllable stiffness, micropatterned substrates for spreading, and the use of primary podocytes as they migrate from freshly isolated glomeruli.

Results: When cultured on micropatterns of physiologically relevant extracellular matrix proteins and appropriate stiffness, myosin- and synaptopodin-positive stress fibers developed over two days of culture, then disappeared after six days, and the appearance of these stress fibers was sensitive to substrate stiffness and could be disrupted by inhibiting actomyosin contraction (blebbistatin), culturing cells with stiffness outside of the physiologic range, or presenting cells with substrates associated with pathology.

Conclusions: These results reveal the role of mechanobiological factors in podocytes represented by the mechanoresponsive sarcomere-like structure and establish a novel system for characterizing this mechanobiology in vitro.

Funding: Private Foundation Support



(a) Protocol for preparing the micropatterns of ECM proteins. (b, c) Primary podocytes prefer surfaces with laminin-521, the normal GBM laminin. (d, e) Sarcomere-like structures were observed at the early stages of podocyte spreading on micropatterns. (f, g) The sarcomere-like structure is mechanosensitive: a soft substrate (0.9 kPa) or myosin inhibition (Blebbistatin) increases the periodicity in the pattern.

PO1681

Primary Cilia in Podocyte Health and Disease

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Background: Primary cilia are highly specialized elaborations of the plasma membrane that direct many of the signaling cascades critical for pre- and post-natal development and disease. While renal primary cilia are recognized as key genetic and cellular targets in polycystic kidney disease, the presence and function of primary cilia within the renal corpuscle and glomerulus have yet to be fully characterized. The purpose of our study was to perform a focused and quantifiable characterization of primary cilia of glomerular cell populations in health and disease.

Methods: Renal biopsy samples were obtained from patients with Minimal Change Disease (MCD; N=6), Focal Segmental Glomerular Sclerosis (FSGS; N=3), and control renal tissue (CON; N=4). Immunofluorescence analyses (IF) were used to quantify primary cilia number and length, as well as the expression of Sonic Hedgehog (SHH) protein, the ligand component of the Hedgehog signaling pathway and one measure of primary cilia function.

Results: Mean percent ciliation was significantly increased in MCD and FSGS when compared to CON. Analysis of individual glomerular primary cilia revealed increased ciliary length (μm) in both MCD and FSGS when compared to CON. Further analysis comparing primary cilia length in WT-1-positive nuclei (WT-1+; podocytes) also revealed a pronounced increase in cilia length in MCD and FSGS podocyte primary cilia versus CON. Despite increased length of primary cilia, glomerular SHH expression was significantly decreased in both MCD and FSGS when compared to CON. Glomerular diseases MCD and FSGS are therefore associated with an overall increase in podocyte primary cilia length and ciliation, an effect which corresponded to a decrease in SHH expression.

Conclusions: These data provide evidence in support of a role for primary cilia in glomerular disease pathogenesis. Ongoing and future research is needed to establish a mechanistic explanation for these changes observed in glomerular and podocyte cilia number and length. A more thorough understanding of the role(s) of primary cilia in glomerular cells, and specifically in podocytes, remains critical for to both our understanding of disease pathogenesis as well as for the pharmacologic treatment of glomerular chronic kidney disease.

Funding: Private Foundation Support

PO1682

Establishing a Podocyte-PEC Cross-Talk Model Using an Open Microfluidic Co-Culture Device

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Background: Although focal segmental glomerulosclerosis (FSGS) is initially caused by podocyte injuries, their neighboring parietal epithelial cells (PECs) also undergo molecular changes that further damage the glomerulus. The cross-talk between podocytes and PECs is poorly understood, in part due to a lack of appropriate experimental models for study. Our goal is to establish an in vitro coculture model to induce podocyte injury and determine the mediators and responses of PECs.

Methods: Mouse podocytes labeled with EGFP and PECs labeled with tdTomato were cocultured in two neighboring chambers of an open microfluidic device that we engineered. The chambers remain separated until more media is added to overflow the half wall in between. To induce injury, podocytes were exposed to increasing concentrations

of cytotoxic sheep anti-glomerular antibodies (or media alone as control) for 2 hours. The two chambers were then allowed to communicate passively for 1 to 4 days. Diffusion calculations suggested moderate sized (10 kDa) signaling molecules take approximately 2 days to reach the other chamber. Immunocytochemistry characterized podocyte injury and PEC activation and epithelial-mesenchymal transition (EMT).

Results: By day 1, the normal contiguous monolayer of podocytes was disrupted, accompanied by a dose-dependent increase in the de novo expression of the injury marker desmin. In contrast to F-actin staining of the control group exhibiting thick bundles of cortical actin at cell edges, resembling primary processes, the level of F-actin decreased predominantly along the cell borders in injured podocytes, consistent with the destruction of podocyte cytoskeletal structures. By day 4, the percentage of PECs expressing the EMT marker SM22 increased significantly. $SM22^{+}$ PECs were larger and exhibited cellular protrusions, implying enhanced migration and invasion characteristics of the mesenchymal state. The protein expression of CD44, a marker for the activated profibrotic migratory PEC phenotype, was also increased. Levels of SSeCKS remained unchanged in PECs. A time course of bulk RNA seq results from both podocytes and PECs are pending.

Conclusions: This novel in-vitro microfluidic model for coculturing mouse podocytes and PECs has the potential to study many pathways involved in podocyte-PEC crosstalk, glomerular disease mechanisms, and drug screening.

Funding: NIDDK Support, Other NIH Support - NIA, R35, Other U.S. Government Support

PO1683

C-Type Lectin-Like Receptor (CLEC) 2, the Ligand of Podoplanin, Induced Dynamic Change of F-Actin Filaments in Podocytes

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Background: Podoplanin is intensely expressed on podocyte membrane in an evolutionally conserved manner. Podoplanin is connected to F-actins through phosphorylated (p-)ERM in podocytes. CLEC-2, the endogenous ligand of podoplanin, is highly expressed in platelets and also exists in the plasma as a soluble form. Normally, podocytes are sequestered from CLEC-2, but when the glomerular barrier is injured, podocytes can have access to CLEC-2. We studied potential actions of CLEC-2 on podocytes.

Methods: Fc-CLEC-2, a fusion of Fc and human CLEC-2 (51-229), which can bind to mouse podoplanin, was generated in HEK293 cells and purified by Protein A chromatography. The changes of podocytes were evaluated 1 hr after the treatment with Fc or Fc-CLEC-2 (10ug/mL). StrepTagII-FLAG-CLEC-2, a fusion of double-tags and mouse CLEC-2 (51-229), was generated in HEK293 cells and purified by StrepTactin Sepharose column. Kidneys of C57BL/6 mice were perfused with 5 ug/g BW of FLAG-CLEC-2 through the aorta. Kidney samples were collected 1hr after the perfusion.

Results: Cultured podocytes treated with Fc showed an elongated morphology with numerous F-actin filaments, while podocytes with Fc-CLEC-2 showed a round shape with degradation of F-actin. Western blot revealed that pERM/ERM ratio was 0.47-fold decreased in podocytes with Fc-CLEC-2, indicating that CLEC-2 induced dephosphorylation of ERM. Immunostaining depicted abundant moesin, which we found the major ERM in cultured podocytes, around cell protrusions in podocytes with Fc, while moesin staining was reduced in podocytes with Fc-CLEC-2. Next, we evaluated *in vivo* podocytes perfused with FLAG-CLEC-2. In SEM, podocytes perfused with FLAG-CLEC-2 exhibited retraction of foot processes in 18.5% of visual fields. Western blot of glomerular lysate revealed that phosphorylation of Ezrin, the major ERM in *in vivo* podocytes, was 0.50-fold decreased by FLAG-CLEC-2. Double immunostaining of pERM and podocalyxin confirmed dephosphorylation of ERM in podocytes.

Conclusions: These results collectively suggest that CLEC-2 induced dephosphorylation of ERM, which then caused dissociation of podoplanin from F-actin, degradation of F-actin, leading to retraction of foot processes in podocytes. Thus, leakage of CLEC-2 may exaggerate podocyte injury.

Funding: Government Support - Non-U.S.

PO1684

A Direct CLIC5A/Ezrin Interaction Accounts for CLIC5A Plasma Membrane Localization and CLIC5A-Stimulated Rac1 Activation in Renal Glomeruli

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Background: CLIC5A is part of the Podocalyxin/Ezrin complex at the apical domain of podocyte foot processes. Ezrin binds membrane phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) inducing its activation and C-terminal (T567) phosphorylation. Activated Ezrin bridges membrane-spanning proteins to cortical actin, shaping the cellular architecture. We reported that CLIC5A stimulates Rac1-GTP-dependent PI(4,5)P2 generation and Ezrin activation and that CLIC5A deletion disrupts the foot process architecture (J. Cell Sci. 127:5164, 2014 & Kidney Int. 89:833, 2016). Here, we investigated the mechanism by which CLIC5A interacts with Ezrin.

Methods: Direct protein-protein interactions were established by Yeast two-hybrid (Y2H) assay and confirmed by GST pull-down and reciprocal co-immunoprecipitation. Subcellular localization of endogenous proteins was determined by differential detergent fractionation of mouse glomeruli. Ezrin was released from glomerular membranes by stimulating phospholipase C-mediated PI(4,5)P2 hydrolysis with m-3M3FBS.

Results: We found that CLIC5A interacts directly with the Ezrin C-terminal domain, but only if Ezrin was in the activated state. The extreme 16 C-terminal amino acids of Ezrin were necessary for the interaction and Ezrin phosphorylation at T567 increased CLIC5A binding. Expression of a C-terminal ezrin fragment (Ezrin 432-586, phosphomimic T567D), but not C-terminally truncated Ezrin 432-570 effectively blocked CLIC5A-stimulated Ezrin and Rac1 activation. In glomeruli 49 +/- 4 % of endogenous CLIC5A was in the cytoplasmic, 33 +/- 3% in membrane and 18 +/- 1 % in the cytoskeleton-associated fraction. As expected, PI(4,5)P2 hydrolysis reduced Ezrin phosphorylation and shifted Ezrin from membrane and cytoskeletal fractions into the soluble pool. Similarly, PI(4,5) P2 hydrolysis shifted CLIC5A from membrane- and cytoskeletal fractions, increasing the soluble component to 72 +/- 13% ($p = 0.041$, $n= 3$, mean +/- STD).

Conclusions: CLIC5A interacts directly with active Ezrin, and this interaction is required for CLIC5A-dependent Rac1 activation. The release of CLIC5A together with Ezrin from the membrane fraction in response to PI(4,5)P2 hydrolysis suggests that CLIC5A localizes to the plasma membrane because of its direct interaction with Ezrin.

Funding: Government Support - Non-U.S.

PO1685

The Mechanosensitive Ion Channel Piezo Activates Rho1 in Drosophila Nephrocytes

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Background: Podocytes constantly face biomechanical forces such as shear stress and hydrostatic pressure. Increasing forces result in morphological changes, detachment from the glomerular basement membrane and loss into the primary urine. This highlights a requirement for podocytes to sense changes in their physical environment and induce a response to react to increased biomechanical force.

Methods: Here, we investigated the functional role of the mechano-sensitive ion channel Piezo in *Drosophila* nephrocytes.

Results: First, we confirmed Piezo expression and localisation at the nephrocyte diaphragm. Acute activation of the channel with the chemical compound YODA revealed significantly increased Ca^{++} signalling and Rho1 activation, suggesting a functional role of Piezo in nephrocytes and delineating the putative Piezo mechanosensitive pathway. For further analysis, we used knockout flies and observed a filtration phenotype, while morphology and GTPase activation was not altered. In addition, we also studied the impact of elevated Piezo levels and could show, that in line with the YODA effect, Piezo overexpression revealed severely increased Rho1-GTP levels and FITC uptake, while morphology was not changed. Because of this severe pathological phenotype, we tried to rescue the effects of Piezo overexpression with pharmacological inhibition by using tarantula toxin. Intriguingly, treatment with tarantula toxin reversed the elevated Rho1-GTP levels observed upon Piezo overexpression.

Conclusions: Taken together, our data confirms the functional expression of Piezo in nephrocytes, its role in regulating GTPases and the beneficial effect of tarantula toxin to reverse the pathological effects caused by increased Piezo levels.

PO1686

Drosophila Filamin Exhibits a Mechanoprotective Role During Nephrocyte Injury via Hypertrophy

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Background: Podocytes are constantly exposed to biomechanical forces such as shear stress and hydrostatic pressure. These forces increase during disease like diabetes and hypertension, resulting in adaptive mechanisms such as podocyte hypertrophy. But how do podocytes sense changes in biomechanical forces and how does the molecular response look like?

Methods: To investigate this, we utilized *Drosophila* nephrocytes and studied the functional role of the mechanosensor Cheerio (dFilamin). FilaminB is upregulated in podocyte injury models and upon increased biomechanical stress, therefore serving as an ideal candidate for mediating mechano-protection in response to injury.

Results: Expression of an over-active mechanosensor region variant of Cheerio resulted in a significant hypertrophy phenotype, while morphology and filtration function were only mildly affected. Interestingly, the expression of over-active Cheerio caused a rescue of filtration function after depletion of the nephrocyte diaphragm proteins Duf (dNEPH) and Sns (dNephrin). Additional analysis with human FilaminB confirmed this mechano-protective role and the involvement of the mechanosensor region in the hypertrophy phenotype. To delineate the mechano-protective pathway acting downstream to Cheerio we studied the candidates: TOR, WNT and YAP. Activation of these pathways result in nephrocyte hypertrophy. Interestingly, TOR repression reversed the hypertrophy in over-active Cheerio expressing cells, suggesting TOR to be a novel downstream target of Cheerio and to be responsible for the hypertrophy phenotype.

Conclusions: Although Cheerio and FilaminB mediate a mechano-protective role in the face of injury, their excessive expression resulted in a severe morphological and functional phenotype, emphasizing the need of a tight control of expression levels.

PO1687

Characterization of a Novel FSGS-Associated ACTN4 Mutation in Drosophila melanogaster

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Background: Decisive for podocyte morphology and homeostasis during health and disease is a specialized and highly regulated organization of the actin cytoskeleton. In this context, the actin cross-linking protein Alpha-actinin4 (ACTN4) has been shown to play a crucial role in podocyte architecture and function. Mutations in the *ACTN4* gene are associated with focal segmental glomerulosclerosis (FSGS). Here, performing gene panel sequencing in a pediatric patient presenting with steroid resistant nephrotic syndrome and FSGS, a *de novo*, potentially disease causing variant of *ACTN4* was identified, which was previously undescribed and not found in available genome or exome databases. Our aim is to elucidate the pathogenic potential of this variant for podocytes and FSGS progression.

Methods: To elucidate pathogenic effects of the newly identified ACTN4 variant, we employed the genetic toolbox of *Drosophila*. The fly holds podocyte-equivalent cells called nephrocytes, which are responsible for filtration and detoxification of the hemolymph. Cell-specific genetic manipulation enabled us to analyze RNAi-mediated knockdown of Actinin, the single fly homolog, in nephrocytes and its impact on cell morphology and function. Rescue experiments with the novel human ACTN4 variant will now give indication about possible pathogenic consequences of the mutation when compared to wildtype as well as previously described disease-associated variants of ACTN4.

Results: Knockdown of *Drosophila* Actinin in nephrocytes leads to severe functional defects, as filtration capacity is diminished by up to 50%. Morphologically, mislocalization of the ZO-1 homolog Polychaetoid was observed as well as overall reduction of nephrocyte diaphragms. First rescue experiments with wildtype human ACTN4 led to partial rescue of functional and morphological phenotypes observed upon Actinin knockdown.

Conclusions: Our results underline the importance of Actinin for nephrocyte biology. Capacity of wildtype human ACTN4 in rescuing the knockdown associated phenotypes indicates the model's suitability. Further experiments will be performed to elucidate the pathogenicity of the novel ACTN4 variant also in comparison to previously described pathogenic mutations.

PO1688

The Calcium-Sensing Receptor Restores Podocyte Function in Proteinuric Humans and Mice

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Background: Calcimimetic agents allosterically increase the calcium (Ca^{2+}) sensitivity of the calcium-sensing receptor (CaSR), which suppresses the secretion of parathormone in the parathyroid gland and therefore regulates Ca^{2+}-homeostasis. The CaSR is furthermore expressed in the tubular system and to a lesser extend in podocytes. Activation of CaSR reduces glomerular proteinuria and podocyte damage in animals. However, the precise role of the podocyte CaSR is still unclear.

Methods: A CaSR knockdown (KD) in murine podocytes and podocyte-specific CaSR knockout (KO) in BALB/c mice were generated to study its role in proteinuria.

Results: Podocyte CaSR KD abolished the calcimimetic R-568 mediated Ca^{2+}-influx, reduced the number of actin fibers, cellular attachment and migration velocity in podocytes. In contrast, the activation of the CaSR with R-568 protected the wildtype cells from Adriamycin (ADR)-induced cytoskeletal rearrangement and reduction in adhesion capacity. *In vivo* ADR-induced proteinuria enhanced glomerular CaSR expression in wild type mice (control vs ADR: 33.5±2.0 vs 75.8±7.8 CaSR positive podocytes (%); p=0.0286). In podocyte-specific CaSR KO ADR treatment resulted in a higher albuminuria (control vs KO: 27.9±38.1 vs 85.9±52.7 g/galbumin/creatinine; p=0.023 at day 7), podocyte foot process effacement, podocyte loss (control vs KO: 3504±283.1 vs 2969±547.2 p57+cells/mm^2; p=0.0238 at day 8) and glomerular sclerosis compared to wild type littermates. In addition, four children with nephrotic syndrome, objecting glucocorticoid therapy, were treated with the calcimimetic cinacalcet for 1 to 33 days. Proteinuria declined transiently by up to 96 %, serum albumin increased and edema resolved.

Conclusions: The activation of CaSR regulates key podocyte functions and protects from ADR induced cellular damage *in vitro*. The CaSR reduces toxin induced proteinuria, podocyte loss and glomerular damage in mice. Our findings suggest a major role of CaSR signaling in glomerular disease.

PO1689

Selective PPARγ Modulator with Reduced Adipogenic Potential Ameliorates Experimental Nephrotic Syndrome

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Background: Glomerular disease, often manifesting as nephrotic syndrome (NS) with high proteinuria, can be refractory to standard treatment and is typically associated with hypoalbuminemia, hypercholesterolemia, and hypercoagulopathy. We hypothesized that the nuclear receptor PPARγ can be selectively modulated using a novel partial agonist, GQ-16, to gain therapeutic advantage over traditional PPARγ agonists for NS treatment

Methods: Pio and GQ-16 were administered daily to male Wistar rats with puromycin amino-nucleoside (PAN)-induced nephropathy. Serum and urine chemistries were performed and kidneys, glomeruli, liver, and white adipose tissue (WAT) were harvested for RNA and protein extraction. Blood was collected for determination of thrombin generation parameters.

Results: PAN induced robust proteinuria, which was significantly reduced with Pio to 64% of PAN-value, and robustly with GQ-16 to 81% of PAN, which was comparable to controls. Podocyte hypertrophy also returned to normal with Pio and GQ-16. While both GQ-16 and Pio restored glomerular *Nphs1* and hepatic *Pcsk9* expression and reduced hypercholesterolemia, GQ-16 also restored glomerular *Nrf2*, and reduced disease-associated hypoalbuminemia and hypercoagulopathy. Furthermore, RNA-seq analysis identified both common and distinct glomerular genes altered by Pio and GQ-16 treatments. Moreover, Pio but not GQ-16 significantly induced aP2 (fatty acid binding protein) in adipocytes and in WAT. Both, Pio and GQ-16 induced insulin sensitizing adipokines in WAT with varying degrees

Conclusions: Selective modulation of PPARγ by a partial agonist may be a more beneficial approach than a full PPARg agonist in reducing proteinuria, hypoalbuminemia, and hypercoagulopathy in NS and in decreasing drug-associated side effects such as adipogenesis and weight gain.

Funding: Other NIH Support - NIH Clinical and Translational Science Award to The Ohio State University (Award Number UL1TR002733 from the National Center for Advancing Translational Sciences), Private Foundation Support

PO1690

Simultaneous Loss of Podocyte Insulin Receptor (IR) and Insulin-Like Growth Factor 1 Receptor (IGF1R) Is Detrimental and Associated with Spliceosome Dysfunction

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Background: Insulin signalling to the podocyte via the insulin receptor (IR) is crucial for kidney function. Insulin-like growth factor 1 (IGF1) signalling through the structurally related insulin-like growth factor 1 receptor (IGF1R) is also known to directly affect the podocyte. Since the IR and IGF1R may act redundantly in some contexts, this study sought to elucidate the compound role of the insulin/IGF1 axis in podocyte function using mouse and cell culture models deficient in both receptors.

Methods: To examine the effects of combined receptor loss *in vivo*, a transgenic mouse model with conditional inactivation of podocyte IR and IGF1R was generated. *In vitro*, conditionally immortalised genetic IR knockout, IGF1R knockout and IR/IGF1R dual knockout podocytes were characterised using global proteomic and transcriptomic analysis.

Results: Podocyte specific IR/IGF1R knockout mice developed significant albuminuria and a severe renal phenotype with global sclerosis, renal failure and death occurring between 4 and 24 weeks. >90% loss of IR/IGF1R in cultured mouse podocytes was also detrimental resulting in >50% cell death 7 days after gene knockdown. Enrichment analysis of total proteomic data revealed a striking downregulation of gene ontology terms associated with splicing and RNA processing activity in IR/IGF1R knockout cells. Western blot analysis was used to validate the reduced expression of proteins responsible for spliceosome synthesis and regulation in dual knockout podocytes, including polypyrimidine tract-binding protein 2 (PTBP2), eukaryotic initiation factor 4A (EIF4A) and splicing factor 3B subunit 4 (SF3B4).

Conclusions: This work underlines the critical importance of podocyte insulin/IGF signalling and reveals a novel role for this signalling axis in RNA processing by regulating spliceosome activity.

Funding: Government Support - Non-U.S.

PO1691

Regression of Severe Preexisting Glomerular Pathology in a Mouse FSGS Model in Response to Treatment with Macula Densa-Derived Biologicals

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Background: Macula densa (MD) cells localized at the glomerular vascular pole synthesize and release numerous vasoactive autocoids and newly identified angiogenic (e.g. CCN1) and glomerulotrophic factors that act in a paracrine fashion to maintain high renal/glomerular blood flow and endogenous tissue remodeling. The present study aimed to test the tissue regenerative therapeutic potential of MD-derived biologicals in vivo in a mouse model of focal segmental glomerulosclerosis (FSGS).

Methods: BalbC mice with Adriamycin-induced stable, severe FSGS and albuminuria (albumin/creatinine ratio ACR>10,000mg/g) were randomized into 5 groups and started daily ip injections (150ul each) of either saline (S), human recombinant (hr) CCN1 in low-dose (0.3 ng/mouse) (L), hrCCN1 high-dose (2 ug/mouse) (H), DMEM/F12 control (D), and conditioned culture media of the new MD cell line mMD^{Geo} (MD) for 4 weeks. Transcutaneous GFR (MediBeacon) and ACR were measured weekly. Terminal histological analysis was performed using PAS and Trichrome staining.

Results: Kidney injury was severe at the onset (GFR 1160±51 μL/min/100 g BW, ACR 11219±637) and was sustained throughout the 4 weeks of treatment in control S and D groups (GFR: 1080±143, 992±164; ACR: 10227±5869, 3958±1638, respectively). In contrast, a progressive and significant improvement in kidney function was observed in response to both L, H, and MD treatment (ACR reduced to 1342±573, 921±270, 1113±151, respectively; GFR increased to 1453±100 μL/min/100 g BW in MD group). Similarly, p57+ podocyte number per glomerular area (11±0.4 in L, 12±0.6 in H vs 3.9±0.43 in S;14±0.6 in MD vs 5.5±0.9 in D), GS index (131±2.4 in L, 130±2.3 in H vs 173±3.4 in S; 113±1.9 in MD vs 152±3 in D based on PAS staining) and tissue fibrosis index (67±2 in L, 57±2 in H vs 83±3 in S; 47±2 in MD vs 80±3 in D based on Picrosirius staining density) improved significantly in response to treatment with MD biologicals.

Conclusions: This in vivo preclinical study confirmed that the supplementation of key MD cell-derived factors in the form of injectable biologicals can augment endogenous kidney tissue repair and restores kidney function in a mouse model of FSGS. Targeting MD cell mechanisms is a new potent tissue regenerative therapeutic strategy for kidney diseases.

Funding: NIDDK Support

PO1692

Insulin-Like Growth Factor 1 Receptor (IGF1R) Suppression in the Glomerular Podocyte Has Beneficial and Detrimental Consequences Dependent on the Level of Inhibition

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Background: Insulin signalling to the glomerular podocyte via the insulin receptor (IR) is known to be critical for normal kidney function. This study aimed to define the physiological importance of the closely related insulin-like growth factor 1 receptor (IGF1R) in podocytes.

Methods: Transgenic mice with conditional inactivation of podocyte IGF1R were generated to determine the effects of IGF1R suppression *in vivo. In vitro,* conditionally immortalised genetic IGF1R knockout and wild-type podocytes treated with the IGF1R inhibitor picropodophyllin (PPP) were characterised using global proteomic analysis.

Results: Transgenic mice with partial podocyte-specific IGF1R knockout, generated using conventional Cre recombinase, had no apparent basal renal phenotype but unexpectedly, were protected from doxorubicin-induced nephropathy. An additional mouse model using an epigenetically resistant podocyte Cre driver designed to increase receptor knockout efficiency, exhibited mild basal albuminuria by 24 weeks. Our *in vitro* models revealed that the degree of IGF1R inhibition in the podocyte is important. Greater than 90% knockout caused ~50% cell death after 7 days and did not protect against doxorubicin-induced cell death whilst wild-type podocytes treated with PPP (partial inhibition) showed enhanced survival when stressed with doxorubicin. Proteomic analysis revealed that near complete IGF1R suppression results in downregulation of mitochondrial respiratory complex I and DNA damage repair proteins whilst partial IGF1R inhibition promotes expression of respiratory complexes.

Conclusions: Altered mitochondrial function, impairment of DNA damage responses and resistance to oxidative stress in podocytes is dependent on the level of IGF1R suppression and determines whether receptor inhibition is protective or mildly detrimental.

Funding: Government Support - Non-U.S.

PO1693

Calcium/Calmodulin Kinase 4 Induces FSGS by Promoting Apoptosis While Inhibiting Autophagy in Podocytes

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Background: Podocyte injury and death precede the development of focal segmental glomerulosclerosis(FSGS), but the involved mechanisms remain poorly understood. Calcium/calmodulin kinase 4 (CaMK4), a serine threonine kinase, is increased in podocytes of people with FSGS and in mice models of FSGS.

Methods: B6, B6 *Camk4.fl/fl.podocin*$^{cre-}$ or *Camk4.fl/fl.podocin*$^{cre+}$ mice were created and injected with i.v. adriamycin. Urine was collected on days 0, 3, 7, or 14, and kidney samples were collected on day 7 or 14 after adriamycin injection. Cultured human podocytes in the presence and absence of CAMK4 inhibitor (KN93) were exposed to adriamycin after which immunofluorescence and western blot was performed. Pull down mass-spectrometry and co-immunoprecipitation analysis was performed to identify proteins involved in cell death and those that directly interact with CaMK4 in FSGS.

Results: We found that lack of CaMK4 in podocytes suppressed the development of kidney pathology including the presence of hyaline deposits in glomeruli, podocytopenia and tubulointerstitial damage with intratubular casts in mice injected with adriamycin. Proteinuria in mice lacking CaMK4 in podocytes exposed to adriamycin, was reduced at 7 days and remained low through the 14th day when compared to control mice. Mechanistically we found that CaMK4 phosphorylates 14-3-3, releasing pro-apoptotic protein BAD which in turn binds to the antiapoptotic protein BCL-2, thereby allowing BAX, to aggregate on mitochondria and induce release of cytochrome c through mitochondrial pore formation, followed by caspase activation and apoptosis. In parallel, CaMK4 inhibits autophagy, a process needed for the renewal of damaged organelles, through the mTOR pathway, by directly phosphorylating AKT and S6 kinase.

Conclusions: We demonstrate that mice lacking CaMK4 specifically in podocytes are protected from FSGS-like disease after exposure to adriamycin. These mice also demonstrate markedly reduced proteinuria and podocytopenia. We found that apoptosis leads to cell death while autophagy is protective in FSGS. The characterization of the specific molecular events which lead to podocyte loss and glomerulosclerosis point to putative therapeutic targets and biomarkers for FSGS.

Funding: NIDDK Support, Other NIH Support - NIAID

PO1694

A Noncanonical Role for IRE1α in Podocyte Endoplasmic Reticulum (ER)-Phagy

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Background: Glomerular diseases involving podocyte (glomerular epithelial cell; GEC) injury feature endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR). Inositol requiring enzyme-1α (IRE1α), a UPR transducer, mediates chaperone production and autophagy in podocytes during ER stress. Selective autophagy of the ER (ERphagy) is dependent on ER-resident adaptors (e.g. RTN3L) and is stimulated by ER stress. ER-derived coat protein complex II (COPII) vesicles may participate in the delivery of ER cargo to autophagosomes; however, regulation and importance of ERphagy in glomerular disease are not understood.

Methods: We employed mice with podocyte-specific deletion of IRE1α and littermate controls. IRE1α knockout (KO) and control GECs were produced from these mice. GECs were incubated with tunicamycin (TM) to induce ER stress.

Results: Mass spectrometry analysis of TM-stimulated control and IRE1α KO GECs showed that in addition to ER chaperones, proteins in the secretory pathway, including the COPII component Sec23B, were increased in an IRE1α-dependent manner. By immunoblotting, TM enhanced Sec23B and RTN3L expression in control, but not IRE1α KO GECs. By immunofluorescence microscopy, in control GECs, TM increased the biogenesis of LC3 and Sec23B particles, as well as colocalization of Sec23B with LC3 and RTN3L with LC3; increases were attenuated in IRE1α KO GECs. Thus, deletion of IRE1α impaired delivery of COPII vesicles and RTN3L-coated ER fragments to autophagosomes. Knockdown of Sec23B with siRNAs reduced autophagosome formation in TM-treated control GECs. After blocking protein synthesis with cycloheximide, TM stimulated degradation of RTN3L in control GECs, consistent with ERphagy flux, but RTN3L degradation was impaired in IRE1α KO cells. Similarly, TM induced degradation of α3,4,5 collagen IV in control, but not IRE1α KO GECs, suggesting that collagen IV is an IRE1α-dependent ERphagy substrate. In adriamycin nephrosis, where IRE1α activates an adaptive UPR and autophagy, expression of Sec23B and RTN3L was increased in glomeruli of control, but not IRE1α KO mice.

Conclusions: During ER stress, IRE1α redirects a subset of Sec23B-positive COPII vesicles to deliver RTN3L-coated ER fragments to autophagosomes. ERphagy is a novel outcome of the IRE1α pathway in podocytes and may play a cytoprotective role in glomerular diseases.

Funding: Government Support - Non-U.S.

PO1695

ACE Inhibition Modulates Insulin-Like Growth Factor 1 (IGF-1) Filtration to Regulate Compensatory Kidney and Glomerular Hypertrophy

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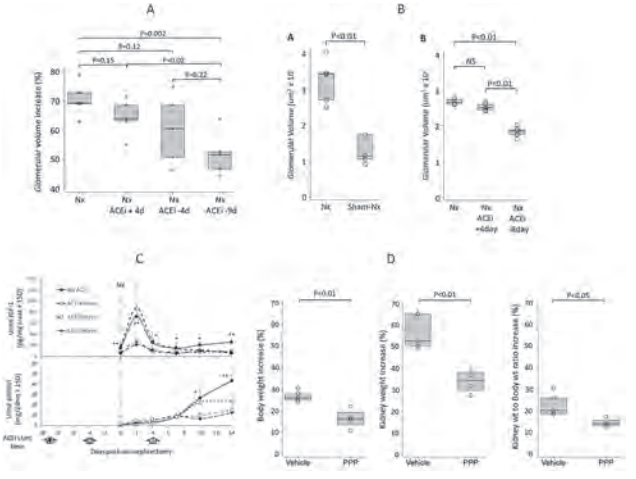
Background: Modeling suggests that preventing glomerular volume (GV) increase could serve as a therapeutic target to mitigate hypertrophy-associated progressive glomerulosclerosis (GS). We, therefore, evaluated how GV is regulated, and how Angiotensin-Converting Enzyme inhibition (ACEi) could reduce compensatory GV increase.

Methods: Uni-nephrectomized (Uni-Nx) wild-type Fischer344 rats were used to model progressive GS triggered by the single kidney state, and the effect of ACEi started either before or after Uni-Nx. Urine IGF ELISA assay, computer-assisted morphometry, single-cell, bulk transcriptomics, immunofluorescence, and human databases were analyzed.

Results: ACEi started *before,* but not *after* Uni-Nx, reduced short (Panel A) and long-term (Panel B) compensatory GV increase, and the associated 8-fold peak of urine IGF-1 post-nephrectomy (Panel C). An IGF-1R inhibitor (picropodophyllin) also reduced compensatory kidney hypertrophy (Panel D). Post-Uni-Nx, a decrease in both serum IGF-1 and glomerular/kidney IGF-1 transcript were noted, and IGFBP3 (the major blood IGFBP) was present in podocyte cytoplasm in the absence of detectable podocyte IGFBP3 transcript, suggesting that IGF-1 and IGF-IGFBP3 complexes had come from blood. A model was developed to predict how IGF-1, IGF-2, and IGF-IGFBP protein complexes would interact with the glomerular filter, and its predictions were confirmed in ERCB database. The importance of hyperfiltered IGF-1 as a driver of glomerular failure in single kidney states was further supported by human kidney allograft half-life analysis.

Conclusions: Hyperfiltered IGF-1 drives compensatory GV increase leading to long-term proteinuria and GS. Timing of ACEi in relation to uni-Nx can reduce both IGF-1 hyperfiltration and GV increase, thereby prolonging single kidney lifespan.

Funding: NIDDK Support



PO1696

Angiotensin II Induces Oxidative Podocyte Injury via the Upregulation of Nox4

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Background: Angiotensin II (Ang II) induces glomerular and podocyte injury via systemic and local vasoconstrictive or non-hemodynamic effects including oxidative stress. The release of free radicals from podocytes may participate in the development of glomerular injury and proteinuria. We studied the pathophysiologic roles of oxidative stress in Ang II-induced podocyte apoptosis.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times and transfected by Nox4 or AT1R siRNAs or negative control scrambled siRNA for 24 h. The changes of podocyte oxidative stress and apoptosis were observed by confocal imaging, western blotting, realtime PCR, FACS and TUNEL assay according to the presence of Ang II.

Results: Ang II increased the generation of superoxide anions and intracellular reactive oxygen species levels but suppressed superoxide dismutase activity that was reversed by an antioxidant, probucol. Ang II also increased Nox4 protein and expression in podocytes, measured using western blotting and real-time PCR analysis that was also reversed by probucol. Nox4 suppression by small interference RNA (siRNA) reduced the oxidative stress induced by Ang II. These results suggest that Ang II induced oxidative stress via the upregulation of Nox4 protein in a transcriptional mechanism. Ang II promoted podocyte apoptosis that was reduced significantly by probucol and Nox4 siRNA. Ang II-induced podocyte apoptosis were also recovered by Ang II type 1 receptor (AT1R) siRNA.

Conclusions: Our findings suggest that Ang II induced podocyte oxidative stress and apoptosis through AT1R and Nox4. These findings suggest that Ang II promoted podocyte oxidative stress and apoptosis through AT1R and via the upregulation of Nox4, which could be preventive by Nox4 inhibition and/or antagonizing AT1R as well as antioxidants.

PO1697

Anillin Serves a Protective Function in a Mouse Model of HIV-Associated Nephropathy

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Background: HIV associated nephropathy (HIVAN) is characterized by a rapid progression to end stage kidney disease with limited treatment options. We previously demonstrated that mutations in the gene encoding anillin (*ANLN)* can cause FSGS and showed that ANLN is upregulated in the glomerulus of HIVAN patients as well as the HIVAN Tg26 mouse model. ANLN is an F-actin binding protein that affects cell proliferation and survival, two cell processes that are predicted to play a key role in the phenotype associated with HIVAN. We hypothesized that ANLN upregulation is one of the drivers of glomerular disease in HIVAN mice, therefore modulating ANLN expression may present an alternative therapeutic strategy for HIVAN.

Methods: To evaluate the therapeutic potential of reduced functional ANLN in a HIVAN mouse model, we created a mouse line using CRISPR Cas9 mediated gene editing that contains an early stop codon in the *Anln* gene (ANLNx). We then bred heterozygous ANLNx mice with Tg26 HIVAN mice and evaluated proteinuria and mortality over 16 weeks for each genotype. Sclerotic glomeruli from 3 mice in each group were evaluated and quantified at 16 weeks of age by pathologists blinded to genotype.

Results: There was no improvement in glomerular disease phenotype associated with the reduction of functional ANLN in the Tg26 HIVAN model. Urine albumin and creatinine ratio at 8, 12, and 16 weeks were similar between double ANLNx Tg26 heterozygotes compared to Tg26 HIVAN mice (p=1.038, 0.0863. 0.0761 for each time-point). Mice heterozygous for both the ANLNx and Tg26 alleles also did not display any increase in survival compared to mice carrying only the Tg26 allele (p=0.361). Evaluation and scoring of PAS stained kidney sections by independent pathologists revealed similar levels of sclerosis between Tg26 HIVAN mice and mice heterozygous for both the ANLNx and Tg26 alleles.

Conclusions: Genetic ablation of ANLN does not improve kidney disease phenotypes in Tg26 HIVAN mice. ANLN upregulation likely represents a survival mechanism in Tg26 HIVAN mice and not a cause of injury.

Funding: NIDDK Support

PO1698

The Role of LRP1 in Podocytes

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Background: Recent studies have demonstrated the importance of endocytosis for podocyte health. However, little is known about the function of the internalized cargo proteins. We investigated the role of the low-density lipoprotein receptor-related protein 1 (LRP1), a large endocytic scavenger receptor, in podocytes *in vitro* and *in vivo*.

Methods: We used immunoblotting and -fluorescence to determine quantity and localization of LRP1 in cultured human podocytes. siRNA knockdown (KD) of LRP1 and an antagonist were used to investigate potential functional importance *in vitro*. We used zebrafish morpholino knockdown models of LRP1 homologs to study the function of LRP1 *in vivo*. LRP1 expression in healthy and diseased human renal tissue was determined by immunohistochemistry.

Results: LRP1 is highly expressed in cultured podocytes where it localizes to the membrane and perinuclear region. It colocalizes with early and late endosomes, in line with its role in endocytic trafficking. Interaction with β1-Integrin (ITB1) was confirmed by immunoprecipitation and colocalization. siRNA KD of LRP1 resulted in a reduction of podocyte number and cell size. Morpholino KD of both Lrp1 isoforms in zebrafish led to pericardial effusion and generalized edema, hinting at a renal phenotype. Interestingly, LRP1 has nearly absent baseline expression in healthy human glomeruli. Glomerular expression is significantly increased in human biopsies of various podocytopathies. However, LRP1 does not colocalize with the podocyte marker nephrin in human tissue.

Conclusions: LRP1 is a highly expressed endocytic receptor in cultured podocytes. Aberrant LRP1 function caused by siRNA KD or pharmacological inhibition resulted in disarrangement of podocyte shape, implicating a crucial role in adhesion and cytoskeletal regulation *in vitro*. Colocalization and immunoprecipitation with ITB1 suggests involvement in integrin trafficking. The importance of LRP1 for kidney function is corroborated by our zebrafish experiments where Lrp1 silencing led to a renal phenotype. Since glomerular LRP1 expression is increased in proteinuric diseases, it could function as a mediating or compensating factor in glomerular injury. However, its absence from podocytes *in vivo* makes its function for podocytes outside of the culture environment unclear. Our findings thus exemplify the difference in podocyte adhesion regulation between podocytes *in vitro* and *in vivo.*

Funding: Private Foundation Support, Government Support - Non-U.S.

PO1699

Dach1 Is Essential for Maintaining Normal Podocytes

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Background: Dach1 is a transcription factor, determining cell fates in various organs. Dach1 polymorphism has been reported to be associated with nephrotic syndrome and chronic kidney diseases. We previously found that Dach1 was highly expressed in normal podocytes and rapidly disappeared after induction of podocyte injury, similarly to WT1. We aimed to elucidate the function of Dach1 in podocytes *in vivo*.

Methods: Because *Dach1* null mice die shortly after birth, kidneys were harvested at P0 and histologically examined. To study the role of Dach1 in mature podocytes, podocyte-specific *Dach1* deleted mice were generated by mating *Dach1*$^{fl/fl}$ mice with *Nphs1*-Cre or *Nphs2*-CreERT2 mice. Eleven *Nphs1*-Cre/*Dach1*$^{fl/fl}$ mice were analyzed at 8-35 weeks of age. 14 *Nphs2*-CreERT2/*Dach1*$^{fl/fl}$ mice were treated with tamoxifen (0.1mg/g BW/day, p.o. 5 days 3 courses) and analyzed 7 days later.

Results: In neonatal wild-type mice, Dach1 is faintly expressed in the cap mesenchyme and increased in the renal vesicles/S-shaped bodies and further intensified and concentrated in mature podocytes. Dach1 is also intensely expressed in the ureteric bud. In *Dach1* null mice, negative Dach1 staining was confirmed. Kidneys of *Dach1* null mice were 14.2 % smaller than those of control mice but showed normal structure. Podocytes in *Dach1* null mice showed normal phenotypes in SEM and TEM with normal slit membrane, and no abnormal leakage of albumin. Immunostaining for WT1, nephrin, podocin, synaptopodin and nestin was normal. Only a small number of podocytes lacked Dach1 staining in *Nphs1*-Cre/*Dach1*$^{fl/fl}$ and *Nphs2*-CreERT2/*Dach1*$^{fl/fl}$ mice, indicating inefficient Cre-mediated recombination. Nevertheless, all *Nphs1*-Cre/*Dach1*$^{fl/fl}$ exhibited abnormal albuminuria (UACR 4.7±1.6 mg/mg vs 0.06±0.007), which increased with age, and seven (63%) mice showed FSGS. Seven (50%) *Nphs2*-CreERT2/*Dach1*$^{fl/fl}$ mice exhibited abnormal albuminuria, and three (21%) mice showed early sclerotic lesions. Immunostaining showed that sclerotic lesions lacked Dach1 as well as WT1, synaptopodin and nephrin. Most of Dach1 negative podocytes in non-sclerotic glomeruli had normal staining for podocyte marker proteins.

Conclusions: These results indicate that Dach1 does not determine the fate of differentiation into podocytes but is indispensable for maintaining normal integrity of mature podocytes.

Funding: Government Support - Non-U.S.

PO1700

TAZ Is Important for Structural and Functional Integrity of Podocytes

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Background: Podocyte is an important component of glomerular filtration barrier (GFB). Maintenance of integrity of slit-diaphragm(SD) structure is critical for normal kidney function. Podocytes lost most epithelial cell tight junction components except for Zonula occludens-1 and -2 (ZO-1 and ZO-2). In podocytes, ZO-1 is an important binding partner of Neph1, and mice with podocyte-specific ZO-1 deletion showed significant growth retardation and severe proteinuria starting at 2 weeks of age, but the regulation of ZO-1 expression in podocytes are not clear. TAZ (transcriptional coactivator with PDZ-binding motif) and its paralog Yes-associated protein (YAP) are two crucial effectors of Hippo signaling pathway. Recent study has shown that podocyte-specific YAP deletion causes FSGS and progressive renal failure, but the potential role of TAZ in podocytes has not been studied.

Methods: Mice with podocyte-TAZ deletion (TAZ^{podKO}) were generated by crossing TAZ$^{flox/flox}$ mice with podocin-Cre recombinase transgenic mice. Urinary albumin excretion and kidney histology and podocyte number per glomerulus were evaluated in TAZ^{podKO} and WT mice. Immunoblotting analysis of isolated glomerulus lysates of TAZ^{podKO} or TAZ^{podWT} mice were performed. In primary cultured mouse podocytes and immortalized mouse podocytes cell morphology and cell lysates were evaluated after silencing TAZ with specific siRNAs.

Results: 41.7% of TAZ^{podKO} mice develop mild proteinuria at age of 3-4 weeks (n=36), with a urine albumin/creatinine ratio of 89.57 ± 12.67 vs 27.86 ± 1.55 (μg/mg, n=7). At 9 weeks of age, compared to TAZ^{podWT} mice, the glomeruli of TAZ^{podKO} mouse kidney had focal sclerosis and significant podocyte loss (WT1+ cells: 13.23 ± 0.699 vs. 17.85 ± 0.608 (n=13). Expression of Bcl2, ZO-1, ZO-2 and synaptopodin were decreased, but expression of cleaved-caspase 3 in the isolated glomeruli from TAZ^{podKO} mice compared with TAZ^{podWT} mice. In cultured podocytes, silencing TAZ by siRNA altered cell morphology and F-actin distribution, and downregulation of Bcl2, ZO-1, ZO-2 and synaptopodin expression and up-regulation of cleaved-caspase 3 expression.

Conclusions: This study demonstrates that TAZ expression plays an important role in regulating podocyte structural protein expression, which cannot be compensated by its paralogue YAP.

Funding: NIDDK Support, Other NIH Support - American Diabetes Association

PO1701

Neurexin1α Containing Splice Site 4 Interacts with Nephrin and Contributes to Maintenance of the Integrity of Podocyte Slit Diaphragm

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Background: Neurexins (NRXNs) are synaptic cell adhesion molecules having essential roles in the assembly and maturation of synapses. It is known that NRXN1α contains 6 splicing sites (SS)s, and multiple splicing variants were diffusely expressed in neuronal tissues. We have previously reported that NRXN1α is expressed at slit diaphragm (SD), a cell-cell junction of podocyte, and is downregulated in injured podocytes. The report also showed that NRXN1α expressed in podocytes is a unique variant containing SS1, 3, 4, and 5, which is a rare variant in neural tissues (Am J Physiol, 300:R340, 2011). However, the role of NRXN1α at SD is not well understood yet.

Methods: The interaction of NRXN1α with SD-associated molecules was analyzed by the immunoprecipitation (IP) assay. The function and structure of SD of NRXN1α KO mice were precisely analyzed.

Results: The interaction of NRXN1α with SD molecules such as nephrin and ephrin-B1 was detected by the IP assay with rat glomerular lysates. IP assay with the HEK cell expression systems showed NRXN1α containing SS4 interacted with nephrin, but NRXN1α lacking SS4 did not. The interaction between NRXN1α and nephrin was dissociated, if nephrin was phosphorylated. The interaction of NRXN1α with ephrin-B1 was not detected in the HEK system, suggesting NRXN1α interacts with ephrin-B1 via nephrin. Abnormal proteinuria (92.1 mg/day vs. 23.8 mg/day, $p<0.05$) and clear alterations in the expression of major SD components including nephrin, ephrin-B1 and podocin were detected at the age of 20 weeks of NRXN1α KO mice (IF score; nephrin, 2.68 vs. 3.83, $p<0.05$: ephrin-B1, 2.68 vs. 3.84, $p<0.05$: podocin, 2.78 vs. 3.58, $p<0.05$), although these alterations were not detected at the age of 10 weeks. The phenotypes of the KO mice suggest NRXN1α does not play a major role for formation of SD but contributes to the maintenance of the integrity of SD at an elderly age.

Conclusions: Neurexin1α containing SS4 interacts with nephrin, and is a novel SD component. NRXN1α contributes to maintenance of the function and the molecular integrity of SD. It is conceivable that downregulation of NRXN1α participates in the development of podocyte injury onset at an elderly age.

Funding: Government Support - Non-U.S.

PO1702

Possible Role of the Cytosolic RNase Inhibitor in Maintaining the Integrity of the Glomerular Filtration Barrier

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Background: The ribonuclease inhibitor (RI) is a cytoplasmic protein encoded by the *RNH1* gene. The RI forms a tight non-covalent bond with members of the RNaseA superfamily and therefore it's considered that its main function is to act as a sentinel for dysregulated RNases. The ratio of RI to substrate has also been shown to vary according to the proliferative and metabolic status of the cell suggesting that the balance in the protein-protein interactions between the RI and its substrates plays a role in maintaining cell homeostasis by impacting processes such as protein synthesis and various signaling pathways. However, the entirety of the biological roles fulfilled by the RI are yet to be described.

Methods: Immunofluorescence staining of human kidney tissue and protein detection by western blot from samples of immortalized podocytes were carried out to confirm the presence of the RI in glomerular cells. As an initial injury model, podocytes were treated with PAN to determine if changes in RI expression occur as a response. RNH1 inhibition was performed in a transgenic zebrafish line that allows for the detection of proteinuria via a GFP-tagged protein in the circulation. At 96hpf the severity of the edema phenotype and the fluorescence levels were recorded.

Results: Our preliminary data shows that the RI is present in human podocytes both in vitro and in vivo, as its expression domain coincides with glomerular cells labelled with synaptopodin. Additionally, the RI is present in cultured podocytes both before and after the temperature shift used to induce quiescence, and it appears to increase after differentiation. There is also expression modulation of RNH1 in response to PAN treatment of podocytes. In our zebrafish model, RNH1 knockdown resulted in up to a 40% increase in mild to severe edema and over 30% decrease in fluorescence suggesting that a reduction in RI might compromise the filtration barrier enough to lead to proteinuria.

Conclusions: Taken together our initial data show a promising avenue for research where the balance between members of the RNaseA superfamily and their cytoplasmic inhibitor may represent a powerful mechanism that allows the cells to modulate the proteome in response to stimuli. An imbalance in this relationship might ultimately affect the integrity of the cells in the kidney.

Funding: Government Support - Non-U.S.

PO1703

Atypical Caspase 3-Dependent Death in Podocytes

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Background: Apoptosis of podocytes has been widely reported in many *in vitro* studies, but definitive apoptosis has never been documented *in vivo* podocytes. To elucidate this discrepancy, we analyzed dying process in podocytes *in vitro* and *in vivo*.

Methods: Primary mouse podocytes were transiently transfected with hCD25 and EGFP expression plasmids and treated with a hCD25-targeting immunotoxin, LMB2 (1nM), and observed 1 day later. In some experiments, the cultured podocytes were transfected with Bak1 or Bax siRNA before treatment with LMB2. In *in vivo* experiments, podocyte injury was induced by injecting LMB2 (1.25ng/gBW) into NEP25 mice, which express hCD25 in podocytes, and analyzed 7 days later.

Results: In *in vitro* studies, administration of LMB2 caused loss of co-introduced EGFP in 56.8±13.6%, incorporation of propidium iodide in 13.6±2.5%, activation of caspase 3 (Casp3) in 19.6±2.6% and TUNEL staining in 4.5±1.3% without significant increase in LDH activity in the culture medium. These phenomena were not observed in cells without hCD25 or without LMB2. Ac-DEVD-CHO (10μM), a Casp3 inhibitor, attenuated the loss of EGFP by 38.2%. Inhibition of Bak1 and Bax using siRNAs attenuated EGFP loss by 77.6% and 28.4%, respectively. These indicate that LMB2 induced the typical Casp3 dependent intrinsic apoptosis in podocytes *in vitro*. In *in vivo* studies, kidneys of NEP25 mice contained podocytes positive for cleaved (c) Casp3 and those for cLaminA, a product of Casp3, but no TUNEL+ podocytes. EM analysis showed no apoptotic body, but occasionally rupture of plasma membrane of podocytes. The urinary sediments contained podocalyxin-positive podocytes (2.5±0.3/μl). Among these, 39.1±3.7% were stained for cCasp3 and 21.7±5.5% were stained for TUNEL. To evaluate the effect of glomerular filtration, NEP25 mice were similarly injected with LMB2 and subjected to UUO 1 day before sacrifice. The obstructed kidney contained significantly more cLaminA+ podocytes than the contralateral kidney. In addition, detaching podocyte cell bodies were frequently observed in the contralateral kidney by SEM analysis, but never in the obstructed kidney.

Conclusions: Thus, due to physical force of glomerular filtration, podocytes doomed to Casp3 dependent death are quickly lost by detachment or plasma membrane rupture before completing full apoptotic processes. This accounts for the absence of podocyte apoptosis *in vivo*.

PO1704

Mice Deficient in Aminopeptidase A Have Worse Glomerular Injury in Response to Chronic Renal Mass Reduction

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Background: Aminopeptidase A (APA) is a membrane-bound metalloproteinase expressed in podocytes and tubular epithelia. It is a key enzyme in metabolizing angiotensin (Ang) II and diverting Ang I from the formation of Ang II. A recent finding suggests that APA also plays a role in the maintenance of glomerular structure. We have previously shown that global deficiency in APA augmented albuminuria in the early phase of remnant nephropathy. We sought to determine the effect of APA deficiency in a later phase of remnant nephropathy.

Methods: We measured urinary albumin (Alb) and creatinine (Cr) excretion, podocyte morphology and kidney histopathology in 129Sv/C57Bl6 wild type (WT, n=6) and APAKO mice (n=6) subjected to renal mass reduction. Twenty-four hour (24h) urine collections were obtained prior to, and then 2, 4, 6 and 8 weeks following 5/6 nephrectomy. Podocyte density was assessed by immunofluorescence utilizing synaptopodin and Dachshund Family Transcription Factor 1 as podocyte markers.

Results: Baseline median UAlbV was 15 (13-24) and 16 (11-46) μg/24 for the WT and APA mice respectively. Renal mass reduction induced albuminuria in both groups at 2 weeks. However, 24h albumin excretion (UAlbV) was markedly higher for the APAKO compared to the WT mice at all time points post 5/6 nephrectomy ($p = 0.0035$). Median UAlbV at 8 weeks was 104 (33-536) and 1556 (1154-3890) μg/24 ($p=0.0159$) for the WT and APAKO mice. Similar findings were observed when albumin levels were expressed as urine Alb/Cr. The percentage of glomeruli with segmental or global hyalinosis/sclerosis was greater for APAKO mice compared to the WT (36% vs. 4%, $p<0.01$). Further, APAKO mice had a higher level of glomerular collapse (32% vs. 2%, $p<0.005$), parietal epithelial hyperplasia (pseudo-crescents) (28% vs. 2%, $p<0.01$), and a greater degree of tubular injury and microcystic tubular dilatation (45% vs. 5%, $p<0.01$). Affected glomeruli from APAKO mice showed a marked decrease in podocyte number ($p<0.01$). Among glomeruli with preserved architecture, podocyte size was reduced in APAKO mice ($p<0.001$). Neither BUN nor plasma Ang II levels were different between the 2 groups at 8 weeks.

Conclusions: Our findings further support a role for APA in attenuating glomerular injury following 5/6 renal ablation.

Funding: Private Foundation Support

PO1705

Glomerular Endothelial Cell-Derived MicroRNA-192 Regulates Podocyte Nephronectin in Membranous Glomerulonephritis

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Background: Autoantibodies binding to podocyte antigens cause idiopathic membranous glomerulonephritis (iMGN). It remains elusive how autoantibodies reach the subepithelial space because the glomerular filtration barrier (GFB) is normally size-selective and impermeable for antibodies.

Methods: Kidney biopsies from patients with iMGN, cell culture, zebrafish and mice models were used to investigate the role of nephronectin (NPNT) regulating microRNAs (miRs) for the GFB.

Results: Glomerular endothelial cell (GEC)-derived miR-192-5p and podocyte-derived miR-378a-3p are upregulated in glomeruli of patients with iMGN whereas NPNT expression is reduced. Overexpression miR-192-5p as well as morpholino-mediated npnt knockdown induced edema, proteinuria and podocyte effacement similar to podocyte-derived miR-378a-3p in zebrafish. Moreover, structural changes of the glomerular basement membrane (GBM) with increased lucidity, slicing and lamellation especially of the lamina rara interna similar to ultrastructural findings seen in advanced stages of iMGN were found (Fig. 1). IgG size nanoparticles accumulated in lucidity areas of the lamina rara interna and lamina densa of the GBM in npnt knockdown zebrafish models. Loss of slit diaphragm proteins and severe structural impairment of the GBM were further confirmed in podocyte-specific Npnt knockout mice. GECs downregulate podocyte NPNT by secretion of miR-192-5p containing exosomes in a paracrine manner.

Conclusions: Podocyte NPNT is important for proper GFB function and GBM structure and is regulated by GEC-derived miR-192-5p and podocyte-derived miR-378a-3p. We hypothesize that loss of NPNT in the GBM is part of the pathophysiology of iMGN and enables subepithelial immune complex deposition in iMGN.

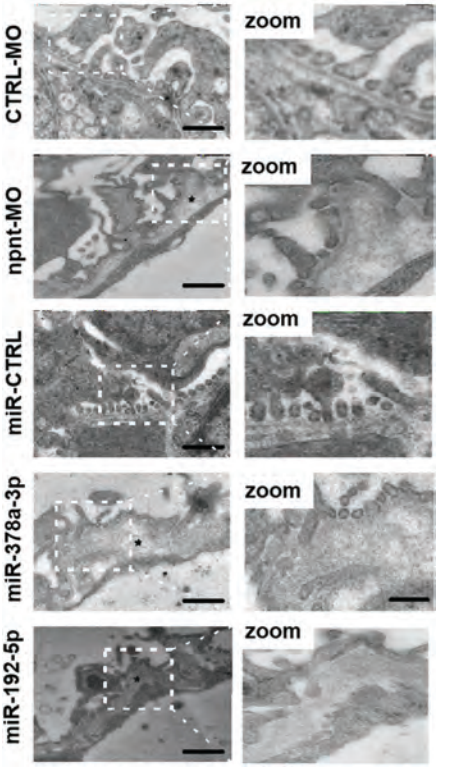

Fig. 1

PO1706

Identification of the Mechanism Underlying the Toxicity of Systemically Administered miR-145-5p on Podocytes Based on Podocyte Essential Genes

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Background: MicroRNAs are emerging as effective therapeutic agents. MiR-145-5p dysregulation has been shown to be involved in kidney injury. To determine whether supplement of miR-145-5p would alleviate kidney injury in mouse models, we first tested the miR-145-5p enriched extracellular vesicles (miR-145-5p EVs) sample for toxicity or side effects on healthy control mice.

Methods: miR-145-5p EVs were injected to mice intravenously every day for a total of 6 days. A group of mice were simultaneously injected with miR-145-5p inhibitor using TransIT®-EE Delivery Solution. Cultured cells were transfected with RNAiMAX or Fugene.

Results: miR-145-5p EVs resulted in proteinuria and podocyte foot process effacement in normal control mice, and this effect was abolished by miR-145-5p inhibitor. We demonstrated that systemically administered miRNA can enter podocytes. miR-145-5p EVs could enter cultured podocytes and cause F-actin loss. miR-145-5p mimic caused a similar reduction of F-actin in the cells. We speculated that miR-145-5p is toxic to podocytes because it is not normally expressed in podocytes and exogenous miR-145-5p can effectively target genes essential for podocytes. By using the concept that genes commonly expressed in all individual podocytes are likely podocyte essential genes, we predicted 611 podocyte essential genes when expression cutoff was set as > 0.1 RPKM. We found that 32 of them are predicted to be targeted by miR-145-5p. Functional annotation of the 32 genes revealed small GTPase mediated signal transduction as the top function. Among genes associated with the small GTPases pathway, Arhgap24 is known to cause podocyte injury and regulate Rac1/Cdc42 activities, and we found miR-145-5p significantly repressed Arhgap24 expression in podocytes *in vivo* and *in vitro*. miR-145-5p- increased activity of both Rac1 and Cdc42.

Conclusions: MiR-145-5p induced podocyte injury through targeting podocyte essential genes associated with small GTPase mediated pathway. Our study provides a novel approach to investigate how a miRNA affects a given cell type, allowing not only identification of the molecular mechanism underlying an observed side effect of a miRNA drug but also prediction of miRNA drug toxicity on various cell types.

Funding: Government Support - Non-U.S.

PO1707

Glomerular mRNAs Are Alternatively Spliced and Polyadenylated During Podocyte Injury in Animal Models of Nephrotic Syndrome

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Background: Glomerular disease, often manifesting as nephrotic syndrome (NS) with high proteinuria, is characterized by podocyte loss and injury. Furthermore, alternative mRNA processing, such as alternative splicing (AS) and alternative polyadenylation (APA) play important roles in physiology, development, and disease; however, there is very limited knowledge of their roles in glomerular disease. We hypothesized that AS and APA events of glomerular RNAs is associated with podocyte injury and proteinuria in NS.

Methods: Glomerular damage characterized by proteinuria was induced by puromycin aminonucleoside (PAN) or adriamycin (ADR) to mimic human minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), respectively. Urine and serum chemistries, kidney histology and glomerular RNA-seq analyses were performed. APATrap and JunctionSeq bioinformatics analyses software were used to detect APA and AS glomerular events. Correlation of differentially expressed genes (DEGs) was performed with known glomerular disease genes and polyadenylation and splicing factors.

Results: Robust proteinuria was induced in both PAN-MCD and ADR-FSGS models, accompanied by hypoalbuminemia, hypercholesterolemia and histological alterations in the kidneys (protein casts and podocyte hypertrophy). Out of 13,265 genes, MCD model resulted in 1033 and FSGS model in 1308 glomerular DEGs with abs(log2FC)>1 and P_{adj}<0.05. Of 80 analyzed genes with established roles in glomerular disease, 30 were altered in both MCD and FSGS. Significant APA was identified in 71 and 746 genes in MCD and FSGS nephrosis, respectively, and of 173 polyadenylation factors analyzed, 21 were altered in MCD and 24 in FSGS. Significant AS was identified in 136 and 1875 genes in MCD and FSGS models, respectively. In accordance, of 50 splicing factors analyzed, 3 were altered in MCD and 5 in FSGS. Specifically, the identified APA and AS events affected genes of the slit diaphragm complex such as *Nphs1, Nphs2, and Tjp1,* which are critical determinants of podocyte structure and function.

Conclusions: Association of global glomerular mRNA alteration due to AS and APA with podocyte and glomerular injury is a newly recognized phenomenon, with potential implications for therapy and molecular understanding of the disease.

Funding: Other NIH Support - NIH Clinical and Translational Science Award to The Ohio State University (Award Number UL1TR002733 from the National Center for Advancing Translational Sciences), Private Foundation Support

PO1708

Continuous Non-Mutagenic DNA Damage in Podocytes Activates Inflammatory Response and May Accelerate Kidney Aging

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Background: Podocytes are suggested to contribute to kidney aging because of their terminally differentiated features. We have previously reported the association of KAT5-mediated DNA damage repair with altered DNA methylation in podocytes (Cell Rep 2019). However, the role of podocyte DNA damage itself on DNA methylation changes and kidney aging has remained to be adequately elucidated.

Methods: To investigate the significance of DNA double-strand breaks (DSBs) in podocytes, we generated podocyte-specific I-PpoI-expressing mice (podocin-Cre ROSA26-STOP- I-PpoI). I-PpoI is a homing endonuclease which causes non-mutagenic DSBs. RNA-seq and MeDIP-seq analysis were performed using isolated podocytes in I-PpoI mice and wildtype controls.

Results: I-PpoI mice showed severe albuminuria (WT 43±34.4 mg/gCr, Ip-Po1 2224±7.3 mg/gCr, p<0.01) with diffuse foot process effacement in podocytes but glomerulosclerosis and interstitial fibrosis were not observed at 12 weeks of age. Interestingly, infiltration of CD11b-positive cells was shown in I-PpoI mice, which is a similar finding in 2-year-old aged mice. The aged mice showed increased DNA damage and DNA methylation. In I-PpoI mice, rapid deterioration of renal function with glomerulosclerosis and tubulointerstitial fibrosis developed around the age of 20 weeks. RNA-seq analysis revealed that inflammatory-related genes were upregulated in podocytes of I-PpoI mice. Senescent-associated secretory phenotype (SASP)-related gene expression was also increased. MeDIP-seq analysis revealed that 5219 differentially methylated regions (DMRs) were identified in I-PpoI mice compared with controls. Interestingly, there was no significant correlation between the distance from the I-PpoI cutting site and DMRs. DNA methylation was increased in genes containing I-PpoI cutting sites or podocyte epithelial genes such as nephrin and podocin, whereas it was decreased in inflammatory related genes, suggesting gene-specific DNA methylation changes following DNA damage.

Conclusions: The phenotype of the I-PpoI mice may reflect one aspect of accelerated kidney aging. Repeated DNA damage repair in podocytes may cause altered DNA methylation independent of primary DNA damaged sites with promoted inflammation and podocyte morphological changes.

PO1709

Deletion of MCP-1 in Podocytes Does Not Protect Against Glomerular Injury

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Background: Over the past three decades, the global burden of chronic kidney disease (CKD) has nearly doubled straining healthcare budgets. Understanding the role of podocytes in the pathophysiology of proteinuric disease is important for development of novel treatments. Prior studies implicate monocyte chemoattractant protein-1 (MCP-1) in podocyte injury, but the source of MCP-1 has not been definitely identified. Both MCP-1 and its cognate receptor, CCR2, are expressed in podocytes. Therefore, using podocyte-specific MCP-1 knockout mice (PODO-MCP-1$^{-/-}$), we evaluated whether autocrine MCP-1 signaling by podocytes contributes to proteinuric CKD.

Methods: PODO-MCP-1$^{-/-}$ mice were generated by crossing MCP-1 floxed mice with mice harboring Cre recombinase under the control of the podocin promoter. Knockout mice and wild-type littermates were subjected to angiotensin II by osmotic minipumps (Ang II; 1.5mg/kg/day) for 28 days. Weekly spot urines were collected, assessed with ELISA for albuminuria, and results normalized to urinary creatinine. After 28 days, kidneys were harvested and histologic, immunofluorescent, immunoblot, and quantitative PCR analyses were performed. Results are reported as mean ± S.E.M. Threshold for significance was P<.05.

Results: There were no baseline differences in bodyweight, histology, and urinary albumin levels between the two groups. Following 28 days of Ang II infusion, histologic analysis revealed renal pathology particularly glomerulosclerosis. There were no significant differences in bodyweight, albuminuria, renal function, expression of nephrin and WT1, and number of podocytes. *Ccr2* gene expression also revealed no significant difference.

Conclusions: Our results demonstrate that podocyte-specific MCP-1 production is not a major contributor to Ang II-induced glomerular injury as demonstrated by lack of protection in the podocyte-specific MCP-1 knockout mice. Future studies will evaluate other sources of MCP-1 that may impact disease.

Funding: NIDDK Support, Private Foundation Support

PO1710

Delayed Treatment with a Novel Highly Selective Small-Molecule Agonist of MC5R Attenuates Podocyte Injury and Proteinuria in Puromycin Aminonucleoside Nephrosis

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Background: Clinical studies indicate that the melanocortin peptide ACTH is effective in inducing remission of nephrotic glomerulopathies like MCD and FSGS, even those resistant to steroids, suggesting that a steroid-independent melancortinergic mechanism might contribute. However, the type of melanocortin receptor (MCR) that conveys this beneficial effect as well as the underlying mechanisms remains controversial. Recently, burgeoning evidence suggests that MC5R is likely involved in glomerular pathobiology. This study aims to test the effectiveness of a novel highly selective MC5R agonist (MC5RA) in puromycin aminonucleoside (PAN) nephrosis.

Methods: MC5RA was generated by N-terminal modification of the melanocortin core tetrapeptide His-D-Phe-Arg-Trp-NH2 with an aromatic group, resulting in a triphenylpropionyl melanocortin analog with a 100-fold selective agonistic activity on MC5R. Rats were injured with a tail vein injection of PAN, and 5 days later, were randomized to daily MC5RA or vehicle treatment.

Results: Upon PAN injury, rats developed heavy proteinuria on day 5, entailing an established nephrotic glomerulopathy. Following vehicle treatment, proteinuria continued to progress on day 14 and was sustained till day 21, accompanied by evident histologic signs of podocytopathy, marked by ultrastructural lesions of glomeruli, including extensive effacement of podocyte foot processes and podocyte microvillus transformation, and concomitant with loss of podocyte homeostatic markers, such as synaptopodin and nephrin, and *de novo* expression of podocyte injury marker desmin. Rescue treatment with MC5RA significantly attenuated urine albumin excretion and mitigated the loss of podocyte marker proteins, resulting in improved podocyte ultrastructural changes. *In vitro* in cultured podocytes, MC5RA prevented the PAN-induced disruption of actin cytoskeleton integrity and apoptosis. Mechanistically, MC5RA treatment reinstated inhibitory phosphorylation and thus averted hyperactivity of GSK3β, a convergent point of multiple podocytopathic pathways, in PAN-injured podocytes *in vitro* and *in vivo*.

Conclusions: Pharmacologic targeting of MC5R by using the highly selective small-molecule agonist is likely a promising and feasible therapeutic strategy to improve proteinuria and podocyte injury in glomerular disease.

Funding: NIDDK Support

PO1711

Tadalafil, a PDE5 inhibitor, Exhibits Renoprotective Effects Preventing Podocyte Damage in an Adriamycin-Induced Nephrotic Syndrome Model

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Background: Phosphodiesterase (PDE)-5 inhibitor is reportedly a renoprotective compound. Although PDE5 expression is confirmed in the glomeruli, its relationship with renal dysfunction remains elusive. We have previously investigated the renoprotective effects of tadalafil in a CKD model (Tomita N, et al. *Physiol Rep.* 2020), suggesting that such an effect would be related to podocyte damage attenuation. In this study, we investigated how tadalafil, a PDE5 inhibitor, could affect a rat nephrotic syndrome model.

Methods: Wistar ST rats were established as nephrotic syndrome models by administrating adriamycin (ADR) injection. The animals were divided into 3 groups: control (n = 6), ADR (n = 5), and ADR + tadalafil (n = 5). Tadalafil was administered 10 mg/kg daily. After 2 weeks of treatment, the urinary protein and serum albumin levels were evaluated, and the kidney tissue was harvested. WT1-positive cells were identified as podocytes by WT1 immunostaining. Moreover, human renal glomerular epithelial cell damage was induced *in vitro* by ADR supplementation. After 24 h of ADR treatment with or without tadalafil, cell viability was determined using CCK-8.

Results: The ADR injection induced high urinary protein and low serum albumin levels. Two weeks of tadalafil treatment attenuated proteinuria compared to the ADR group ($P<0.01$). ADR reduced the WT1-positive cell number and the tadalafil treatment prevented the reduction ($P<0.05$). Moreover, the ADR treatment resulted in reduced cell viability *in vitro*. The tadalafil treatment improved cell viability compared to the ADR treatment only ($P<0.05$).

Conclusions: This study suggests that the treatment with tadalafil, a PDE5 inhibitor, could effectively prevent podocyte damage in the case of nephrotic syndrome.

PO1712

Targeting mTOR Signaling Improved Kidney Function in APOL1 Risk Variant Mice with Chronic Exposure to Inflammatory Stimuli

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Background: Inheriting two copies of APOL1 risk variants significantly increases the likelihood of developing chronic kidney disease in African Americans. Many different mechanisms of disease have been proposed using cell-based model systems. Here we try to understand risk variant pathophysiology using a transgenic mouse model.

Methods: Transgenic mice with a single copy of human APOL1 G0 and G2 were generated using bacterial artificial chromosome (BAC) on a FVB background. Mice were injected with interferon gamma (IFN-g) plasmid via hydrodynamic tail vein injections to induce APOL1 expression. Since mTOR activation has been frequently observed in podocytes during FSGS, we blocked the pathway using rapamycin to see if it could improve disease outcomes. Mice were injected with 2mg/kg of rapamycin every other day (3 days/week, intraperitoneally) for a total of 2 weeks. Paraffin embedded tissue sections were used for immunohistochemistry and Periodic acid–Schiff (PAS) staining. Glomerular isolations were performed using Dynabeads. APOL1 oligomerization was assessed using blue native PAGE.

Results: 7 Days after IFN-g plasmid injection, the podocytes of G2 mice stained positive for phospho-S6 ribosomal protein indicating mTOR activation accompanied by proteinuria. Blocking mTOR activation using rapamycin reversed ribosomal protein S6 phosphorylation, reduced proteinuria, and improved tissue histology as seen by PAS staining. We hypothesized that rapamycin might be activating autophagy and clearing APOL1 oligomers, but found no evidence for this mechanism of rescue. Instead, we were able to replicate the rescue we had observed with rapamycin using a cell cycle inhibitor, suggesting that rapamycin might be rescuing G2 phenotype by inhibiting podocyte cell cycle entry downstream of risk variant mediated injury.

Conclusions: Persistent expression of APOL1 risk variants pushes podocytes into cell cycle entry. Inhibiting mTOR signaling and subsequent cell cycle entry alleviated injury.

Funding: Other NIH Support - NIMHD, Other U.S. Government Support

PO1713

Plin5 Deficiency in Podocyte Negatively Affects the Communication Between Lipid Droplets and Mitochondria in Alport Syndrome

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Background: Alport Syndrome (AS) is a hereditary disease caused by mutations in collagen type IV. We and others have demonstrated pathogenic renal lipid droplets (LD) and triglyceride (TG) accumulation in experimental AS (Col4a3KO mice). Excessive FFA catabolism resulting from excessive lipolysis of TG is a major contributor to cell lipotoxicity. Perilipin 5 (PLIN5) is an LD-related protein that plays a critical role in regulating TG lipase activity and the interactions between LD and mitochondria, where it protects mitochondria from excessive exposure to FFA. Here we test the hypothesis that PLIN5 is expressed in podocytes and that PLIN5 deficiency in AS causes excessive TG breakdown and the loss of LD-mitochondrial contact, thus contributing to kidney failure.

Methods: *In vitro*, Immortalized AS podocytes and WT podocytes were established and characterized in our laboratory by breeding the Col4a3KO mice (Jackson Laboratory) to H-2kb-tsA58 transgenic mice (Charles River). PLIN5 expression was determined by RT-PCR and western blot analysis in AS podocytes and kidney cortex in AS mice when compared to controls. TG lipolysis and FFA quantification were determined and normalized to protein content. LD-Mitochondrial contact was determined by TEM analysis.

Results: PLIN5 deficiency was observed in the kidney cortex of Col4a3KO mice when compared to controls ($p<0.001$). We demonstrate that PLIN5 is expressed in podocytes, and the expression of PLIN5 is significantly decreased in AS podocytes compared to WT podocytes ($p<0.01$). AS podocytes also showed significantly increased rates of TG lipolysis ($p<0.05$), intracellular free fatty acids ($p<0.05$) and apoptosis ($p<0.01$) when compared to WT podocytes. AS podocytes had reduced number of LD-mitochondrial contacts ($P<0.05$), implying that and apoptosis. Moreover, Ezetimibe, which restored LD-Mitochondrial contact *in vitro* ($P<0.05$) and improved kidney function *in vivo*, was found to restore PLIN5 expression *in vitro* and *in vivo (P<0.05)*.

Conclusions: Our study suggests that podocyte PLIN5 deficiency may cause podocyte injury in AS through excessive TG lipolysis and inefficient FA transfer from LD to Mitochondria, leading to mitochondrial dysfunction and contributing to disease progression.

PO1714

UCP2 Regulates Mitochondrial Dynamics and Podocyte Injury by OMA1-Dependent Proteolytic Processing of OPA1

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Background: Podocyte injury and loss are pivotal events in the progression of glomerular diseases, such as diabetic kidney disease (DKD) and focal segmental glomerulosclerosis (FSGS). Disordered mitochondrial dynamics leads to mitochondrial dysfunction, which is extensively involved in podocyte injury. The mitochondrial inner membrane uncoupling protein, UCP2, is involved in the regulation of mitochondrial dynamics, but the specific mechanism is unknown.

Methods: The function and structure of podocyte were detected by electron microscopy, immunofluorescent staining, PAS staining, and urinary albumin. A Seahorse Bioscience XF24 Extracellular Flux Analyzer was used to measure dissolved oxygen in culture medium around adherent cells. Mitochondrial membrane potential was detected using TMRM dye. The content of ATP in cells of each well was determined with an ATP Assay Kit.

Results: We reported that the mitochondrial inner membrane UCP2 expression in podocyte was corelated with proteinuria level in patients. Mice with podocyte-specific *Ucp2* deficiency developed podocytopathy with proteinuria with aging. Furthermore, those mice exhibited increased proteinuria in experimental models evoked by diabetes or adriamycin. Our findings suggest that UCP2 mediates mitochondrial dysfunction by regulating mitochondrial dynamic balance. *Ucp2* deleted podocyte exhibited increased mitochondrial fission and deficient in ATP production. Mechanistically, opacity protein 1 (OPA1), a key protein in fusion of mitochondrial inner membrane, was regulated by UCP2. *Ucp2* deficiency promoted proteolysis of OPA1 by activation OMA1 which belongs to mitochondrial inner membrane zinc metalloprotease. Those finding demonstrate the role of UCP2 in mitochondrial dynamics in podocyte and provide new insights into pathogenesis associated with podocyte injury and proteinuria.

Conclusions: Our findings suggest that UCP2 protects mitochondrial dynamics balance by OMA1-dependent proteolytic processing of OPA1.

Funding: Government Support - Non-U.S.

PO1715

L-WNK1 Inhibition Protects from Glomerular Injury in Mice

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Background: The With No lysine (K) kinase L-WNK1 plays a key role in the maintenance of cellular homeostasis in response to variations in osmolarity, intracellular chloride concentration or cell volume. We have shown that L-WNK1 activation in the distal nephron results in hypertension. Other studies showed that the inhibition of L-WNK1 could be beneficial in epileptic diseases and to prevent the metastatic process. However, the preclinical study of a L-WNK1 inhibitor was discontinued due to unacceptable side effects. Therefore, L-WNK1 inhibition can be either beneficial or deleterious depending on the pathology and affected tissue. It is necessary to better define the signalling pathways controlled by L-WNK1 in order to develop targeted therapies with limited secondary effects. In that context, we chose to define the roles played by the kinase in the glomerulus, its predominant site of expression within the kidney.

Methods: We used mice carrying an ubiquitous and heterozygous (*L-WNK1*$^{+/-}$) or podocyte-specific homozygous inactivation of L-WNK1 (*NPHS2-Cre;WNK1*$^{lox/lox}$). We characterised their renal function (plasma urea, creatinine, urine albumin/creatinine) and glomerular structure at baseline and in a model of crescentic glomerulonephritis (CGN) induced by the administration of nephrotoxic serum (NTS-CGN).

Results: L-WNK1 inactivation, either global or podocyte-specific, did not impair glomerular function and structure. After induction of NTS-CGN, the renal function of *L-WNK1*$^{+/-}$ mice was improved compared to control ones. We observed a decreased infiltration of macrophages and a lesser stimulation of the expression of fibrotic genes. The same improvement of renal function, associated with a reduced number of glomerular lesions, was observed in *NPHS2-Cre;WNK1*$^{lox/lox}$ mice during NTS-CGN. To uncover the underlying mechanisms, we used the immortalised AB8/13 cell line of human podocytes. Our hypotheses were the stimulation of autophagy, a decreased capacity for proliferation and migration and a reduced stimulation of the TRPC6 calcium channel. We have shown that the pharmacological inhibition of L-WNK1 activity by WNK463 resulted in an increased autophagic flux and a decreased migration/proliferation in a wound-healing assay.

Conclusions: In conclusion L-WNK1 inhibition represents a new target for the protection of the podocytes during CGN.

Funding: Government Support - Non-U.S.

PO1716

Protective Role of the Epithelial STAT5 Pathway in Kidney Injury

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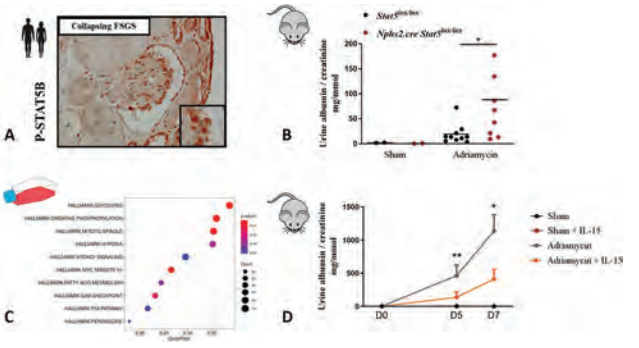
Background: During kidney diseases, diverse tissue-specific pathways can regulate kidney injury and prognosis. Thus, therapeutic targeting of these pathways could improve the management and prognosis of chronic kidney diseases. The Janus Kinase/ Signal Transducer and Activator of Transcription (JAK/STAT) pathway, classically described in immune cells, has been recently described in intrinsic kidney cells.

Methods: We 1) analyzed STAT5 activation in kidney biopsies from patients with focal segmental glomerulosclerosis (FSGS) and acute tubular injury (ATI), 2) used experimental models of glomerular and tubular injury in mice with podocyte- or tubular-specific STAT5 deficiency, 3) studied transcriptomic modifications related to *STAT5* deletion in human kidney epithelial cells, 4) explored interleukin-15 mediated STAT5 activation in podocytes and glomerular injury.

Results: Here, we show, for the first time, that STAT5 is activated in both human podocytes (Figure 1A) and tubular cells in FSGS and ATI, respectively. Additionally, STAT5 deficiency in *either* glomerular or tubular epithelium aggravates the functional and structural alterations in a range of experimental models of glomerular (Figure 1B) or tubular disease. STAT5 deficiency in kidney epithelial cells resulted in dysregulation of multiple metabolic pathways, including glycolysis and oxidative phosphorylation (Figure 1C). Interleukin 15 (IL-15), a classical activator of STAT5 in immune cells, increases STAT5 phosphorylation in human podocytes and alleviates glomerular injury *in vivo* (Figure 1D) by activating anti-apoptotic pathways.

Conclusions: In conclusion, activating renal epithelial STAT5 represents a new therapeutic avenue with the potential for a range of beneficial effects in kidney diseases.



A. STAT5B activation in human podocytes in FSGS. B. STAT5 podocyte deficiency aggravates adriamycin-induced proteinuria. C. CRISPR-Cas9 induced deletion of *STAT5B* from human kidney epithelial cells leads to disruption of metabolic pathways. D. IL-15 alleviates adriamycin-induced glomerular injury in mice

PO1717

Shiga Toxin Targets the Podocyte in Haemolytic Uraemic Syndrome (HUS) Resulting in Glomerular Endothelial Cell Complement Dysregulation

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Background: Haemolytic uraemic syndrome (HUS) is a thrombotic microangiopathy (TMA) that has a predilection to present in the kidney. It is a triad of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. In 90% of cases, HUS follows gastroenteritis secondary to infection with Shiga toxin (Stx) producing bacteria such as Escherichia coli. Stx HUS is the leading cause of acute kidney injury in children with a mortality of 5%. However, the precise pathophysiological mechanisms following Stx infection leading to TMA remain poorly understood. Here we show that the podocyte is a key initiator in Shiga toxin HUS, which could explain why the glomerulus is the prime target of systemic Shiga toxin driven infection.

Methods: To demonstrate that the podocyte Shiga toxin receptor (Gb3) is sufficient to trigger the development of HUS, we used conditional gene targeting to engineer human Gb3 expression specifically in the podocytes of adult mice.

Results: Following intraperitoneal Shiga toxin challenge, these mice developed thrombocytopenia, haemolytic anaemia and uraemia (Figure 1) with evidence of glomerular TMA on histology. Interrogation of this model revealed evidence of glomerular endothelial cell complement activation, with loss of local complement factor H protection. Furthermore, C5 inhibition was found to rescue the Shiga toxin HUS phenotype.

Conclusions: Together, these observations provide compelling evidence for the importance of podocyte-glomerular endothelial cell cross-talk within the kidney in the development of Shiga toxin associated HUS and suggest a possible therapeutic role for complement inhibition in patients with this devastating disease.

Funding: Other NIH Support - Charity support - Kidney Research UK

Shiga toxin targets the podocyte in Haemolytic Uraemic Syndrome (HUS) resulting in glomerular endothelial cell complement dysregulation: supporting Figure 1

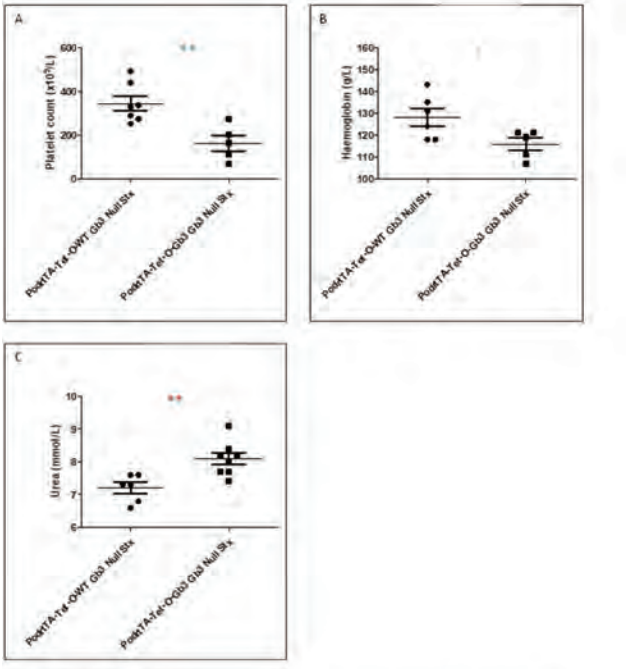

Figure 1: Podocyte Gb3 expressing mice (PodrtTA-Tet-O-Gb3 Gb3 null mice) develop HUS following intraperitoneal Shiga toxin

PodrtTA-Tet-O-Gb3 Gb3 null mice given 10ng/g of IP Shiga toxin show a drop in platelet count (A), drop in haemoglobin (B) and rise in plasma urea (C) vs. age matched control mice (PodrtTA-Tet-O-WT Gb3 null) at Day 10.

These differences were statistically significant A: * Unpaired T test p value 0.004; B: * Unpaired T test p value 0.041; C: **Unpaired T-test p value 0.0052 Note urea results pooled from day 10 to day 16.

PO1718

Nephronectin Expression Is Controlled by the Non-Canonical TGF-β Pathway in Podocytes

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Background: Within the glomerulus, podocytes, glomerular endothelial cells (GEC) and the glomerular basement membrane (GBM) build the glomerular filtration barrier. Extracellular matrix (ECM) of the GBM is mainly composed of proteins synthesized by GECs and podocytes. Our interest focuses on nephronectin (NPNT), an ECM protein mainly produced by podocytes. Recently, it has been described that NPNT expression patterns vary in different glomerular diseases. For example, in focal segmental glomerulosclerosis (FSGS) and membranous glomerulonephropathy (MGN) NPNT expression was decreased compared to healthy controls, while it was increased in diabetic nephropathy (DN). In addition, transforming growth factor beta (TGFβ) is able to down-regulate NPNT on both mRNA and protein level. Our aim is to further analyze this TGFβ-mediated regulation of NPNT in human podocytes.

Methods: Immortalized human podocytes were differentiated for 10 to 12 days at 37°C and pre-incubated with inhibitors for components of the canonical and the non-canonical TGFβ signaling pathway with subsequent culture in the presence or absence of TGFβ. We used cell culture supernatants for ELISA, as well as cell lysates for qPCR and western blot analyses.

Results: While treating differentiated immortalized human podocytes with TGFβ decreased NPNT on both mRNA and protein level, we observed that inhibition of single components of the TGFβ pathway did not alter NPNT mRNA expression and excretion. On protein level, we noted no change after blockade of either Smad2 or Smad3 under baseline conditions. However, TGFβ was still able to decrease NPNT expression when canonical pathway components were inhibited, suggesting a minor role for this pathway in NPNT regulation via TGFβ. If single components of the non-canonical pathway were blocked, we observed an increase in NPNT protein expression, which was not further altered by TGFβ addition.

Conclusions: Taken together, our data suggest that in podocytes NPNT expression is fine-tuned via the non-canonical TGFβ pathway with additional regulation on the post-translational level.

Funding: Government Support - Non-U.S.

PO1719

Podocyte Damage in Chimeric Kidney Organoids

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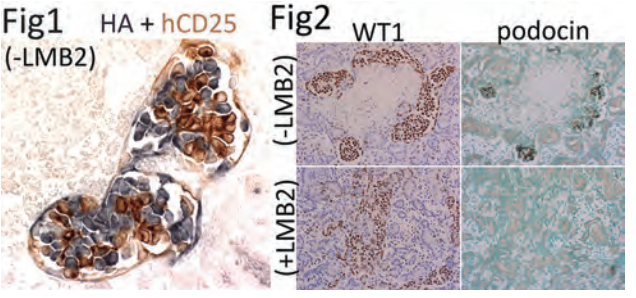
Background: We previously found that when a portion of podocytes are injured, other podocytes are secondarily injured in a mouse model, which may underlie the relentless progression of chronic renal failure. In the present study, we tested whether this phenomenon is observed in kidney organoids.

Methods: Nephron progenitor cells (NPCs) were established by culture-dependent purification (CDP) method from 12.5 dpc NEP25 and RiboTag mouse kidneys (*Cell Stem Cell*. 2016, 19, 516-29). Podocytes of NEP25 mice express hCD25 and can be injured by hCD25-targeted immunotoxin, LMB2. Podocytes of RiboTag mice express hemagglutinin (HA)-tagged ribosomal protein. Kidney organoids were generated by transient stimulation with FGF2 and CHIR99021 of NPC aggregates and subsequent 8-day culture. On day 8, LMB2 (20 nM) was added to induce injury in hCD25+ podocytes.

Results: We confirmed that podocytes in both organoids are stained for nephrin, podocin and WT1. Podocytes derived from NEP25 NPC expressed hCD25 and were injured by LMB2, and those from Ribotag NPC expressed HA and were resistant to LMB2. When two types of NPCs were mixed at 1:1 ratio, organoids showed a chimeric pattern containing hCD25+ and HA+ podocytes (Fig1). 2 days after LMB2 treatment, hCD25 staining completely disappeared accompanied by cleaved (c) lamin A staining, a cell death marker. HA staining was retained, but WT1 was diminished and podocin disappeared (Fig 2). Occasionally, c-lamin A was positive in HA+ cells. RNA of Ribotag podocytes can be obtained by immunoprecipitation with anti-HA antibody. Q-PCR revealed that *Nphs1* (0.31), *Nphs2* (0.04), *Wt1* (0.37) were decreased to the indicated fold by LMB2 and that *Gadd45b* was increased to 4.82-fold.

Conclusions: Thus, podocyte damage damages podocytes in kidney organoids that lack glomerular filtration.

Funding: Government Support - Non-U.S.



PO1720

Increased Old Astrocyte Specifically Induced Substance (OASIS) in Podocytes Leads to the Progression of Nephrotic Syndrome

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Background: Old astrocyte specifically induced substance (OASIS) is a transcription factor of the CREB/ATF family. Previously, we found that OASIS was expressed in podocytes in murine kidneys. However, the pathophysiological roles of OASIS in podocytes remain unclear. The aim of this study is to elucidate the role of OASIS in podocytes.

Methods: To assess the relevance of OASIS to renal pathology, the expression of OASIS in glomeruli of lipopolysaccharide (LPS)-treated mice or streptozotocin (STZ)-treated diabetic mice was examined by laser capture microdissection, followed by immunoblotting. To further investigate the functional roles of OASIS in podocytes, podocyte-restricted OASIS overexpressing transgenic (OASIS TG) mice were established. Urinary albumin-creatinine ratio (uACR) was measured. Podocyte injury was assessed by electron microscopy. Tubular injury was evaluated by PAS staining and by measuring *LCN2* mRNA expression. Masson's trichrome staining and quantitative PCR for fibrosis-related genes, *COL1A1* and *FN1*, were performed to analyze tubulointerstitial fibrosis. To explore the effect of OASIS on podocyte actin cytoskeleton in vitro, phalloidin staining was performed on lentivirus-induced OASIS overexpressing murine cultured podocytes.

Results: OASIS expression was increased in glomeruli of both LPS-treated and diabetic mice. uACR was significantly increased in OASIS TG mice (uACR (μg/mg): control; 35.1±24.9, OASIS TG; 8930.0±8461.4, n=9 for control, n=7 for OASIS TG), and electron microscope analysis showed that OASIS overexpression in podocytes caused foot process effacement. In addition, damaged tubules and *LCN2* upregulation were observed in OASIS TG mice. Furthermore, Masson's trichrome staining showed that OASIS overexpression in podocytes evoked kidney fibrosis, and the expression of *COL1A1* and *FN1* were upregulated in OASIS TG mice. Consistent with in vivo study, OASIS overexpressing podocytes showed the reduction in actin stress fiber formation.

Conclusions: The increased OASIS in podocytes contributes to nephrotic progression.

PO1721

Podocyte-Derived RARRES1 Aggravates Kidney Disease Progression by Inducing Both Glomerular and Tubular Injury

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Background: Our previous study demonstrates that the expression of retinoic acid receptor responder protein 1 (RARRES1) increases in glomeruli of patients with diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS). The glomerular expression of RARRES1 also correlates with eGFR slope and predicts glomerular disease progression. Single-cell RNA-sequencing of the kidney showed that RARRES1 expressed mostly in podocytes within the kidney. Mechanistically, WT-RARRES1 is cleaved into a soluble form which subsequently induces podocyte apoptosis whereas mutant RARRES1 with cleavage defect failed to induce podocyte apoptosis *in vitro*. Here, we further determined whether increased expression of WT-RARRES1 in the podocytes aggravated progression of glomerular disease.

Methods: Mice with podocyte-specific overexpression of human WT- RARRES1 or mutant RARRES1 with cleavage defect were generated and then subjected to aging, adriamycin (ADR) administration or streptozotocin (STZ) injection. To identify the role of podocyte-derived soluble RARRES1 in tubular cells, HK2 cells were treated with soluble RARRES1 obtained from podocyte supernatants.

Results: In vivo, podocyte-specific overexpression of WT-RARRES1 resulted in severe proteinuria and marked glomerular cell injury in mice with aging, adriamycin-induced nephropathy, or STZ-induced diabetic nephropathy as compared to the control mice with overexpression of mutant RARRES1. Interestingly, tubular vacuolation and interstitial injury were also observed in these mice with podocyte-specific overexpression of RARRES1. In addition, we showed that soluble RARRES1 collected from podocyte supernatants was endocytosed in HK2 cells to induce cellular injury. Similarly, cleaved form of human RARRES1 in the mice with podocyte-specific human RARRES1 overexpression was found in the tubular compartments, indicating that soluble RARRES1 generated from podocytes may act on tubular cells through glomeruli-tubule crosstalk.

Conclusions: Our study suggests that RARRES1 is a risk gene for glomerular disease progression through its direct effects in podocytes as well as indirect effects in tubular cells probably via glomeruli to tubules crosstalk.

Funding: NIDDK Support, Veterans Affairs Support

PO1722

Podocyte-Specific Extracellular Vesicles Yield Novel Insight into Intercellular Signaling in the Glomerulus

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Background: Extracellular vesicles (EVs) have been identified to play an essential role in basic pathological processes such as priming of the metastatic niche, autoimmunity and propagation of insulin resistance. Nevertheless, knowledge about their role in kidney health and disease remains scarce. A new group of EVs, shed upon apoptosis with the ability to induce a proliferative effect in neighboring cells, was recently identified in cell culture models as well as experimental glomerulonephritis. This study aimed to characterize these medium-sized EVs and the signaling propagated by them in podocyte damage.

Methods: Using differential centrifugation and filtration we established a protocol to separate medium-sized EVs from cell culture supernatants, kidney tissue and urine samples. With Western Blot, immunofluorescence microscopy and image flow cytometry we investigated the release dynamics of podocyte-specific vesicles in different models of murine podocyte damage *in vitro* and *in vivo*. Furthermore, cross culture experiments and life microscopy were used to determine the effect of podocyte-specific medium-sized EVs on parietal epithelial cells.

Results: Podocyte-specific medium-sized EVs were detected in baseline podocyte culture supernatant, untreated murine kidney tissue as well as the urine of healthy human volunteers. Vesicle quantification revealed a drastic increase of vesicle release upon podocyte damage both *in vitro* and *in vivo*. Interestingly, podocyte-specific EVs exerted different effects on the proliferative and migratory behavior of primary parietal epithelial cells.

Conclusions: Our study represents the first investigation of podocyte-specific medium-sized extracellular vesicles, their release dynamics and functional implications in health and disease. Ongoing analyses aim to characterize their proteomic content and effect other renal epithelial cells. As these vesicles can be separated without advanced equipment such as ultracentrifuges, we believe they could also be a valuable source for biomarker research in various nephropathies.

PO1723

Effects of Varying Mild Tubular Injury on Subsequent Glomerular Injury

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Background: Tubular injury predisposes to CKD, including glomerular injury. We analyzed effects of mild tubular injury on subsequent glomerular injury.

Methods: Double transgenic, Nep25/DTR$^+$ male and female mice (with human CD25 receptor on podocytes and Diphtheria toxin (DT) receptor on proximal tubules) received DT (25, 50, or 100ng/kg; 2x one week apart, n=5/group) to induce tubular injury, or vehicle (VEH). Uninephrectomy was done 4 wks later; 5 wks later glomerular injury was induced by LMB2 toxin (CD25 ligand) and mice were sacrificed 10 days later.

Results: In males, urinary KIM-1 was significantly higher vs VEH with all DT doses on d3 after DT injections, lowest in DT25 and similar with DT50 and DT100. KIM-1 levels were only numerically higher in DT50 and DT100 vs VEH by wk 6. Urinary NGAL was significantly increased at d3 only in DT100 vs VEH. NGAL levels normalized in all DT groups by week 6. In females, KIM-1 levels were increased by d3 with highest level with DT100. KIM-1 levels were only numerically higher vs VEH in a dose-dependent manner by wk 6. Urinary NGAL on day 3 was significantly higher in DT50 and DT100, normalized by wk 6, with numerically highest level in DT100. Males had higher levels of KIM-1 vs females at all timepoints, while NGAL showed similar levels in males and females at DT100 on d3, but higher levels in females at DT100 dose at wk 6. In males, albuminuria at sacrifice after additional podocyte injury showed numerically higher levels by 67% in DT100 vs VEH. In females, albuminuria gradually increased, with levels lower than in males in all groups. Ultrastructural analysis after podocyte injury showed similar significant foot process effacement, glomerular capillary fenestration loss and increased GBM thickness in all groups.

Conclusions: Sex differences in response to tubular injury and albuminuria were observed. Even very mild tubular injury, recovered by assessment of KIM-1 and NGAL-1 led to numerical increase in albuminuria after second hit glomerular injury in both sexes. The sex-dependent differences in KIM-1 and NGAL-1 further support differential susceptibility of nephron segments to injury in females vs males, which may play a role in glomerular sensitization to injury.

Funding: NIDDK Support

PO1724

Effect of Glomerular Disease on the Podocyte Cell Cycle

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Background: Progression of glomerulosclerosis is associated with loss of podocytes and subsequent glomerular tuft instability. A decreased number of podocytes may be able to preserve tuft stability through cell hypertrophy associated with cell cycle re-entry. At the same time, re-entry into the cell cycle can lead to podocyte detachment from the glomerular basement membrane, if podocytes cross the G1/S checkpoint and undergo abortive cytokinesis.

Methods: To study cell cycle dynamics during CKD development, we used a FUCCI mouse model (fluorescence ubiquitination-based cell cycle indicator) affected by X-linked Alport Syndrome (AS). This model has progressive CKD and expresses cell cycle fluorescent reporters exclusively in podocytes. We quantified podocytes cell cycle distribution in WT and AS mice at different ages and collected podocytes in G0 and G1 for proteomics studies.

Results: We showed that with the development of CKD, an increasing fraction of podocytes *in vivo* are in G1 or later cell cycle stages. G1 and G2 podocytes are hypertrophic. Heterozygous female mice, with milder manifestations of CKD, show G1 fraction numbers intermediate between WT and male AS mice. Proteomic analysis showed differences in cytoskeleton re-organization and metabolic processes between podocytes in G0 and G1 in disease vs. WT and indicate alteration of specific proteins also identified in human AS podocytes.

Conclusions: Our data showed that, during progressive CKD, the podocyte cell cycle distribution changes dramatically, suggesting that cell cycle manipulation may have a role in the treatment of various progressive glomerular diseases characterized by podocytopenia.

Funding: Private Foundation Support

PO1725

Glucocorticoid- and Pioglitazone-Induced Proteinuria Reduction Correlates with Glomerular Extracellular Matrix Remodeling in Experimental Nephrotic Syndrome

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Background: Nephrotic Syndrome (NS) is a common glomerular disease in children. While glucocorticoids (GC) are the mainstay of childhood NS treatment, pioglitazone (Pio; an FDA-approved PPARg agonist to treat type 2 diabetes) has been reported to reduce proteinuria in experimental NS and to directly protect podocytes from injury. Since both GC and Pio activate nuclear receptors (NR3C1 and PPARG, respectively) we hypothesized that their proteinuria-reducing effects result from overlapping glomerular gene transcriptional patterns.

Methods: We performed transcriptome analyses on glomeruli isolated from GC (immunosuppressive)- and Pio (non-immunosuppressive)-treated rats 11 days after induction of NS with PAN (n=4/group).

Results: Unsupervised clustering revealed partial reversibility of PAN-associated mRNA dynamics by treatment with either GC or Pio. IPA analyses + web-based bioinformatic platforms identified 29 genes-of-interest common to GC- and Pio-induced proteinuria reduction, which included ECM remodeling, lipid metabolism, DNA-binding and cytoskeletal organization. Based on expression differences using real-time PCR,

29 genes-of-interest were selected for further analysis, which on clinical correlation with a human FSGS database (*Nephroseq*) suggested a direct relevance of glomerular ECM regulation in NS. Also, glomerular cell deconvolution using published single-cell glomerular transcriptome profiles identified podocyte- and mesangial cell-specific perturbations in gene expression during NS and with treatments. Finally, validation of selected genes-of-interest using PAN-induced injury of human podocytes and mesangial cells confirmed significant upregulation of *LGALS3 (primary role in cell adhesion)* and *MMP2/ACTA2 (primary role in ECM degradation/cell motility or integrity)* respectively.

Conclusions: These studies identified podocyte- and mesangial cell-specific transcripts common to both proteinuria-reducing treatments that identify possible targets for future treatment for NS

PO1726

Alteration of Intestinal Microbiota in Patients with ESRD Undergoing Hemodialysis

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Background: The alteration in the intestinal microbiota is reported to be associated with various diseases, indicating that the development and progression of end-stage kidney disease also might be associated with dysbiosis.

Methods: The stool samples were collected from patients with hemodialysis (n = 41, HD group) and those with normal renal function (n = 40, NRF group). Both groups are comprised of patients with (HD_DM, n = 20; NRF_DM, n = 19) and without diabetes (HD_non-DM, n = 21; NRF_non-DM, n = 21). We conducted 16S rRNA gene amplicon sequencing using stool samples to analyze the intestinal microbiota.

Results: The reduced abundance of the genera *Megamonas* and *Fusicatenibacter*, and the enriched abundance of the genera Family_XIII_AD3011_group (*Anaerovoracaceae* family), UBA_1819 (*Ruminococcaceae* family), and *Pseudomonas* in the stool samples of HD patients were observed significantly compared with those of NRF patients. Compared with patients with NRF_DM, the relative abundance of the genera *Megamonas* was decreased and that of Family_XIII_AD3011_group was increased significantly in patients with HD_DM, although those relative abundance did not alter between NRF_non-DM and HD_non-DM. The relative abundance of the genera *Suterella* in HD_non-DM was significantly decreased than that in NRF_non-DM, although that relative abundance did not differ between NRF_DM and HD_DM. In the microbial beta diversity, there was no difference between NRF_DM and NRF_non-DM by weighted and unweighted Unifrac analysis, however, there was significant difference between HD_DM and HD_non-DM by unweighted Unifrac analysis ($p = 0.007$). These results suggest that the gut microbiota alters with renal function decline, and varies depending on the presence or absence of diabetes.

Conclusions: The intestinal microbiota might be varied substantially depending on renal function and the presence or absence of diabetes.

PO1727

Nutritional Intervention in Intensive Care Unit Patients Undergoing CRRT

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Background: Providing adequate calories and protein constitutes an important part of critical care, and inadequate nutrition for critically ill patients is associated with poor prognosis. Therefore, increased loss of amino acids, electrolytes, and water-soluble vitamins during continuous renal replacement therapy (CRRT) could be a therapeutic target. We evaluated whether enforcing protein, trace elements and vitamin supply could improve the prognosis of CRRT patients.

Methods: A nutritional intervention (100 mg/day of Thiamine, 25–30 kcal/kg of energy, 1.8 g/kg of protein, and 50–100 mcg/day of microelement with selenium) was conducted in patients subject to CRRT from May 2020 to December 2020. The primary outcomes were 28-day mortality, CRRT day, ICU stay, and ventilator-free day, and the outcomes before and after the intervention were compared.

Results: Total 88 patients were included during the study period and compared with 88 patients in the previous year. The average age was 68.05 years old, 56 (63.5%) patients were male. At day 1 APACHE-II score was 35.45±9.2, SAPS3 88.1±16.8, SOFA 10.4±2.7. There were 9 (10.2%) patients with ECMO, 78 (88.6%) using ventilator. There were 19 (21.6%) pneumonia with ARDS patient, 18 (20.5%) cardiac disease, 9 (10.2%) UTI sepsis, 11 (12.5%) gastrointestinal bleeding and sepsis, 6 (6.8%) cerebral hemorrhage, and others. The main reason for CRRT was hemodynamic instability. Baseline characteristics including APACHE-II score, SAPS 3, and SOFA were not significantly different between the nutritional intervention and the non-intervention patients. Nutritional intervention did not induce significant changes in 28-day mortality (36 versus 37, $p = 0.56$) and CRRT days (7.3 ± 6.9 versus 6.3 ± 5.2, $p = 0.29$). However, nutritional intervention showed minimal improvement in ICU stay (22.1 ± 23.9 vs 20.7 ± 22.1, $p = 0.05$) and ventilator-free days (17.8 ± 22.3 vs 12.4 ± 14.4, $p = 0.05$).

Conclusions: This study suggests that support for protein, trace elements, and vitamins may have a positive effect in CRRT patients. Therefore, the nutritional requirements of patients with CRRT should be carefully assessed, individualized, and considered as an important axis of CRRT treatment.

Primary outcome

Variables	Conventional (2019) n=88	Intervention (2020) n=88	p-value
28-day mortality, n (%)	36 (40.9%)	37 (42.0%)	0.56
Duration of CRRT, day (mean±SD)	7.32 ± 6.9	6.34 ± 5.2	0.29
Duration of ventilator, day (mean±SD)	17.84 ± 22.37	12.47 ± 14.43	0.05
Length of stay, day (mean±SD)	22.14 ± 23.9	20.74 ± 22.18	0.05
ICU stay	45.06 ± 40.13	41.3 ± 46.91	0.57
Total hospital stay			

PO1728

Nutritional Phenotypes and Variation in Nutritional Parameter Trajectories Among Non-Dialysis CKD (CKD-ND) Patients Prescribed Oral Nutritional Supplements

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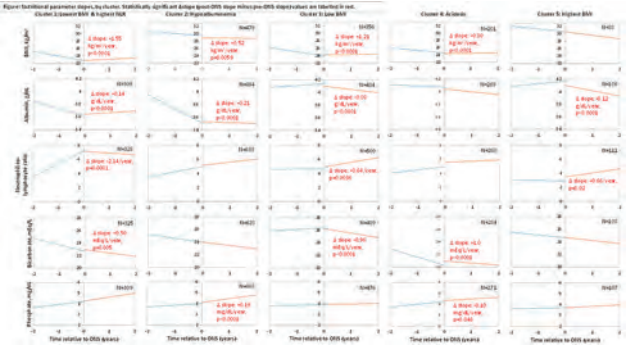
Background: Among CKD-ND patients at risk of undernutrition/protein-energy wasting, the definition of patient subgroups most likely to benefit from ONS treatment is not known. Therefore, our aims were to identify phenotypes of non-dialysis CKD patients prescribed ONS, and to assess nutritional parameter slopes before and after ONS use, by phenotype.

Methods: This longitudinal cohort study included 2543 adult CKD-ND patients who entered multidisciplinary CKD clinics across British Columbia during 2010- 2019, met weight and/or dietary intake criteria for ONS prescription based on dietitian assessment, received ≥1 ONS prescription. Hierarchical cluster analysis was used to identify phenotypes using baseline nutritional parameters. Using linear mixed models, slopes for body mass index (BMI), serum albumin, bicarbonate, phosphate, and neutrophil-to-lymphocyte ratio (NLR), an inflammation marker, were assessed in the 2-year periods before and after the first ONS prescription.

Results: Cluster analysis identified five nutritional phenotypes. Changes in parameter slopes (Δslope = post-ONS slope - pre-ONS slope) varied by cluster (Figure). Cluster 1 (characterized by the highest mean NLR and the lowest mean BMI among clusters) demonstrated statistically significant positive Δslopes for BMI, albumin and bicarbonate, and a negative Δslope for NLR. Cluster 2 (hypoalbuminemia) demonstrated positive Δslopes for BMI, albumin, and phosphate. Cluster 3 (low mean BMI) demonstrated a positive Δslope for BMI, accompanied by negative Δslopes for albumin and bicarbonate, and a positive Δslope for NLR. Cluster 4 (acidosis) demonstrated positive Δslopes for BMI and bicarbonate. In Cluster 5 (highest BMI), a negative Δslope for albumin and a positive Δslope for NLR were observed (no improvement with ONS).

Conclusions: The variation in response to ONS by cluster subgroup lends support to an individualized approach to nutritional management of patients at risk of undernutrition/protein-energy wasting.

Funding: Government Support - Non-U.S.



PO1729

Association of Muscle Mass and Protein Intake with Risk of ESKD in Patients with CKD

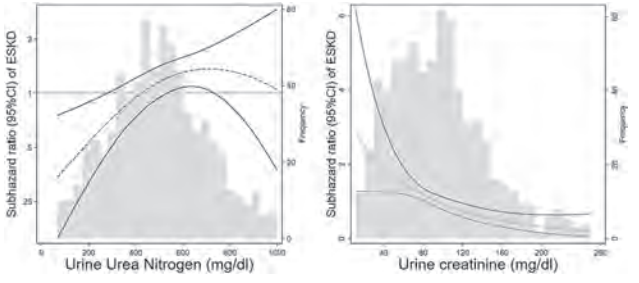
Atif Ibrahim,[1] Neeharika Mettupalli,[1] Waleed Hassan,[1] Yoshitsugu Obi,[1] Mahmoud M. Mohamed,[1] Keiichi Sumida,[1] Miklos Z. Molnar,[2] Barry M. Wall,[1,3] Csaba P. Kovesdy.[1,3] *[1]The University of Tennessee Health Science Center, Memphis, TN; [2]University of Utah Health, Salt Lake City, UT; [3]VA Memphis Medical Center, Memphis, TN.*

Background: Better nutritional status is favorably associated with clinical outcomes, but high protein intake may have deleterious effects on kidney function by virtue of mechanisms unrelated to nutritional status. We hypothesized that dietary protein intake and muscle mass (two markers of nutritional status) have opposite associations with progression of CKD when examined together.

Methods: We examined a cohort of 702 US veterans with stage 3-5 CKD followed at a single institution. We used spot urea nitrogen (UUN) and urine creatinine (UC) and adjusted for urine specific gravity as surrogates of dietary protein intake and muscle mass, respectively. We examined the concomitant association of UUN and UC with ESKD using multivariable adjusted competing-risks regression with adjustment for demographic characteristics, comorbidities, eGFR, proteinuria, smoking status, and body mass index.

Results: Patients were 68±10 years old, 96% were male, 60% were African American and their baseline eGFR was 32±13 mL/min/1.73 m². There were 178 ESKD events (event rate, 72.8/1000 PY; 95%CI, 62.8-84.4) over a median follow-up of 3.5 years. In a multivariable adjusted model including both nutritional markers, higher UUN was associated with a higher risk of ESKD (subhazard ratio [SHR] and 95%CI associated with 100 mg/dl higher UUN: 1.15, 1.00-1.35), while UC was associated with a lower risk of ESKD (SHR and 95%CI associated with one standard deviation higher UC: 0.50, 0.32-0.78) [**Figure**].

Conclusions: Higher protein intake is associated with higher risk of ESKD, while higher muscle mass is associated with a lower risk of ESKD in patients with stage 3-5 CKD. While observational in nature, these results suggest that renoprotection with dietary protein restriction should be pursued with close attention to maintaining optimal nutritional status.



PO1730

The Beneficial Effects of Intradialytic Parenteral Nutrition in Malnourished Hemodialysis Patients: A Randomized Controlled Trial

Athiphat Banjongjit, Kamonchanok Metta, Yingyos Avihingsanon, Somchai Eiam-Ong, Piyawan Kittiskulnam. *Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Background: Intradialytic parenteral nutrition (IDPN) is an intermittently supplemental nutrition support administered during hemodialysis (HD). IDPN has been suggested as a trial option after a failure response to oral nutritional supplements (ONS). However, the extent to which IDPN contributes to improve protein-energy status remains unclear.

Methods: Maintenance HD patients having spontaneous energy and protein intake of ≥ 20 kcal/kg/day and ≥ 0.8 g/kg/day, respectively and intolerance to ONS were randomly assigned 1:1 to receive IDPN or intensive dietary counselling. In IDPN group, 3-in-1, anti-inflammatory omega 3-rich parenteral nutrition was infused during HD for 3 months followed by a treatment-free period of 3 months. The control group received an individualized dietary counselling once a week for 3 months to target the required nutrient intake. The outcomes were changes in serum albumin, muscle parameters and nutritional biomarkers. Serious adverse events were also monitored.

Results: A total of 38 patients were completed the study (age 67±11). Baseline characteristics were not different between groups. After 3 months, serum albumin were significantly higher in the IDPN (n=18) compared with control group (from 3.5±0.3 to 3.8±0.2 *vs* 3.6±0.2 to 3.5±0.3 g/dL, p=0.01, respectively). The infusion volume was 14.2±3.9 ml/kg/HD session. Total energy and protein intake (p=0.04), weight (p=0.01), subjective global assessment (p=0.03), and malnutrition inflammation score (p=0.01) were significantly improved in IDPN group, but not in control group (all p>0.05). Among nondiabetic patients, IDPN significantly reduced serum IL-6 as an inflammatory marker (p=0.03) but unaltered serum acylated ghrelin as an orexigenic hormone (p=0.31). Muscle mass, strength, and serum prealbumin were not different between both groups. Participants in IDPN group reverted to baseline albumin levels after 3-month post-intervention follow-up. Neither volume overload nor uncontrolled hyperglycemia was found throughout the study.

Conclusions: A short-term IDPN supplementation significantly increased serum albumin level, a survival surrogate among HD patients. The impact of IDPN therapy on clinical outcomes may require larger scale with longer period of study.

PO1731

An Itch to Scratch: The Problem with Pruritus

Tucker B. Hurtado, Skylar Malone, Jennifer Robinson. Spherix Advanced Analytics Group *Spherix Global Insights, Exton, PA.*

Background: Dialysis patients often suffer from some level of associated pruritus and nephrologists generally recognize the condition's impact on patient lives, rating pruritus as a high unmet need for new therapeutic options. However, official diagnosis of CKD-associated pruritus and physician-reported estimates may be highly underestimated.

Methods: Using a HIPAA-compliant, online chart review tool, 177 nephrologists submitted de-identified clinical and non-clinical demographic information for 1,008 dialysis patients in Fall 2020. These data were then merged with physician demographic profiles and attitudinal responses; the full data set was analyzed in SPSS.

Results: When thinking generally, nephrologists estimate that nearly one-half of end-stage renal disease (ESRD) patients on dialysis have some level of pruritus, making it extremely prevalent in this population. However, chart reviews reveal that only 3.2% of dialysis patients are diagnosed with uremic pruritus (3.4% of HD patients and 1.4% of PD patients). On their last visit with their dialysis patients, nephrologists noted that only 4% of patients reported (or they observed) a skin rash, itch, or pruritus (3.7% of HD patients and 5.6% of PD patients). Interestingly, only approximately one-third of those patients were diagnosed with uremic pruritus, indicating there are more patients presenting with a rash or itch who are not actively being diagnosed. Despite the impact on patient lives, nephrologists report that only 25% of HD patients diagnosed with uremic pruritus are pharmacologically treated; this drops to 17% of PD patients with uremic pruritus. Treatments vary wildly and have varying levels of reported success among physicians. Nephrologists do recognize the impact pruritus can have on a patient's quality of life, making this high rate of underdiagnosis especially troubling. On a 1-10 scale rating unmet need for a new therapeutic agent, 62% of nephrologists rated a high unmet need (8-10) for pruritis in dialysis patients.

Conclusions: While many recognize that itching impacts many dialysis patients, actual diagnoses and treatment are rare, driven by a lack of effective treatment options. Elevating awareness among nephrologists will help with patient identification and treatment, especially as new treatment options are available on the market to help patients.

PO1732

Long-Term Safety of Tenapanor for the Control of Serum Phosphorus in Patients with CKD on Dialysis: Serum Electrolytes and Albumin

Pablo E. Pergola,[1] Jeanene Fogli,[2] Yang Yang,[2] David M. Spiegel.[2] *[1]Renal Associates PA, San Antonio, TX; [2]Ardelyx Inc, Fremont, CA.*

Background: Tenapanor, an investigational first-in-class phosphate absorption inhibitor (PAI), blocks the paracellular absorption of phosphate in the gastrointestinal tract by local inhibition of the sodium-hydrogen exchanger (NHE3). Tenapanor is being studied as a non-binder approach for the management of hyperphosphatemia in patients on dialysis and it is dosed as one pill (10, 20, or 30 mg) twice daily. Due to its novel mechanism of action, it is important to understand its safety profile, including any potential effects on serum electrolytes and albumin.

Methods: This report evaluates the effects of tenapanor on serum electrolyte and albumin concentrations using data from 3 pivotal trials in which tenapanor met its primary phosphorus-lowering endpoint. Trials included a 12-week monotherapy study (BLOCK), a 52-week monotherapy study (PHREEDOM), and a 4-week tenapanor + phosphate binder combination study (AMPLIFY). Serum electrolytes and albumin were measured per study protocol in central research laboratories.

Results: Tenapanor was generally well tolerated, with diarrhea being the only adverse event reported by >5% of patients. Diarrhea was typically mild to moderate in severity, was transient, and resolved with continued treatment. Data from all 3 trials showed that tenapanor treatment, either alone or in combination with phosphate binders, resulted in no clinically meaningful changes in measured serum electrolytes or albumin at any time point. Data from patients treated with tenapanor continuously for 52 weeks in the longest trial, PHREEDOM, are shown in the table.

Conclusions: In these clinical trials, tenapanor inhibited paracellular absorption of phosphate and decreased serum phosphorus with an acceptable safety profile, with no observed effect on serum electrolytes or albumin in patients on maintenance dialysis with hyperphosphatemia.

Funding: Commercial Support - Ardelyx, Inc.

Laboratory parameter	Baseline (mean ± SD)	Week 26 (mean ± SD)	Week 52 (mean ± SD)
Bicarbonate (mmol/L)	23.6 ± 3.1	24.4 ± 2.9	24.5 ± 3.2
Calcium (mg/dL)	8.2 ± 0.8	8.4 ± 0.8	8.7 ± 0.7
Chloride (mmol/L)	96.9 ± 4.0	97.2 ± 3.7	97.1 ± 3.8
Magnesium (mg/dL)	2.5 ± 0.3	2.5 ± 0.3	2.5 ± 0.3
Potassium (mmol/L)	4.8 ± 0.8	4.9 ± 0.7	4.8 ± 0.7
Sodium (mmol/L)	136.4 ± 3.8	136.1 ± 3.4	136.3 ± 3.2
Albumin (g/dL)	4.0 ± 0.3	4.0 ± 0.3	3.9 ± 0.3

PO1733

Patient-Reported Experience with Tenapanor in the OPTIMIZE Trial

Susan A. Edelstein, Yang Yang, Brett Stephenson, Suling Zhao, Lynae Pagliaro, Jeanene Fogli. *Ardelyx Inc, Fremont, CA.*

Background: Tenapanor (TEN), a first-in-class phosphate absorption inhibitor (PAI) that works via the paracellular pathway, provides a novel approach for hyperphosphatemia management. The primary goal of this study is to evaluate how to optimize the treatment of hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis with the use of TEN and its novel mechanism of action.

Methods: Patients with serum phosphorus (sP) >5.5 and ≤10.0 mg/dL during stable phosphate binder (PB) treatment were randomized 1:1 to 2 different treatment cohorts: Cohort 1 (straight switch; n=151) – discontinued current PB and began TEN 30 mg twice daily (BID); or Cohort 2 (50% PB reduction; n=152) – decreased current PB dose by 50% (or more if taking an odd number of PB tablets) and began TEN 30 mg BID. After week 2 investigators could increase PB doses to achieve sP ≤5.5 mg/dL with TEN as the core therapy. Additionally, patients on TEN with sP >5.5 mg/dL could add low dose PB, and patients on TEN and PBs with sP <5.0 mg/dL could reduce PB dose. Participants were monitored for safety and efficacy at weeks 1, 2, 3, 4, 6, 8, and 10. At week 10 or the early termination visit, patients were asked about their experience with their sP management routine during OPTIMIZE compared to before the study. Here we report findings from a selection of questions from the patient experience questionnaires completed by a total of 179 patients (Cohort 1, n=94; Cohort 2, n=85).

Results: When interviewed, 85.1% of patients in Cohort 1 and 83.5% of patients in Cohort 2 reported an improved perception of their sP management routine. Overall,

64.2% of patients (63.8% and 64.8% in Cohort 1 and Cohort 2, respectively) identified an improvement in their sP medication regimen as the top reason for the improved perception, and 30.5% of patients (31.3% and 29.6% in Cohort 1 and Cohort 2, respectively) reported an improved perception of the form or frequency of bowel movements as the top reason for improved perception of their treatment routine.

Conclusions: Patients who were switched to TEN or added TEN to a reduced PB therapy regimen reported improved experience with their sP management. The findings from this analysis show that TEN may improve patient experience with sP management regimens. Further research is needed to elucidate what factors affect a patient's perspective of sP management.

Funding: Commercial Support - Ardelyx, Inc.

PO1734

Apparently Paradoxical Relations of Serum Phosphate and Albumin Variability with Outcomes Are Explained by the Directional Change

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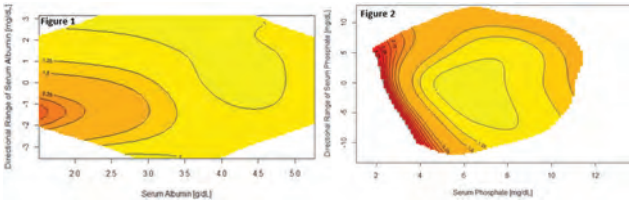
Background: Evidence indicates that variability of serum phosphate (P) and albumin (Alb) is associated with higher risk of mortality. We aimed to study the variability of P and Alb with all-cause mortality taking into account the interaction with the averaged levels.

Methods: All adult incident HD patients (pts) treated in Fresenius Medical Care NA clinics between 2010&2018 were included. Serum P and Alb levels were averaged from month(mo) 1 to 6 after HD initiation. Variability of P and Alb were described by standard deviation(SD) and directional changes(DR). All-cause mortality was recorded between mo 7 and 18. Cox proportional hazards models with spline terms were applied to explore the association between variability of P & Alb and all-cause mortality. Additionally, tensor product smoothing splines were computed to study the effect of interactions between averaged values of parameters and their variability with outcomes.

Results: We enrolled 353,142 pts. Averaged P was 4.98 mg/dL, median SD and DR were 0.92 and 1.10. Baseline Alb was 3.61 g/dL, median SD and DR were 0.21, and 0.40. Across different levels of P, higher SD of P were associated with higher risk of mortality, especially in those pts with lower averaged P. Contrasting, in pts with low Alb, higher SD was associated with reduced mortality. Regarding Alb, an unidirectional relation between DR and outcome was observed, whereas the relation between DR with outcomes was bidirectional for P (Fig1&2).

Conclusions: The relationship between P variability and mortality was apparent at all levels of P. In well-nourished pts, higher P variability are associated with increased risk of mortality, which is related to the adverse effects of both an increase and a decline of this parameter. In pts with low Alb, the apparently paradoxical association between higher levels Alb variability and better survival due to an improvement of nutritional and inflammatory status, related to a positive DR. Due to possible nonlinear relations between risk factors and outcomes in patients on HD, variability should ideally be explored by various metrics.



PO1735

Restrict Dietary Phosphorus to Decrease Proteinuria and Prevent Decline in Glomerular Filtration Rate in CKD Stages 1 and 2

Anita Saxena. Renal Nutrition Group *Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.*

Background: Though dietary phosphorus restriction is therapeutic for disordered phosphorus homeostasis, early restriction of dietary phosphorus is not advised in CKD. Aim: Does early control of dietary phosphorus ameliorates proteinuria, prevent decline in glomerular filtration rate and prevent rise in FGF-23.

Methods: One year longitudinal study on 79 CKD stages 1 and 2 patients. eGFR, serum creatinine, phosphorus, calcium, FGF-23, soluble α-Klotho iPTH FGF 23, blood pressure, were evaluated and compared with 35 controls. 3 days dietary intake was taken using standard methodology on first visit, 6 and 12 months. CKD patients were grouped based on dietary phosphorus intake: Group 1 (n 42): normal phosphorous intake (<1000mg/day) and Group 2 (n=37): high phosphorous intake (>1000mg/d). Patients in Group 2 were educated on high and low phosphorus foods and counselled to adopt a plant-based diet, for low phosphorus absorption with directed diet plan. Data were analysed using SPSS.

Results: At baseline there was no significant difference in the GFR (group1 85.00±18.64 ml/min vs group 2 82.53±16.30ml/min), serum creatinine between groups. In group2 ; GFR, sKlotho, serum phosphorus and FGF-23 correlated significantly with dietary phosphorus intake. In group 2, FGF-23, serum phosphorus, dietary protein and phosphorus intake were significantly higher and sKlotho was significantly lower than group 1. There was significant difference in serum phosphorus (p 0.000), iPTH, (p 0.004), FGF23 (p0.000), Klotho (p0.000), urinary protein (p0.000), dietary protein (Group 1 37.57±3.40; Group 248.79±5.86 p 0.000) and phosphorus (Group 1868.96±69.99 mg/d and Group 2 1312.26±137.57 mg/d p 0.000) intake and dietary phosphorous to protein ratio (p 0.000) between groups 1 and 2. On dietary intervention in group 2 GFR increased p 0.012 from 80.93±15.34 to 84.11±15.38; and to 87.43±18.27 ml/min at 6 and 12 months respectively, Urinary protein declined to 22.01±3.39 mg/mL. FGF 23 declined from 60.67±6.26 to 58.00±7.07 to 53.29±9.48 pg/mL at 12 months. Dietary phosphorus: protein ratio reduced significantly from 27.16±4.35 to 24.75±4.34 p 0.000 at 12 months ((p<0.000)). Urinary phosphorus excretion increased from 574.37±214.22 to 624.64±137.67 at 12 months.

Conclusions: Restricting dietary phosphorus in stages 1 and 2 can prevent progression of CKD and for control proteinuria.

PO1736

Understanding Obesity Management in CKD Patients

Michael Chiu, Kathy Koyle, Arsh Jain. *London Health Sciences Centre, London, ON, Canada.*

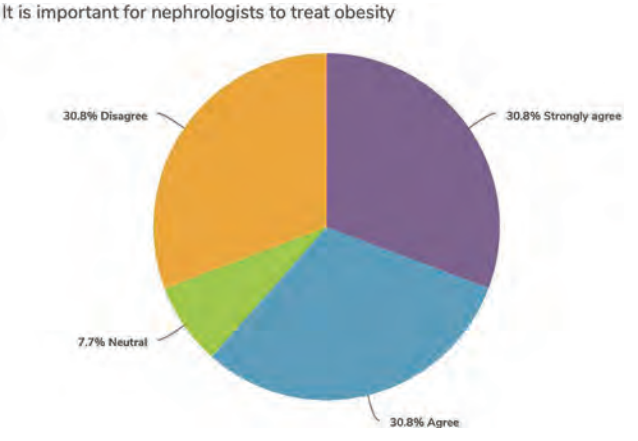
Background: Obesity is a global epidemic that is directly and indirectly linked to progression of chronic kidney disease (CKD). Nephrologists' attitude towards obesity management is not understood.

Methods: We surveyed 14 nephrologists practicing in an academic centre in London, Ontario, Canada to investigate their perception and management of obesity. Then we performed a retrospective chart review of patients in a CKD clinic with obesity (BMI >30kg/m2). Ten follow-up visits were randomly selected for each nephrologist between Jan-Dec 2019. Each chart was assessed for documentation of obesity and a management plan such as lifestyle counselling, pharmacologic intervention, or specialist referral.

Results: There were 13 responses (93%). Responses from a 5-point Likert scale, agree and strongly agree, have been combined. All nephrologists agreed that obesity negatively impacts CKD patients. 92% reported that discussing obesity evokes a negative response and 39% thought patients want to discuss obesity. Interestingly, 0% of nephrologists thought patients know that obesity has effective treatments. 85% of nephrologists talked to their patients about obesity, but 0% felt that they had time to treat it. With regards to management, 54% of nephrologists were comfortable with non-pharmacologic treatment, but only one was comfortable with pharmacologic treatments. 85% of respondents felt that patients should be referred to a specialist. A total of 140 charts were reviewed with a mean age 66 years, weight 105 kg, and BMI 37 kg/m2. Only one chart had obesity as a clinical issue and documented a weight loss discussion using non-pharmacologic strategies.

Conclusions: Our results suggest that obesity is rarely managed despite nephrologists' desire to treat it. This care gap can be addressed using robust Quality Improvement principles. Our centre will improve obesity management by developing a clinical handbook for nephrologists on how to efficiently address obesity with patients as well as a partnership and streamlined referral process to an obesity specialist.

Funding: Clinical Revenue Support



PO1737

Changes over Time in DASH Diet Accordance by Racial/Ethnic Groups Among US Adults

Tanushree Banerjee,[1] Charles E. Mcculloch,[1] Deidra C. Crews,[2] Nilka Rios Burrows,[3] Alain Koyama,[3] Hal Morgenstern,[4] Rajiv Saran,[4] Neil R. Powe.[1] *[1]University of California San Francisco, San Francisco, CA; [2]Johns Hopkins University, Baltimore, MD; [3]Centers for Disease Control and Prevention, Atlanta, GA; [4]University of Michigan, Ann Arbor, MI.*

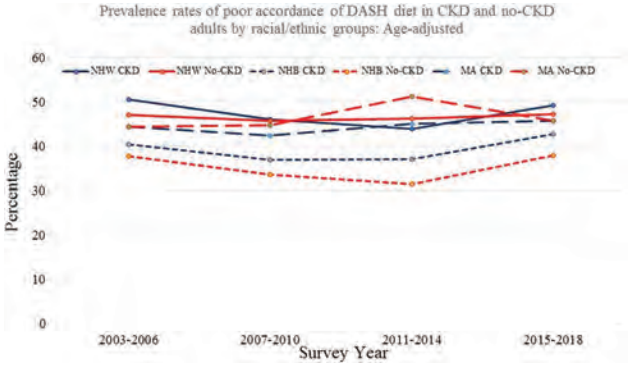
Background: Recommendations for healthy dietary patterns may vary for individuals with and without CKD. Racial/ethnic disparities in dietary quality exist, yet there is limited understanding of how dietary patterns have changed over years in different racial/ethnic groups. We examined trends in accordance to a Dietary Approaches to Stop Hypertension (DASH) diet by different racial/ethnic groups in adults with and without CKD.

Methods: We used data from the 2003-2018 NHANES to estimate the prevalence of DASH diet accordance among individuals aged≥20 years with CKD (ACR≥30mg/g or eGFR 15-59 ml/min) and no-CKD by racial/ethnic group. Self-reported race/ethnicity was categorized as non-Hispanic White (NHW), non-Hispanic Black (NHB), Mexican American (MA), or other. Change in diet composition over 16 years was assessed with a DASH diet agreement score with the years collapsed into 2003-06, 2007-10, 2011-14, 2015-18. We calculated the score based on 9 target nutrients by coding each as 1 for met and 0 for not met and summing to a total score of 9. Lowest tertile of the score was considered poor accordance. Prevalence rates were estimated for racial/ethnic groups after age-standardizing to the 2010 US Census data. Time trends in age-adjusted DASH diet prevalence were assessed using logistic regression with time interval as a predictor.

Results: Overall, the prevalence of poor accordance to a DASH diet was 13.5% and 17.5% in adults with CKD and no-CKD. Throughout the period, the age-adjusted prevalence of poor accordance was higher in NHB with CKD (prevalence did not change significantly, Figure) than in NHB with no-CKD. For MA, a significant change in prevalence was noted among no-CKD (ptrend=0.008), but not in those with CKD.

Conclusions: Poor accordance to a DASH diet was greater in adults with no-CKD. However, prevalence of poor accordance did not change in NHB and MA with CKD. Efforts to further improve promotion and accordance to DASH diets may help address CKD progression and health disparities in the US.

Funding: Other U.S. Government Support



PO1738

Food Purchasing Patterns Among Participants of a Dietary Intervention Trial for African Americans with Hypertension and CKD

Rohin A. Aggarwal, Meghana S. Iragavarapu, Raneitra Grover, Taharat T. Sheikh, Rebecca Brody, Kathryn A. Carson, Chiazam Omenyi, Edgar R. Miller, Deidra C. Crews. Five Plus Nuts and Beans for Kidneys Investigators *Johns Hopkins University, Baltimore, MD.*

Background: Financial resources and the surrounding food environment can impact healthy food purchasing patterns and may play a role in disparities in CKD. We examined predictors of healthy food purchases among control group participants of a clinical trial who were assigned to receive a gift card to a grocer worth $30 per week for 4 months ($480 total) but received no specific guidance on purchases.

Methods: We examined purchasing patterns of 50 participants using receipts linked to a grocer club card. The primary outcome of interest was the number of fresh or frozen fruit or vegetable items purchased, dichotomized at the median to those purchasing <= 6 and > 6 types of fruits/vegetables. Predictors examined included participant sociodemographic factors and food environment factors (i.e. living in a healthy food priority area). Statistical analyses included descriptive statistics and multiple linear regression.

Results: All participants were African American; median age was 63 yrs; 64% were female. Most (78%) were either unemployed or retired; 58% received a H.S. diploma/GED or less. Half had annual income < $25,000. Purchases made included both food and non-food items and many used other funds beyond those from the study. Adjusting for income, women purchased 2.3 more fruit/vegetable items than men (95% CI 0.2-4.5). Those purchasing more fruits/vegetables spent a greater total amount than those purchasing fewer fruits/vegetables.

Conclusions: In a dietary intervention trial for African Americans with CKD, healthy food purchases differed by sex, income level, and dollar amount spent, but not by food security or neighborhood food environment.

Funding: Other NIH Support - NHLBI; NIMHD

Participant Characteristics by Number of Fruits/Vegetables Purchased

	≤ 6 (N=26)	> 6 (N=24)	P value
Age in years, median (IQR)	65 (56-71)	62.5 (55-68)	0.41
Female, %	13 (50)	19 (79)	0.04
Employed full or part time, %	4 (15)	10 (42)	0.06
Income group:	-	-	0.04
< $10,000	6 (29)	2 (11)	
$10,000-24,999	9 (43)	8 (42)	
$25,000-49,999	5 (24)	4 (21)	
$50,000-99,999	1 (5)	3 (16)	
$100,000+	0 (0)	2 (11)	
Lives in Healthy Food Priority Area (limited food access)	8 (31)	4 (17)	0.35
Food insecure (self-reported)	9 (35)	7 (29)	0.77
Total dollars spent, median (IQR)	$355.3 (179.7-467.7)	508.9 (356.5-604.2)	0.003
Dollars spent on fruits/vegetables, median (IQR)	$29.4 (21.5-72.9)	$88.8 (60.2-117.6)	<0.001

PO1739

Experiences of Participants of a Dietary Intervention Trial for African Americans with Hypertension and CKD

Kristal L. Brown, Sophia Lou, Mary Ann C. Stephens, Zehui Zhou, Tahiyat Sheikh, Denise E. Saint-Jean, Chiazam Omenyi, Rebecca Brody, Edgar R. Miller, Deidra C. Crews. Five Plus Nuts and Beans for Kidneys Investigators *Johns Hopkins University, Baltimore, MD.*

Background: African Americans are disproportionately affected by hypertension (HTN) and CKD and evidence suggests dietary modifications towards a more Dietary Approaches to Stop Hypertension (DASH)-accordant diet could improve outcomes for this population. We aimed to explicate barriers and facilitators of healthy eating, and the perceived benefits of the intervention among completed participants of a dietary intervention trial for African Americans with HTN and CKD. Participants were randomized to one of two groups: 1) Self-Shopping DASH (S-DASH) diet group with $30/week grocery allowance for 4 mo. but no specific guidance on purchases, followed by no food allowance for 8 mo.; or 2) Coaching DASH (C-DASH) diet advice group with a $30/week food allowance and assistance in purchasing foods for 4 mo., followed by intermittent coaching without food allowance for 8 mo.

Methods: We performed a content analysis of transcripts from semi-structured interviews with participants who completed the trial (13 C-DASH; 12 S-DASH were randomly selected). Thematic analyses followed 5 stages: 1) reading and rereading all transcripts and utilizing audio recordings as needed for clarity; 2) three coders reading two of the same transcripts, coding them, and comparing codes which were then used to create the initial coding framework; 3) defining codes, coding additional transcripts, discussing/revising the coding framework; 4) formulating initial themes and 5) diagramming relationships among initial themes to merge overlapping themes.

Results: Participants were a mean age of 62 ± 9.3 years, 36% were male. Key themes included healthy diet facilitators (food tracking, motivation, social support, and perception of healthy foods); barriers (transportation, past eating habits, stress and COVID mitigation); and impact of the trial on knowledge and health.

Conclusions: Participants of a dietary intervention trial for African Americans with HTN and CKD identified several facilitators and barriers to healthy eating that could inform future efforts to address disease burden in this population.

Funding: Other NIH Support - NHLBI; NIMHD

Themes	Representative Quotes
Healthy Diet Facilitators	[in reference to materials from the study and grocery allowance] made it easier, I guess, with both phases of it, with giving me all the feedback and stuff like that. You all would give me feedback like doing a good job, keep up the good work, you know, positive reinforcement, whatever you call it. All that made a big difference. (S-DASH) [in reference to support system and ability to eat healthy] Well, like my daughter, she would help, she would go get the foods for me, pick the foods up for me when I couldn't get there. So, she would make sure that, you know, if I couldn't get there, she made sure I would get the foods and get them to me. And she followed me, once I started eating more fruits and vegetables, she started eating more, you know. (C-DASH)
Healthy Diet Barriers	[in reference to things that were difficult to change] … because fresh vegetables are more expensive than canned vegetables. So that was a -- that was another kind of hurdle that I kind of really didn't follow. (S-DASH) [in reference to grocery shopping options and if shopping behaviors changed in the study] And we had a—where I live at now, we had, like, a farmer's market that would come every week as well, but when COVID came, they don't come anymore. (C-DASH)
Impact of Trial on Knowledge and Health	[in reference to how study affected health] Well, it—like I said, it helped me control my pressure a little bit. It's making me more aware and pay attention to my labs plus it's helping me maintain my weight." (C-DASH) [in reference to eating changes since being in the study] And they told me to watch, I started watching my labels as far as the sodium and stuff. (S-DASH)

PO1740

Barriers and Facilitators to DASH Diet Adherence Among Black Adults with CKD: A Qualitative Study

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Background: Black individuals are disproportionately burdened by hypertension and chronic kidney disease (CKD). The Dietary Approaches to Stop Hypertension diet (DASH) improves hypertension in Black individuals and is associated with improved CKD outcomes. Yet, adherence to DASH among Black individuals is low. We conducted a qualitative study to assess barriers and facilitators to DASH adherence in Black adults with CKD.

Methods: We conducted focus groups and individual interviews with Black adults with CKD stages 3 or 4 (n=22). Questions included perceptions of CKD and DASH, the cultural-centeredness of DASH, and barriers and facilitators to adopting DASH. Qualitative content analysis was used to analyze interview transcripts.

Results: Among 22 participants (2 focus groups, 8 individual interviews), 13 (59%) had CKD stage 3, 13 (59%) were female, the median age was 61 years, and 19 (90%) had hypertension. Some participants reported having previously heard of DASH, which they perceived as a healthy diet. Participants perceived DASH as culturally-compatible based on 3 emergent themes: 1) Blacks individuals already eat DASH-recommended foods ("*Blacks eat pretty much like this*"); 2) traditional (e.g., southern or soul-food) recipes can be modified into healthy versions ("*you can come up with decent substitutes to make it just as good)*", and 3) diet is not uniform among Black individuals (*"I can't say that I eat traditional"*). Barriers included unfamiliarity or inexperience measuring portion sizes, inadequate cooking skills, unsupportive household members, and high cost of healthy food. Eleven (52%) reported "rarely" or "never" having leftover money to

purchase healthy food after paying monthly bills. Facilitators included having local access to healthy food, living alone or with supportive household members, and having will power and internal/external motivation for change.

Conclusions: Black adults with CKD were interested in adopting DASH and viewed it as a healthy, culturally-compatible diet. Recognizing that diet in Black adults is not uniform, interventions should emphasize person-centered, rather than culture-centered, approaches that minimize barriers and enhance facilitators to adherence.

Funding: Other NIH Support - NHLBI

PO1741

Priorities for Person-Centered Obesity Management in ESKD

Meera N. Harhay, Brandy-Joe Milliron, Jasmine M. Sweeting, Joanna H. Lee, Sneha S. Hingorany, Jennifer R. Haileselasse, Bengucan Gunen, Ann C. Klassen. *Drexel University, Philadelphia, PA.*

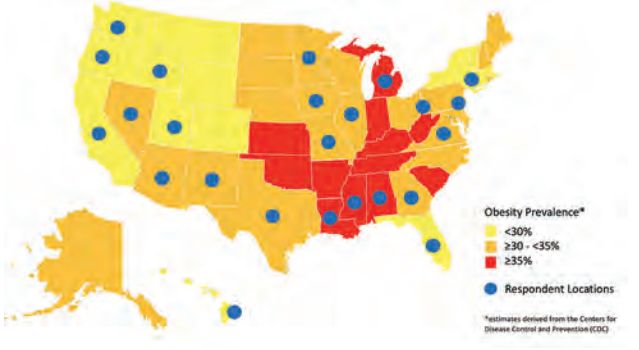
Background: Although obesity is a pervasive kidney transplant barrier, little is known about the social, dietary, and process-of-care challenges to addressing obesity among individuals with ESKD.

Methods: Using purposive sampling we recruited adults with ESKD and obesity (N=40) and ESKD health care professionals (HCPs, N=20) in the United States for semi-structured interviews to elicit perspectives about obesity and barriers and strategies for healthy weight loss. Recorded phone interviews lasting 1.5 hours were transcribed verbatim and analyzed using inductive and deductive thematic analysis.

Results: Median patient age was 55 (interquartile range [IQR] 47,63) years, median dialysis exposure was 5 (IQR 3,10) years, 51% were female, 27% were Black, and median BMI was 37.8 (IQR 33.5, 40.8) kg/m^2. HCPs were renal dietitians, nephrologists, and transplant surgeons. Five themes emerged from patient interviews: 1) obesity-related counseling typically limited to immediate goal (transplant BMI requirements); 2) obesity as a life-long disease or linked to trauma; 3) food choices driven by fatigue and poor sleep quality; 4) existing nutrition programs not transferable to ESKD; 5) absence of culturally-effective nutrition counseling. HCP interviews revealed uncertainty about provider roles and responsibilities for addressing obesity and underscored that poverty and low health literacy are barriers to healthy weight loss.

Conclusions: Obesity-related care for people with ESKD is often limited to addressing BMI limits for transplant. Weight loss interventions for people with ESKD and obesity should be tailored with knowledge of social and financial context and a shift in focus from short-term goals to long-term health.

Funding: NIDDK Support



Geographic distribution of semi-structured interview respondents, including patients with dialysis-dependent kidney disease and obesity, renal dietitians, nephrologists, and transplant surgeons.

PO1742

Association of Nutritional Data and Glycemic Variability in CKD Patients

Nandakishor Kapa, Harshanna Badhesha, Tae Youn Kim, Olivia A. Moss, Chenoa R. Vargas, Seung M. Jin, Henning Langer, Usman Rehman, Jennifer E. Norman, Armin Ahmadi, Thomas Jue, Maryam Afkarian, Baback Roshanravan. *University of California Davis Medical Center, Sacramento, CA.*

Background: Insulin resistance is highly prevalent in chronic kidney disease (CKD) and strongly associated with adverse clinical outcomes. Glycemic variability measured by continuous glucose monitoring (CGM) is a clinical measure of insulin resistance. The association of dietary recalls and healthy eating measures with CGM readings in CKD are unknown.

Methods: We recruited diabetic (n=7) and non-diabetic (n=8) participants with eGFR<60ml/min who had CGM performed over 2 weeks. The ASA24 Dietary Assessment Tool was used to perform dietary recalls on 3 random days over the CGM period. The Healthy Eating Index 2015 (HEI-2015) was used to determine how closely an individual's eating pattern matched Dietary Guidelines for Americans' recommendations. A linear mixed model adjusting for diabetes status was used to determine association of dietary measures from ASA24, HEI-2015 scores, and CGM readings over 3 days.

Results: Participants had a mean age 59±11years, eGFR 35.5±4.6ml/min/1.73m^2 and BMI 32.8±4.6kg/m^2. Greater dietary added sugar, total carbohydrate, and carbohydrate to fiber ratio was associated with higher average daily blood sugar (P<0.001, P<0.001, and P=0.006, respectively). Each 1-point greater HEI score (healthier eating) was inversely associated with average daily blood sugar for fatty acid (-1.09 mg/dL; 95% CI -2.11, -0.07), added sugar (-1.76 mg/dL; CI -3.11, -0.4), vegetable (-2.85 mg/dL; CI -5.5, -0.2), and fruit (-2.63 mg/dL; CI -5.03, -0.22). HEI total score did not show significant association with the CGM readings.

Conclusions: Greater added sugar, saturated fats, and dietary carbohydrate to fiber ratio are strongly associated with greater average daily blood sugar. Sugar, carbohydrates, and saturated fats contribute to glycemic variability. Healthy eating centered on low sugar, low fat, and high vegetable and fruit intake may improve glycemic control in both diabetic and non-diabetic CKD patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

HEI-2015 Scores Associated with CGM in Non-Diabetic and Diabetic CKD Patients

	CGM Value (β (95% CI))	
HEI-2015 (n=15)	Average daily blood sugar (mg/dL)	Percent time above target (%)
HEI Fatty Acid	-1.09 (-2.11, -0.07)	-0.34 (-1.19, 0.5)
HEI Added Sugar	-1.76 (-3.11, -0.4)	-1.13 (-2.24, -0.02)
HEI Total Vegetable	-2.85 (-5.5, -0.2)	-1.18 (-3.36, 0.98)
HEI Total Fruit	-2.63 (-5.03, -0.22)	-1.39 (-3.37, 0.59)

PO1743

Late Stage 3 CKD Is an Independent Risk Factor for Sarcopenia, but Not Proteinuria

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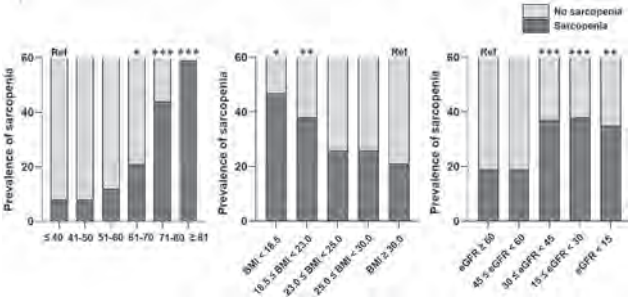
Background: Most epidemiologic studies assessing the relationship between chronic kidney disease (CKD) and sarcopenia have been performed in dialysis patients. This study aimed to evaluate the relationship between estimated glomerular filtration rate (eGFR), proteinuria, and sarcopenia in patients with non-dialysis-dependent CKD.

Methods: A total of 892 outpatients who did not show any rapid changes in renal function were enrolled in this observational cohort study. We measured the muscle mass using bioimpedance analysis and handgrip strength (HGS), and sarcopenia was defined as low HGS and low muscle mass.

Results: Sarcopenia was found in 28.1% of the patients and its prevalence decreased as body mass index (BMI) increased; however, in patients with BMI ≥ 23 kg/m^2, the prevalence did not increase with BMI. As eGFR decreased, the lean tissue index and HGS significantly decreased. However, the eGFR did not affect the fat tissue index. The risk of sarcopenia increased approximately 1.6 times in patients with eGFR < 45 mL/min/1.73 m^2. However, proteinuria was not associated with sarcopenia. With a decrease in eGFR, the lean muscle mass and muscle strength decreased, and the prevalence of sarcopenia increased.

Conclusions: In patients with late stage 3 CKD, further assessment of body composition and screening for sarcopenia may be needed.



PO1744

Association of Serum Selenium Levels with the Response to Erythropoiesis-Stimulating Agents in Maintenance Hemodialysis Patients

Minoru Yasukawa, Shigeyuki Arai, Michito Nagura, Daigoro Hirohama, Osamu Yamazaki, Yoshifuru Tamura, Yoshihide Fujigaki, Shigeru Shibata. *Teikyo Daigaku Igakubu Daigakuin Igaku Kenkyuka, Itabashi-ku, Japan.*

Background: Reduced response to erythropoiesis-stimulating agent (ESA) has been shown to be associated with poor outcomes in maintenance hemodialysis (MHD) patients. Selenium is a trace element that modulates diverse physiological processes, such as immune responses and cardiovascular function. Previous studies also indicate that selenium and selenoproteins are involved in erythropoiesis. However, its role in the control of anemia in chronic kidney disease patients remains unclear. In this study, we determined serum selenium levels in MHD patients and analyzed their association with hemoglobin levels and the doses of ESA.

Methods: The study included 174 patients who received MHD from four dialysis facilities. We obtained data on demographics, laboratory, comorbidities, hemodialysis prescription and medication by medical record abstraction. Concentration of selenium was measured in serum using ICP-MS.

Results: The mean age was 67.2 years, 77% were male, and 44% of patients received dialysis at least for five years. The average serum selenium concentrations in our cohort were 10.7 ± 2.9 μg/dL, and 88 patients (51%) had a selenium levels of less than 10.5 μg/dL (a lower limit of normal serum selenium levels for adult Japanese population). Patient characteristics, including age, sex, BMI, dialysis vintage, and comorbidities were not significantly different between the low selenium (Low) group and normal selenium (Normal) group. However, the percentage of patients receiving ESA tended to be higher in Low group than in Normal group, whereas hemoglobin levels as well as percentage of patients receiving iron therapy were similar between the groups. In a subgroup analysis involving 146 patients who received ESA, we found a significant negative correlation between serum selenium levels and ESA-resistance index (ERI) (r = -0.25, p = 0.002).

Conclusions: Our study indicates that low levels of serum selenium are associated with poor response to ESA. The relationship between selenium and response to ESA in MHD patients merits further evaluation in larger populations.

PO1745

Serum Irisin and Prediction of Cardiovascular Events in Elderly Patients with CKD Stage 3-5

Teresa Del Mastro, Teresa Arcidiacono, Monica Avino, Arianna Bologna, Nadia Edvige Foligno, Federico Persico, Giuseppe Vezzoli. *IRCCS Ospedale San Raffaele, Milano, Italy.*

Background: Irisin is a circulating myokine released from skeletal muscles after physical exercise. Irisin production decreases during the course of chronic kidney disease (CKD) as a potential consequence of sarcopenia and physical inactivity.

Methods: This observational study explored the relationship of serum irisin with cardiovascular outcome in 79 patients with stage 3-5 CKD.

Results: Serum irisin was significantly higher in healthy subjects (n=20) than CKD patients (7±2 vs 3.1±0.9 μg/ml; p=0.0001) and was higher in patients with CKD stage 3 (3.2±1 μg/ml) compared with patients at stage 4 and 5 taken together (n=36, 2.8±0.7 μg/ml, p=0.05). Patients in the lowest serum irisin tertile had lower serum 1,25(OH)$_2$D levels (21±11 pg/ml) than patients in the middle (30±13 pg/ml; p=0.005) and the highest tertile (27±14 pg/ml; p=0.047). Patients in the highest tertile had lower Kauppila score (10.6±6.9) than patients in the middle (11.8±5.5; p=0.007) and the lowest tertile (6.9±6.8; p=0.043). Twenty patients suffered from cardiovascular events during a 3-year follow-up. A Cox regression model using age, body weight, presence of diabetes mellitus, gender, Kauppila calcification score, serum values of FGF23 (as logarithm), phosphate, sclerostin, albumin and cholesterol, eGFR and serum irisin tertiles as covariates showed that patients in the highest tertile of serum irisin had a lower cardiovascular risk than patients in the middle tertile (B 2.38, OR 10.8, 95%CI 1.65-58.13; p=0.013) or in the lowest tertile (B 1.61, OR 5, 95%CI 1.09-22.83; p=0.038).

Conclusions: These findings suggest that serum irisin may be a marker of cardiovascular outcome in CKD patients.

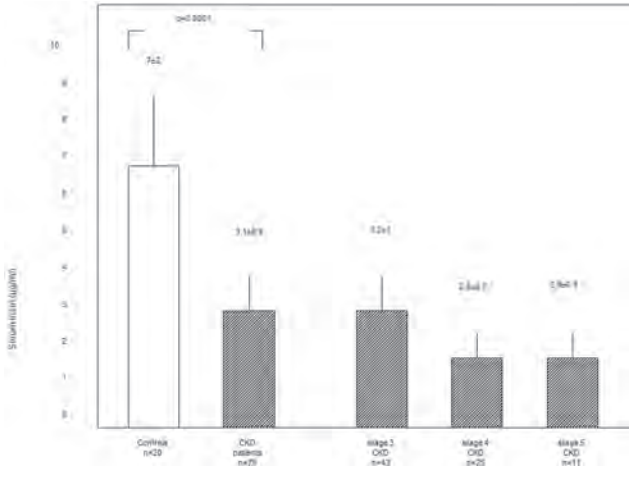


Image 1

	Tertiles of serum irisin		
	The lowest tertile	the middle tertile	the highest tertile
N (M/F)	27(20/7)	25(16/9)	27(17/10)
Age (yrs)	70±7	71±6	67±14
Body weight (kg)	80±13	76±15	73±16
Serum calcium (mmol/l)	2.33±0.12	2.33±0.12	2.33±0.12
Serum phosphate (mmol/l)	1.18±0.22	1.09±0.21	1.13±0.24
Serum creatinine (mg/dl)	2.49±1.21	2.15±0.65	2.20±1.24
GFR (ml/min)	30±14	31±11	35±16
Serum Alkaline phosphatase (U/l)	83±34	115±65	102±56
Serum 1,25(OH)2D (pg/ml)	21±11[a]	30±13	27±14
Serum PTH (pg/ml)	38±30	46±27	54±74
Serum FGF23 (pg/ml)	106±94	90±60	236±587
Serum albumin (g/dl)	4.05±0.32	4.11±0.36	3.97±0.4
Serum irisin (μg/ml)	2.2±0.3	3±0.2	4.0±0.8
Kauppila score	10.6±6.9	11.8±5.5	6.7 ±6.8[b]

[a]p=0.005 vs patients in the middle tertile and p=0.047 vs patients in the highest tertile
[b]p=0.007 vs patients in the middle tertile and p=0.043 vs patients in the lowest tertile

Image 2

PO1746

Deoxycholic Acid (DCA) and Cognitive Impairment and Decline in the Chronic Renal Insufficiency Cohort (CRIC) Study

Kristen L. Nowak,[1] Makoto Miyazaki,[1] Michel Chonchol,[1] Anand Srivastava,[2] Michael J. Fischer,[3] Ana C. Ricardo,[3] Jiang He,[4] Katherine T. Mills,[4] Katherine L. Wolfrum,[5] Amanda H. Anderson,[4] Manjula Kurella Tamura,[6] Harold I. Feldman,[5] Tamara Isakova,[2] Anna Jovanovich.[7] *[1]University of Colorado Health, Aurora, CO; [2]Northwestern University Feinberg School of Medicine, Chicago, IL; [3]University of Illinois at Chicago, Chicago, IL; [4]Tulane University, New Orleans, LA; [5]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [6]Standford University, Palo Alto, CA; [7]VA Eastern Colorado Health Care System, Aurora, CO.*

Background: Cognitive impairment is common in chronic kidney disease (CKD). The secondary bile acid, DCA, is associated with endothelial dysfunction and oxidative stress, characteristics of cognitive impairment. DCA is also associated with cognitive impairment and risk of Alzheimer's dementia among older adults without CKD. Whether DCA is associated with cognitive impairment in CKD is unknown.

Methods: We used multivariable-adjusted regression models to cross-sectionally and longitudinally evaluate the association between fasting serum DCA levels measured at visit 5 (considered baseline) and cognitive impairment. Among 2836 CRIC Study participants, cognitive impairment was assessed by the Mini-mental State Exam (MMSE). Among 698 participants enrolled in the CRIC Cognitive (COG) Study, cognitive impairment was further assessed by Trails A&B, Category Fluency, Buschke Recall, and Boston Naming tests. Cognitive impairment was defined by a test score >1 standard deviation (SD) worse than the test mean.

Results: Mean age was 59 ± 10 years, 45% were female, and 39% were black. In cross-sectional analyses, there was no association between DCA and cognitive impairment assessed by MMSE in the total cohort after adjustment for demographics and clinical factors (prevalence ratio per 1-SD increase ln DCA: 1.03, 95% CI 0.91-1.17). In longitudinal analyses, DCA was associated with progressive impairment (mean annual % change MMSE per 1-SD increase ln DCA: -0.15, 95% CI -0.34 - -0.02), but not with incident impairment. Among CRIC COG Study participants, in cross-sectional analyses DCA was associated with cognitive impairment based on Category Fluency (prevalence ratio per 1-SD increase ln DCA: 1.36, 95% CI 1.05-1.76) but not with other measures of impairment. In longitudinal analyses among CRIC COG Study participants, DCA was not associated with progressive or incident cognitive impairment.

Conclusions: Among individuals with CKD stages 2-4, higher DCA levels were independently associated with prevalent cognitive impairment in Category Fluency and progressive cognitive impairment assessed by MMSE.

Funding: NIDDK Support, Veterans Affairs Support

PO1747

The Association of Sodium Intake and Albuminuria According to Cotinine-Verified Smoking Status: Korean National Health Examination Survey (KoNHES)

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Background: Smoking and high sodium intake are reported about the association with chronic kidney disease. Smoking and sodium intake are modifiable risk factors and the implementation of life style changes in the broad population could have a beneficial effect on public health. We assessed the association of sodium intake and smoking on the presence of albuminuria.

Methods: An observational study from the Korean National Health and Nutrition Examination Survey (2008-2011, 2014-2018) was performed. We included 38,161 adults with eGFR≥60 ml/min/1.73m^2 and had urine cotinine/creatinine ratio (Ucot/Ucrea). Smoking status was assumed by Ucot/Ucrea. 24 hour sodium intake was estimated from spot urine sodium using Kawasaki formula. Albuminuria was defined as urine albumin creatinine ratio ≥ 30mg/g.

Results: Ucot/Ucrea level was significantly higher in current smokers than those in ex-smokers and non-smokers (920.22±9.00, 48.30±2.46, vs. 23.83±1.29 ng/mg, P<0.001). Non-smokers who were exposed to secondhand smoke showed significantly higher Ucot/Ucrea levels than those who were not exposed to secondhand smoke (37.74±3.14 ng/mg vs 16.71±1.13 ng/mg, P<0.001). Ucot/Ucrea level was significantly associated with sodium intake. Sodium intake of 2nd and 3rd Ucot/Ucrea tertile were significantly higher than that of 1st Ucot/Ucrea tertile (4.15±1.31, 4.13±1.43 vs. 3.73±1.15 mg, P <0.001). The quartile groups of sodium intake had a linear relationship with albuminuria (5.2, 5.8, 7.5, and 9.7%, P<0.001). The highest quartile of sodium intake was significantly associated with risk of albuminuria (OR 1.43, 95% CI 1.05-1.93, P=0.022). We evaluated the association of sodium intake with albuminuria according to smoking status estimated by Ucot/Ucrea. In the group with the highest Ucot/Ucrea level, the highest sodium intake quartile indicated significantly higher risk of albuminuria compared to that of lowest quartile (OR: 2.05, 95% CI: 1.20-3.52, P=0.009).

Conclusions: High dietary sodium intake is an independent risk factor for albuminuria and this association was highlighted in high Ucot/Ucrea group. The synergistic effects of cigarette smoking and high salt intake might increase the risk of albuminuria.

PO1748

Interplay Between Serum Thyrotropin, Free Thyroxine, and Thyroid Autoantibody Levels and Survival in a Prospective Hemodialysis Cohort

Amy S. You,[1] Gregory Brent,[2] John J. Sim,[3] Yalitzi Guerrero,[1] Sara S. Kalantar,[4,1] Rebecca Ahdoot,[1] Yoko Narasaki,[1] Matthew D. Nguyen,[1] Csaba P. Kovesdy,[5] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh,[1] Connie Rhee.[1] *[1]University of California Irvine, Irvine, CA; [2]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [3]Kaiser Permanente Southern California, Pasadena, CA; [4]University of California Berkeley, Berkeley, CA; [5]The University of Tennessee Health Science Center College of Medicine, Memphis, TN.*

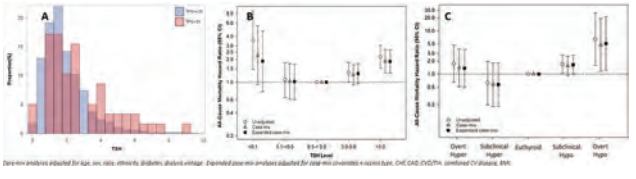
Background: CKD patients have a high prevalence of hypothyroidism (elevated serum thyrotropin [TSH]) which has been associated with worse survival. In patients with altered protein-hormone binding states (uremia, low/high circulating proteins) among whom routine "indirect" free thyroxine (FT4) assays are not as accurate, little is known about the impact of subclinical (high TSH+normal FT4) and overt (high TSH+low FT4) hypothyroidism and thyroid autoimmune status on hemodialysis (HD) survival.

Methods: In a multicenter prospective cohort of 1117 HD patients from the "Hypothyroidism, Cardiovascular Health, and Survival (HyCARDS)" Study, we conducted protocolized TSH, "direct" FT4 by equilibrium dialysis/tandem mass spectrometry (robust FT4 assessment method in altered protein-hormone binding), and anti-thyroid peroxidase antibody (anti-TPO Ab) assays every 6 months from 2011-19. We examined associations of severity of thyroid dysfunction ascertained by TSH gradations (subclinical vs. overt hypothyroid-range TSH levels) and pairings of TSH+FT4 (subclinical vs. overt hypothyroidism), as well as presence of elevated anti-TPO Abs with mortality using time-varying Cox models.

Results: TSH distributions were higher in those with elevated anti-TPO Abs. In analyses of TSH gradations, elevated TSH was associated with higher mortality (ref: 0.5-<3.0): HRs (95%CI) 1.30 (0.96-1.77) and 1.88 (1.31-2.68) for TSH 3.0-5.0 and >5.0. In analyses of paired TSH+FT4, overt hypothyroidism was associated with higher mortality (aHR [95%CI] 5.11 [1.23-21.28]), while subclinical hypothyroidism trended towards higher mortality (aHR [95%CI] 1.63 [0.98-2.72]). Elevated anti-TPO Abs were not associated with death.

Conclusions: In a prospective cohort of HD patients who underwent rigorous thyroid status assessment, both mild (subclinical) and severe (overt) hypothyroidism were associated with higher mortality. Further studies are needed to determine if correction of thyroid status with thyroid hormone replacement therapy improves survival in this population.

Funding: NIDDK Support



PO1749

Effect of Water Intake and Water Balance on All-Cause and Cardiovascular Mortality Based on a Nationwide Population Study

Seonmi Hwang,[1] Yaerim Kim,[3] Jeonghwan Lee,[2] Jae Yoon Park,[5] Kyung Don Yoo,[4] Yong Chul Kim,[1] Dong Ki Kim,[1] Yon Su Kim,[1] Chun Soo Lim,[2] Jung Pyo Lee.[2] *[1]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [3]Keimyung University School of Medicine, Daegu, Daegu, Republic of Korea; [4]Ulsan University Hospital, Ulsan, Republic of Korea; [5]Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea.*

Background: The water balance consists of loss of water and intake of water. Healthy people maintain a good physiological water balance in their daily lives. The aim of this study was to investigate whether fluid intake is independently correlated with all-cause mortality among the general US adult population. In addition, we evaluated the relationship between fluid intake and the participants' hydration status.

Methods: We conducted a prospective cohort study using 1999 to 2015 data from the National Health and Nutrition Examination Survey. A total of 39,039 patients aged over 19 years who had water consumption data using 24-hour dietary recall were enrolled. Participants' hydration status was measured by bioelectical impedance analysis (BIA). The all-cause mortality were calculated using the multivariable Cox model adjusting for comorbidities, body mass index, glomerular filtration rate, serum albumin, and total cholesterol representing nutritional status.

Results: In weighted multivariable Cox models, compared to people with lowest quartile of water intake, the adjusted hazard ratios (aHRs) for all-cause mortality in people with other quartiles 2nd, 3rd, and 4th were 0.83 (95% confidence interval [CI], 0.75-0.91), 0.76 (95% CI, 0.68-0.84) and 0.80 (95% CI, 0.72-0.88), respectively. Restricted cubic spline regression also found a U-shaped relationship between total body water and all-cause mortality. In the correlation analysis, as the water intake increased, the total body water amount measured by BIA increased. Additionally, participants showed lower mortality rates as the total amount of water in the body was higher (1st vs.2nd aHR 0.928 [95% CI, 0.622-1.384] and 1st vs. 3rd aHR 0.542 [95% CI, 0.315-0.933]).

Conclusions: In the general population, which is not in a disease state, too little water in the body and water intake are associated with increased mortality. It is important to maintain adequate hydration status through adequate water consumption.

PO1750

Serum Cystatin C-to-Creatinine Ratio Is a Potential Biomarker for Sarcopenia in Patients with Non-Dialysis-Dependent CKD

Illeon Cho, Yong Seon Choi, Jung Nam An, Sung gyun Kim, Young rim Song. *Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.*

Background: Sarcopenia is a prevalent complication in patients with chronic kidney disease (CKD) and linked with quality of life, morbidity and mortality. Sarcopenia is defined as clinical, functional and body compositional parameters, although several candidate biomarkers for this condition have been evaluated. This study aimed to evaluate serum cystatin C to creatinine (Cr) ratio as a potential biomarker for sarcopenia in patients with non-dialysis dependent CKD.

Methods: A total of 517 outpatients were enrolled in this observational cohort study. We measured the muscle mass (lean tissue index, LTI) using bioimpedance analysis and handgrip strength (HGS), and sarcopenia was defined as low HGS and low muscle mass.

Results: Sarcopenia was observed in 25.5% patients. The serum cystatin C/Cr ratio was significantly higher in patients with sarcopenia regardless of age, sex, eGFR, and BMI; and showed a positive correlation with age and pulse pressure, but LTI, HGS, hemoglobin, and serum albumin level showed a negative correlation with serum cystatin C/Cr ratio. Especially in patients with eGFR ≥ 45 mL/min/1.73 m^2, serum cystatin C/Cr ratio showed high negative predictive value in predicting sarcopenia (90.5%) and low LTI (90.4%). As the serum cystatin C/Cr ratio increased by 1, the prevalence risk of sarcopenia and low LTI increased by about 5.8 times and about 9.9 times even after adjusting for sex, age, BMI, underlying disease, albumin, Hb, and eGFR. The association between serum cystatin C/Cr ratio and sarcopenia was maximized in patients with eGFR less than 30, resulting in an increased prevalence risk of about 22.7 times, and in the case of low LTI, an independent association was found in patients with eGFR less than 45, and among them, a 43.9-fold increase in risk was identified. However, there was also no significant result for low HGS.

Conclusions: Serum cystatin C/Cr ratio is inexpensive and easily, quickly, and repeatedly measured; therefore, quick screening and management of sarcopenia will be possible, which will be of great help in the treatment of CKD patients.

PO1751

Prevalence of Inflammation and Associated Healthcare Resource Utilization in Patients with CKD

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Background: Many patients with chronic kidney disease (CKD) suffer from inflammation, which often increases as CKD progresses. Inflammation is a risk factor for comorbidities and complicates the treatment of anemia, which is common in CKD. Inflammation has been associated with reduced red blood cell and erythropoietin production, as well as increased hepcidin levels, which can lead to functional iron deficiency. Because data on the impact of inflammation on healthcare utilization (HCRU) in patients with CKD are limited, we aimed to assess HCRU in these patients.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a point-in-time survey of physicians and their patients with CKD (stage 3-5D) collected in the United States in 2018. Physician and patient reported HCRU-related information, such as the number of healthcare visits, hospitalizations, and tests conducted to diagnose and monitor patients. Inflammation was defined as C-reactive protein ≥4.9 mg/L, ferritin ≥700 ng/mL, or albumin ≤3.6 g/L. Fisher's exact and t-tests were conducted to assess differences in HCRU between patients with and without inflammation.

Results: There were 227/703 (32%) patients with inflammation; inflammation was present in 136/491 (28%) non-dialysis-dependent, and 91/212 (43%) dialysis-dependent patients. HCRU, including the mean number of healthcare visits, tests conducted, and hospitalizations in the last 12 months, number of pills and injections taken per day, and incidences of requiring a carer were greater in patients with inflammation vs those without (all p<0.05; Table 1).

Conclusions: We found that inflammation was common in patients with CKD and associated with greater HCRU across multiple measures in a real-world setting. Novel treatment approaches in CKD that are effective in patients with inflammation may help to reduce HCRU.

Funding: Commercial Support - FibroGen Inc

Table 1: Comparison of HCRU between patients with and without inflammation

	Patients with inflammation N, Mean (SD)	Patients without inflammation N, Mean (SD)	p-value
Number of healthcare visits in last 12 months for CKD[1]	215, 8.9 (8.4)	467, 6.7 (6.8)	0.0002
Number of tests conducted in last 12 months to monitor CKD[1]	223, 18.4 (7.4)	469, 15.5 (6.5)	<0.0001
Number of hospitalizations in last 12 months for CKD[1]	216, 0.3 (0.6)	469, 0.1 (0.5)	0.0010
Number of pills taken per day for CKD[2]	80, 3.2 (2.5)	197, 2.1 (2.6)	0.0014
Number of injections per day for CKD[2]	56, 0.7 (1.1)	135, 0.4 (0.6)	0.0061
Someone is responsible for the patient's daily needs[1]	227, 18% (*)	476, 11% (*)	0.0055

SD, standard deviation
* SD not applicable
[1] – physician reported data
[2] – patient reported data

PO1752

Effects of Home BP-Based Behavioral Guidance on Urinary Albumin Excretion in School Workers with Microalbuminuria-Miyagi Karoshi Prevention Study

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Background: Prevention of work-related cardiovascular events, or Karoshi is an important social issue in Japan. This study aimed to examine if home-BP based behavioral guidance is effective to reduce CV event risk in school staffs associated with microalbuminuria, a marker of endothelial damage.

Methods: Subjects were 3868 Miyagi prefectural school workers. Urinary albumin excretion adjusted for creatinine (UAE) and daily sodium intake based on Tanaka method were examined together with usual annual health check-up in 2019. Among them, 169 were diagnosed as having microalbuminuria (30-299.9mg/gCr). Ninety-one subjects agreed to receive the home-BP based health guidance. Guidance was given according to 5 days mean of home BP measurements, or encouraging medical consultation and lifestyle guidance for subjects with ≧135/85mmHg, lifestyle guidance for subjects with 125-134/80-84mmHg and adequate lifestyle guidance for subjects <125/80mmHg if necessary. Outcomes were UAE and frequency of microalbuminuria in the next year. Data were compared between guided and non-guided subjects. Subjects with menstruation were excluded from analysis. Final analysis number was 48 and 43 for guided and non-guided groups.

Results: Guided group demonstrated similar baseline data as compared with non-guided group for age, male gender, body mass index, cardiovascular risk factors and UAE level. Prescription rate for hypertension and diabetes also was similar between them. LogUAE was significantly and similarly decreased in both groups. One year later, microalbuminuria was present in 31.2% for guided group and 30.2% for non-guided group (n.s.). Systolic BP was lowered significantly as compared with baseline in the guided group but not in non-guided group. HbA1C level and daily sodium intake were increased as compared with baseline in guided group but not in non-guided group. Sensitivity analysis excluding treated patients for hypertension or diabetes from baseline demonstrated essentially similar results.

Conclusions: Reduction in UAE did not differ between groups with or without home-BP based behavioral guidance. Our data suggest that notification of microalbuminuria per se have considerable degree of favorable behavioral effects in school workers with microalbuminuria.

Funding: Government Support - Non-U.S.

PO1753

Weight Changes Following Diabetes Medication: A Population-Based Study

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Background: The majority of patients with type 2 diabetes are obese, with greater percentages in those with concomitant CKD. Clinical trials suggest that the newer glucose-lowering medications, including sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor antagonists (GLP1RA), provide an added benefit of weight loss in people with type 2 diabetes. We evaluated the magnitude of weight change associated with diabetes medication prescription in real-world practice in persons with and without CKD (eGFR <60 vs. ≥60 ml/kg/1.73 m^2).

Methods: We identified patients with diabetes who initiated SGLT2i (n=925), GLP1RA (n=810), dipeptidyl peptidase-4 inhibitors (DPP4i, n=1899), or sulfonylurea (SU, n=3285) between 2015 and 2018 in Geisinger Health System. Outcomes were percent weight change per year among all patients within 1 year after medication initiation and time to first achieving 5% weight loss among patients with overweight/obesity at medication initiation. Inverse probability of treatment weighting (IPTW) based on multinomial propensity scores was used to account for differences in baseline patient characteristics by medication class.

Results: The mean (SD) age of the 6919 patients was 58 (14) years and 3381 (49%) were female. Compared with SU, SGLT2i, GLP1RA, and DPP4i were associated with significant weight loss, with stronger associations for SGLT2i and GLP1RA (**Table**). Similarly, SGLT2i, GLP1RA, and DPP4i users were more likely to achieve 5% weight loss compared with SU (HR [95% CI]: 1.47 [1.28, 1.69] for SGLT2; HR: 1.55 [1.32,1.82] for GLP1; HR: 1.31 [1.19,1.44] for DPP4i). The associations were consistent across CKD status.

Conclusions: In patients with and without CKD, SGLT2i and GLP1RA were associated with significant weight loss compared with SU. These results may further motivate uptake of SGLT2i and GLP1RA, two classes of medications with proven renal benefit, among patients with overweight or obesity.

Funding: NIDDK Support

Percent weight change (%/year) within 1 year associated with diabetes medications

	Before IPTW	After IPTW
Sulfonylureas (n=3281)	0 (Ref)	0 (Ref)
SGLT2 (n=925)	-3.17 (-3.76, -2.57)	-3.02 (-3.63, -2.13)
GLP1 (n=810)	-2.94 (-3.56, -2.32)	-2.87 (-3.51, -2.22)
DPP4 (n=1899)	-1.69 (-2.14, -1.25)	-1.71 (-2.15, -1.27)

PO1754

Effects of Caloric Restriction and Aerobic Exercise on Circulating Cell-Free Mitochondrial DNA in Patients with Moderate-to-Severe CKD

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Background: Understanding mechanisms for increased oxidative stress and inflammation in patients with chronic kidney disease (CKD) is vital due to their role in the pathophysiology of this population. Circulating cell-free mitochondrial DNA (ccf-mtDNA) is released to the plasma and believed to promote inflammation by acting as a damaged-associated molecular pattern. Previous studies suggested that in patients with kidney disease, ccf-mtDNA increases and may induce inflammation. Past investigations in patients with CKD have found that aerobic exercise decreases inflammation. We hypothesized that in patients with moderate to severe CKD, aerobic exercise would reduce plasma levels of ccf-mtDNA.

Methods: We performed a post hoc analysis of a multi-center pilot randomized trial of aerobic exercise and caloric restriction (NCT01150851). We measured ccf-mtDNA in plasma at baseline and two and four months after four interventions (aerobic exercise (EX), caloric restriction (CR), EX + CR, usual activity and usual diet). A multivariable model adjusted for age, race, sex, systolic BP, BMI, diabetes, and eGFR was done

Results: Of a cohort of 111 participants who were randomized, 99 had baseline ccf-mtDNA levels, and 92 completed the study. The median age was 57 years old, 44% were female, and 92% had diabetes. Plasma ccf-mtDNA median concentrations at baseline, two, and four months were 3.62, 3.08, 2.78 pM for the usual activity group, and 2.01, 2.20, 2.67 pM for the aerobic exercise group. There was a 16.1% increase per month in ccf-mtDNA in the aerobic exercise group compared to the usual activity group ($p = 0.024$), especially with the combination of aerobic exercise and caloric restriction (29.5% increase per month). After four months of intervention, ccf-mtDNA increased in the aerobic exercise group by 81.6% (95% confidence intervals [CI] 8.2-204.8; $p = 0.024$) compared to the usual activity group, but it was only observed in the aerobic exercise and caloric restriction group (181.7% increase, 95% CI 41.1-462.2; $p = 0.003$)

Conclusions: Our data suggest that aerobic exercise increases plasma ccf-mtDNA levels in patients with CKD stages 3-4, more profoundly in ones with a combination of caloric restriction.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIEHS, NCATS

PO1755

Physical Activity in Patients Undergoing Dialysis: A Pilot Study

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Background: Patients on chronic dialysis have impaired physical function and poor quality of life. Slow gait speed and handgrip strength are indicators of increased all-cause mortality and cardiovascular events in dialysis patients. The relationship between physical activity and gait speed is inconsistent in prior studies. "Cadence", a gait characteristic measured as steps/minute by accelerometer is strongly associated with the intensity of physical activity. We hypothesized that cadence will be lower in dialysis patients compared to healthy adults and that cadence will be correlated with their gait speed.

Methods: Physical activity was measured in N=20 subjects incident to dialysis over 7 days using a validated wrist worn tri-axial accelerometer (ActiGraph). The 7 days included dialysis and non-dialysis days. Average daily cadence (steps/sec) was extrapolated from accelerometer data utilizing a published algorithm. Subject demographics were recorded by self-report or from medical records. Gait speed (meter/sec) was measured over 4 meters. Data on cadence from healthy subjects (N=32) were obtained from a prior study.

Results: Of twenty subjects (4 peritoneal dialysis, 16 hemodialysis), no one recorded any vigorous activity in the entire period, while most (59.4%) of their time was spent in sedentary behavior. Median average daily cadence across subjects was 1.38 [IQR = (1.31 – 1.48)] steps/second. Dialysis subjects had lower average daily cadence than healthy subjects (1.38 vs 1.66 steps/second, p <0.001). When adjusted for age and sex, being "on dialysis" was associated with a 0.24 (95% CI -0.34, -0.14) steps/second lower cadence compared to healthy subjects. For patients on hemodialysis, average daily cadence was not significantly different between HD days and non-HD days, with no significant correlation between 4m speed and cadence (r=-0.28).

Conclusions: In this prospective study, we show that cadence is low in dialysis patients, that dialysis patients are sedentary and cadence does not correlate with gait speed. Thus gait speed alone may not be an accurate representation of intensity of daily physical activity. This pilot study supports the need for detailed studies of gait characteristics in dialysis patients, which will help in the development of personalized exercise and activity programs in patients undergoing dialysis.

PO1756

Physical Activity Scores in Hemodialysis Patients with Thyroid Dysfunction: A Substudy of the NIH THYROID-HD Trial

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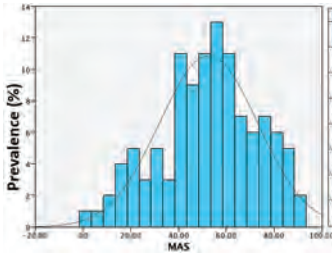
Background: Low physical activity is common in hemodialysis (HD) patients and is associated with adverse outcomes in this population (poor health-related quality of life, cardiovascular [CV] disease, death). Prior studies show that hypothyroidism is highly prevalent in HD patients, and is associated with worse self-reported physical function.

Methods: In a substudy of the ongoing multi-center NIH THYROID-HD Trial, we examined baseline physical activity scores determined by the Human Activity Profile (HAP), a validated 94-item instrument assessing daily activities across a wide range of energy expenditures, in HD patients with TSH levels in the high-normal (TSH >3-5 mIU/L) and subclinical hypothyroid range (TSH >5-10 mIU/L). The HAP was used to derive the Maximum Activity Score (MAS) and Adjusted Activity Score (AAS), representing greatest and mean estimated energy expenditures, respectively (range 0-94, segmented to low [<52], moderate [54-73], and high [>74] scores).

Results: Among 57 HD patients who underwent baseline HAP assessment, the mean±SD MAS and AAS scores were 52±21 and 26±27, respectively; median (IQR) MAS and AAS scores were 52 (40, 68) and 22 (0, 49), respectively. In the overall cohort, 79% had low, 14% moderate, and 7% high AAS scores. MAS scores were lower in patients who were older (≥65 yrs), female, White, Hispanic, of longer (>1 yr) vintage, diabetic, or with underlying CV disease. A similar trend was observed for AAS scores.

Conclusions: In this substudy of the NIH THYROID-HD Trial, HAP scores in HD patients with high-normal and subclinical hypothyroid range TSH levels were lower than observed in prior historical dialysis cohorts that did not have underlying thyroid dysfunction. Further research is needed to determine the impact of thyroid hormone replacement on improving physical activity and function in this population.

Funding: NIDDK Support



Human Activity Profile Scores Across Characteristics		
	MAS score Median (IQR)	AAS score Median (IQR)
Age <65	54 (40, 68)	22 (0, 50)
Age ≥65	51 (27, 69)	8 (0, 46)
Males	56 (41, 70)	22 (0, 50)
Females	52 (39, 62)	20 (0, 47)
White	54 (39, 66)	21 (0, 45)
Non-White	58 (41, 75)	32 (0, 61)
Hispanic	54 (39, 68)	22 (0, 47)
Non-Hispanic	57 (44, 71)	31 (1, 54)
Vintage <1 year	63 (50, 76)	47 (17, 65)
Vintage ≥1 year	51 (37, 63)	17 (0, 42)
Diabetes	52 (37, 63)	22 (0, 43)
No Diabetes	57 (45, 78)	25 (0, 69)
CV Disease	51 (32, 68)	15 (0, 46)
No CV Disease	55 (45, 70)	24 (0, 54)

PO1757

In Vivo Muscle Mitochondrial Function Is Associated with Exercise Capacity and Efficiency in CKD

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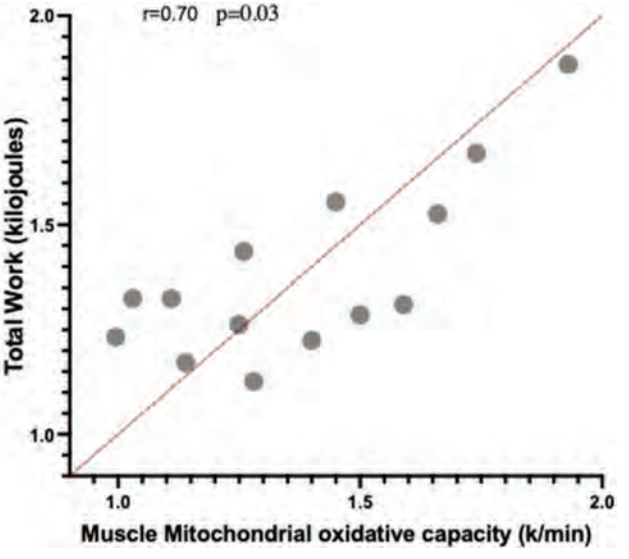
Background: CKD is associated with skeletal muscle dysfunction increasing risk for frailty. Muscle mitochondrial dysfunction may underly impaired physical performance. The associations of in vivo muscle mitochondrial function with exercise capacity and efficiency in CKD is unknown.

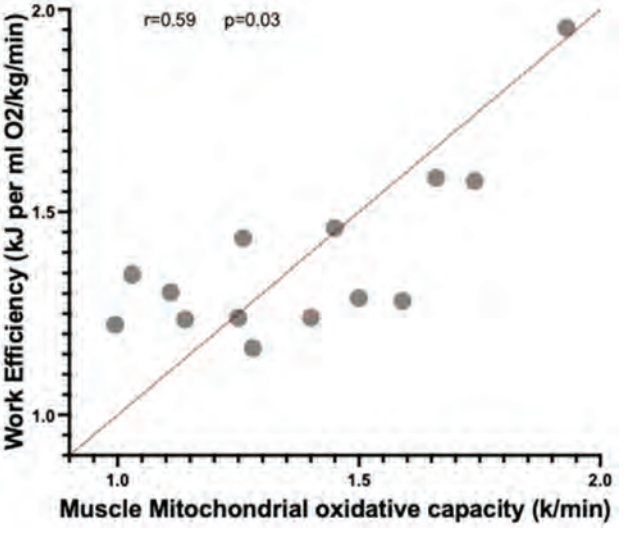
Methods: We recruited 8 diabetic and 6 non-diabetic patients with CKD. Leg muscle mitochondrial oxidative capacity was measured by exercise recovery kinetics of [PCr] using ^{31}Phosphorus Magnetic Resonance Spectroscopy (^{31}P MRS). Cardiorespiratory fitness (CRF, VO_2 peak), total work, and work efficiency (total work/VO2peak) were assessed by cycle ergometry. We tested associations of ^{31}P MRS measures with endpoints using Pearson correlations.

Results: Participants had a mean age was 61±10yrs, eGFR of 35±12ml/min with 43% females. Faster PCr recovery rate correlated with VO_2 peak (r=0.58, p=0.03), total work (r=0.70, p=0.03) and work efficiency (r=0.59, p=0.03) (Figure). Associations of PCr recovery with work and work efficiency were independent of age, sex, and weight (both p=0.03).

Conclusions: Muscle mitochondrial oxidative capacity is a major determinant of exercise efficiency and capacity. Therapeutics targeting muscle mitochondria function in CKD may improve physical performance and CRF.

Funding: NIDDK Support, Other NIH Support - DCI - Dialysis Clinics Incorporated





PO1758

Comparisons of In-Clinic and Free-Living Measures of Physical Function in Predicting Hospitalization in Patients with CKD

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Background: Physical function is associated with risk of hospitalization; however, comparisons of in-clinic and free-living measures of physical function and their associations with risk of hospitalization has not been well established.

Methods: In this secondary analysis of the Sit Less, Interact, Move More (SLIMM) pilot study, we compared in clinic and free-living measures using accelerometry data. Participants with CKD were randomized to the SLIMM intervention or standard of care and asked to wear a thigh worn accelerometer 7 days before a visit to capture their physical activity. In clinic measures of physical function like 6-minute walk distance were performed during visits. Free-living measures were determined from accelerometry. Free-living 6-minute steps were defined as the number of steps taken during the most active recorded 6-minute period. Free-living measures of physical function were compared to in clinic measures using cox proportional hazards models adjusted for age, sex, smoking, alcohol use, BMI, diabetes, CKD, hypertension, heart failure, and peripheral vascular disease.

Results: 106 participants were randomized, the mean age was 69 ± 12 and 69 ± 14, baseline eGFR was 44 ± 12 and 45 ± 14, and 48% and 37% were female for the standard of care and SLIMM groups respectively. When adjusted for covariates, both in clinic and free-living 6-minute walk distance and steps respectively were associated with hospitalizations (table). In comparisons between in clinic and free-living measures, in clinic measures were not significantly associated with hospitalizations while free-living measures were (table).

Conclusions: Both in clinic and free-living measures of physical function were predictors of hospitalization in patients with CKD.

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

Adjusted cox proportional hazard model for hospitalization in in clinic and free-living 6-minute walk

	In clinic alone	Free-living alone	Joint model
In clinic	0.55 (0.34, 0.88)		0.73 (0.45, 1.16)
Free-living		0.49 (0.32, 0.76)	0.58 (0.37, 0.92)

PO1759

Blood Pressure Trends in a Cohort of 9- and 10-Year-Old Children in Iceland: A 10-Year Follow-Up Study

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Background: Although there is significant evidence for an association between childhood and adult office blood pressure (BP), data on the correlation of childhood BP and ambulatory BP (ABP) in young adults are missing. The aim of this study was to examine the association between childhood office BP and both ABP and office BP indices in young adults.

Methods: Subjects were recruited from a cohort of 970 young adults aged 20-21-years who participated in a population-based study of BP in 9-10-year-old Icelandic school children. All participants underwent a minimum of 4 resting BP measurements at the childhood BP screening. A total of 121 individuals have completed their participation in the follow-up study, which included office and ambulatory BP measurements. Pearson correlation and linear regression analysis were used to examine the relationship between childhood and follow-up BP.

Results: A significant positive correlation was observed between childhood mean systolic BP (SBP) and systolic office and ambulatory BP at follow-up (r=0.386, p<0.001 and r=0.370, p<0.001, respectively). The correlation between childhood mean systolic office BP and follow-up mean systolic office BP was stronger for males (r=0.580, p<0.001) than for females (r=0.298, p=0.012), and the same applied for mean systolic ABP (r=0.491, p<0.001 and r=0.323, p=0.006, respectively). The correlation of mean childhood diastolic office BP (DBP) with mean DBP indices at follow-up was insignificant for males (office DBP: r=0.244, p>0.05; ABP: r=0.258, p>0.05) but remained significant for females (office DBP: r=0.355, p=0.0026; ABP: r=0.449, p<0.001). In adjusted analysis, childhood mean office SBP significantly associated with mean office SBP at follow-up in both males (beta=0.69, p<0.001) and females (beta=0.26, p<0.001). Each mmHg increment in mean childhood office SBP predicted an increase of mean ambulatory SBP by 0.52 mmHg (p<0.001), unaffected by sex. Childhood DBP did not significantly predict office or ambulatory BP at follow-up in adjusted analysis.

Conclusions: These preliminary results indicate that childhood SBP significantly predicts both systolic office and ambulatory SBP in young adults and these associations are stronger in males.

Funding: Government Support - Non-U.S.

PO1760

Preterm Birth and Its Association with Altered Renal Sodium Handling in Response to Mental Stress in Young Adults

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Background: Early-life programming events such as preterm birth and very low birth weight (VLBW; <1500 g) contribute to later hypertension development, but the underlying mechanisms are unknown. Experimental data suggest that altered pressure natriuresis and renal sodium handling may be important contributing mechanisms. Adults with primary hypertension exhibit blunted pressure natriuresis in response to sympathetic arousal, but this has not been described in adults born preterm. We investigated renal sodium excretion relative to the change in blood pressure (BP) in response to stress in a cohort of young adults born preterm with VLBW. We hypothesized that young adults born preterm will have a blunted pressure natriuresis response to mental stress compared to those born term with normal birth weight.

Methods: In this long-term prospective cohort of 161 individuals, 129 (80%) born preterm with VLBW and 32 (20%) term-born controls, we measured spot urine sodium/creatinine before and after a 30-min mental stress test and non-invasive continuous BP every 2 min during the stress test. We defined our outcome, pressure natriuresis, as the change in sodium excretion relative to the change in mean arterial pressure (MAP) before and after the stress test with a blunted response being < 0 mg/dL per mmHg. We used generalized linear models to estimate the association between prematurity and the outcome.

Results: The mean age of study participants was 19.8 (SD 0.9) of whom 56% were female. Among those born preterm, median change in sodium excretion relative to change in MAP was 0.022 mg/dL per mmHg [IQR -0.021, 0.12], while the change in term-born counterparts was 0.04 mg/dL per mmHg [-0.005, 0.184]. On unadjusted analyses, the preterm/term difference in pressure natriuresis was B=0.068 mg/dL per mmHg (-0.092 to 0.228), and the relative risk of blunted pressure natriuresis was 1.3 (0.71 to 2.36).

Conclusions: We observed no statistically significant difference in pressure natriuresis response in adults born preterm with VLBW when compared to those born term. Ongoing analyses include investigating other measures of pressure natriuresis in adjusted multivariable models.

Funding: NIDDK Support

PO1761

The Cardiovascular Risk Analysis According to Different Pediatric Hypertension Guidelines: Data from the Korea National Health and Nutrition Examination Survey, 2016-2018

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Background: Worldwide pediatric hypertension (HTN) prevalence is increasing. Pediatric HTN predicts adulthood HTN, the modifiable leading factor of cardiovascular disease (CVD). Therefore, pediatric HTN is important for CVD risk prevention. There are two well-known pediatric HTN guidelines, the 2017 American Academy of Pediatrics (AAP) and the 2016 European Society for Hypertension (ESH). Also, Korea Center for Disease Control established the blood pressure (BP) classification in 2008 (K-CDC). There is discordance of HTN prevalence in each BP classification. However, no study evaluated the CVD risk according to each BP criteria in the Korean pediatric population. This study evaluated the difference in prevalence and pediatric CVD risk factors according to each BP criteria.

Methods: The data of 2060 children and adolescents aged 10-18 years from the Korea National Health and Nutrition Examination Survey 2016-2018 was reviewed. The BP was classified by AAP, ESH, K-CDC and modified AAP (K-AAP, applying the normal weight Korean children BP reference table in AAP definition). The high BP was defined when BP was above normotension. To analyze the difference in CVD risk, AAP and ESH, AAP and K-AAP, and K-AAP and K-CDC were compared. In each comparison, those newly defined as high BP are compared to those with consistent normotensive - age, sex, height matched. Finally, the BP criteria reflecting more CVD risk was used to analyze data from Korea School Health Examination Survey 2018.

Results: The prevalence of high BP in Korean children and adolescents was generally high in AAP than ESH (19.5% vs 10.6%, p<0.0001). However, there were some differences in prevalence according to age, sex and obesity. AAP reflected more CVD risk factors, including obesity and metabolic risk, than ESH. K-AAP well-screened non-obese children with metabolic risk than AAP and children with obesity and metabolic risks than K-CDC. The prevalence of high BP and HTN in Korean school students with K-AAP was 13.7% and 5.1%, respectively.

Conclusions: The K-AAP classifies Korean children and adolescent with more CVD risk factors as high BP. Therefore, for early CVD risk control, K-AAP could be used to define pediatric HTN in Korea. Further study is warranted for actual CVD association.

PO1762

Clinical Event Reductions in Hypertension Patients with and Without CKD Treated with Renal Denervation: A Model-Based Estimate Based on Data from the Global SYMPLICITY Registry

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Background: Estimates of clinical event reductions following renal denervation (RDN) were modelled for patients with and without chronic kidney disease (CKD) based on 3-year follow-up data from the Global SYMPLICITY Registry (GSR).

Methods: CKD (eGFR<60 ml/min/1.73m^2; n=630) and No CKD (eGFR ≥60 ml/min/1.73m^2; n=1,860) cohorts of the GSR were analyzed. Reductions in office systolic blood pressure (oSBP) at 6, 12, 24, and 36 months follow-up were averaged and relative risks (RR) for death, cardiovascular (CV) death, myocardial infarction (MI), stroke, and new-onset end-stage renal disease (ESRD) were obtained from published meta-regression analysis of randomized trials of blood pressure lowering in hypertensive patients. Using the derived RRs, clinical event estimates for maintained baseline oSBP were calculated, facilitating estimation of 36-month absolute event reductions and resulting numbers needed to treat (NNT) for the individual endpoints.

Results: Baseline oSBP and oSBP reductions for the CKD and No CKD cohorts were 163.6 ± 25.7; -11.1 and 166.7 ± 24.6; -15.5 mmHg, respectively. RR ranged from 0.65 for stroke in the No CKD cohort to 0.93 for death in the CKD cohort. There was a numerically higher absolute reduction in major adverse cardiac events (MACE: composite of CV death, MI and stroke) within 3 years of RDN treatment in the CKD vs. No CKD patients (4.0% vs. 3.2%, p=0.12), in part due to higher overall 3-year MACE rates observed in CKD patients (18.8% vs. 11.7%, p<0.001) (Table).

Conclusions: Model-based projections provide a directional estimate of the potential clinical events avoided following RDN treatment and suggest clinically meaningful risk reduction in patients with and without CKD.

Funding: Commercial Support - Medtronic

Observed and projected events for the CKD and No CKD cohorts

	CKD				No CKD			
	GSR-observed (36M)	Calculated RR	Calculated control (BL oSBP)	Calculated NNT	GSR-observed (36M)	Calculated RR	Calculated control (BL oSBP)	Calculated NNT
Death	10.0%	0.93	10.8%	135	4.0%	0.92	4.3%	298
CV death	5.2%	0.87	5.9%	131	2.2%	0.83	2.6%	229
MI	3.4%	0.82	4.2%	130	2.3%	0.78	2.9%	160
Stroke	6.1%	0.71	8.6%	40	4.0%	0.65	6.2%	46
New-onset ESRD	6.4%	0.92	6.9%	185	0.2%	0.91	0.3%	4,170
MACE	14.7%	0.79	18.8%	25	8.4%	0.72	11.7%	31

BL: baseline; 36M: 36 months

PO1763

Achievement of Blood Pressure Target and Risk of Major Adverse Cardiovascular and Cerebrovascular Events in Patients with Metabolic Syndrome

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Background: Metabolic syndrome (MetS) is closely related to adversely cardiovascular morbidities and mortality. Among the components of MetS, controlling the hypertension might provide the highest yield in reducing major cerebro-cardiovascular events (MACCE). Herein, we aimed to investigate the impact of control of hypertension on the development of MACCE and all-cause mortality according to the presence of MetS.

Methods: We performed a nationwide population-based study using the national health insurance database of South Korea. Among 2,998,127 subjects with hypertension who received more than 3 times national health screenings from 2003 to 2011, a total of 1,920,601 subjects were included in the study. The study group was divided by the presence of the MetS and the degree of control of blood pressure (BP), 1) intensive well-controlled (well-C) (SBP <120 and DBP <70), 2) standard well-C (SBP 120-130 and DBP 70-80), 3) uncontrolled subgroup 1(U-S1) (SBP 130-159 or DBP 80-99), and 4) uncontrolled subgroup 2 (U-S2) (SBP ≥160 or DBP ≥100). The main study outcome was all-cause mortality and composite MACCE. The study outcomes were investigated using multivariable Cox-regression analysis after adjusting for clinical variables.

Results: There were 945,243 (49.2%) subjects with 2 or more components of MetS. Among them, 142,991, 179,041, 562,725, and 60,486 subjects were grouped in the well-C intensive, well-C standard, U-S1, and U-S2, respectively. Compared to the well-C standard group, both intensively controlled group (hazard ratio [HR]; 1.123, 95% confidence interval [95% CI]; 1.062-1.186) and uncontrolled group (HR: 1.106; 95% CI 1.061-1.153 in U-S1, and (HR: 1.353; 95% CI 1.265-1.448) in U-S2 group) was associated with increased risk of composite MACCE. In addition, the risk of all-cause mortality in subjects with MetS was increased in well-C intensive group (HR: 1.197; 95% CI 1.143-1.254) and U-S2 group (HR: 1.211; 95% CI 1.211-1.138-1.287), compared to the well-C standard group.

Conclusions: Uncontrolled hypertension increased risk for MACCE and all-cause mortality in patients with or without MetS, whereas intensive control of BP also increased risk. Therefore, proper targeting the blood pressure is important to reduce the risk of major clinical outcomes irrespective of the presence of MetS.

PO1764

Vascular Function Indices Are Strong Predictors of the Severity and Characteristics of Carotid Atherosclerosis

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Background: Vascular functional indices strongly predict adverse cardiac outcomes in CKD. However, few have examined the link between vascular function and the severity and characteristics of carotid atherosclerosis in CKD. Management of Cardiovascular disease in cKd(MaCK, NCT03636152) is a randomized controlled study aimed to evaluate the effects of hydroxychloroquine on inflammation, vascular dysfunction and carotid atherosclerosis in Veterans with high-CV risk CKD. Analyzing the baseline parameters of enrollees, we aim to evaluate the predictors of carotid atherosclerosis in CKD patients.

Methods: All randomized participants of MaCK study underwent detailed clinical and laboratory evaluations, including evaluation of inflammation (hsCRP), vascular function (central aortic pressure(CAP), augmentation index(AI) and aortic pulse wave velocity(APWV) by sphygmocore™ XCEL) and detailed evaluation of carotid atherosclerosis 15 mm around bifurcation (total plaque volume (TPV), lipid-rich necrosis, calcification, fibrous cap, and intraplaque hemorrhage by 3T MRI analyzed with Plaquiview™ software).

Results: Initial 17 randomized participants(age 73±4years, all male, 41% with pre-existing CVD and 88% on statins, with eGFR 40±4.7ml/min, microalbumin/creatinine ratio 855±1207mcg/gm, hsCPR 10.6±20.6mg/L total cholesterol 168±40mg/dl, and LDL/HDL ratio 2-1±0.7) with full analyzable MRI were included in the analysis. Significant vascular stiffness was evident at baseline with CAP:98.3±12.6 mm of Hg, Augmentation Index:15.5±7.6 and APWV:9.3±2.4 m/s. Atherosclerotic burden was high, carotid TPV:2207±802mm^3 and Normalized Wall Index:71.7±6, with necrotic core, calcification, fibrous cap, and intraplaque hemorrhage volumes of 357.6±289, 556.2±478, 153.8±122 and 49.6±78 mm^3 respectively. Univariate analysis showed that detailed baseline clinical and laboratory parameters had no significant correlations with TPV or its individual components whereas, vascular functional indices had strong positive correlations with TPV and individual plaque components(p<0.01), especially the CAP, which had among the strongest correlations with lipid-rich necrotic core (p<0.000).

Conclusions: Non-invasively measured central aortic pressure and aortic pulse wave velocity are strong predictors of carotid atherosclerosis and unstable plaques.

Funding: Veterans Affairs Support

PO1765

Relation Between Waist Circumference and Renal Hemodynamic in Healthy Individuals

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Background: Abdominal adiposity, measured by waist circumference (WC), is associated with increased mortality in individuals with chronic kidney disease. Little is known about the impact of abdominal obesity on the renal perfusion and function in humans. We analyzed whether abdominal adiposity changes renal hemodynamics in 80 healthy, young, male individuals without cardiovascular (CV) disease.

Methods: We analysed the renal hemodynamic using steady state input clearance with infusion of paraaminohippuric acid and inulin, respectively. Intraglomerular pressure and resistances of the afferent (RA) and efferent (RE) arterioles were calculated according to the Gomez equation. The study population was divided in into two groups based on median of WC of the total study population.

Results: The study cohort consisted of male, non-smoking individuals, aged 27 ± 9 years. Mean of WC in the total study cohort was 84.75 ± 9 cm and just 9 patients showed WC > 94 cm (threshold for CV risk according to 2018 hypertension guidelines). Table 1 shows the renal hemodynamic in patients related to mean WC of the total study population. After adjustment for age and mean arterial blood pressure (MAP) using multivariate regression analysis the difference between both WC groups remained significant for the following parameters: RPF (p = 0.006), GFR (p = 0.017), RBF (p = 0.006), RVR (p = 0.006), IP (p = 0.018), RA (p = 0.005).

Conclusions: Increased WC in healthy young, male individuals without cardiovascular disease was associated with reduced GFR and reduced RPF. This effect is likely to be mediated by increased renal vascular resistance, more precisely vasoconstriction of the renal vas afferens.

Renal parameters	Waist circumference (WC)			Waist circumference (WC) / body height		
	≥ median	< median	p-value	≥ median	< median	p-value
Renal plasma flow (ml/min)	620 ± 109	700 ± 104	0.001	630 ± 115	693 ± 103	0.011
Glomerular filtration rate (ml/min)	131 ± 11	140 ± 15	0.003	132 ± 12	140 ± 15	0.013
Filtration fraction (-)	22 ± 2.6	20 ± 2.1	0.017	21 ± 2.7	20 ± 1.9	0.054
Renal blood flow (ml/min)	1096 ± 193	1245 ± 197	0.001	1115 ± 207	1231 ± 193	0.013
Renal vascular resistance (mmHg/(ml/min))	85 ± 19	70 ± 12	< 0.001	83 ± 19	71 ± 13	0.001
Intraglomerular pressure (mmHg)	36.7 ± 2.3	38.5 ± 3.1	0.003	36.8 ± 2.5	38.4 ± 3.1	0.014
Resistance vas afferens (dyn*s/cm5)	4034 ± 1177	3069 ± 786	< 0.001	3953 ± 1164	3106 ± 852	< 0.001
Resistance vas efferens (dyn*s/cm5)	2283 ± 339	2118 ± 280	0.021	2263 ± 361	2131 ± 254	0.062

Table 1: Data are presented as mean ± SD

PO1766

Framingham Risk Score and ACC/AHA Pooled Cohort Equation for Prediction of Atherosclerotic Cardiovascular Events in CKD

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Background: The Framingham Risk Score and the ACC/AHA Pooled Cohort Equation are used clinically to identify patients at high risk for atherosclerotic cardiovascular disease (ASCVD). The performance of these equations (alone or with clinically available cardiac biomarkers) is unclear in patients with chronic kidney disease (CKD), particularly at more advanced stages. We tested the discrimination of these risk scores and cardiac biomarkers to predict ASCVD in CKD.

Methods: We studied 1027 participants in the Chronic Renal Insufficiency Cohort without ASCVD who were not taking aspirin or statins. Framingham Risk Score, Pooled Cohort Equation, N-terminal pro-brain type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hsTnT) were measured at baseline. Outcomes were the composite of fatal and non-fatal myocardial infarction (MI) and cardiac death, with or without stroke, over 10 years. We estimated internally valid C-indices using 10-fold cross validation for each risk score and cardiac risk marker overall, and across categories of eGFR.

Results: Among 1027 participants, the mean age was 52 years, and the mean eGFR was 48 mL/min/1.73 m2. The C-index (95% CI) was 0.74 (0.69, 0.79) for the Framingham Risk Score, and 0.72 (0.67, 0.78) for the Pooled Cohort Equation. Both risk scores had better discrimination for predicting ASCVD at eGFR >60 mL/min/1.73 m2 compared with lower eGFR. HsTnT had comparable discrimination to both risk scores overall. HsTnT alone had comparable discrimination across the spectrum of CKD severity (difference in C-index for lowest vs highest eGFR category for ASCVD -0.04; 95% CI -0.21, 0.14) (**Table**).

Conclusions: The Framingham Risk Score and Pooled Cohort Equation had moderate discrimination for prediction of ASCVD in CKD and performed better at eGFRs >60 versus <60 mL/min/1.73 m2. HsTnT alone had discrimination comparable to each risk score overall, and comparable discrimination across the spectrum of CKD severity. Further work is needed to develop novel risk scores including cardiac biomarkers specifically for use in CKD.

Funding: NIDDK Support

Discrimination of Framingham Risk Score, Pooled Cohort Equation, and hsTnT by C-indices, by eGFR					
Predictor	Overall (N=1027)	eGFR >60 mL/min/1.73 m2 (N = 235)	eGFR 45-59 mL/min/1.73 m2 (N = 298)	eGFR 30-44 mL/min/1.73 m2 (N = 301)	eGFR <30 mL/min/1.73 m2 (N = 148)
ASCVD (Framingham Risk Score composite outcome: first fatal or non-fatal MI or cardiac death					
C-index: Framingham Score	0.74 (0.69, 0.79	0.93 (0.86, 1)	0.64 (0.53, 0.75)	0.65 (0.55, 0.74)	0.76 (0.67, 0.84)
C-index: hsTnT	0.76 (0.70, 0.81)	0.80 (0.65, 0.96)	0.73 (0.60, 0.86)	0.64 (0.53, 0.75)	0.77 (0.68, 0.85)
C-index difference for each eGFR category vs. eGFR > 60 mL/min/1.73 m2					
Framingham Score	N/A	Referent	**-0.29 (-0.42, -0.16)**	**-0.29 (-0.40, -0.17)**	**-0.17 (-0.29, -0.06)**
hsTnT	N/A	Referent	-0.07 (-0.27, 0.14)	-0.16 (-0.36, 0.03)	-0.04 (-0.21, 0.14)
ASCVD and Stroke (Pooled Cohort Equation composite outcome: first stroke, fatal or non-fatal MI, or cardiac death)					
C-index: Pooled Cohort Equation	0.72 (0.67, 0.78)	0.94 (0.89, 1)	0.58 (0.47, 0.70)	0.63 (0.54, 0.72)	0.75 (0.66, 0.85)
C-index: hsTnT	0.78 (0.71, 0.81)	0.81 (0.68, 0.94)	0.74 (0.62, 0.86)	0.65 (0.54, 0.76)	0.76 (0.67, 0.84)
C-index difference for each eGFR category vs. eGFR > 60 mL/min/1.73 m2					
Pooled Cohort Equation	N/A	Referent	**-0.36 (-0.49, -0.23)**	**-0.31 (-0.42, -0.21)**	**-0.19 (-0.30, -0.08)**
hsTnT	N/A	Referent	-0.07 (-0.25, 0.14)	-0.16 (-0.33, 0.01)	-0.05 (-0.21, 0.10)

Bold numbers indicate statistically significant differences between C-indices

PO1767

Patients with CKD and Multiple Chronic Conditions Are at Increased Risk of Cardiovascular Events

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Background: Major adverse cardiovascular events (MACE) are the leading cause of mortality in chronic kidney disease (CKD). We studied the relationship between the number and type of multiple chronic conditions (MCCs) and the risk of MACE in patients with CKD.

Methods: We retrospectively examined the SAIL Databank: a cohort consisting of the population of Wales, UK (2011-2018). Patients were categorised by the number of MCCs additional to CKD: the primary analysis included all MCCs (e.g. asthma, depression), and a secondary analysis excluded cardiometabolic conditions (hypertension, ischaemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation, peripheral vascular disease, diabetes). The outcome was MACE: myocardial infarction, stroke, heart failure hospitalisation. The risk of MACE associated with number of MCCs was calculated using cox proportional hazards models. Adjustments were made for age, sex, smoking, deprivation, eGFR and cholesterol.

Results: Of the 173,388 patients with CKD, median age was 78 years, 57% were female, 98.6% were of white ethnicity and median eGFR was 51ml/min/1.73m². There was a graded rise in the risk of MACE by MCC count (Figure 1): 1 condition adjusted hazard ratio (aHR) 1.15 (1.02-1.29), 2 MCCs aHR 1.37 (1.22-1.53), 3 MCCs 1.68 (1.50-1.88), ≥4 MCCs 2.61 (2.34-2.92). For non-cardiometabolic conditions, MACE risk was lessened, but the trend persisted: 1 condition aHR 1.16 (1.12-1.20), 2 MCCs aHR 1.30 (1.25-1.35), 3 MCCs 1.43 (1.38-1.49), ≥4 MCCs aHR 1.65 (1.59-1.71).

Conclusions: Patients with CKD and MCCs are at high risk of MACE, even when cardiometabolic conditions are excluded. Cardiovascular risk stratification and preventative strategies in patients with CKD should take into account the number and type of other chronic conditions.

Funding: Other NIH Support - Medical Research Council (UK)

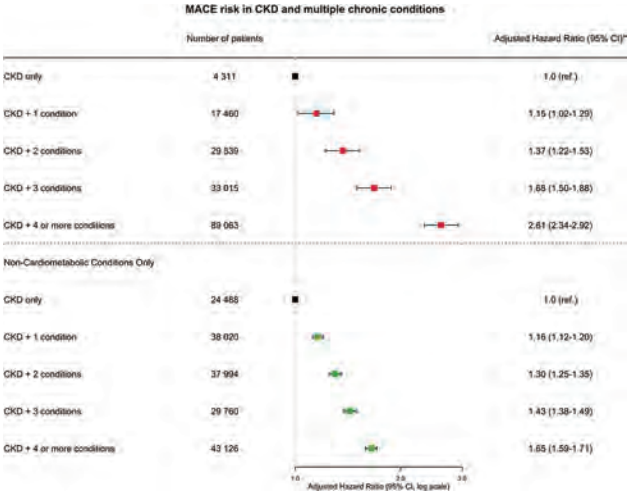

Figure 1. Cox regression for MACE. *Adjusted for age, sex, smoking, deprivation, eGFR & cholesterol

PO1768

Nondipping Heart Rate in Patients with CKD

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Background: A decrease in the nocturnal heart rate (HR) decline, nondipping HR (NHR), was reported to be 14% in the general population and related to cardiovascular events and all-cause mortality, however, the clinicopathologic features of chronic kidney disease (CKD) patients with NHR is still unclear. Previous studies have reported that interstitial and/or tubular atrophy (IF/TA) was significantly associated with both daytime and nighttime hypertension observed with ambulatory blood pressure monitoring (ABPM). We aimed to investigate the clinicopathologic findings associated with NHR status in patients with CKD.

Methods: We retrospectively identified 135 subjects who underwent ABPM and kidney biopsy simultaneously at our institution, from 2016 to 2019. We excluded patients with age <20 years, end-stage kidney disease, less than 5 glomeruli in the kidney biopsy, and patients taking β-blockers. NHR status was defined as (daytime HR – nighttime HR)/ daytime HR <0.1. The percentage of global glomerulosclerosis (GS%), IF/TA, and the severity of arteriosclerosis were scored semi-quantitatively according to the Mayo Clinic/ Renal Pathology Society Chronicity Score (CS).

Results: The median age was 51 years [interquartile range: 35–63], 54.0% of which were male, and the median eGFR was 53.0 [30.0–75.0] mL/min/1.73m². NHR status was found in 39 out of 135 patients (28.9%). Patients with NHR were older and had worse renal function, higher blood pressure, lower hemoglobin level, and a larger amount of urinary protein excretion than patients with dipping HR. In terms of histopathological parameters, patients with NHR had more severe GS%, IF/TA, arteriosclerosis, and higher CS (**Table 1**). In multivariable analysis, GS% was established as an independent determinant of NHR status after its adjustment according to age, sex, and other statistically significant parameters (β = 1.03 [1.00–1.05], *P* = 0.02).

Conclusions: NHR status was observed in 28.9% of CKD patients. This study indicates that GS% is the most relevant histopathological parameter associated with NHR in this population.

Table 1. Characteristics of the subjects according to dipping and nondipping heart rate pattern

	All (n = 135)	DHR (n = 96)	NHR (n = 39)	*P* value
Clinical parameters				
Age (years)	51 (35-63)	46 (33-59)	62 (49-74)	<0.01
Male, n (%)	73 (54)	50 (52)	23 (59)	0.47
eGFR (mL/min/1.73m²)	53.0 (30.0-75.0)	59.0 (36.5-79.0)	36.0 (14.0-53.0)	<0.01
24h MAP (mmHg)	93 (85-102)	90 (84-100)	102 (90-112)	<0.01
Diabetes, n (%)	21 (16)	13 (14)	8 (21)	0.31
Dyslipidemia, n (%)	48 (36)	28 (29)	20 (51)	0.02
BMI (kg/m²)	22.2 (20.4-24.7)	22.0 (20.2-24.6)	22.9 (20.8-25.3)	0.43
Hb (g/dL)	13.0 (11.1-14.7)	13.6 (11.8-14.9)	11.2 (10.1-13.1)	<0.01
UA (mg/dL)	6.3 (5.1-7.3)	6.1 (5.0-7.1)	7.0 (5.2-7.5)	0.05
EPI/IBW (g/kg/day)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.6-1.0)	0.13
NaCl (g/day)	6.1 (4.4-8.5)	5.8 (4.4-7.8)	7.0 (4.3-9.8)	0.58
UPE (g/day)	0.9 (0.4-2.1)	0.7 (0.3-1.6)	1.8 (0.6-4.3)	<0.01
Histological parameters				
GV (x10⁶μm³)	2.3 (1.8-3.4)	2.3 (1.8-3.2)	2.6 (1.7-3.8)	0.43
GS (%)	13.6 (4.3-39.5)	10.7 (2.6-27.0)	38.9 (13.5-58.3)	<0.01
IF/TA (%)	10.0 (5.0-30.0)	10.0 (5.0-20.0)	30.0 (10.0-60.0)	<0.01
Arteriosclerosis grade				0.02
No intimal thickening	29 (21)	23 (24)	6 (15)	
Intima < Media	34 (25)	29 (30)	5 (13)	
Intima = Media	72 (53)	44 (46)	28 (72)	
Renal Chronicity Score				<0.01
Minimal (score 0-1)	42 (31)	37 (39)	5 (13)	
Mild (score 2-4)	39 (29)	29 (30)	8 (21)	
Moderate (score 5-7)	40 (30)	25 (26)	15 (38)	
Severe (score ≥8)	14 (11)	5 (5.2)	11 (28)	

Abbreviations: DHR, dipping heart rate; NHR, nondipping heart rate; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; BMI, body mass index; Hb, hemoglobin; UA, uric acid; EPI/IBW, estimated protein intake/ideal body weight; NaCl, sodium intake; UPE, urinary protein excretion; GV, mean glomerular volume; GS, glomerular sclerosis; IF/TA, interstitial fibrosis and/or tubular atrophy.

PO1769

Turning the Page on Page Kidney with Dual RAAS Blockade

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Introduction: Page kidney is a rare form of secondary hypertension from activation of the renin-angiotensin-aldosterone (RAAS) axis by compression of renal parenchyma. It can occur with blunt abdominal trauma/procedures, but it can occur spontaneously. Initial treatment is an ACE inhibitor (ACE) or angiotensin receptor blocker (ARB). Surgical intervention is pursued if more conservative measures fail. Procedures carry their own intrinsic risk for morbidity and mortality, particularly in the setting of uncontrolled hypertension. This report details the case of a patient with Page kidney responsive to an unconventional conservative management approach: dual RAAS blockade with ACE + ARB after a lack of response with other agents.

Case Description: The patient is a 55M with a history of end stage renal disease (ESRD) on hemodialysis (HD), atrial fibrillation, and type 2 diabetes mellitus admitted for anemia. The patient was dyspneic and weak with right flank pain. He denied hematemesis, melena, or hematuria. Hemoglobin on admission was 4.7 g/dL with INR of 4.8 (on Coumadin for atrial fibrillation). Vitals were normal except a fever to 38.4 C. A CT scan of the abdomen showed a 16.5cm right retroperitoneal hematoma adjacent to the right kidney with anterior dislocation of the kidney. A CT angiogram showed active extravasation within the hematoma. Coumadin was held and a dose of Vitamin K and two units of blood were given. The patient underwent renal artery embolization. Hemoglobin was stable therafter. The patient soon developed hypertensive urgency with blood pressure reaching 190/100 mmHg. The patient's only home medication for blood pressure was Carvedilol. Lisinopril 20mg PO daily was added and increased to maximum dosage, only partially relieving the hypertension. Losartan was added and uptitrated to 100mg PO daily. The patient's blood pressure normalized with average in 120s systolic by discharge. The patient was continued on this regimen as an outpatient. No hyperkalemia was observed.

Discussion: Page kidney is a rare but serious form of secondary hypertension from RAAS activation from renal parenchymal compression. Historically, a trial of either an ACE or ARB is indicated, with refractory cases being managed surgically. In this case, dual RAAS blockade was required for blood pressure control, which allowed surgical interventions, and their associated risk of morbidity and mortality, to be avoided.

PO1770

ESRD Risk Predicting Using Cumulative Hypertension Burden

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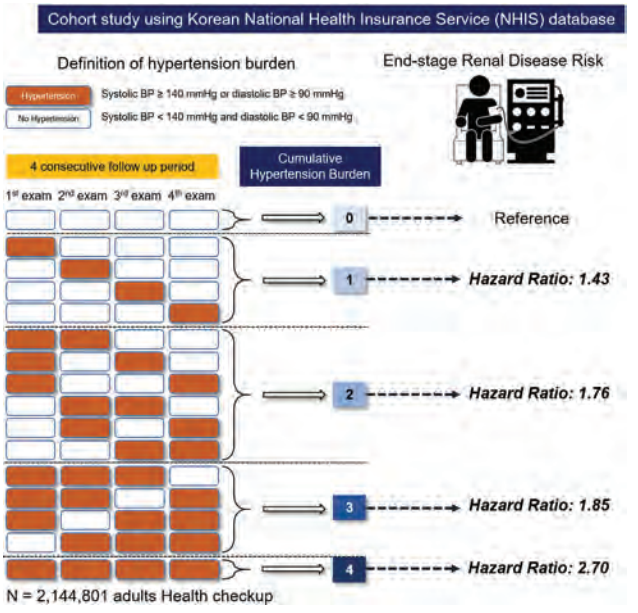
Background: Hypertension is the leading risk factor for end-stage renal disease (ESRD). However, the association between sustained exposure of increased blood pressure (BP) and ESRD is not well-established. This study investigated whether the cumulative hypertension burden is a substantial risk factor for ESRD.

Methods: The incidence of ESRD among 2,144,801 participants identified from the Korean National Health Insurance Service database, who had documented BP assessments for annual health checkup data between 2006 and 2010, was determined. Over a median follow-up of 7.2 years, ESRD was identified in 1,758 participants. Hypertension burden was defined as the cumulative exposure of hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) during 4 consecutive follow up period, and scaled 0 to 4.

Results: Hypertension burden was as follows: 0 (n = 1,164,488), 77.6%; 1 (n = 292, 377), 13.6%; 2 (n = 114,397), 5.3%; 3 (n = 52,671), 2.5%; and 4 (n = 20,886), 1.0%. Compared to the hypertension burden of 0, adjusted hazard ratio for ESRD was increased to 1.43, 1.74, 1.85, and 2.70 in hypertension burden of 1, 2, 3, and 4, respectively. A positive dose-dependent relationship between the hypertension burdens and ESRD was found (*P* for interaction < 0.001). This association was maintained for the sustained exposure of both systolic and diastolic hypertension burden. In conclusion, hypertension burden increases the risk of ESRD.

Conclusions: Our study underlines the usefulness of a new assessment of the hypertension burden over a certain period for predicting the risk of ESRD from a large population-based cohort.



PO1771

Hypertension in the US Veterans Health Administration: Updated Prevalence and Risk Factors for Poor Blood Pressure Control

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Background: The Veterans Health Administration (VHA) management guideline recently redefined the blood pressure (BP) cut-off for hypertension diagnosis as ≥130/90 mmHg and recommended a BP goal of <130/90 mmHg for patients with known hypertension. We evaluated the impact of the new definition on the prevalence of hypertension and explored the clinical predictors for uncontrolled BP based on the new treatment goal.

Methods: We retrospectively analyzed data from VHA including Veterans with ≥2 office BP measurements between January 2016 and December 2017. If more than one BP value was available, we used the lowest of the day. Prevalent hypertension was defined as diagnostic codes related to hypertension, prescribed anti-hypertensive drugs, or based on office BP values. We then evaluated the clinical variables associated with uncontrolled BP (mean BP ≥130/90 mmHg) via multivariable logistic regression with risk estimates expressed as relative risk.

Results: Of the 1,959,337 Veterans eligible for inclusion in the analysis, we found that 1,394,230 (71%) and 1,594,093 (81%) met the hypertension diagnosis criteria including ≥140/90 and ≥130/90 mmHg, respectively. Among those who met the diagnosis hypertension criteria including BP ≥130/90 mmHg (n=1,594,093), 34% (n=538,947) had controlled BP (mean BP <130/90 mmHg) and 66% (n=1,054,939) had uncontrolled BP (mean BP ≥130/90 mmHg). Older age, Black race, obesity, kidney disease, and prior cerebrovascular disease (CVD) were associated with increased risk of uncontrolled hypertension (Table 1).

Conclusions: Applying the new 130/90 cut-off to the definition of hypertension increased the prevalence of hypertension by 10% in VHA. Among those with hypertension, 66% of Veterans did not meet the new BP goal of <130/90 mmHg. In addition, our findings indicate the need for targeted interventions in high-risk individuals such as Veterans with obesity, kidney disease, CVD, or of Black race.

Funding: Veterans Affairs Support

Table 1. Clinical Variables Associated with Uncontrolled Hypertension

Variable	Relative Risk of Uncontrolled Hypertension
Age (years)	-
<40	1.0 (REF)
40-49	1.09 (1.08-1.10)
50-59	1.18 (1.17-1.19)
60-69	1.27 (1.26-1.28)
70-79	1.31 (1.29-1.32)
≥80	1.36 (1.35-1.37)
Race	-
White	1.0 (REF)
Black	1.08 (1.07-1.08)
Kidney Disease	1.04 (1.03-1.05)
Cerebrovascular Disease	1.05 (1.04-1.06)

PO1772

Persistence of Uncontrolled Hypertension Among Older Women Post Implementation of Hypertension Improvement Program

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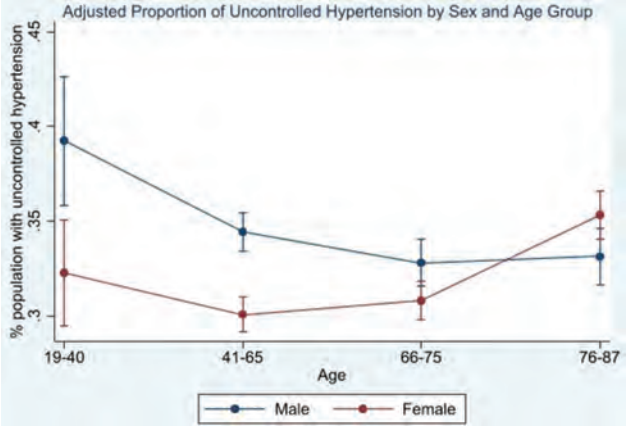
Background: Age-dependent sex differences in hypertension control have been demonstrated in multiple populations. Four large primary care (PC) practices at Loyola adopted the Target:BP hypertension improvement program in 2018; hypertension control rates increased after adoption. Our study evaluated the impact of the Target:BP program on hypertension control by sex and by age group.

Methods: Analysis used data from 21,864 patients age ≥ 18 years with a hypertension diagnosis and > one outpatient visit in 2019 to a PC clinic enrolled in Target:BP program. Uncontrolled hypertension was defined as blood pressure ≥140/90 mmHg based on last visit. Mixed effects models were used to calculate adjusted odds of uncontrolled hypertension after adjustment for demographics and co-morbidities. Interaction term of sex* age group (≤ 65, 66-75, > 75 years) in fully adjusted mixed effects models was significant (P < 0.001) so adjusted odds of uncontrolled hypertension were calculated by sex and by age group. Adjusted proportion of patients with uncontrolled hypertension by sex and by age group was calculated using marginal effects.

Results: Mean age of patients with hypertension was 64.8 ± 12.7 years; 56.3% were female, 66.6% were White, 21.4% were Black and 11.0% were of Hispanic ethnicity. Among the 5973 (27.3%) with uncontrolled hypertension, 54.7% were female; mean age was 65.2 ± 12.9 years. Adjusted odds of uncontrolled hypertension was significantly higher among women vs. men age 66-75 years (OR 1.33; 95% CI 1.30, 2.28) and age 76+ years (OR 1.73; 95% CI 1.31, 2.28) vs. age ≤ 65 years. Figure 1 shows the adjusted proportion of patients with uncontrolled hypertension by sex and by age group.

Conclusions: Despite implementation of a hypertension improvement program, sex disparities in hypertension control persist among older adults.



PO1773

Influence of Biological Sex on Brachial Cuff Blood Pressure Accuracy

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Background: Females have higher risks of cardiovascular events compared to males with similar BP. Our objective was to assess if the accuracy of brachial cuff and central BP measurements towards intra-aortic BP is influenced by biological sex.

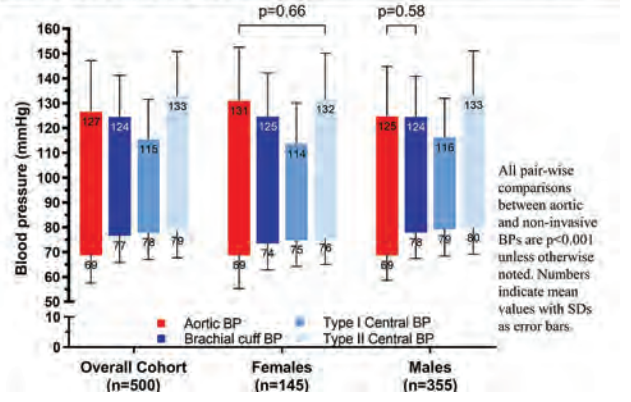
Methods: We enrolled 500 patients undergoing coronary angiography for simultaneous measurements of invasive aortic BP with brachial cuff and central BP (Mobil-o-Graph device). Acceptable accuracy was defined as a mean difference between non-invasive and aortic BPs ≤5 ± ≤8 mmHg. Linear regression and mediation analyses were used to adjust for potential confounders in the relationship between biological sex and BP accuracy.

Results: Of 500 participants, 145 were females. Several characteristics were different in males and females (Table). Brachial cuff systolic BP (SBP) was identical in both groups whereas aortic SBP was 6.2 mmHg higher in females (p<0.001). As such, the brachial cuff appreciably underestimated the aortic SBP in females but not in males. Type II central SBP was the most accurate BP in females, whereas it was brachial cuff SBP in males. In an adjusted linear regression model, only height and pulse pressure were independently associated with the accuracy of brachial cuff SBP. This effect of sex on accuracy was mostly mediated by height (3.5 mmHg; 95% CI 1.4 to 5.6; 57% mediation) to an extent that the direct effect of sex became non-significant (2.9 mmHg; 95% CI -0.3 to 6.2).

Conclusions: Females have higher aortic SBPs than males with identical brachial cuff SBP, which is mostly mediated by a lower height. This could partly explain why females are at higher risk of cardiovascular diseases than males at similar brachial cuff SBP levels.

Clinical characteristics	Female (n=145)	Male (n=355)	p-value
Age	66 ± 11	66 ± 10	0.6
Height (cm)	159 ± 7	174 ± 7	<0.001
Weight (kg)	74 ± 18	86 ± 18	<0.001
BMI (kg/m²)	29 ± 6	28 ± 5	0.3
Active smoking	26%	24%	0.6
Diabetes	26%	29%	0.5
eGFR (mL/min/1.73m²)	79 ± 18	81 ± 17	0.5
Anti-hypertensive medication	76%	81%	0.2
Cuff Brachial SBP (mmHg)	125 ± 18	124 ± 16	1.0
Cuff brachial DBP (mmHg)	74 ± 11	78 ± 11	<0.001
Brachial cuff PP (mmHg)	51 ± 13	47 ± 11	<0.001
Heart rate (bpm)	71 ± 13	66 ± 11	<0.001
Aortic pulse wave velocity (m/s)	9.4 ± 2.1	9.4 ± 1.7	0.9
Augmentation index @ 75 bmp	26 ± 13	17 ± 13	<0.001
Accuracy			
Invasive Aortic SBP	131 ± 22	125 ± 20	<0.001
Difference with Invasive Aortic SBP			
Cuff Brachial SBP	-6.5 ± 12.1	-0.3 ± 11.7	<0.001
Cuff Type I central SBP	-17.3 ± 13.1	-8.8 ± 13.1	<0.001
Cuff Type II central SBP	0.6 ± 15.3	8.3 ± 14.2	<0.001

Mean differences represent the difference between non-invasive BP and aortic BP and are expressed with ± SD. Type I central BP is obtained through calibration with brachial cuff SBP and DBP. Type II central BP is obtained through calibration with brachial cuff mean BP and DBP.



PO1774

Sex-Specific Associations Between Potassium Intake, Blood Pressure, and Cardiovascular Outcomes in the EPIC-Norfolk Cohort Study

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Background: High potassium intake is associated with lower blood pressure and lower risk of cardiovascular disease. Whether these associations differ between men and women and whether they depend on daily sodium intake is unknown.

Methods: We performed an analysis in 11,267 men and 13,696 women from the Epic-Norfolk cohort. Daily sodium and potassium consumption was estimated from sodium and potassium concentration in spot urine samples by using the Kawasaki formula. Linear and Cox regression were used to explore the association between potassium intake, systolic blood pressure and cardiovascular events (defined as hospitalization or death due to cardiovascular disease).

Results: After adjustment for cofounders, interaction between potassium intake and sex was significantly associated with systolic blood pressure (p=0.001) and cardiovascular events (p=0.035). In women, but not in men, the inverse slope between potassium intake and systolic blood pressure was steeper in those within the highest quintile compared to the lowest quintile of sodium intake (p<0.001 for interaction). In women within the highest quintile of sodium intake, every 1-gram increase in potassium intake was associated with a 2.9 mmHg lower systolic blood pressure. These associations were paralleled with lower hazards of cardiovascular disease in women (highest vs. lowest potassium intake tertile: HR 0.88, 95% CI 0.93-0.94). Conversely, in men, the inverse association between potassium intake and cardiovascular disease was not statistically significant (highest vs. lowest potassium intake tertile: HR 0.94, 95% CI 0.88-1.01).

Conclusions: We demonstrate that the association between potassium intake and both systolic blood pressure and cardiovascular disease is sex-specific. Our data suggests that particularly women may benefit most from a high potassium intake.

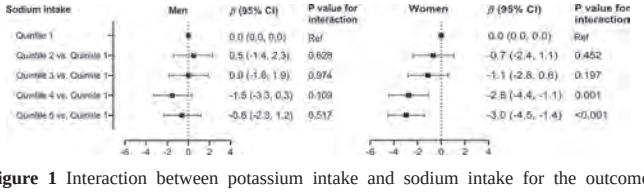

Figure 1 Interaction between potassium intake and sodium intake for the outcome systolic BP in men and women

PO1775

Tryptophan Metabolites Associate with Subclinical and Incident Cardiovascular Disease in CKD

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Background: Inflammation and oxidative stress contribute to the increased cardiovascular disease (CVD) burden in CKD patients. Altered tryptophan catabolism via the kynurenine pathway associates with CVD, but the ability of these specific metabolites to act as biomarkers of CVD risk in CKD warrants further research.

Methods: We measured tryptophan metabolites using targeted mass spectrometry in moderate to severe CKD patients (n=325; median follow-up 3 years). Vascular calcification at the coronary artery and aorta was measured using a 4-slice LightSpeed QXi and reported as Agatston scores. Incident CVD events included myocardial infarction, coronary revascularization procedures, stroke, transient ischemic attack, new-onset heart failure, sudden cardiac death, and peripheral vascular disease requiring revascularization or amputation. Multiple linear regression and Cox proportional hazard analyses assessed the relationship of tryptophan metabolites to subclinical markers of CVD and CVD events.

Results: We found that lower baseline tryptophan levels predicted increased aortic calcification in a fully adjusted model controlling for demographics, CVD history, traditional risk factors, renal function, CRP, and serum albumin (p=0.006). Higher baseline levels of anthranilic acid and hydroxyanthranilic acid predicted increased coronary calcification and higher total Agatston score, respectively, in the fully adjusted model (p=0.03 and p=0.03). One unit decrease in serum tryptophan at baseline is associated with 70% decrease in time to incident CVD event when adjusting for demographics, CVD history, risk factors, and renal function (HR: 0.31, p = 0.04). Increased anthranilic acid and quinolinic acid independently reduced time to incident CVD event (HR: 1.88, p=0.02; HR: 1.56, p=0.02 respectively), but were not significant in the fully adjusted model.

Conclusions: Lower tryptophan levels are associated with increased aortic calcification and decreased time to incident CVD events. Higher levels of anthranilic acid, hydroxyanthranilic acid, and quinolinic acid are associated with subclinical CVD. Together, these data demonstrate that catabolism of tryptophan via the kynurenine pathway is associated with subclinical CVD and predicts cardiovascular events in CKD.

Funding: Other NIH Support - UL1TR002240 NCATS

PO1776

Abstract Withdrawn

PO1777

High Level of Uromodulin Increases the Risk of Hypertension: A Mendelian Randomization Study

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Background: The association of uromodulin and hypertension was clinically observed, but not proved as a causal relationship. We conducted a two-sample Mendelian randomization analysis to investigate the causal relationship between uromodulin and blood pressure based on the public datasets.

Methods: We selected two SNPs for the uUMOD exposure from the Genome-Wide Association Studies (GWAS) meta-analysis study(N=10884) and sixteen SNPs for sUMOD based on the open studies in Pubmed(N=4147). Six summary level studies based on the UKbibank and ICBP served as outcomes with the sample of hypertension is 46188, a total sample size of SBP is 1194020, and the DBP is 1194025. We used the Wald ratio to estimate the causal effect of urinary uromodulin(uUMOD) and the inverse variance weighted (IVW) method to combine each SNP's effect. Three methods (IVW, MR-Egger, and Weighted median) were used to access the causal effect of serum uromodulin(sUMOD) on blood pressure. We also adopted Cochran's Q statistic to test the heterogeneity and MR-PRESSO to confirm the horizontal pleiotropy.

Results: MR analysis of the IVW method shows uromodulin could elevate blood pressure and enhance the risk of hypertension. Odds Ratios(OR) of the uUMOD to hypertension (ukb-b-14057 and ukb-b-14177) is 1.04(95% Confidence Interval (CI), 1.03-1.04), while in sUMOD is 1.01(95%CI 1.01-1.02). Both sUMOD and uUMOD can predict the elevation of the SBP and DBP. The effect sizes of the uUMOD to SBP are 1.100 and 0.028 in ieu-b-39 and ukb-b-20175 respectively. The causal relationship between uUMOD and DBP of the ieu-b-39 is 0.88(p-value=4.38E-06) and 0.05 of the ukb-b-7992(p-value=2.13E-10). The β coefficient of sUMOD IVW in ieu-b-38 is 0.371 and 0.011 in ukb-b-20175. For DBP in ieu-b-39 are β=0.313 (SE=0.050) and β=0.018 (SE=0.003)in ukb-b-7992.

Conclusions: Our results solidly indicated that high urinary and serum uromodulin level is a causal risk factor for hypertension.

PO1778

Follistatin Is a Potential Novel Therapeutic Agent for Essential Hypertension

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Background: Follistatin (FST) is an inhibitor of several members of the profibrotic TGFb superfamily. It is highly effective at neutralizing activins, without activity against TGFb1 itself. Activins are known to induce inflammation, oxidative stress and fibrosis, all of which contribute to the vascular dysfunction characteristic of hypertension (HTN). We previously showed that FST inhibits kidney fibrosis, improves kidney function and lowers blood pressure (BP) in a hypertensive chronic kidney disease mouse model. While this is a model of secondary HTN, here we seek to analyze the efficacy of FST in improving BP and vascular structure and function in a model of essential HTN.

Methods: Telemeters were implanted in the abdominal aorta of spontaneously hypertensive rats (SHR), a model of essential HTN, and normotensive control Wistar Kyoto (WKY) rats for wireless BP monitoring. Rats were treated with 0.075mg/kg FST or vehicle IP every other day from 12-20 weeks of age (8 weeks). BP was recorded weekly. First branch mesenteric arteries were harvested for analysis of vascular function using myography, assessed for oxidative stress by DHE, or formalin fixed for IHC.

Results: By the end of the study, FST significantly lowered both systolic and diastolic BP in SHRs (200 +/- 9 over 132 +/- 4 mmHg in control and 189 +/- 2 over 123 +/- 2 mmHg in FST-treated SHRs, $P < 0.04$ and $P < 0.03$ respectively). SHR vessels showed increased contractility with the *a*1 adrenergic agonist phenylephrine, which was attenuated by FST. Impaired endothelium-dependent relaxation in SHR vessels was also improved by FST. Structurally, FST-treated vessels had less collagen deposition, assessed by Trichrome, which was accompanied by a reduction in medial thickness. Increased oxidative stress seen in SHR vessels was inhibited by FST.

Conclusions: FST lowers BP in SHR with established HTN, at least in part by reducing vascular oxidative stress and medial thickening. This manifests as improved vascular function, with decreased hypersensitivity to contractile agents and improved endothelial function. Future work will identify the effects of FST on inflammation, and the role of specific activins in essential HTN.

Funding: Private Foundation Support

PO1779

Age and Sex Disparities in Hypertension Treatment Inertia After Implementation of Target: BP

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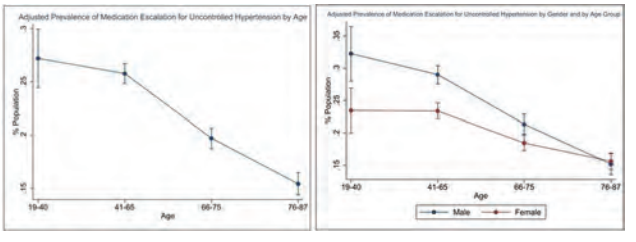
Background: Blood pressure (BP) control decreases with advancing age among women but not men, but reasons for sex disparities remain uncertain. Our institution enrolled four large outpatient primary care clinics in the Target:BP hypertension improvement program in 2018. This hypertension improvement program included audit and feedback of physician prescribing practices of BP lowering medications. We examined the adjusted association of medication escalation, a measure of treatment inertia, with age group among adults with uncontrolled hypertension and determined whether this association is modified by sex. We hypothesized that medication escalation for BP control differs by age group and by sex.

Methods: Adults age ≥ 18 years with uncontrolled hypertension (BP ≥ 140/90 mmHg at last visit) receiving primary care at a clinic enrolled in Target:BP and ≥ 1 primary care visit during 2019 were included. Medication escalation was defined as a change in BP lowering medication class or dose during a visit when hypertension was uncontrolled. Mixed effects models were used to calculate adjusted odds of medication escalation by age group (≤ 65, 66-75, ≥ 76 years) after adjustment for demographics and co-morbidities. Interaction term of sex* age group was then fitted in fully adjusted mixed effects models and was significant ($P < 0.001$). Adjusted odds of medication escalation were then calculated by sex and by age group and adjusted prevalence of medication escalation by age group and by sex was calculated using marginal effects.

Results: Mean age of 5973 adults with uncontrolled hypertension was 65.2 (SD 6.2) years; 54.7% were women; 64.7%% were White, 24.0% were Black and 9.9% were Hispanic ethnicity. Figure (left panel) shows that adjusted prevalence of medication escalation declined with advancing age group among men and women combined. Right panel shows the decline in medication escalation with advancing age group differed by sex until age 76+ years.

Conclusions: Medication escalation for uncontrolled hypertension declines with advancing age and this age associated treatment inertia differs by sex.



PO1780

Oscillometric vs. Auscultatory Blood Pressure Measurements and the Impact of Atrial Fibrillation

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Background: The Hypertension literature recognizes a difference in Oscillometric Blood pressures compared to Auscultatory Blood pressure measurements. Theses differences are small but increased in patients with Atrial fibrillation. This difference varies in previous studies. Again this Difference is larger in subjects with atrial fibrillation. Current Blood pressure measurement guidlines emphasize the use of an Auscultatory method or repeated oscillometric measures to measure blood pressure in patient with arrythmias including atrial fibrillation. This recommendation is not consistently implemented in clinical medicine. We aim to quantify the differences in blood pressure readings between oscillometric and auscultatory method and correlate that to presence or absence of atrial fibrillation.

Methods: This is a retrospective study that involved adult patients seen in the outpatient nephrology clinic by one of the investigators (CM) between january 2016 and january 2020. Data collection included age, sex, BMI, atrial fibrillation (AF), CKD stage, diabetes mellitus, blood pressure readings (by both methods, which were done by the investigator (CM) in all antihypertensive patients) and number of blood pressure medications. Information on a total of 200 patients were collected. 100 of those had hypertension with AF while the other 100 had hypertension but no AF to achieve a power of 80% and P value of 0.05.

Results: After using Unpaired t test, the average difference between two methods in hypertensive patient without atrial fibrillation were around 0.29 mmHg in systolic blood pressure (P value of 0.9 and 95% CI from -5.5 to 6.12) and 5.39 mmhg in diastolic blood pressure (P value of 0.0068 and 95% CI from 1.5 to 9.24). On the other hand, the average difference between two methods in hypertensive patients with atrial fibrillation were 6.8 mmHg in systolic blood pressure (P value of 0.018 and 95% CI from 1.18 to 12.5) and 5.04 mmHg in diastolic blood pressure (P value of 0.002 and 95% CI from 1.87 to 8.21).

Conclusions: This study showed a statistical difference between the two methods in measuring the blood pressure of hypertensive patients with atrial fibrillation. A larger study is needed to show the no difference between the two methods. For now we need to encourage the use of auscultatory method in measuring the Blood pressure in this group of patients.

PO1781

Single-Nephron Salt Excretion and Nighttime Hypertension: A Cross-Sectional Study in Patients with IgA Nephropathy

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Background: Abnormalities in diurnal blood pressure variability and renal salt handling may contribute to poor disease outcomes in patients with IgA nephropathy (IgAN). This study examined the relationships between diurnal blood pressure variability and single-nephron urinary salt excretion (SNUSE) in IgAN patients.

Methods: The subjects were IgAN patients who underwent ambulatory blood pressure (ABP) monitoring and 24-h urine collection during hospitalization for a diagnostic biopsy. In all patients, dietary salt intake was restricted to 6 g/day during hospitalization. Daytime and nighttime hypertension were defined as daytime ABP ≥135/85 mmHg and nighttime ABP ≥120/70 mmHg, respectively. The total nephron number per kidney was estimated by a combined cortical volume assessment of unenhanced computed tomography images and stereology-based measurements of non-sclerotic glomerular density in a biopsy. SNUSE was calculated by dividing urinary salt excretion per day by the total nephron number of both kidneys.

Results: Among the 112 patients (42 years old, 63.4% male, estimated glomerular filtration rate [GFR] 62.4 mL/min/1.73 m^2) included, daytime and nighttime hypertension were noted in 33.0% and 50.9%, respectively. There was no marked difference in the total nephron number or SNUSE in relation to the daytime hypertension. In patients with nighttime hypertension, the total nephron number per kidney was lower (490,000 vs. 796,000/kidney, p = 0.01) and SNUSE was higher (6.53 vs. 4.22 μg/day, p=0.003) than in normotensive patients during nighttime. An increase in SNUSE in patients with nighttime hypertension was associated with advanced tubulointerstitial injury, defined as a T score in the Oxford histopathological classification of IgAN. The single-nephron GFR was comparable among patient groups with and without hypertension both during the daytime and nighttime and was not associated with a T score.

Conclusions: These results provide evidence that salt excretion per nephron is increased in IgAN patients presenting with nighttime hypertension. The difference in SNUSE was identified in relation to the tubulointerstitial injury without producing a difference in single-nephron GFR values among ABP categories, indicating compensatory changes in tubular salt handling at the single-nephron level.

Funding: Other U.S. Government Support

PO1782

Small Changes in eGFR Are Associated with Different Patterns of 24-Hour Ambulatory Blood Pressure Monitoring in the General Population

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Background: Alteration of circadian blood pressure (BP) rhythm such as non-dipper and reverse-dipper pattern is associated with cardiovascular diseases and chronic kidney disease (CKD). However, most studies did not control for kidney function even though kidney function is an important risk factor. In this study, we tried to show 24-h ambulatory blood pressure monitoring (ABPM) patterns based on an eGFR in patients without CKD.

Methods: This study was a cross-sectional study from the data of the Korean Genome and Epidemiology Study, which is ongoing prospective cohort study. A total of 1733 participants (60.0±7.00 years, 938 women) who had an eGFR > 60 ml/min/1.73m2 were included. Dipping status was stratified as reverse dipper (<0%), non-dipper (0% to <10%), and dipper (≥10%) based on the night to day ratio of mean BP. They were divided into 4 groups based on quartile of an eGFR (Q4, 128.6-101.6; Q3, 101.5-95.7; Q2, 95.6-87.4; Q1, 87.3-60.5).

Results: The proportion of dipper was progressively decreased from the highest to the lowest eGFR whereas that of reverse dipper and non-dipper significantly increased. (P<0.001). We analyzed the data using logistic regression model in relation to dipper, non-dipper, reverse dipper, and non-dipper plus reverse dipper according to the quartile groups of an eGFR. The highest quartile group (Q4) was fixed as the reference. In univariate analyses, Q1 and Q2 groups were significantly associated with increasing odds ratio (OR) with non-dipper, reverse dipper, and non-dipper plus reverse dipper. After full-adjustment with age, sex, hypertension, diabetes, body mass index, smoking status, exercise, and alcohol consumption, the lowest eGFR group was significantly associated with reverse dippers and non-dipper plus reverse dippers compared to the highest eGFR group (OR=1.689, 95% CI, 1.005-2.840; OR=1.427, 95% CI, 1.027-1.985, respectively). The significant linear trend of non-dipper plus reverse dipper with a decrease in eGFR was confirmed with the test for trend (P=0.024).

Conclusions: Small changes in eGFR are associated with different pattern of 24-h ABPM in general population. ABPM could be useful tool to detect patients with non-dipper in these population.

PO1783

Blood Pressure Control and Undiagnosed Hypertension: A Randomized Diagnostic Study Comparing Clinic, Home, and Kiosk Methods

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Background: Undiagnosed hypertension is common and contributes to CKD and cardiovascular morbidity and mortality. We compared prevalence of blood pressure (BP) control and undiagnosed hypertension at 6 months according to different BP measurement methods.

Methods: BP CHECK was a randomized diagnostic study of 510 adults aged 18-85 without diagnosed hypertension or antihypertensive medications, with elevated BP in clinic and at baseline, conducted 2017-2019 in primary care centers of an integrated healthcare system. Randomization occurred into one of three diagnostic regimens: (1) Clinic BP (usual care), (2) Home BP (twice daily for 5 days), or (3) Kiosk BPs (triplicate BPs on 3 days). All participants completed ABPM at baseline. Primary outcomes were changes in systolic BP and diastolic BP; BP control and receipt of a new hypertension diagnosis at 6 months. We further examined whether changes in patient-reported outcomes relating to physical and psychological well-being and behavior were associated with BP control or a new hypertension diagnosis.

Results: Mean baseline BP was similar across groups (150/88 mmHg). Overall, 93% (472/510) of study participants completed the 6-month visit. All groups experienced a reduction in BP (mean reduction: systolic BP –11.5 mmHg, diastolic BP –5.5 mmHg) with no significant differences by randomization group. Among 323 participants with hypertension based on ABPM, 156 (48%) achieved BP control (<140/90 mmHg) and 130 (40%) had a new hypertension diagnosis recorded in the EHR at 6-months. Participants with undiagnosed hypertension at 6 months experienced significantly lower reductions in both systolic and diastolic BP, compared to individuals with a new hypertension diagnosis (difference in mean change SBP [95% CI], -5.1 mmHg [-7.8,-2.3], P<0.001; DBP -2.4 mmHg [-4.2, -0.5], P=0.01). Changes in patient-reported outcomes from baseline to 6 months were small, with no significant differences in body weight, intake of fruits/vegetables, or measures of physical health according to randomization group or presence of hypertension diagnosis.

Conclusions: Irrespective of BP measuring method, most participants with high BP on screening and ABPM diagnostic testing did not receive a hypertension diagnosis or adequate BP control. New strategies are needed to enhance uptake of BP diagnostic testing into clinical practice.

Funding: Other U.S. Government Support

PO1784

Crit-Line Monitoring Effect on Blood Pressure Control in ESRD Patients Undergoing In-Center Hemodialysis

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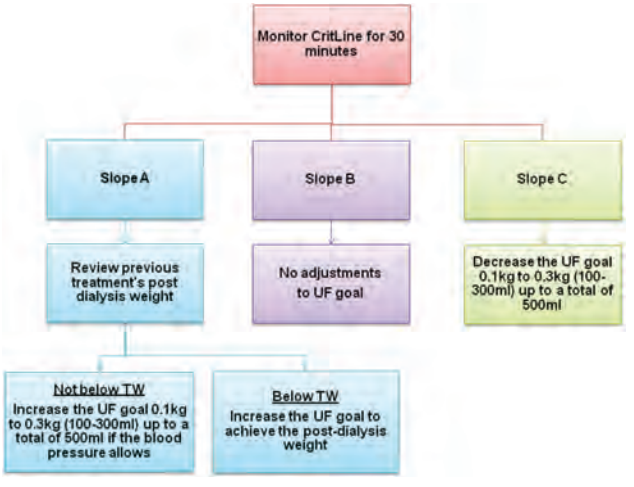
Background: Patients with end stage renal disease (ESRD) are admitted to the hospital about twice per year, with a 35% readmission rate. Cardiovascular disease (CVD) makes up 28% of admissions; 38% of patients with CVD admissions have pulmonary edema. Fluid overload in ESRD increases morbidity and mortality. Fluid management improvements have potential to positively impact clinic outcomes in dialysis patients.

Methods: This was a prospective cohort study with adult patients at two outpatient dialysis facilities on the Washington University in St Louis Campus. Our inclusion criteria were patients with consistent 3x weekly in center hemodialysis defined as 80% attendance in the 30 days prior to the study. A critline protocol was implemented by the treatment team (Figure 1).

Results: Among 58 qualified patients, average age was 59. 77% were African American with male predominance (57%). Average BMI was 29. In the Critline cohort, systolic blood pressure trended down (Figure 2). In the initial 25 weeks, average number of antihypertensive medications per patient decreased from 2.6 to 1.8. The number of admissions for fluid overload stayed stable at 10, however readmissions decreased from 4 to 1.

Conclusions: Implementing a Critline protocol trended towards improvements in blood pressure and reduced number of antihypertensives medications. Our findings suggest that a protocolized approach to fluid management using critline will improve our patients outcomes.



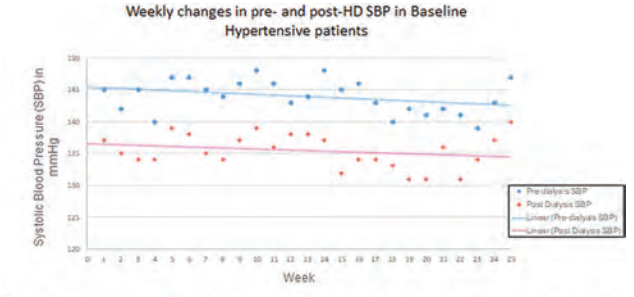


Figure 1. Weekly changes in pre- and post-HD SBP in Baseline Hypertensive patients. Pre- and post-dialysis SBP in hypertensive groups are shown through Week 12. Values given in mmHg. Weekly average post-dialysis SBP is denoted by the filled diamond and the pre-dialysis SBP by the filled circle.

PO1785

Cardiovascular Functional Changes in Transplant Waitlist Dialysis Patients

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Background: The transition to dialysis is a crucial time in patients with advanced chronic kidney disease (CKD), conferring an increased risk for cardiovascular death. We recently showed that VO_2Peak, an index of cardiovascular functional capacity (CFC) significantly declined in advanced CKD patients following 1-year follow-up in the absence of changes in left ventricular mass index (LVMI). Herein, we hypothesized that initiating dialysis and continuing dialysis could worsen an individual's CFC over time.

Methods: We conducted a cross-sectional study of 241 CKD stage 5 patients from the Cardiopulmonary Exercise Testing in Renal Failure (CAPER) cohort. VO_2Peak (primary endpoint) was assessed by cardiopulmonary exercise testing (CPET) in parallel with transthoracic echocardiography.

Results: Of the 241 patients (mean age [SD] age, 48.9 [14.9] years; 154 [63.9%] male), n=42 patients were pre-dialytic (mean eGFR [SD], 14 [3.4] ml/min/1.73m^2), n=66 were in tertile 1 of dialysis vintage (0-17 months), n=69 in tertile 2 (18-50 months) and n=64 in tertile 3 (≥51 months). Predialysis patients had an impaired VO_2Peak of 22.7 [5.2] ml/min/kg, and this significantly declined to 18.5 [5.5] ml/min/kg in tertile 1 dialysis patients. Compared to the pre-dialysis group, tertile 1 dialysis patients exhibited reduced maximal workload (p=0.003), impaired maximal heart rate (p=0.02), increased LVMI (p<0.001) and markedly elevated FGF23 levels (p=0.01). On assessment of the effects of dialysis vintage, we found an incremental downward trend in VO_2Peak across the groups (19.1 [5.2] tertile 1, 18.0[4.7] tertile 2, 16.9[4.2] ml/min/kg) following exclusion of patients who had prior kidney transplants, however this did not reach statistical significance (p=0.2).

Conclusions: Initiating dialysis in advanced CKD patients is associated with impaired CFC comparable to declines seen in new onset heart failure, making this a critical time for these patients.

PO1786

Major Adverse Limb Events and Mortality After Peripheral Artery Revascularization in Hemodialysis Patients

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Background: Revascularization is important for symptom relief and limb salvage in peripheral artery disease, yet limited information exists on the prognosis of hemodialysis patients who receive the procedure. This study sought to determine the incidence and associated factors of major adverse limb events (MALE) after peripheral artery revascularization among hemodialysis patients.

Methods: Hemodialysis patients undergoing peripheral artery revascularization between July 1, 2005, and December 31, 2019, in the Taipei Tzu Chi Hospital were examined for the primary outcome of MALE, defined as severe limb ischemia leading to an intervention or amputation. The secondary outcomes included major adverse cardiovascular events (MACE) and all-cause mortality. Multivariable-adjusted Cox proportional hazards models were used to explore risk factors associated with development of MALE.

Results: A total of 402 hemodialysis patients were included in the final analysis. Overall, the mean age was 68 years, 56.5% (n = 227) were male, 83.3% (n = 335) had diabetes, and 58.0% (n = 233) had coronary artery disease. During a median follow-up of 2.2 years, 54.0% (n = 217) experienced a subsequent MALE, 33.6.0% (n = 136) had a MACE, and 54.5% (n = 219) died. Diabetes, coronary artery disease, current smoking, lower body mass index, and higher platelet count or total cholesterol were significantly associated with increased risk of post-procedure MALE.

Conclusions: A significant proportion of hemodialysis patients undergoing peripheral artery revascularization developed a subsequent MALE and MACE or died. Strategies that address risk factors for MALE should be evaluated to improve the outcomes of revascularized hemodialysis patients.

PO1787

Central Blood Pressure Calibration Method and Cardiovascular Risk Prediction According to Sex

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Background: The accuracy of central BP is improved when calibrated on the mean BP and diastolic BP (C2SBP) compared to calibration on the systolic BP and diastolic BP (C1SBP). Furthermore, preliminary data suggest C2SBP may have the best accuracy in females. We aim to assess whether this enhanced accuracy translates into improved cardiovascular (CV) risk prediction when compared to brachial SBP (bSBP) and C1SBP in the general population and stratified by sex.

Methods: 12,927 participants exempt of known CV disease, with prospective follow-up from administrative databases and central BP measurements were included. The SphygmoCor Px device was used to estimate C1SBP. C2SBP was derived from unprocessed radial pressure waveforms extracted from SphygmoCor output data, which was recalibrated with diastolic BP and 40% form factor derived mean BP. Participants with heart rate <60 were excluded due to incomplete waveforms. Major adverse CV events (MACE) comprised myocardial infarction, stroke, heart failure with hospitalization and CV death. Multivariable Cox regressions, differences in area under the curve, net reclassification index and integrated discrimination index were calculated comparing C2SBP to C1SBP and to bSBP.

Results: Over a median follow-up of 10.1 years (IQR 9.9-10.3), there were 2125 MACE (723/7013 females and 860/5934 males). All BP parameters were significantly associated with MACE, regardless of sex. In the overall cohort, risk prediction metrics marginally favored C2SBP compared to bSBP, but were similar to C1SBP. No significant improvement of CV risk prediction was found in sex-stratified analyses (see Table).

Conclusions: C2SBP marginally improved CV risk prediction when compared to bSBP but not C1SBP in the overall cohort only. All three BP parameters were similarly predictive in both sex, although this analysis possibly lacked power. This may be related to the FF-derived MAP (rather than oscillometric MAP), which is highly dependent on the brachial SBP.

Table 1. Central blood pressure calibration method and cardiovascular risk prediction

Cohort	Calibration method	ΔAUC (95% CI)	NRI (95% CI)	IDI (95% CI)
All	C2SBP vs Brachial SBP model	0.05 (-0.12, 0.12)	0.11 (0.03, 0.17)	0.0002 (-0.0001, 0.0007)
	C2SBP vs C1SBP model	-0.01 (-0.10, 0.07)	-0.01 (-0.10, 0.09)	-0.0004 (-0.0006, 0.0003)
Males	C2SBP vs Brachial SBP model	0.05 (-0.05, 0.13)	0.08 (-0.05, 0.14)	0.0003 (-0.0001, 0.0010)
	C2SBP vs C1SBP model	0.04 (-0.03, 0.11)	-0.03 (-0.11, 0.07)	-0.0001 (-0.0010, 0.0007)
Females	C2SBP vs Brachial SBP model	0.06 (-0.06, 0.18)	0.11 (-0.03, 0.19)	0.0001 (-0.0004, 0.0010)
	C2SBP vs C1SBP model	0.03 (-0.11, 0.17)	0.03 (-0.11, 0.14)	-0.0000 (-0.0007, 0.0009)

Each model includes the relevant BP parameter and age, BMI, smoking status, diabetes, HDL-c, total cholesterol, eGFR, heart rate and use of aspirin, statin, β-blockers, calcium channel blockers, diuretics and renin-angiotensin system blockers. C1SBP, central SBP calibrated on brachial SBP and DBP; C2SBP, central SBP calibrated on brachial SBP and MAP; ΔAUC, difference in area under the receiver operating characteristic curve; NRI, net reclassification index; IDI, integrated discrimination index.

PO1788

Suppressed Renin Activity in CKD: Are We Missing Primary Hyperaldosteronism?

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Background: Primary hyperaldosteronism (PA) is more prevalent than once thought and associated with adverse kidney and cardiovascular outcomes. A prior analysis of the CKD registry at the Cleveland Clinic in patients without a diagnosis of PA showed that the lowest quartile of plasma renin activity (PRA) had more severe hypertension and faster eGFR decline. We hypothesized that some of these patients with suppressed PRA may have undiagnosed PA.

Methods: We reviewed patients in the Cleveland Clinic CKD registry with documented PRA and absolute plasma aldosterone concentration (PAC). Patients in the lowest PRA quartile were identified and stratified by PAC/PRA ratio. A cutoff ratio of ≥20 was considered suggestive of PA regardless of the PAC. Characteristics and outcomes of these two subgroups were compared using t-tests, chi-square tests, Kaplan-Meier analyses and Cox models.

Results: 276 patients were identified for this analysis. Median PRA and PAC were 0.5 ug/L/hr and 8.7 ng/dl respectively. 141 (51%) patients had a PAC/PRA ratio of ≥20 with a median PAC of 14.6 ng/dl in this subgroup. Patients with PAC/PRA of ≥20 vs. <20 had significantly lower eGFR (mean: 50.7 vs. 55.4 mL/min/1.73 m^2; p=0.009), more resistant hypertension (63.1% vs. 48.9%; p=0.044), lower serum potassium values (mean: 3.9 vs. 4.2 mmol/L; p<0.001), and higher serum bicarbonate levels (mean: 26.4 vs. 25.3 mmol/L; p=0.001). With median follow up of 4.2 years, there was no difference in mortality between the two subgroups on adjusted cox model analysis (HR for ≥20 vs.<20: 0.83, 95%CI: 0.47,1.47). No difference in ESKD-free survival at 5 years was noted but the event rate was low (92.6 vs. 91.9 for ≥20 vs.<20; p=0.77).

Conclusions: Our analysis indicates that some CKD patients with suppressed PRA may have underlying PA. More than half of our suppressed PRA cohort had elevated PAC/PRA ratio ≥20 suggestive of PA. The biochemical profile and severe hypertension further supports this diagnosis. We hypothesize that the diagnosis of PA was possibly ruled out because of the "not very high" PAC. Given the limitations of the spot PAC/PRA screen owing to diurnal PAC variations, a suppressed PRA should merit an in-depth evaluation for undiagnosed PA regardless of the PAC. Making this diagnosis is critical since it has significant therapeutic implications.

PO1789

Higher Plasma Renin Activity Level Is Associated with the Severe Intrarenal Arterial Injury in Patients with Hypertensive Emergency

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Background: It is well known that most patients with hypertensive emergencies have high plasma renin activity (PRA) levels, which indicates the pathophysiology of organ damage. However, the association with intrarenal arterial injury and PRA level has not been well documented.

Methods: We herein investigated this association retrospectively in patients who were diagnosed with hypertensive emergency and were also evaluated the PRA and underwent kidney biopsy between April 2001 and September 2019. The severity of intrarenal arterial injury was classified into stage 0 to stage 3 based on the report by Kohagura et al (Hypertens Res. 2013).

Results: A total of 13 patients (mean age; 39.2±11.2 years, male; 92.3%, BMI; 26.4±3.9 kg/m^2, history of hypertension; 92.3%) were included in this study. All patients had higher systolic blood pressure (≧180 mmHg), and 12 patients had higher diastolic pressure (≧120 mmHg). At admission, 12 patients had kidney injuries, 12 patients had hypertensive retinopathy, 6 patients had acute heart failure, and 1 patient had lacunar infarction. The average PRA levels at admission was 20.0±2.8 ng/mL/ hr. The average duration from diagnosis to kidney biopsy were 14.4 days. The median eGFR on the day of kidney biopsy was 15.3 [IQR 9.1, 21.7] mL/min/1.73m^2. PRA was significantly and positively correlated with severity of intimal edema of intrarenal small arteries (r^2=0.42, p=0.02). However, no association was found between PRA and other histological kidney injury.

Conclusions: Since vascular injury directly leads to organ damage, its presence calls for urgent need for blood pressure lowering with caution for ischemia. Since biopsy is often not available, PRA can be a good substitute to assess vascular injury in the management of those with acute severe hypertension.

PO1790

Cardiovascular and Renal Outcomes of the New Intensive Blood Pressure Target in a CKD Population in Korea

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Background: Hypertension is one of the most important modifiable risk factors of cardiovascular disease (CVD) including ischemic heart disease (IHD) and stroke. The 2021 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure (BP) in CKD recommended a target systolic BP (SBP) <120 mmHg regardless of albuminuria, using standardized office BP measurement. We evaluated the prevalence of cardiovascular events and CKD progression to assess the effects of this intensive BP target for CKD patients in Korea.

Methods: The data of 166,397 adults whose baseline estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 were extracted from the Korean National Health Insurance Service database between 2009 and 2011. The data were adjusted for multiple factors such as age, sex, smoking, eGFR, and anti-hypertensive medications in multivariate Cox proportional hazards regression models. All participants were divided into four SBP categories (<120 mmHg, 120-129 mmHg, 130-139 mmHg, ≥140 mmHg). The primary outcome was CVD risk, and the secondary outcome was the risk of progression to end-stage renal disease (ESRD), especially in need of intermittent hemodialysis (HD).

Results: The mean ages of the each group of CKD patients were 45.1±15.71 years in SBP <120 mmHg group and 52.13±16.00 years in SBP 120-129 mmHg group. 11.1% in SBP <120 mmHg group and 24.6% in SBP 120-129 mmHg group of the participants were already taking anti-hypertensive medications. 112,012 patients (67.3%) had SBP ≥120 mmHg, and 78,119 patients (46.9%) had SBP ≥130 mmHg. Participants with SBP 120-129 mmHg exhibited a significantly high risk for IHD (hazard ratio (HR), 1.29; 95% confidence interval (CI), 1.03-1.61; P = 0.03) and stroke (HR, 1.57; 95% CI, 1.13-2.18; P <0.001) when compared with the participants with SBP <120 mmHg. Also, the risk of progression to ESRD was also higher (HR, 1.67; 95% CI, 1.46-1.91; P <0.001). Similar statistical findings were observed between the group with SBP <120mmHg and the other groups.

Conclusions: Therefore, the new intensive BP target can be applied to the real clinical practice in CKD population with proper BP monitoring in Korea, and it may eventually reduce the risk of CVD and progression to ESRD in a number of CKD outpatients.

PO1791

Intensive Blood Pressure Control, Age, and All-Cause Mortality in the US Veterans Health Administration

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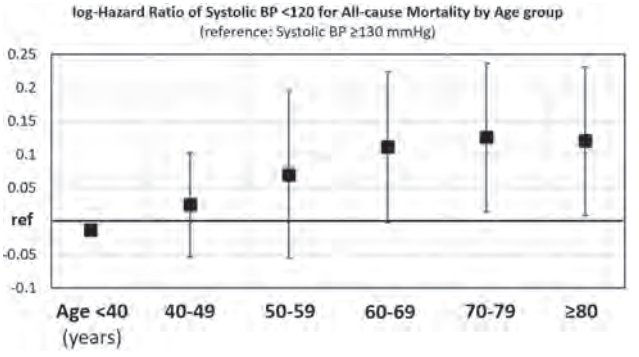
Background: Intensive blood pressure (BP) control has been shown to improve survival in large clinical trials. It is unknown if intensive BP control is associated with improved outcomes amongst older adults in the real-world setting. We examined the association of intensive BP control with all-cause mortality in U.S. Veterans.

Methods: This retrospective analysis of Veterans Health Administration (VHA) data included Veterans with ≥2 systolic blood pressure (SBP) readings between January 2016 and December 2017 excluding those with mean SBP <100 mmHg to minimize reverse causation. Prevalent hypertension was defined as diagnostic codes related to hypertension, prescribed antihypertensive drugs, or ≥2 office BP of ≥130/90 mmHg. The following SBP categories were examined: <120, 120-129, and ≥130 mmHg (reference). We estimated the potential effect of SBP control on all-cause mortality and evaluated the potential interaction with age using a random-effect Cox regression model.

Results: Of the 1,959,003 Veterans, 18% had SBP <120 mmHg (n=352,684), 26% had SBP 120-129 mmHg (n=507,907), and 56% had SBP ≥130 mmHg (n=1,098,412). Mean SBP <120 and 120-129 mmHg associated significantly with mortality (the adjusted hazard ratio [aHR] was 1.30; 95% confidence interval [CI] 1.28-1.32 for SBP <120 mmHg and 1.03 [95% CI 1.01-1.04] for SBP 120-129 mmHg). There was a significant interaction between SBP category and age (p<0.01). Specifically, we observed a graded association of SBP <120 mmHg with all-cause mortality across increased age categories; this association was significant in the age categories ≥70 years (Figure 1).

Conclusions: Based on the analysis of real-world data of approximately 1.9 million Veterans, intensive BP control (SBP <120 mmHg) was associated with higher mortality specifically among older Veterans. These data have implications for BP management and suggest that intensive control of SBP may be harmful in older adults.

Funding: Veterans Affairs Support



PO1792

Markers of Kidney Tubular Secretion and Risk of Cardiovascular Disease and Mortality in Persons with CKD in SPRINT

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Background: Tubular secretion of organic solutes is essential to the clearance of many drugs, metabolites, and toxins. Whether novel measures of tubular secretion have prognostic value for cardiovascular and mortality risk among hypertensive, nondiabetic persons with CKD is uncertain.

Methods: In 2089 SPRINT (Systolic Blood Pressure Intervention Trial) participants with baseline eGFR <60 ml/min/1.73m2, we created a summary secretion score from 10 tubular secretion biomarkers by averaging across their urine-to-plasma ratios. We used multivariable Cox proportional hazards models to evaluate associations between secretion scores and risk of cardiovascular disease (CVD) and all-cause mortality.

Results: Mean age at baseline was 73 ±9 years and mean eGFR was 46 ±11 ml/min/1.73m2. There were 272 CVD events and 144 deaths during a median follow-up of 3.26 years. In unadjusted analyses, a 1-SD higher secretion score was associated with a lower risk of CVD (hazard ratio [HR] per: 0.87; 95% CI: 0.76, 0.99), but not all-cause mortality (HR: 0.95, 95% CI: 0.80, 1.13) (Table). In multivariable analyses adjusting for baseline eGFR, albuminuria, and CVD risk factors, the association between higher secretion score and CVD risk attenuated and was no longer significant (HR: 0.94, 95% CI: 0.81, 1.08), while higher secretion appeared to be associated with an increased risk of all-cause mortality that did not reach statistical significance (HR: 1.12, 95% CI: 0.95, 1.33).

Conclusions: Among SPRINT participants with CKD, higher tubular secretion was not significantly associated with risk of CVD or mortality after adjustment for eGFR and albuminuria.

Funding: NIDDK Support

Associations of summary tubular secretion score* with CVD events and all-cause mortality in persons with CKD in SPRINT

	Events/N	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
CVD events			
Per 1-SD higher score	272/2089	0.87 (0.76, 0.99)	0.94 (0.81, 1.08)
Quartile 1	85/523	Reference	Reference
Quartile 2	75/528	0.85 (0.62, 1.16)	0.83 (0.60, 1.15)
Quartile 3	55/535	0.61 (0.43, 0.85)	0.68 (0.47, 0.98)
Quartile 4	57/503	0.65 (0.47, 0.91)	0.75 (0.51, 1.10)
All-cause mortality			
Per 1-SD higher score	144/2089	0.95 (0.80, 1.13)	1.12 (0.95, 1.33)
Quartile 1	45/523	Reference	Reference
Quartile 2	38/528	0.82 (0.53, 1.26)	0.92 (0.58, 1.46)
Quartile 3	26/535	0.55 (0.34, 0.89)	0.81 (0.48, 1.38)
Quartile 4	35/503	0.75 (0.48, 1.17)	1.24 (0.73, 2.10)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; SD, standard deviation SPRINT, Systolic Blood Pressure Intervention Trial.
*Summary score calculated from averaging normalized urine-to-plasma ratios of adipic acid, cinnamoylglycine, p-cresol sulfate, 1,7-dimethyluric acid, 2-furoylglycine, hippuric acid, m-hydroxy hippurate, indoxyl sulfate, phenylacetylglutamine, tiglylglycine, and 1,3,7-trimethyluric acid.
†Model 1 is unadjusted.
‡Model 2 adjusts for baseline age, sex, race, intervention arm, smoking, body mass index, systolic blood pressure, number of antihypertensive medications, prevalent cardiovascular disease, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, statin use, baseline eGFR and urine albumin

PO1793

Markers of Kidney Tubular Secretion and Risk of Adverse Events in Persons with CKD in SPRINT

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Background: Tubular secretion is an essential mechanism for the elimination of many drugs, metabolites, and toxins. Impaired tubular secretion may contribute to the high burden of adverse events (AEs) in persons with CKD. Whether novel measures of tubular secretion have prognostic value for AEs during hypertension treatment is unknown.

Methods: In 2089 SPRINT (Systolic Blood Pressure Intervention Trial) participants with baseline eGFR <60 ml/min/1.73m2, we created a summary secretion score from 10 tubular secretion biomarkers by averaging across their urine-to-plasma ratios. Multivariable Cox proportional hazards models were used to evaluate associations between secretion scores and risk of a composite of pre-specified serious AEs (hypotension, syncope, bradycardia, acute kidney injury, electrolyte abnormalities, and injurious falls) and two outpatient AEs (hyperkalemia and hypokalemia).

Results: Mean age was 73 ±9 years and mean eGFR was 46 ±11 ml/min/1.73m2. Overall, 30% of participants experienced at least one AE during a median follow-up of 3.0 years. The association between secretion score and composite AE risk followed a curvilinear pattern. Compared to the lowest secretion score quartile, the highest quartile was associated with reduced risk of the composite AE in analyses adjusting for demographics and clinical characteristics (hazard ratio [HR]: 0.63; 95% CI: 0.44, 0.91) (Table). After additionally adjusting for baseline eGFR and albuminuria, the association attenuated and was no longer significant (HR: 1.01, 95% CI: 0.67, 1.50). In multivariable analyses of the individual AEs, higher secretion was independently associated with higher risk of syncope or hypotension (HR per 1-SD higher secretion score: 1.30, 95% CI: 1.10, 1.54) and lower risk of ambulatory hyperkalemia (HR: 0.71, 95% CI: 0.54, 0.95).

Conclusions: Among SPRINT participants with CKD, higher tubular secretion was associated with lower AE risk, but this association was not independent of eGFR and albuminuria.

Funding: NIDDK Support

Table. Association of summary tubular secretion score* with a composite of adverse events in persons with CKD in SPRINT

	HR (95% CI)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Events/N	212/523	163/522	137/523	125/522
Model 1†	Reference	0.73 (0.57, 0.93)	0.65 (0.49, 0.88)	0.59 (0.41, 0.84)
Model 2‡	Reference	0.76 (0.59, 0.97)	0.70 (0.52, 0.95)	0.63 (0.44, 0.91)
Model 3§	Reference	0.92 (0.70, 1.19)	1.01 (0.73, 1.41)	1.01 (0.67, 1.50)

Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; SPRINT, Systolic Blood Pressure Intervention Trial.
*Summary score calculated from averaging normalized urine-to-plasma ratios of adipic acid, cinnamoylglycine, p-cresol sulfate, 1,7-dimethyluric acid, 2-furoylglycine, hippuric acid, m-hydroxy hippurate, indoxyl sulfate, phenylacetylglutamine, tiglylglycine, and 1,3,7-trimethyluric acid.
†Model 1 adjusts for baseline age, sex, race, intervention arm, and urine creatinine.
‡Model 2 adjusts for covariates in model 1 and smoking, body mass index, systolic blood pressure, number of antihypertensive medications, prevalent cardiovascular disease, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, and statin use.
§Model 3 adjusts for covariates in model 2 and baseline eGFR and urine albumin.

PO1794

Longitudinal Changes in FGF-23 and High-Sensitivity C-Reactive Protein with Incident CKD in the Accord-BP Trial

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Background: In adults over 50 with increased cardiovascular (CV) risk, intensive systolic blood pressure (SBP) lowering reduces the risk of death and major CV events, but increases the risk of incident CKD. Metabolic manifestations of incident CKD related to intensive SBP lowering are unknown. Here we explored the relation between incident CKD and FGF23, an early marker of bone and mineral metabolism, in participants enrolled in the ACCORD-BP trial.

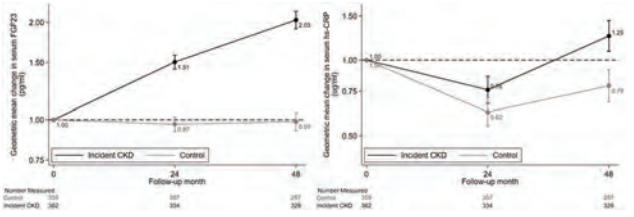
Methods: We included 362 ACCORD BP participants with incident CKD during follow-up along with 359 control participants without any kidney events. Control participants were matched for age, sex, race/ethnicity, SBP intervention and glycemia intervention arms. Incident CKD was defined as a >30% decrease in eGFR to <60 ml/min/1.73m2. Serum concentrations of FGF23 and hs-CRP were measured using Meso Scale Discovery Immunoassay platform at baseline, month 24 and 48/ close-out. Differences from baseline were estimated for the average of month 24 and 48/ close-out using mixed effect models with fixed effects for group and visit.

Results: Mean age was 63±6 yrs, 55% women, and 30% non-white. Baseline duration of diabetes was 11±8 yrs; baseline eGFR, FGF23 and hsCRP in the incident CKD and control groups were 87±17 and 92±19, 76(55,107) and 52(40,76) pg/ml and 3.2 (1.3,7.2) and 3.8(1.3,12.0) μm/ml, respectively. Longitudinal changes in these parameters are summarized in the Table and Figure.

Conclusions: Compared to controls, incident CKD was associated with increase in serum FGF23 and hsCRP levels. The long-term implications of incident CKD with intensive BP control needs further study.

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

	Within incident CKD	Within control group	Between groups differences
	Geometric mean change from baseline (95% CI)		
FGF23, pg/ml	1.75 (1.67,1.83)	0.98 (0.93,1.03)	1.79 (1.68,1.91)
hs-CRP, µm/ml	0.97 (0.87,1.09)	0.70 (0.62,0.79)	1.39 (1.20,1.61)
MDRD eGFR	0.61 (0.60,0.62)	0.90 (0.89,0.92)	0.67 (0.66,0.69)



PO1795

Carotid Plaque Characteristics and Incident Cognitive Impairment in Hypertensive Adults

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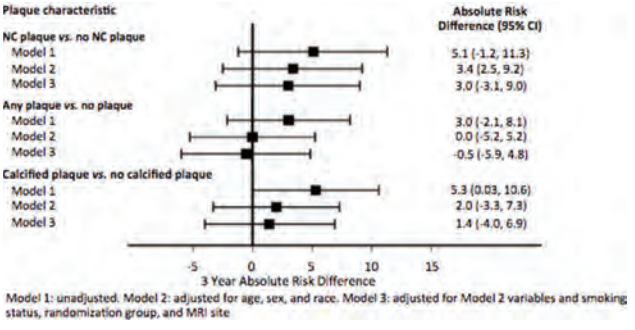
Background: Carotid atherosclerosis is associated with cognitive impairment. We investigated associations of plaque characteristics on carotid magnetic resonance imaging (MRI) with the development of mild cognitive impairment (MCI) or probable dementia.

Methods: In an ancillary study to the Systolic Blood Pressure Intervention Trial (SPRINT), carotid plaque was identified by MRI and characterized as having a lipid-rich necrotic core (NC) or calcification. In the parent study, adjudicated MCI and probable dementia were adjudicated on the basis of neuropsychological testing and proxy reports of cognition-related decline in functional status. We related baseline plaque presence and characteristics of NC or calcification with the incidence of MCI/probable dementia at 3 years of follow-up.

Results: Of 465 participants, 137 (29.5%) had NC plaque. Those with NC plaque were older and more likely to have cardiovascular disease than those without NC plaque. There were 38 MCI/probable dementia outcomes in the entire cohort over 2220 person-years of follow-up. The incidence (95% CI) of a composite outcome of MCI or probable dementia at 3 years was 12.0% (7.5, 18.9) in the NC group and 7.0% (4.6, 10.4) in the no NC group with an absolute risk difference of 5.1% (95% CI -1.2, 11.3, P=0.11). With further adjustment, the absolute risk difference attenuated but the point estimate remained high (Figure). Results for the presence of any plaque or calcified plaque with MCI/probable dementia are also summarized in the Figure.

Conclusions: We observed large differences in risk for MCI/probable dementia associated with the presence vs. absence of NC plaques, but the significance of this finding is uncertain due to the small number of incident cases of cognitive impairment. Nonetheless, our observations indicate the need to study NC plaque as a novel and potentially more relevant marker of vascular health in future studies of cognitive impairment in hypertensive adults.

Funding: NIDDK Support, Veterans Affairs Support



Model 1: unadjusted. Model 2: adjusted for age, sex, and race. Model 3: adjusted for Model 2 variables and smoking status, randomization group, and MRI site

PO1796

Associations of CKD with Dementia Before and After Transient Ischemic Attack and Stroke in a Population-Based Cohort Study

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Background: Individuals with chronic kidney disease (CKD) appear to have a greater risk of developing cognitive disorders than the general population. Both vascular and neurodegenerative hypotheses have been proposed to underlie this cognitive burden. To explore the vascular hypothesis further, we investigated the association between CKD and dementia before and after transient ischaemic attack (TIA) and stroke.

Methods: In a prospective, population-based cohort study of TIA and stroke (Oxford Vascular Study; 2002-2012), pre-event and new post-event dementia were ascertained through direct patient assessment and follow-up for 5 years, supplemented by review of hospital/primary care records. Associations between pre-dementia and CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m²) were examined using logistic regression, and between post-event dementia and CKD using both Cox and competing risk regression models, adjusted for age, sex, education, cerebrovascular burden (stroke severity, prior stroke, white matter disease), diabetes mellitus, and dysphasia.

Results: Among 2305 TIA/stroke patients (median [IQR] age, 77 [67-84] years, 1174 [51%] male, 688 [30%] TIA), 1174 (50.9%) had CKD. CKD initially appeared to be associated with both pre-event (odds ratio [OR], 2.04 [95% CI, 1.52–2.72]; P<0.001) and post-event dementia (hazard ratio [HR], 2.01 [95% CI, 1.65–2.44]; P<0.001); however, these associations attenuated and became non-significant after adjustment for the above covariates (OR=0.92 [0.65-1.31]; p=0.65 and HR=1.09 [0.85-1.39]; p=0.50). The results were similar when a competing risk model was used (subdistribution HR [SHR] =1.74 [1.43-2.12; p<0.001, attenuating to 1.01 [0.78-1.33]; p=0.92 with complete adjustment). CKD was more strongly associated with late (>1 year) post-event dementia (SHR=2.32, 1.70-3.17; p<0.001), particularly in the minor events subgroup (SHR=3.08, 2.05-4.64; p<0.001), but not significantly so after complete adjustment (SHR=1.53, 0.90-2.60; p=0.12).

Conclusions: In patients with TIA and stroke, CKD was not independently associated with either pre- or post-event dementia, suggesting that age, sex, education, and cerebrovascular burden may play a more important role in the relationship than renal-specific neurodegenerative mechanisms.

PO1797

Microvascular Endothelial Dysfunction in Women Living with HIV Represents Premature Aging

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Background: Combined antiretroviral therapy has permitted HIV-infected subjects to survive to old age yet many develop premature cardiovascular disease (CVD) characteristic of small vessel dysfunction though the causes are unclear. We reported that young HIV-infected individuals had endothelial dysfunction in their subcutaneous microarterioles (SMAs) dissected from a gluteal biopsy. We now test the hypothesis that this represents premature microvascular aging due to inflammation and reactive oxygen species (ROS).

Methods: SMAs from young (n=24) and old (n=18) virally-suppressed, HIV-infected and propensity-matched young (n=18) and old (n=16) HIV-negative controls were preconstructed on a myograph and relaxed with acetylcholine (Ach) to assess endothelium-dependent relaxation factor (EDRF*). Circulating IL-6 and urinary* 8-isoprostane $F_{2\alpha}$ were measured to access markers of inflammation and ROS.

Results: Young HIV infected (vs uninfected) subjects had significantly (p< 0.05) reduced EDRF (26±3% vs 39±2%) and significantly (p<0.05) increased circulating IL-6 (13±2 vs 6±2 pg/ml) and urinary 8-isoprostane $F_{2\alpha}$ (2.7±0.5 vs 1.3±0.3 ng/ ml.mg creatinine). Amongst controls, EDRF was reduced significantly (p< 0.05) in old vs young (26±2 % vs 38±3 %), accompanied by increased IL-6 (15±3 vs 6 ± 1 pg/ml) and 8-isoprostane $F_{2\alpha}$ (3.4±0.5 vs 1.3± 0.3 pg/ml). These variables were not significantly different between young and old HIV-infected individuals such that, amongst the old subjects, there was no difference (P=NS) between HIV infected (vs uninfected) subjects for EDRF, IL-6 or 8-isoprostane $F_{2\alpha}$.

Conclusions: Young subjects living with HIV have inflammation and ROS that impair their endothelial function but normal subjects develop age-dependent endothelial dysfunction sufficiently to abolish any difference with subjects who have HIV. Thus, microvascular disease in HIV represents the effects of inflammation and oxidative stress to cause premature aging.

Funding: Other NIH Support - NIH National Heart, Lung, and Blood Institute, NIH 5RO1-HL134511

PO1798

Platelet Activity Mediates Enhanced Cardiovascular Risk in Patients with CKD and Peripheral Artery Disease

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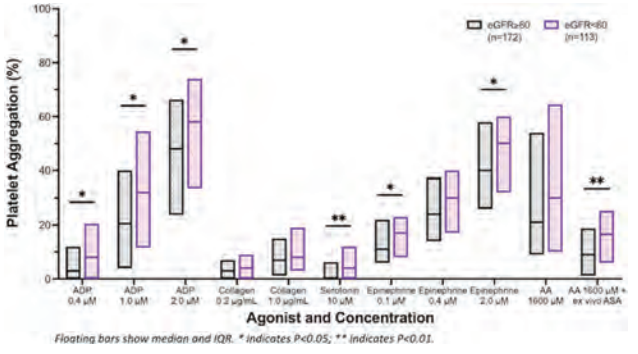
Background: Chronic kidney disease (CKD) is common in patients with peripheral artery disease (PAD), and both are associated with poor cardiovascular (CV) outcomes. Platelets drive PAD pathogenesis and mediate atherothrombosis. Platelet function in CKD and the related CV risk is unclear. We investigated relationships between CKD, platelet activity, and incident CV events in a cohort of patients with PAD

Methods: The Platelet Activity and Cardiovascular Events (PACE) study enrolled 289 patients with PAD undergoing lower extremity revascularization (LER). CKD was defined as eGFR<60 mL/min/1.73m^2 by the CKD-EPI equation. We measured platelet activity via light transmission aggregometry (LTA) in response to submaximal ADP, collagen, serotonin, epinephrine, and arachidonic acid (AA) prior to LER, and followed patients for a median of 18 months. The primary clinical endpoints were myocardial infarction (MI) and a composite of major adverse CV events (MACE; MI, stroke, death).

Results: There were 113 (40%) patients with and 172 (60%) without CKD. Patients with CKD (vs. non-CKD) were older and more likely to be female, Hispanic, have diabetes, heart failure, and critical limb ischemia (P<0.05 for each). There were no significant differences in prevalent coronary artery disease or use of antiplatelet therapy between groups. Platelet aggregation in response to submaximal ADP, serotonin, epinephrine, and AA was elevated in the CKD group (**Figure**). After multivariable adjustment, patients with CKD were at greater risk of MI (aHR 2.2 [95% CI: 1.02-4.9]; P=0.045) and MACE (1.9 [1.2-3.3]; P=0.01) than those without CKD. Platelet aggregation in response to submaximal agonist stimulation had a 25% and 12% mediating effect on the association of CKD with MI and MACE, respectively

Conclusions: In patients with PAD, CKD was associated with increased platelet activity and CV events. Heightened platelet activity is an important mechanism underlying increased CV risk in CKD



*Floating bars show median and IQR. * indicates P<0.05; ** indicates P<0.01.*

PO1799

Circulating Vascular Adhesion Protein-1 Level Predicts Risk of Cardiovascular Events and Mortality in Hemodialysis Patients

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Background: Vascular adhesion protein-1 (VAP-1) is an oxidative enzyme of primary amines that facilitates the transmigration of inflammatory cells. The oxidative and inflammatory effects of VAP-1 are prominently increased in pathological conditions such as metabolic, atherosclerotic, and cardiac diseases. However, the clinical significance of circulating VAP-1 levels in hemodialysis (HD) patients is unclear.

Methods: A total of 434 HD patients were prospectively enrolled between June 2016 and April 2019 as part of a prospective multicenter cohort study. Plasma VAP-1 levels were measured at the time of study data entry, and the primary endpoint was defined as a composite of cardiovascular (CV) events and cardiac events.

Results: Circulating VAP-1 levels were positively correlated with plasma levels of cardiac remodeling markers, including brain natriuretic peptides, galectin-3, and matrix metalloproteinase-2. Multivariate logistic regression analysis revealed that patients with higher circulating VAP-1 levels were more likely to have left ventricular (LV) diastolic dysfunction (odds ratio, 1.40; 95% confidence interval [CI], 1.04–1.88). The cumulative event rate of the composite of CV events was significantly greater in VAP-1 tertile 3 than in VAP-1 tertiles 1 and 2 (P = 0.009). Patients with VAP-1 levels in tertile 3 were also associated with an increased cumulative event rate of cardiac events (P = 0.015). The VAP-1 tertile 3 was associated with a 2.06-fold higher risk of the composite of CV events (95% CI, 1.10–3.85) and 2.06-fold higher risk of cardiac events (95% CI, 1.03–4.12) after adjustment for multiple variables.

Conclusions: Plasma VAP-1 levels had the positive relationship with circulating levels of cardiac pathology markers and LV diastolic dysfunction. Higher VAP-1 levels were also associated with an increased risk of incident CV events and cardiac events in HD patients. Our results indicate that VAP-1 help clinicians identify those at high risk of CV events

PO1800

Circulating Neprilysin Level Predicts the Risk of Cardiovascular Events in Hemodialysis Patients

Hyeon Seok Hwang,[1] Jin sug Kim,[1] Yang gyun Kim,[1] Yu ho Lee,[2] Dong-Young Lee,[3] Shin-Young Ahn,[4] Ju young Moon,[1] Sangho Lee,[1] Kyung hwan Jeong.[1] *[1]Kyung Hee University Medical Center, Seoul, Republic of Korea; [2]CHA Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea; [3]Korea Veterans Health Service, Seoul, Republic of Korea; [4]Korea University Medical Center, Seoul, Republic of Korea.*

Background: Neprilysin inhibition has demonstrated impressive benefits in heart failure treatment, and is the current focus of interest in cardiovascular (CV) and kidney diseases. However, the role of circulating neprilysin as a biomarker for CV events is unclear in hemodialysis (HD) patients.

Methods: A total of 439 HD patients from the K-cohort were enrolled from June 2016 to April 2019. The plasma neprilysin level and echocardiographic findings at baseline were examined. The patients were prospectively followed up to assess the primary endpoint (composite of CV events and cardiac events).

Results: Plasma neprilysin level was positively correlated with left ventricular (LV) mass index, LV end-systolic volume, and LV end-diastolic volume. Multivariate linear regression analysis revealed that neprilysin level was negatively correlated with LV ejection fraction (β = -2.14; p = 0.013). The cumulative event rate of the composite of CV events was significantly greater in neprilysin tertile 3 (p = 0.049). Neprilysin tertile 3 was also associated with an increased cumulative event rate of cardiac events (p = 0.016). In Cox regression analysis, neprilysin tertile 3 was associated with a 2.61-fold risk for the composite of CV events (95% confidence interval [CI], 1.37–4.97) and a 2.72-fold risk for cardiac events (95% CI, 1.33–5.56) after adjustment for multiple variables.

Conclusions: Higher circulating neprilysin levels independently predicted the composite of CV events and cardiac events in HD patients. The results of this study suggest the importance of future studies on the effect of neprilysin inhibition in reducing CV events.

PO1801

Serum Cathepsin-S Concentration Is Not Related to Arterial Calcification Severity Among Hemodialysis Patients

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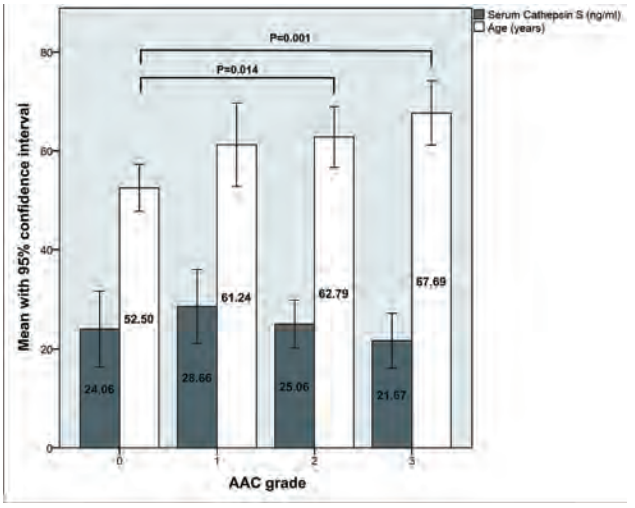
Background: Vascular calcification is prevalent among hemodialysis patients and is strongly correlated to their cardiovascular and total mortality. Cathepsin S, a lysosomal cysteine protease that is elevated in CKD patients, has shown its critical role of vascular calcification in cell culture experiments and in uremic animal model. To validate the relationship of Cathepsin S and vascular calcification in clinical practice, we conducted the current cross sectional study.

Methods: 88 patients on maintenance hemodialysis were enrolled and their serum Cathepsin S and its natural inhibitor Cystatin C were measured. Severity of vascular calcification was semi-quantified by aortic arch calcification (AAC) score on chest X-rays. Patients were divided into groups according to their AAC score, and the serum Cathepsin S level, Cathepsin S / Cystatin C ratio and other factors were compared between groups.

Results: There was no significant difference in the level of Cathepsin S (p=0.778) or Cathepsin S to Cystatin C ratio (p=0.417) between patients with different aortic arch calcification score. Only age was associated with the severity of AAC score (p=0.014). Increasing serum triglyceride level is significantly associated with higher serum Cathepsin S level (Pearson Correlation p=0.001, R square=0.133).

Conclusions: Despite a pre-clinical study supporting the role of Cathepsin S in the development of vascular calcification under uremic and phosphate-rich conditions, serum Cathepsin S was not found to be associated with vascular calcification severity among hemodialysis patients in this study. Serum triglyceride is the strongest predicting factor for higher Cathepsin S levels in these patients. Further study is needed to confirm these findings using a different grading system.



Mean age and serum Cathepsin S with 95% confidence interval between groups of patients, categorized by their Aortic arch calcification (AAC) grade.

PO1802

Kidney Function Trajectory Following Left Ventricular Assist Device Implantation

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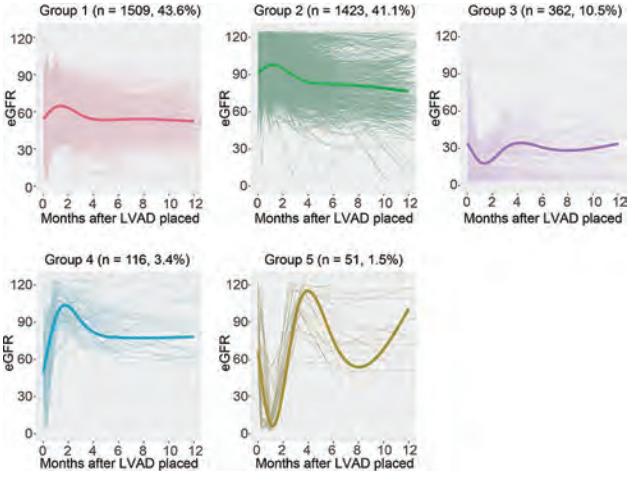
Background: LVADs have variable effects on kidney function. Identification of distinctive eGFR trajectory groups after LVAD placement, by applying unsupervised techniques to longitudinal eGFR measures, may enable insights into diverse pathophysiology.

Methods: From a national cohort, we identified persons who underwent isolated, primary continuous flow LVAD implantation in the US, 2016-17. eGFR values from pre-LVAD implantation to 12 months post were used. Latent class mixed models using cubic splines were applied to derivation and validation subsets, and models with 2-9 distinct groups were evaluated to find the optimal number.

Results: In the cohort (3,461 in derivation subset, 1,154 in validation), we identified 5 distinct trajectory groups. The 2 largest groups (1,2) are similar to previously reported cohort averages, with early eGFR increase followed by decline, but differed by baseline eGFR. Three smaller groups (3-5, ~15% of the cohort) demonstrated novel trajectories: group 3 had early worsening with sustained low kidney function; 4 had early and sustained eGFR improvement, and 5 had substantial eGFR variation. These groups differed in baseline factors (groups 3 and 4 had the most pre-LVAD acute dialysis, 4 and 5 the most cardiogenic shock) and outcomes (groups 2 and 4 had the highest survival, 3 and 5 had the lowest).

Conclusions: Novel eGFR trajectories after LVAD implantation were identified in a national cohort. Group 4, with early and sustained increase in eGFR, may reflect type 1 cardiorenal syndrome. Group 3 may reflect chronic kidney disease with early complications, and group 5 may reflect intact kidney parenchyma but post-LVAD right ventricular failure. These results demonstrate the feasibility of identifying previously unobserved heterogeneity in kidney outcomes. The novel trajectory groups may reveal potential for tailored care, in addition to pathophysiologic insights.

Funding: NIDDK Support



Trajectory groups. Bold lines are class-specific predicted means; thin lines are individuals

PO1803

Which Loop Is Best? Comparing the Effect of Loop Diuretic Prescribing on Mortality and Heart Failure Readmission

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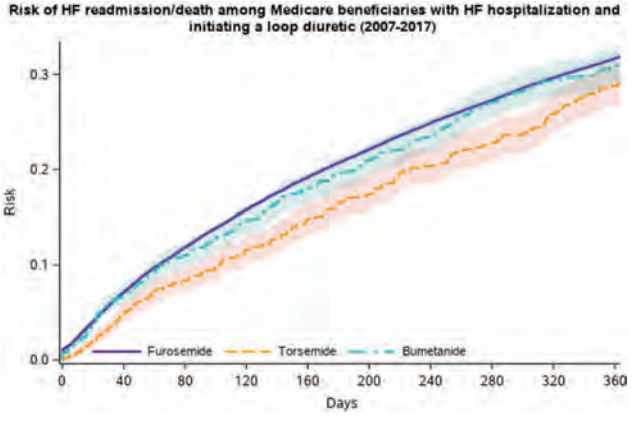
Background: Loop diuretics are a mainstay of heart failure (HF) management. While furosemide is most commonly prescribed, torsemide and bumetanide are increasingly being prescribed, possibly due to their superior bioavailability. Few trials or real-world evidence studies have compared the effectiveness of prescribing these loop diuretics while adequately addressing critical study design biases.

Methods: We identified beneficiaries initiating the study loop diuretics by using an active comparator, new-user cohort design and Medicare claims data from 2007-2017. We estimated 1-year risks of death and a composite outcome (HF readmission/death) using inverse probability of treatment weighting to adjust for relevant confounders. We calculated a dose equivalency based on furosemide to adjust for disease severity.

Results: We identified 45,310 furosemide, 1,148 torsemide, and 1,630 bumetanide new users. In the total weighted population, 24.3% had a reduced ejection fraction, 27.1% had CKD (> Stage 2), with a mean age of 80.1 years and a mean furosemide dose equivalent of 50.8 mg/mL. The 1-year risk of death across all study loop diuretics was similar (19.9%-20.6%), whereas the risk of the composite outcome was more varied (29.1%-32.0%). The 1-year risk difference (95% CI) of the composite outcome was -2.9% (-6.2, 0.4) for torsemide vs. furosemide and -1.1% (-3.8, 1.6) for bumetanide vs. furosemide.

Conclusions: Among Medicare beneficiaries, the risk of HF readmission/death varies meaningfully with torsemide having a reduced risk compared to other study loop diuretics. This study leverages claims data and causal methodology to generate a less biased and more generalizable estimate than previous studies. While additional trial and real-world evidence studies are needed, this study suggests initial loop diuretic prescription after HF hospitalization may produce long-term differences in risk of death and HF readmission.

Funding: NIDDK Support



PO1804

Diuretic Resistance in Acute Decompensated Heart Failure with Preserved vs. Reduced Ejection Fraction

Akash Sharma, Rahul Patel, Chakradhar Velagapudi, Shweta Bansal. *The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: Loop diuretic resistance (DR) is one of the common causes of inadequate decongestion in patients hospitalized with acute decompensated heart failure (ADHF). However, DR has not been characterized in patients with HF with preserved ejection fraction (HFpEF).

Methods: In a post hoc analysis of a pilot study which evaluated the role of high-dose spironolactone in hospitalized ADHF patients with DR, we analyzed the prevalence and potential pathophysiologic factors of DR in HFpEF (n=20), and compared those with HF with reduced EF (HFrEF) (n=27). DR was defined as weight loss<1lb/day despite intravenous furosemide>160mg/day (at least one dose of 80mg/day) or no change in dyspnea 48H after admission with usual care.

Results: DR was observed in 10 (50%) of HFpEF subjects as compared to 10 (37%) of HFrEF subjects (p=ns). In general, patients with HFpEF were older, more female and obese, had more diabetes, higher systolic blood pressure and lower brain natriuretic peptide compared to HFrEF (Table 1). There was no difference in clinical presentation, eGFR and pulmonary arterial systolic pressure in DR-HFpEF vs. DR-HFrEF. However, urine sodium/potassium ratio, plasma renin activity and aldosterone were lower in DR-HFpEF as compared to DR-HFrEF, though still higher than diuretic responsive-HFpEF patients (Table 1). Weight loss in response to high-dose spironolactone was similar in DR-HFpEF and HFrEF (14±8.6 vs.14±13 lb).

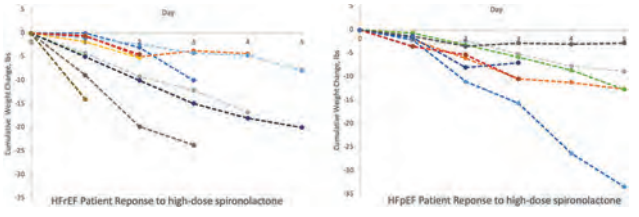
Conclusions: Although the comparisons were not statistically significant due to small sample size; the results suggest that DR is more prevalent in HFpEF. Despite similar clinical features of congestion and response to high-dose spironolactone, a state of reduced neurohormonal activation points that additional factors might be contributing to DR in HFpEF compared to HFrEF patients.

Funding: Commercial Support - Relypsa Education Grant

Table 1: Baseline characteristics of HFrEF vs. HFpEF patients

	RS-HFrEF (n=17)	DR-HFrEF (n=10)	Total, HFrEF (n=27)	RS-HFpEF (n=10)	DR-HFpEF (n=10)	Total, HFpEF (n=20)	p-value
Age	55 (11.1)	56 (14.8)	55 (12.3)	55 (11.6)	68 (15.7)	61 (15.0)	ns
Male (%)	88	80	85	60	50	55	<0.001
Body Mass Index (kg/m2)	28.7 (4.2)	28.7 (8.3)	28.7 (6.0)	38 (9.3)	36.8 (7.6)	37.4 (8.4)	ns
Systolic blood pressure (mmHg)	125 (20.7)	115 (18.5)	121 (20.2)	138.2 (14.9)	131.6 (21.8)	134.9 (18.5)	ns
Diastolic blood pressure (mmHg)	78 (15.5)	76 (14.8)	77 (15.0)	76.9 (17.2)	69 (10.6)	73 (14.5)	ns
Peripheral Edema (%)	64.7	100	77.8	100	90	95	ns
Pulmonary rales (%)	82.4	60	74	80	80	80	<0.001
Diabetes	29	30	30	60	70	65	<0.001
CKD (eGFR <60 ml/min)	59	60	59	50	70	60	ns
eGFR (ml/min/1.73m2)	61.6 (17.8)	60.2 (22.8)	61.0 (19.4)	68.4 (22.5)	54.3 (29.6)	61.4 (26.6)	ns
Urine Sodium/potassium ratio	7.59 (4.9)	4.25 (3.9)	6.26 (4.8)	5.30 (4.5)	2.48 (1.2)	3.89 (3.5)	ns
Pulmonary congestion on X-ray (%)	88.2	80	85.2	80	80	80	ns
PASP on ECHO (mmHg)	43 (10.0)	45 (9.9)	44 (9.9)	40 (8.4)	50 (13.5)	45 (12.1)	ns
Brain natriuretic peptide (pg/mL)	1637 (2224)	1255 (783)	1527 (1973.5)	467 (604)	406 (310.8)	449 (330.5)	
Renin activity (ng/mL/hour)	2.50 (8.6)	10.6 (37.1)	6.90 (12.8)	0.65 (3.9)	3.75 (9.7)	1.15 (9.6)	ns
Aldosterone (ng/dL)	5.20 (3.6)	42.20 (32)	7.90 (20.3)	3.95 (3.6)	14.30 (17.6)	7.55 (12.3)	ns
Antidiuretic hormone (pg/mL)	4.00 (4.3)	4.10 (4.1)	4.00 (4.6)	1.15 (1.7)	1.35 (1.5)	1.35 (1.9)	ns
Epinephrine (pg/mL)	35.50 (43.8)	74 (116)	42.00 (58)	16.00 (19.8)	31.00 (22)	18.00 (26)	ns
Norepinephrine (pg/mL)	730.5 (840.3)	1557 (410)	849.50 (1005.3)	533.50 (295.3)	864.50 (322.8)	734.50 (443.3)	ns

RS=Responsive, DR=Diuretic Resistant



PO1805

Renal Outcomes and Safety of Angiotensin Receptor Neprilysin Inhibitors in Patients with Heart Failure: A Meta-Analysis

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Background: Angiotensin receptor neprilysin inhibitors (ARNIs) are an effective treatment for heart failure. However, their safety profile compared with angiotensin converting enzyme-inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) with respect to renal outcomes has not been clearly established.

Methods: We conducted a literature search of MEDLINE, Cochrane library, Embase, and clinical trials registries using relevant search terms (last search date May 7, 2021). The primary renal outcome was kidney function decline and the safety outcome was hyperkalemia. Only studies with at least 12 weeks of follow up were included in the renal outcome analysis to better capture CKD.

Results: Ten randomized controlled trials were eligible for inclusion (n=22,174 participants). ARNIs were associated with a lower risk of kidney function decline compared with ACEIs or ARBs: RR 0.65 (95%CI 0.53-0.81). The risk of hyperkalemia was similar in both treatment groups: RR 0.96 (95%CI 0.81-1.13).

Conclusions: ARNI use in patients with heart failure is associated with a lower risk of kidney function decline and a similar risk of hyperkalemia compared to ACEIs or ARBs.

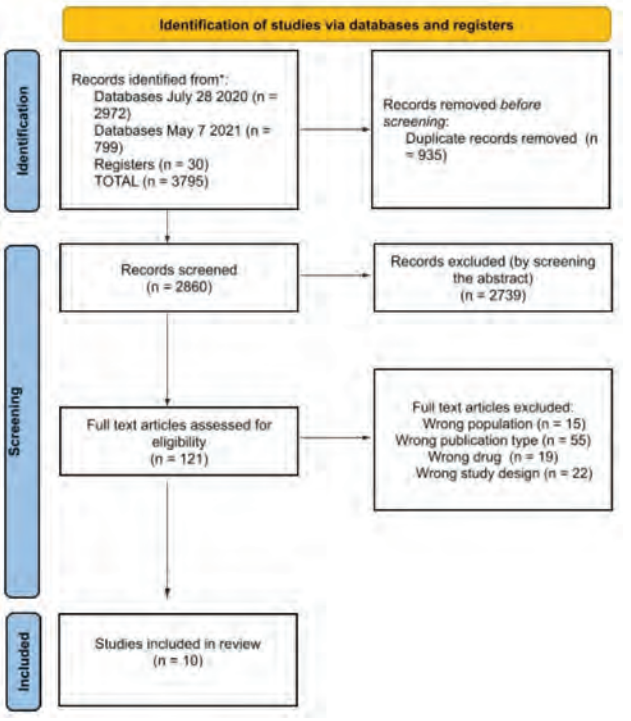

Fig 1. PRISMA Flow Diagram

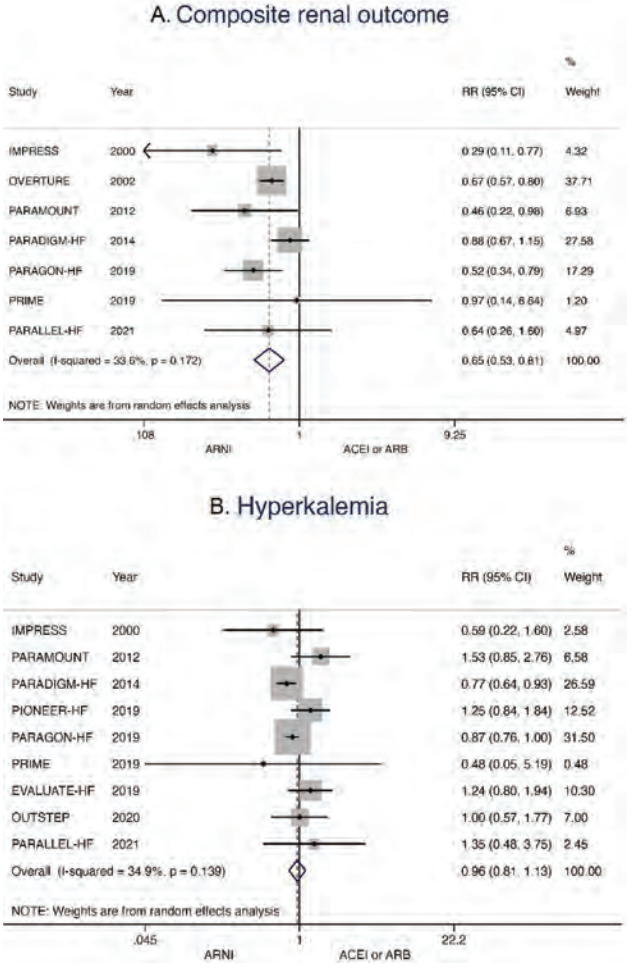

Fig 2. Forest plots

PO1806

Hydralazine-Isosorbide Dinitrate Associated with Reduced All-Cause and Cardiovascular Mortality in Patients on Dialysis with Heart Failure

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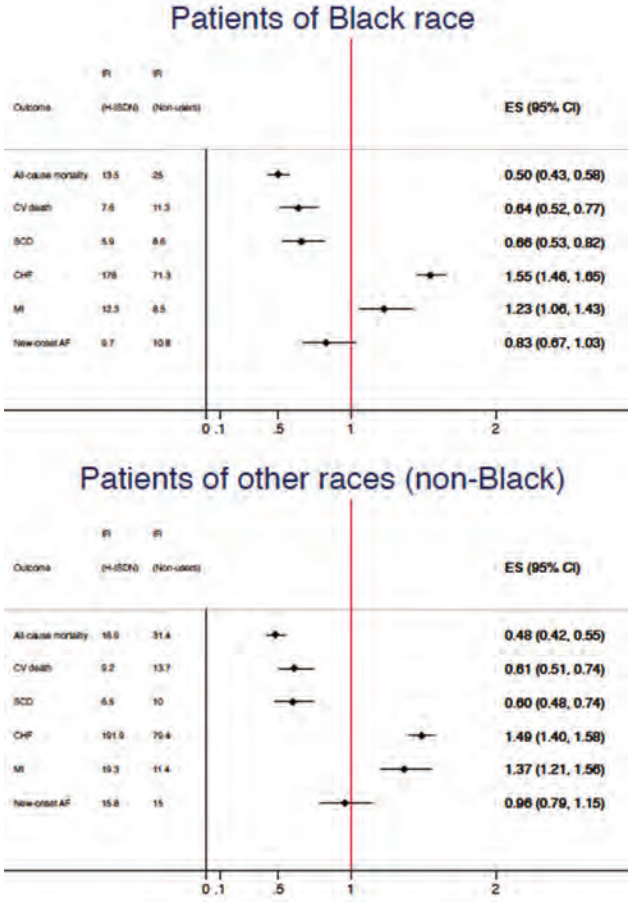
Background: Heart failure (HF) is an important contributor to the increased cardiovascular (CV) mortality incidence in ESKD. Therapies targeting HF's unique pathophysiology in ESKD are lacking. Hydralazine-isosorbide dinitrate (H-ISDN) targets reduced nitric oxide bioavailability and could improve CV mortality in ESKD

Methods: Adult patients with HF on maintenance dialysis between January 2011 and December 31, 2016 were identified using the United States Renal Data System. There were 6306 patients with at least one prescription for H-ISDN and 75,851 non-users. The primary outcome was death from any cause. Secondary outcomes included cardiovascular death and sudden death. Treatment effects were estimated using stabilized inverse probability weights in Cox proportional hazards regression. Because H-ISDN has been shown to improve outcomes in Black HF patients, we investigated effect modification by race

Results: Age was similar in H-ISDN users (66 ± 13 years) and non-users (69 ± 13 years) with 50% and 51% men, respectively. H-ISDN (51%) users were more likely to be of Black race than non-users (27%). Dialysis vintage was longer in H-ISDN (25 months) users compared with non-users (15 months). All characteristics were well balanced in weighted models. Risks of all-cause mortality, cardiovascular death, and sudden death were significantly reduced in H-ISDN users compared to non-users (Table). We did not identify significant effect modification by race (Figure)

Conclusions: To our knowledge, this is the first analysis of the impact of H-ISDN on mortality in ESKD. Our results suggest that combination H-ISDN improves survival in dialysis patients with HF

Outcome	Incidence rate (events)		Weighted HR (95% CI)	p value
	H-ISDN (N=6306)	Non-Users (N=75851)		
All-cause mortality	16.0 (497)	27.9 (34371)	0.48 (0.43-0.54)	<0.001
CV death	8.9 (275)	12.4 (15214)	0.62 (0.53-0.71)	<0.001
SCD	6.7 (207)	9.2 (11292)	0.62 (0.52-0.73)	<0.001
CHF	195.5 (3352)	73.4 (48324)	1.51 (1.44-1.57)	<0.001
MI	18.0 (532)	10.2 (11602)	1.33 (1.20-1.48)	<0.001
New-onset AF	12.5 (257)	13.0 (9789)	0.92 (0.79-1.06)	0.25



PO1807

Long-Term Outcomes After Renal Revascularization for Atherosclerotic Renovascular Disease in the ASTRAL Trial

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Background: The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial recruited 806 patients with atherosclerotic renal artery stenosis (RAS) between 2000-2007, randomised 1:1 to medical therapy with or without renal artery stenting. The initial results were presented in 2009 at median follow-up 34.6 months when no benefit of revascularization to renal functional outcome or cardiovascular events (CVE) were evident. Surviving patients remained under follow up until 2014.

Methods: All available data were analysed to assess whether there was a later impact of revascularization on renal function, CVE and survival, including a composite outcome of renal and CV outcomes and death (as used in the CORAL trial). Pre-specified sub-group analyses of different categories of renal function, renal length, prior rapid deterioration in kidney function, and severity of RAS. Further post-hoc analysis of patients with severe RAS (defined as bilateral 70% or > 70% RAS in a solitary kidney = global renal ischemia), those with/without proteinuria and a per protocol analysis were performed.

Results: The mean age of the entry population was 70.5 years, mean eGFR 40 ml/min/1.73m^2, with mean RAS 76% and blood pressure 150/76 mmHg; 83% of the revascularization group underwent attempted stenting. Median follow-up was 56.4 months with 108 patients lost to follow up or withdrawn; 50% of the evaluable population had died, 14% had received RRT and 40% had suffered a 1st CVE. No benefit of revascularization was observed for any outcome in the intention to treat and per protocol analyses, either in the whole population or the pre-specified sub-groups. In the severe RAS sub-group (163 patients) revascularization was associated with a hazard ratio (HR) of 0.74 (0.54-1.01; p=0.062) for the composite renal and CV outcome and an HR of 0.70 (0.49-1.0) for death (p=0.051).

Conclusions: The long-term follow-up of the ASTRAL trial population showed no overall benefit of renal revascularization to renal and CV outcomes. It has been highlighted that a proportion of the population had lower risk mild-moderate RAS. The long-term outcomes in patients with severe RAS (global renal ischemia) point to a potential benefit of stenting that may be worthy of further study in a more selected population.

Funding: Government Support - Non-U.S.

PO1808

Revascularization in Atherosclerotic Bilateral Renal Artery Stenosis

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Background: Patients with B/L RAS, if found to have worsening renal failure, refractory HTN or recurrent CHF, are often referred for revascularization despite limited evidence. We hypothesized that revascularization plus medical management prevents adverse outcomes in patients with B/L RAS.

Methods: This was a retrospective single-center cohort study in patients with B/L RAS, RAS in a solitary kidney, U/L RAS with an atrophic or >1cm smaller contralateral kidney or, RAS in a U/L functioning kidney. We excluded patients with non-atherosclerotic RAS, renal artery dissection, atheroembolism and renal transplantation. The primary outcome was Major Adverse Kidney Events (MAKE) at 3 mo. Secondary outcomes were renal events, changes in BP, hospital admissions and all-cause mortality at 1 yr. We used the Chi-square test for the primary outcome and the Chi-square test or two-sample t-tests for the secondary outcomes.

Results: 153 patients were included in the study. There were no differences in the baseline characteristics of the intervention and control groups, except for higher number of smokers in the control cohort (Table 1). There was no difference in MAKE between the 2 groups at 3 mo. At 1 yr, there were fewer admissions for CHF in the intervention group (Table 2). There were no other major differences in secondary outcome measures.

Conclusions: Revascularization for B/L RAS does not improve renal outcomes, BP control or mortality, but may prevent admissions for CHF.

Table 1: Baseline characteristics

Variable	Intervention Group (N=69)	Control Group (N=84)	p value
	no. (%)		
Hypertension	68 (98.6)	81 (96.4)	0.413
Diabetes mellitus	19 (27.5)	22 (26.2)	0.852
CKD stage 3 or more	39 (56.5)	42 (50.0)	0.421
TIA/CVA	11 (15.9)	13 (15.5)	0.937
ASCVD equivalent disease	34 (49.3)	46 (54.8)	0.499
Peripheral vascular disease	29 (42.0)	43 (51.2)	0.259
Congestive heart failure	22 (31.9)	20 (23.8)	0.077
Obesity	20 (29.0)	23 (27.7)	0.862
Dyslipidemia	56 (81.2)	62 (73.8)	0.529
History of smoking	36 (52.2)	61 (73.5)	0.020

Table 2: Primary and secondary outcomes

Variable	Intervention Group (N=69)	Control Group (N=84)	p value
Primary Outcome at 3-months			
Composite of MAKE[‡]	7 (13.7)	5 (8.0)	0.331
Progression to a higher stage of CKD[‡]	6 (11.8)	4 (6.5)	0.322
Need for initiation of renal replacement therapy[‡]	1 (2.0)	1 (1.6)	0.889
All-cause mortality	0	3 (3.6)	0.113
Secondary Outcomes at 1-year			
Renal Events			
Change in eGFR*	0.04±23.74	-0.97±24.55	0.8264
Development of AKI	15 (31.9)	21 (31.3)	0.9485
New diagnosis of CKD	37 (72.6)	37 (55.2)	0.0539
Worsening of stage of CKD	9 (19.6)	10 (14.9)	0.5170
Initiation of dialysis for AKI	0	0	NA
Initiation of dialysis for ESKD	0	1 (1.5)	0.4052
Renal transplantation	0	0	NA
Nephrectomy	0	0	NA
Blood Pressure			
Systolic BP	134.92±20.97	128.07±17.81	0.0485
Diastolic BP	71.14±11.90	67.90±10.56	0.1068
Change in systolic BP*	-20.19±31.80	-12.93±25.53	0.1576
Change in diastolic BP*	-5.05±21.58	-5.79±14.90	0.8256
Number of antihypertensive drug classes[¥]	2.51±1.48	2.37±1.60	0.5840
Prescription for ACE inhibitor or ARB	31 (45)	39 (46.4)	0.8529
Hospital Admissions			
Total number of hospital admissions	2.12±1.93	2.13±1.43	0.9816
Admissions for renal events[¥]	0	2 (6.5)	0.2847
Admissions for accelerated hypertension	2 (11.8)	3 (9.7)	0.8209
Admissions for congestive heart failure	**0**	**8 (25.8)**	**0.0218**
All-cause mortality	2 (2.9)	6 (7.2)	0.2419

[‡]Data was missing in 40 of 153 (26%) patients.
*Change is defined as year 1 minus baseline.

PO1809

Hypertension in a Young Female: A Common but an Intriguing Anecdote

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Introduction: Renal artery stenosis accounts for about 1-10% of the 50 million people with hypertension worldwide. All major trials conducted so far on RAS found no benefit with renal artery stenting. Here we report a case of resistant hypertension in a young female who subsequently found to have bilateral renal artery stenosis and ultimately benefitted from unilateral stenting.

Case Description: A 35 yrs female, married, with no comorbids, presented with 03 months history of intermittent epsiodes of throbbing headache along with dizziness, palpitations, fatigue. Examination revealed BP - 160/100 with no postural drop, and regular pulse with no radio-radial, radio-femoral delays. Her baseline investigations(including blood complete picture, LFTs, RFTs, urine routine examination, PT/PTTK were Normal. Hepatitis B and C serology were negative) USG abdomen showed right shrunken kidney with no renal artery flows on Doppler ultrasound. She was put on four different groups of anti hypertensives including a beta blocker, a calcium channel blocker, thiazide diuretic and an angiotensin receptor blocker but her blood pressure did not settle. Further investigations revealed raised ESR but other tests including autoimmune screening, 2DECHO all negative-CT aortogram revealed a non visualised shrunken right kidney with attenuated right renal artery and a vascular kink in proximal left renal artery. DTPA scan showed estimated GFR of 66.7ml/min with 97% contribution by left kidney and 3% contribution by right kidney. So based on renal imaging findings, a final diagnosis of bilateral renal artery stenosis was made. Percutaneous transluminal angioplasty with stenting to proximal left renal artery was done. She was given dual antiplatelets along with a statin post operatively and advised monthly follow up. Currently she is normotensive without any anti hypertensive medicine.

Discussion: Distinct and new diagnostic and therapeutic innovations for RAS accessible but the best modality for a particular patient remains arduous. Though Renal artery stenting has shown propitious results in few patients but not to the degree many have expected. More RCTs should be contemplated to scrutinize the clinical predictors which will aid in identifying appropriate indications and subgroups of patients that will raise hope of maximum outcome of this intervention and evading gratuitous procedures that wiil not benefit the patient

PO1810

Long-Term Safety and Efficacy of Renal Denervation with the Symplicity Spyral Catheter in the Global SYMPLICITY Registry

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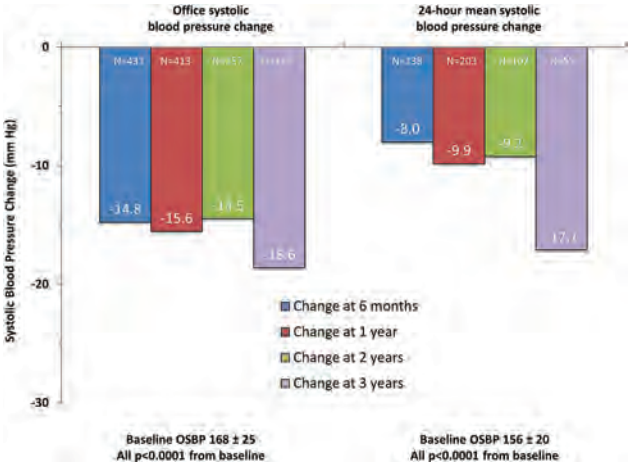
Background: Catheter-based renal denervation (RDN) therapy targets overactivity of the sympathetic nervous system to treat hypertension. Results from recent randomized sham-controlled clinical trials have demonstrated the safety and efficacy of RDN, but long-term safety and durability of the procedure in real-word patients is also important.

Methods: The Global SYMPLICITY Registry (GSR) is a prospective, international registry of patients who receive radiofrequency RDN treatment due to uncontrolled hypertension or conditions associated with excessive sympathetic nervous system activation. Office and ambulatory blood pressure (BP) levels were measured at baseline, 3, 6, 12, 24, and 36 months per standard of care. Adverse events were collected out to 3 years. In this analysis, we present safety and efficacy data for patients who received RDN with the multi-electrode Symplicity Spyral catheter in GSR.

Results: Currently there are 641 patients treated with the Symplicity Spyral catheter (baseline office BP 168±25 mmHg, 4.6±1.5 prescribed anti-hypertensive medication classes, mean age 60.5 ± 12.5 years, 56.9% male, 42.5% history of cardiac disease, 37.2% type II diabetes mellitus, and 19.1% renal insufficiency with eGFR<60 ml/min/1.73m^2). At 3 years, there were no cases of new renal artery stenosis >70% or renal artery re-intervention. Rates of other adverse events at 3 years included new onset end stage renal disease (2.4%), cardiovascular death (1.6%) and myocardial infarction (0.8%). Mean change in eGFR from baseline to 3 years was -6.5±15.7 mL/min/1.73m^2. Changes in mean 24-hour and office BP from baseline to 6, 12, 24 and 36 months are shown in the **Figure**.

Conclusions: Office and 24-hour BP were significantly reduced from baseline at all follow up time-points after RDN with the Symplicity Spyral catheter, with no instances of renal artery re-intervention.

Funding: Commercial Support - Medtronic



PO1811

Endovascular Renal Denervation Efficacy in a Five-Year Follow-Up

João Carvão,[1] Patricia Q. Branco,[2] Catarina Mateus,[2] Pedro Gonçalves,[2] Manuel D. Almeida,[2] Maria augusta C. Gaspar.[2] *[1]Servico de Saude da Regiao Autonoma da Madeira, Funchal, Portugal; [2]Centro Hospitalar de Lisboa Ocidental EPE Hospital de Santa Cruz, Carnaxide, Portugal.*

Background: Endovascular renal denervation (ERD) is a minimally invasive procedure that uses radiofrequency ablation to burn the nerves in the renal arteries. Renal sympathetic nerves can modulate sympathetic activity at the whole body level, playing an important role in essential hypertension. This study aim to evaluate ERD efficacy in the treatment of essential hypertension in a five-year follow-up.

Methods: We conducted a prospective study including 41 patients with essential hypertension. ERD was performed using Simplicity Probe or Spyral. Blood pressure (BP) was evaluated using 24hour ambulatory BP monitoring. Echocardiography was performed using HDI 5000. Clinical and biochemical variables were explored.

Results: A total of 41 patients were included. Overall, 53,7% (n=22) were females with a mean age of 63,6 ± 7,5 years, BMI 30,8 ± 5,2 Kg/m^2, 17,1% (n=7) had an estimated glomerular filtration rate (eGFR) < 60ml/min/1,73m^2 and 68,3% (n=28) diabetes. Proteinuria (>300mg/g) was found in 24,4% (n=10) of the patients. A significant reduction in the number of antihypertensive drugs being taken was found after 5 years' follow-up (p<0,001). Despite this reduction, a significant reduction in diastolic blood pressure

(DBP) (p=0,001) was found, but not in systolic blood pressure (SBP) (p=0,08). Also left ventricle mass index (LVMI) reduced significantly (p<0,0001) and a reduction of acute elevation of left ventricle filling pressure (LVFP) was detected using E/e' (p<0,0001). There was a worsening of eGFR (p<0,0001) as expected by the progressive worsening of kidney function. We have found a non significant reduction in proteinuria (p=0,07). In the group with a reduction in proteinuria, it was not associated with BP and LVMI, when using multivariate analysis. In a multivariate analysis, the reduction in the number of antihypertensive drugs, of the LVMI, SBP and DBP were not related with age, gender, body mass index and proteinuria.

Conclusions: In our population, we managed to reduce the number of anti-hypertensive drugs and still reduce patients DBP with RDN. Also RDN showed benefits in reducing LVMI and LVFP. Reduction of proteinuria, when present, was independent of BP anad LVMI. There was a worsening of kidney function as expected in a long term follow-up. RDN has been showed to be an effective mean of treating essential hypertension.

PO1812

Potential Benefits of Asymptomatic Hyperuricemia Treatment: A Systematic Review and Meta-Analysis of Randomized Control Trials

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Background: Asymptomatic hyperuricemia is strongly associated with an increased risk for chronic kidney disease and cardiovascular conditions. However, many current guidelines suggest no medical treatment for patients with asymptomatic hyperuricemia. We aim to systematically analyze randomized control trials with serum uric acid-lowering medication in the treatment of patients with asymptomatic hyperuricemia.

Methods: A literature review of seven medical databases (Scopus, Clinical Gov, Pubmed, Web of Science, Google Scholar, VHL, and GHL) for randomized controlled trials related to the treatment of asymptomatic hyperuricemia was conducted. Bias was evaluated using the Cochrane Risk of Bias 2 tool. Standard differences of means of variables of interest were combined across studies to compare the effects of uric acid lowering treatment versus control. Using the Comprehensive Meta-Analysis program, fixed-effects and random heterogeneity model, forest plots were created for each variable of interest.

Results: Analysis of eleven studies showed significant decreases in creatinine [-0.302 (95% CI: -0.599, -0.005)], systolic blood pressure [-0.277 (95% CI: -0.5, -0.055)], and serum uric acid [-1.972 (95% CI: -2.145, -1.800)] in the treatment versus control group. Furthermore, significant increases in estimated glomerular filtration rate (eGFR) after sensitivity analysis [0.228 (95% CI: 0.027, 0.428)], and high-sensitivity C-reactive protein [0.588 (95% CI: 0.205, 0.971)] were observed in the treatment versus control group. Lastly, non-significant decreases in carotid intima-media thickness test [-0.113 (95% CI: -0.269, 0.042)], and diastolic blood pressure [-0.312 (95% CI: -0.638, 0.013)], while non-significant increases in hemoglobin A1C [0.394 (95% CI: -0.026, 0.813)] and fasting glucose level [0.117 (95% CI: -0.145, 0.380)] were found in the treatment versus control group.

Conclusions: This study showed that uric acid lowering treatment of patients with asymptomatic hyperuricemia may be beneficial in those with elevated creatinine and blood pressure, and decreased eGFR.

PO1813

Urinary Glycogen Synthase Kinase 3β Level Predicts the Progression of Hypertensive Nephrosclerosis

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Background: Hypertensive nephrosclerosis (HTN) is a serious consequence of prolonged hypertension. In the United States, HTN is the second most common cause of end-stage kidney disease. Recently, emerging evidence suggests that glycogen synthase kinase (GSK) 3β is a key factor in the progression of diabetic kidney disease (DKD). However, it remains uncertain whether the role of GSK3β is specific for DKD or a generic mediator of renal damage irrespective to the underlying cause.

Methods: We studied 32 patients with biopsy-proved HTN patients. Their GSK3β level in urinary supernatant was measured by conventional ELISA, and GSK3β mRNA level in urinary sediment was measured by quantitative polymerase chain reaction. The results were compared to the baseline kidney function and the subsequent risk of renal function deterioration.

Results: The average urinary GSK3β level was 212.67 ± 47.74 ng/L by conventional ELISA, which closely correlated with its mRNA level in urinary sediment (r = 0.821, P<0.0001). Urinary GSK3β level significantly correlated with baseline glomerular filtration rate (GFR) (r=-0.451, p=0.010) and the slope of GFR decline (r=-0.397, p=0.033). Patients with a high urinary GSK3β level has a higher risk of developing 40% kidney function loss and progressing to dialysis-dependent kidney failure than those with a low GSK3β level (log rank test, p=0.028 and p=0.043, respectively). Similarly, urinary GSK3β mRNA level also significantly correlated with baseline GFR (r=-0.582, p<0.0001) and the slope of GFR decline (r=-0.402, p=0.022). Patients with a high urinary GSK3β mRNA level has a higher risk of developing 40% kidney function loss and progressing to dialysis-dependent kidney failure than those with a low GSK3β level (p=0.022 and p= 0.004, respectively).

Conclusions: These results demonstrated that urinary GSK3β level correlates with the rate of kidney function loss in patients with biopsy-proved HTN, and urinary sediment mRNA level appears to be a more accurate prognostic marker than urinary GSK3β level by ELISA. Our results suggest that GSK3β is a generic mediator for the progression of chronic kidney disease and is not specific for DKD.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

PO1814

Deletion of the Dopamine D2 Receptor in the Renal Proximal Tubule Increases Blood Pressure on Low-Salt Diet and Decreases Blood Pressure on High-Salt Diet: A Case of Inverse Salt Sensitivity

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Background: The dopamine D2 receptor D2 (D2R) in the kidney is important in maintaining normal blood pressure (BP) and preventing inflammation and tissue injury. Global D2R gene (*Drd2*) knockdown i or renal-selective D2R downregulation in the mouse increases BP and results in renal inflammation, tubular injury, and fibrosis. To study the function of D2R in the renal proximal tubule, we generated *Drd2*$^{fl/fl}$, P$_{SGLT2}$::*Cre*+ mice (D2R$^{PT-/-}$) that lack D2R only in the renal proximal tubule and *Drd2*$^{fl/fl}$, P$_{SGLT2}$::*Cre*- (D2R$^{PT+/+}$) mice that do not have the deletion.

Methods: Mice were genotyped for *Drd2*$^{fl/fl}$ and a smaller amplicon representing the Cre deletion mutant. We studied male mice on normal salt (NS; 0.4% NaCl), high (HS; 4% NaCl), and low (LS; <0.08% NaCl) diets.

Results: On NS diet, male D2R$^{PT-/-}$ had slightly higher BP, measured under anesthesia, than male D2R$^{PT+/+}$ mice (106±1 vs 101±2 mmHg, n=15/group; P<0.05). On HS diet D2R$^{PT-/-}$ mice had lower BP than D2R$^{PT+/+}$ (100±3 vs 107±2 mmHg; P<0.04; n=12) but on LS diet D2R$^{PT-/-}$ had higher BP than D2R$^{PT+/+}$ mice (126±5 vs 103±4 mmHg; P<0.01; n=7). Both the decrease in BP on HS diet and the increase in BP on LS diet, relative to BP on NS diet, were confirmed by telemetry in conscious mice. These data indicated that D2R deletion only in the renal proximal tubule impairs the normal responses to changes in salt intake. On NS diet the renal mRNA expressions of NHE3, Na^+/K^+ATPase, and NCC were similar in both groups of mice. On HS diet NHE3 and NCC were lower in D2R$^{PT-/-}$ than D2R$^{PT+/+}$ mice (NHE3: 0.7±0.02 vs 1.0±0.03 fold-change; P<0.05, n=4-5/group; NCC: 0.5±0.1 vs 1.0±0.09 fold-change; P<0.05) while Na^+/K^+ATPase was similar in both groups. On LS diet NHE3, Na^+/K^+ATPase, and NCC expression were higher (P<0.05) in D2R$^{PT-/-}$ than in D2R$^{PT+/+}$ mice.

Conclusions: There are marked differences in the response to changes in dietary salt intake on BP and renal expression of sodium exchanger/transporter/pump in mice lacking D2R only in the renal proximal tubule that is accompanied by increased inflammation and fibrosis. There results may have significant clinical implications since in humans, the presence of D2R variants, *DRD2* rs6276 and rs6277, which decrease D2R protein/function, is associated with inverse salt sensitivity.

Funding: Other NIH Support - NIH R01 grants

PO1815

Renal Proximal Tubule-Specific Alteration of the NKA/Src Receptor Complex in the Mouse: Evidence for Sexual Dimorphism

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Background: The Na^+/K^+-ATPase (NKA) expressed on the basolateral membrane of renal proximal tubule (RPT) cells serves an anti-natriuretic enzymatic function through its classically recognized ion-pumping properties. There is also pharmacological evidence that, through a Src-mediated mechanism, Na/K-ATPase α1 serves a counteracting natriuretic receptor function that reduces NKA- and NHE3-mediated transport, leading to decreased transepithelial Na^+ flux.

Methods: To test this genetically, we generated RPT cells and mice expressing wild-type (WT) or Src signaling null mutant (Y260A) forms of NKA α1, both with intact ion-transporting functions. In porcine RPT cells (LLC-PK1) expressing NKA α1 ^{Y260A}, a 50% decrease in phosphorylation-mediated inactivation of NHE3 compared to WT NKA α1^{WT}-expressing cells occurred. In mice, a SGLT2-Cre-driven KO and Rosa26 rescue system was used to selectively express WT NKA α1 (RPTα1^{WT}) or NKA α1Y260A (RPTα1^{Y260A}) in the RPT. For all renal phenotyping and biochemical assessments, we studied 4-month adult mice. Basal and renal characterization was conducted by metabolic cages, lithium clearance, and urine analysis.

Results: The RPT-specific rescue was confirmed by immunohistochemistry in kidney cross-sections from RPTα1^{WT} and RPTα1^{Y260A} mice. Kidney size, morphology, and overall structure assessed by periodic acid shift (PAS) staining was unchanged (n=3). In contrast, RPTα1^{Y260A} mice presented with a RPT-mediated hyper-reabsorptive phenotype of 60% decrease in total daily urine output and 40% decrease in absolute sodium output in females but not in males (n=6-11). This sexual dimorphism in urinary phenotype of RPTα1^{Y260A} mice was supported by a 50% increase in membrane abundance of NHE3 in female renal cortex compared to female RPTα1^{WT}, which was not observed in males (n=4-5).

Conclusions: These observations are compatible with a sexual dimorphism in the NKA/Src mechanism of regulation of NHE3 and Na^+ transport in the RPT. This study highlights the importance of improving our understanding of the natriuretic mechanism of NKA signaling in the RPT and its potential impact on sex-based differences in renal physiology and pathophysiology.

Funding: Private Foundation Support

PO1816

Sex-Dependent Regulation of the WNK-NCC Pathway via Ubiquitination in Response to Dietary High Salt Intake in Young Sprague-Dawley Rats

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Background: The thiazide-sensitive Na^+-Cl^- cotransporter (NCC), located in the apical membrane of distal convoluted tubule, fine-tunes sodium reabsorption and regulates blood pressure. The NCC is downregulated by high salt intake in normotensive salt resistant rats. These studies investigated the potential mechanistic pathways by which NCC is degraded in response to high salt intake in male and female Sprague-Dawley (SD) rats.

Methods: 3-month-old normotensive male and female SD rats were fed a normal salt (NS; 0.6% NaCl) or HS (4% NaCl) diet for 21 days. On day 21, the kidneys were collected and ~200 mg of the renal cortex was used to measure the expression of total NCC, WNK1, WNK4, Nedd4-2, Sortilin, KLHL3, and calcineurin via immunoblotting (N=5~6/group).

Results: A 21-day HS diet evokes the suppression of total NCC protein expression in young normotensive male and female SD rats. A HS diet downregulated WNK1 in male but not female SD rats. A HS diet suppressed the expression of the full-length and short WNK4 variants in female SD rats only. There was a trend for HS to increase Nedd4-2 expression in male SD rats (P=0.06), in contrast female rats downregulated Nedd4-2 in response to HS. The expression of sortilin, KLHL3, and calcineurin was suppressed by a HS diet in female rats only.

Conclusions: These data suggest that in response to a HS diet young female SD rats exhibit greater ubiquitin-dependent proteolytic and lysosomal degradation of the NCC than young male SD rats to regulate sodium homeostasis and blood pressure via a WNK-dependent signaling pathway.

Variables	Male		Female	
	NS	HS	NS	HS
NCC expression (fold change)	1.00 ± 0.12	0.55 ± 0.04*	1.00 ± 0.06	0.43 ± 0.04*
WNK1 expression (fold change)	1.00 ± 0.15	0.48 ± 0.04*	1.00 ± 0.24	1.02 ± 0.23
Full length WNK4 expression (fold change)	1.00 ± 0.16	1.16 ± 0.13	1.00± 0.11	0.26 ± 0.10*
Short WNK4 variants expression (fold change)	1.00 ± 0.11	0.73 ± 0.05*	1.00 ± 0.19	0.12 ± 0.02*
Nedd4-2 expression (fold change)	1.00 ± 0.12	1.43 ± 0.13	1.00 ± 0.12	0.75 ± 0.07*
Sortilin expression (fold change)	1.00 ± 0.16	0.88 ± 0.05	1.00 ± 0.09	0.57 ± 0.13*
KLHL3 expression (fold change)	1.00 ± 0.17	0.92 ± 0.09	1.00 ± 0.08	0.57 ± 0.05*
Calcineurin expression (fold change)	1.00 ± 0.42	0.45 ± 0.09	1.00 ± 0.06	0.58 ± 0.09*

Table 1: NS, 0.6% NaCl; HS, 4% NaCl. *P<0.05 vs. respective NS Group.

PO1817

Renal Denervation Improves Renal Afferent Nerve Activity After High Sodium Intake

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Background: Previous work of ours suggests that the sensitivity of renal afferent neurons is decreased under pathological conditions. Here we tested the hypothesis that pathologically decreased sensitivity of renal afferent neurons due to high salt diet is normalized after renal denervation.

Methods: 6 male Sprague Dawley (SD) rats were put on high salt diet (HS; 8% NaCl) for 10 days. In another group of 18 rats on high salt diet (HS) left kidney were deneravated (DNX) 7 days prior to examination. Rats on standard diet with and without DNX (10 and 7 SD rats) were used as controls. Harvested dorsal root ganglion neurons (DRG Th11-L2) with renal afferents were investigated in primary neuronal cell culture using current clamp mode to assess action potential generation during current injection and to characterize neurons as tonic highly active and phasic less active neurons. Results are mean±SEM.

Results: In renal neurons from rats on HS the relation of tonic to phasic neurons shifted towards less active phasic units (62% tonic neurons in control vs. 42% on HS, p<0.05, z-test). Further, neurons from rats on HS exhibited decreased action potential production upon stimulation (controls 14.8+/-0.9 APs/600ms vs. HS 12.1+/-0.8 APs/600ms, p<0.05, t-test). Denervation (DNX) of the left kidney in rats on high salt diet (HS-DNX) led to a recovery of afferent renal DRG neurons. They regained their ability to generate action potentials as in controls (high salt diet 12.1+/-0.8 APs/600ms vs. HS-DNX 14.8+/-0.7 APs/600ms, p<0.05, t-test) and their electrophysiological property of tonic firing (42% tonic neurons in HS vs. 71% HS-DNX, p<0.05, z-test).

Conclusions: In rats on high salt (HS) diet the *in vitro* proportion of highly active tonic neurons with renal afferents decreased at the expense of less active phasic neurons. Furthermore, their firing rate decreased due to HS. These HS effects could be abolished by renal denervation (DNX). Whether DNX in vivo would be able to reduce HS induced sympathetic nerve activity increases remains to be determined.

PO1818

Empagliflozin Prevents Impaired Sensitivity of Afferent Neurons with Renal Axons During a High-Salt Diet

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Background: Afferent renal nerve pathways likely play a role in salt sensitive hypertension. We recently reported that high salt diet (HS) impairs these afferent renal pathways in rats. Now we tested the hypothesis that during HS a decrease in sensitivity of renal afferent neurons is prevented by the SGLT2 inhibitor empagiflozin.

Methods: Respective groups of rats were put on HS containing 8% NaCl or a normal diet. Two groups (HS, controls) received empagiflozin 20 mg/kg BW/day orally. Renal neurons were retrogradely labeled with DiI. In culture, labeled dorsal root ganglion neurons (DRG Th11-L2) with renal afferents were investigated electrophysiologically using current clamp mode to assess action potential generation during current injection (neurons were characterized as tonic highly active (> 5 action potentials, AP) and phasic less active neurons (≤ 5 AP upon stimulation).

Results: In neurons from rats on HS, the relation of tonic highly active neurons to less active phasic neurons shifted consistently towards phasic units (63,8% tonic neurons in controls vs. 42%* on HS, *p<0.05, z-test). However, continuous treatment with empagiflozin preserved the proportion of tonic neurons as in controls (67,9% on HS with concomitant administration of empagiflocin). In controls, empagiflozin did not affect the proportion of tonic to phasic neurons (63,8% tonic neurons in controls vs. 67,9% on HS & empagliflozin, p=0.7, z-test). Blood pressure and heart rate were not altered by HS and or treatment with any chosen dose of empagiflozin.

Conclusions: In rats, chronically elevated sodium intake (8% NaCl) reduced the sensitivity and stimulability of renal afferent DRG neurons. Under these circumstances, concomitant treatment with the SGLT2 inhibitor empagiflozin preserved the function of renal afferent DRG neurons. SGLT 2 inhibitors may help to treat dysfunction of renal innervation in cardiovascular disease.

PO1819

The Role of Histaminergic System Components in Renal Function During Salt-Sensitive Hypertension

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Background: Up to 50% of hypertensive patients have salt-sensitivity (SS), a condition characterized with an increase in blood pressure in response to salt intake. The abnormal activation of the immune response is a major contributor to SS hypertension and renal injury. Histamine and its receptors (HRs) are a complex system of immunoregulators that have been linked to renal disease development. It is known that the Dahl SS rat fed a high salt diet develops hypertension accompanied with elevated levels of inflammatory factors. We hypothesize that HRs and associated enzymes contribute to renal disease progression during SS hypertension.

Methods: Male Dahl SS rats at 8 weeks of age were placed on either a 0.4% (normal salt; NS, control) or 4% (high salt; HS, hypertensive group) NaCl diet for 21 days to induce SS hypertension. An additional group of animals received 3 injections of ranitidine (RAN; HR2 blocker; 25 mg/kg) or saline (VEH; 2.5 mL/kg) pre- and post- the HS challenge to test the effects of HR2 blockage on renal function.

Results: Using immunohistochemistry, we established the expression of all four HRs as well as histamine-metabolizing and catabolizing enzymes, along the nephron with a pronounced expression in the glomerulus, proximal tubule and the distal tubules. Interestingly, we observed a decrease in histidine decarboxylase, and an increase in histamine N-methyltransferase in the kidney of HS diet fed rats, suggesting a shift in renal histaminergic tone. RAN treatment pre-HS resulted in a significant decrease in urine volume (1.89 ± 0.20 vs 1.60 ± 0.18 mL/100g, p=0.012, in VEH vs RAN groups respectively) and water consumption (14.3 ± 2.25 vs 11.9 ± 1.69 mL), along with elevated Cl^- excretion (728.4 ± 287.4 μM vs 1107.8 ± 416.6 uMol). Post-HS RAN treatment yielded a significant increase in urine osmolality (1313.2 ± 319.7 vs 1659.5 ± 359.2 mOsm).

Conclusions: Thus far, we report a shift in the histaminergic tone toward less histamine production in the Dahl SS rat fed a HS diet. Dahl SS rats acutely treated with H2R blocker exhibit lower water consumption, reduced diuresis, and increased urinary osmolality.

Funding: Other NIH Support - R00DK105160, R01HL148114

PO1820

Salt-Induced Blood Pressure Elevation in Females Is Associated with Increased Arachidonic Acid Metabolites

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Background: Excess dietary sodium (Na^+) intake is a major risk for salt-sensitive hypertension and cardiovascular disease. Several clinical trials have found that women are more salt-sensitive than men, but the contributing sex-specific mechanisms are poorly understood. Arachidonic acid (AA) and its metabolites play a role in the pathophysiology of hypertension. We hypothesized that women have greater blood pressure (BP) elevation in response to Na^+ intake that is associated with higher AA metabolites than men.

Methods: Plasma AA metabolites were measured via a metabolomics analysis in volunteers who completed a validated 3-day food record to estimate dietary Na^+ intake before the study visit where BP was measured. Based on the recommendations by the American Heart Association, we classified daily Na^+ intake <2.3g as normal salt, and high salt for subjects consuming ≥ 2.3g Na^+. Spearman correlation was used to assess the relationship between Na^+ intake and systolic blood pressure (SBP).

Results: Women (n=81) displayed a stronger relationship between BP and Na^+ intake than men (n=49) (r=0.372; p<0.001 vs. r=0.317; p=0.026). The relationship between Na^+ intake and BP was stronger in white (n=46, r=0.4172; p=0.004) than in black (n=22,r=0.338; p=0.124) women and conversely stronger in black (n=7, r=0.790; p=0.034) than white (n=32, r=0.251; p=0.166) men. We measured plasma levels of palmitate and linoleate, both upstream of AA synthesis, AA, and 12-Hydroxyeicosatetraenoic acid (12-HETE) an AA metabolite. In subjects consuming a high Na^+ diet (women 28, men 25) levels of linoleate (1.211 + 0.330 vs. 0.869 + 0.170; p<0.001), palmitate (1.155+ 0.292 vs. 0.924+ 0.233; p= 0.003), AA (1.119 + 0.242 vs. 0.965 + 0.201; p=0.015) and 12-HETE (1.329+ 0.925 vs. 0.902 + 0.520; p=0.0469) were higher in women. In contrast, no sex differences in any of these parameters were observed between men and women consuming a normal salt diet.

Conclusions: Our findings suggest that AA and its metabolites may account for sex and perhaps also racial differences in salt sensitivity of BP. Further study of AA and its metabolites may shed light on the mechanisms of the sex differences in salt sensitivity.

Funding: Other NIH Support - NHLBI

PO1821

Gstm1 Genotype Affects Metabolic Response in Hypertension

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Background: Glutathione S-transferases (GSTs) are a family of enzymes that detoxify electrophiles, including products of oxidative stress. In humans, GST μ-1 (GSTM1) has a common null allele variant, *GSTM1(0)*, which has been linked to elevated oxidative stress in pathophysiological conditions and increased risk and/or accelerated progression of a variety of diseases. Recently, we reported that *Gstm1* knockout (KO) mice had increased oxidative stress and augmented kidney injury in angiotensin II (Ang II)-induced hypertension (HTN).

Methods: Kidney tissue was obtained from 12-20 week old male wild-type (WT) and *Gstm1* knockout (KO) mice at either baseline (no treatment) or following 4 weeks of Ang II-induced HTN via mini-osmotic pump at 1000 ng/kg/min. For each animal, a kidney was excised and snap frozen. For qPCR, mRNA was extracted from an homogenized kidney and used to create cDNA, followed by probing for a panel of 18 *Gst* genes. For metabolomics, frozen tissue was ground to a fine powder and sent to Metabolon (Morrisville, NC) to obtain a global metabolic profile.

Results: Analysis of qPCR results showed no significant alterations in the expression of *Gst* genes between WT and KO mice, except for the expected loss of *Gstm1* in KO mice. Metabolomics analysis yielded data for 926 metabolites, with expected significant differences due to Ang II treatment particularly in inflammatory and oxidative stress pathways. About 10% of detected metabolites (97) showed genotype-based effects and a further 131 (14%) displayed an interaction between genotype and treatment. Comparing Ang II-treated KO and WT mice, there was a significant increase in metabolite abundance in the methionine and glutathione pathways, including the transsulfuration pathway linking them. Furthermore, there was an increase in carnosine and anserine and a decrease in several lipid peroxidation markers.

Conclusions: The loss of GSTM1 in Ang II-induced HTN did not elicit a significant compensatory upregulation of mRNA of other GSTs. It is likely other antioxidant pathways are upregulated based on the altered metabolite abundances. However, based on previous results in treated KO mice, any compensatory mechanism is insufficient to protect against the oxidative stress-induced kidney damage. Further research should be pursued to elucidate the oxidative stress-related specific substrates of GSTM1 that are not detoxified by other pathways.

Funding: NIDDK Support

PO1822

HMGB-1 Activates Mineralocorticoid Receptor-Dependent Endothelial Cell Injury via Receptor for Advanced Glycation End Products

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Background: Endothelial dysfunction plays a central role in the pathogenesis of cardio-renal syndrome. High mobility group box-1 (HMGB-1) is a protein with various roles in different cellular compartments, and indirectly regulates the activity of transcription and DNA repair in the nucleus. On the other hand, during tissue damage, it is released into the extracellular environment as damage-associated molecular patterns (DAMPs). HMGB-1 is reported to elevate in CKD patients and be involved in endothelial dysfunction through binding to toll like receptor (TLR) and receptor for advanced glycation end products (RAGE). In addition, we recently demonstrated that RAGE-mediated Rac1 activated mineralocorticoid receptor (MR) and resulted in podocytes damage. In the present study, we hypothesized that crosstalk between HMGB-1/ RAGE and Rac1-MR pathways could contribute to endothelial dysfunction in kidney diseases.

Methods: In the present study, we investigated whether HMGB-1 could activate Rac1-MR axis and induce endothelial injury in cultured human umbilical vein endothelial cells (HUVECs) by assessing expression levels of genes for MCP-1 and cell adhesion factors (ICAM-1, VCAM-1) with or without administration of RAGE aptamer or MR blocker (esaxerenone, 1μM).

Results: HMGB-1 supplementation significantly increased GTP-bound Rac1 and enhanced MR translocation into the nucleus in HUVECs. We also found that RAGE expression was enhanced by HMGB-1 and RAGE aptamer completely abolished Rac1 activation and MR translocation observed in HMGB-1 exposed HUVECs. HMGB-1 also upregulated MCP-1, ICAM-1, and VCAM-1 in HUVECs, all of which were significantly blocked by pretreatment of RAGE aptamer as well as MR blocker.

Conclusions: These results suggest that there may be a close relationship between HMGB-1/ RAGE axis and Rac1/ MR activation, thus contributing endothelial injury. Using RAGE aptamer or MR blocker could be novel therapeutic strategies against endothelial dysfunction in patients with kidney diseases.

PO1823

The Role of Ketogenic Diet on the Development of Salt-Sensitive Hypertension

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Background: Hypertension is one of the most important risk factors for cardiovascular disease, which is the leading cause of mortality in the US. Two-thirds of hypertension cases are positively correlated with excessive weight gain. The ketogenic diet (KD) may be useful as part of the treatment of cardiovascular complications especially in obese patients. The KD, a low-carb high-fat diet, triggering the body to burn fat for energy instead of carbohydrates, has gained popularity through the weight loss community. We hypothesized that KD can have protective effects during the development of salt-induced hypertension.

Methods: The Dahl salt-sensitive (SS) rats fed a high salt diet develop hypertension accompanied by kidney injury. The Dahl SS rats were given either 4% NaCl diet (HS; Dyets Inc, 113756) or 4% NaCl modified KD (Harland Tekland, TD 190564) with free access to water for 5 weeks. Blood pressure was monitored with telemetry throughout the study, and urine samples were collected in metabolic cages on days 0, 7, 14, 28, and 35. At the end of the protocol animals were sacrificed and blood and kidney tissues were harvested for the analyses.

Results: Dahl SS rats fed a KD had a lower blood pressure compared to control rats fed a HS diet. Mean arterial pressure was 147 ± 5 mmHg vs 179 ± 9 mmHg (KD vs HS, p<0.05). Reduced renal hypertrophy with decreased kidney to body weight ratio (1.00 ± 0.06 vs 1.25 ± 0.04, p<0.05 compared to HS) and smaller kidneys (3.5 ± 0.1 vs 4.5 ± 0.2 g, p<0.05 compared to HS) were found in the KD group. No differences in glomerular damage scores were detected between the groups. The rats on KD experienced hypoglycemia (282 ± 9 vs 335 ± 14 mg/dL, p<0.05 compared to HS) with reduced glucose urinary excretion (5 ± 1 vs 32 ± 7, glucose to creatinine ratio, p<0.05 compared to HS). Microbiome analyses revealed an increase in the relative abundance of putatively beneficial gut microbiota (*Lactobacillus*) and a reduced level of putatively pro-inflammatory taxa (*Turicibacter*).

Conclusions: Therefore, prolonged KD intervention provides a protective effect on the development of SS hypertension. Our data revealed that KD during HS challenge resulted in decreased blood pressure, reduced kidney hypertrophy, and diminished levels of plasma glucose.

Funding: NIDDK Support, Other NIH Support - NHLBI R35 HL135749 to A.S., Veterans Affairs Support, Private Foundation Support

PO1824

Effect of Tochu Extract and Its Component Geniposidic Acid on Renal Hemodynamics and Hypertensive Renal Damage

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Background: Aqueous extract of Eucommia ulmoides (Tochu) leaf is used as Tochu tea in Japan and has the effect of lowering blood pressure. We investigated the effects of Tochu extract and its component geniposidic acid on renal hemodynamics and hypertensive renal damage in Dahl salt-sensitive hypertensive rats (DS).

Methods: DS rats received 1% saline solution from 4 weeks of age. After the blood pressure reached 150 mmHg or higher at 9 weeks of age, the rats were treated with 1% saline solution (DSHS), or 1% saline added 0.5% Tochu extract (DSHS + T) or, 1% saline added 0.2% geniposidic acid (DSHS + G) for another 4 weeks. DS rats fed with tap water were used as controls (DSLS). At 13 weeks, renal plasma flow (RPF) was measured by renal clearance study, and immunostaining and PCR of NADPH oxidase, eNOS, sodium transporters and fibrotic factors were performed.

Results: Blood pressure was significantly increased in DSHS rats compared to DSLS rats (196 vs.144 mmHg, $p<0.01$), which was significantly decreased in DSHS + T rats (158 mmHg) and DSHS + G rats (162 mmHg). Vascular resistance of afferent arterioles was significantly increased in DSHS rats compared to DSLS rats, and was decreased in both DSHS + T and DSHS + G rats. RPF was significantly higher in DSHS + T rats than in DSHS rats associated with decreased renal vascular resistance ($p<0.05$). In DSHS rats, NADPH oxidase expression and superoxide production were increased, with increased TGF-beta, procollagen 1, fibronectin and renal fibrosis. These were suppressed in DSHS + T and DSHS + G rats. NO production by eNOS was decreased in DSHS rats, but the treatment groups increased eNOS expression and NO production in the vascular endothelium, resulting in decreased renal vascular resistance and improved renal blood flow. Urinary sodium excretion was significantly higher in DSHS rats than in DSLS rats with decreased sodium chloride co-transporter (NCC). However, there was no further change in NCC or other sodium transporters in the treatment groups, and the high urinary Na excretion in the treatment groups was due to the effect of increased RPF.

Conclusions: Tochu and geniposidic acid suppressed NADPH oxidase and increased eNOS in DS rats, resulting in improved blood pressure, renal hemodynamics and renal damage.

Funding: Commercial Support - Kobayashi Pharmaceutical Inc., Osaka, Japan

PO1825

Effect of Uremia on Endothelial Cell Damage Is Mediated by Excessive Neutrophil Extracellular Trap Formation

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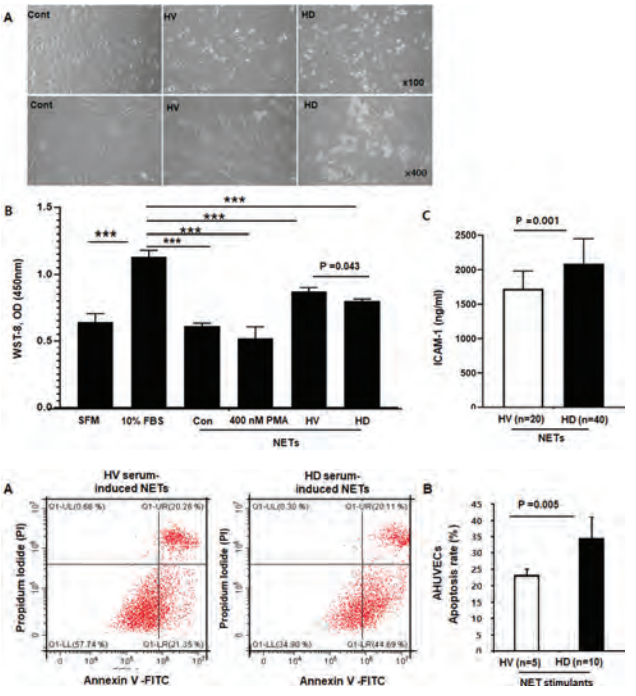
Background: Uremia is a clinical syndrome characterized by accumulation of various uremic toxins and associated metabolic abnormalities in chronic kidney disease (CKD). Patients with CKD are at increased risk for cardiovascular (CV) disease and death, and endothelial dysfunction may be a key uremia-specific risk factor. However, the mechanism by which uremia influences endothelial dysfunction is still unclear. We report a role for excessive neutrophil extracellular trap (NET) formation induced by uremic serum on endothelial cell (EC) injury.

Methods: Plasma nucleosome and myeloperoxidase-DNA, representative markers of *in vivo* NETs, and the intracellular adhesion molecule (ICAM)-1 level were measured in incident hemodialysis (HD) patients and healthy volunteer (HV), and their prognostic role was evaluated. For *in vitro* study, we differentiated HL-60 cells into neutrophil-like cells (dHL-60) by applying retinoic acid, and the effect of uremic serum on dHL-60 and ECs were determined.

Results: The amount of *in vivo* NETs were significantly higher in incident HD patients compared to HV, and the markers were strongly associated with ICAM-1 levels. In particular, nucleosome and ICAM-1 levels were independent predictors of a composite endpoint, all-cause mortality or vascular access failure. *In vitro*, uremic serum derived from HD patients showed significantly increased NETs formation from dHL-60, and these NETs significantly decreased EC viability and induced apoptosis. In addition, the ICAM-1 level in HUVEC supernatant was significantly increased by uremic serum-induced NETs compared to control serum-induced NETs.

Conclusions: Dysregulated neutrophil activities in the uremic milieu may play a key role in endothelial damage and vascular inflammatory responses.



PO1826

Contributions of Obesity and Hypertension to Progression of Cardiorenal Syndrome in Non-Diabetic Obese Female ZSF1 Rats

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Background: Obesity and hypertension are highly prevalent in patients with cardiorenal syndrome (CRS). Insight in how these comorbidities individually contribute to disease progression is required to improve treatment strategy. We dissected the separate contribution of obesity and worsening hypertension by deoxycorticosterone acetate (DOCA) plus high salt diet in the obese female ZSF1 rat, a model of metabolic CRS in the absence of diabetes [Nguyen, PLoS One 2020]. We hypothesize that in obese non-diabetic female ZSF1 rats obesity has a profound effect on functional progression of CRS while hypertension mainly affects fibrosis and inflammation.

Methods: Systolic blood pressure (SBP), renal and cardiac function were assessed biweekly in lean and obese female ZSF1 rats from 12 to 26 weeks of age. From 19 weeks, rats were implanted with either a DOCA pellet and fed a high salt (6% w/w) diet or with a placebo pellet and fed a normal salt diet. At 26 weeks of age, glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were assessed under isoflurane anesthesia. Subsequently, rats were sacrificed and tissues processed for analysis of renal and cardiac damage and inflammation.

Results: Obese versus lean placebo rats showed elevated E/e' ratio from 12 weeks, indicative of diastolic dysfunction. From 24 weeks obese compared to lean placebo rats developed proteinuria with lower GFR at 26 weeks of age. DOCA-salt markedly increased SBP in obese but not lean rats, despite similarly high natriuresis compared to placebo rats. ERPF was increased by DOCA-salt in lean but not obese rats. DOCA-salt worsened proteinuria and glomerulosclerosis in obese rats. Cardiac fibrosis and glomerular hypertrophy, present in obese rats, were not aggravated by DOCA-salt. However, DOCA-salt increased the number of macrophages in heart, but not in glomeruli of obese ZSF1 rats.

Conclusions: Obesity leads to renal and cardiac dysfunction and damage in female ZSF1 rats. Even without worsening of hypertension (DOCA+salt), cardiac dysfunction preceded proteinuria, suggestive of CRS type 2. Our findings suggest that antihypertensive and antiproteinuric treatment at a later stage without initially addressing metabolic risk, even in the absence of diabetes, will not provide adequate functional protection in CRS type 2.

Funding: Private Foundation Support

PO1827

Association Between Kidney Function and Lipid Levels in Older Adults

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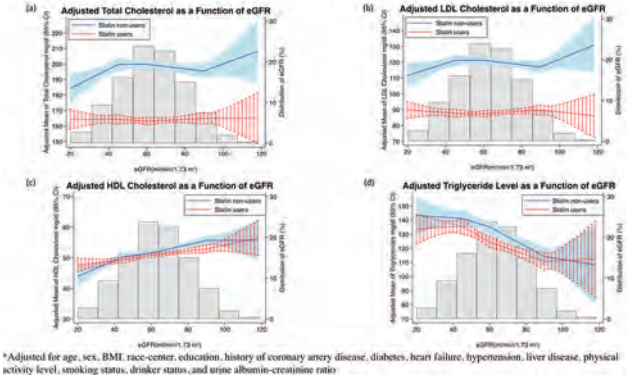
Background: The associations between kidney function and lipid levels in older adults have not been well characterized. Moreover, it is unknown whether residual atherosclerotic cardiovascular disease (ASCVD) risk after statin use differs by lipid levels other than total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), such as triglyceride (TG).

Methods: We conducted a cross-sectional study of older adults (≥65 years) using visit 5 data (2011-2013) of the Atherosclerosis Risk in Communities study. Multivariable linear and logistic regression was used to examine the eGFR-lipid level associations, stratified by statin use. Among statin users without ASCVD who had LDL-C levels <100 mg/dl, we predicted 10-year ASCVD risk after statin use by TG levels (<150 mg/dl vs. ≥150 mg/dl) across eGFR groups.

Results: The mean age of the study population (n=4965) was 75 (SD 5) years, 58% were female, and 22% were Black. The mean eGFR was 63 (SD 18) ml/min/1.73 m^2 and 52% were on a statin. In both statin users and non-users, there were no associations between eGFR and total TC or LDL-C. Low eGFR was associated with low high-density lipoprotein cholesterol (HDL-C) and high TG (**Figure**). Among statin non-users, eGFR <45 (vs. ≥60) was independently associated with low HDL-C (<50 mg/dl) (prevalence=59% vs. 34%, odds ratio=1.86; 95% CI, 1.38-2.51) and high TG (≥150 mg/dl) (31% vs. 20%, 1.54; 1.13-2.09). The results were similar among statin users. Among statins users with LDL-C <100 mg/dl, the prevalence of high predicted ASCVD risk (risk ≥20%) was greater among those with vs. without high TG across all eGFR categories (eGFR ≥60, 66% vs. 59%; 45-59, 78% vs. 73%; eGFR <45, 90% vs. 79%).

Conclusions: We found that low eGFR was associated with low HDL-C and high TG levels, regardless of statin use. Among statin users who achieved adequate LDL-C control, ASCVD risk was still higher among those with high TG compared to those without high TG.

Funding: NIDDK Support



[a]Adjusted for age, sex, BMI, race-center, education, history of coronary artery disease, diabetes, heart failure, hypertension, liver disease, physical activity level, smoking status, drinker status, and urine albumin-creatinine ratio

Adjusted associations between eGFR and lipid levels in older adults

PO1828

Nephroprotective Effects of PDE3A Gene Mutations

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Background: Chronic kidney disease (CKD) affects more than 700 million people worldwide. The molecular mechanisms of CKD are poorly understood and the treatment approaches are non-causal and therefore non-selective. Mutations in the gene coding for phosphodiesterase 3A (PDE3A) cause autosomal-dominant hypertension with brachydactyly type E (HTNB). Despite HTNB patients have decade-long hypertension, their kidneys hardly display any hypertension-induced damage. We hypothesize, understanding how PDE3A mutations protect from CKD development will help to uncover the molecular mechanisms of CKD and pave the way to new strategies for CKD prevention and treatment

Methods: CRISPR/Cas9 was applied to introduce mutations in a regulatory or the catalytic domain encoding segment of the *Pde3a* gene of rats to recapitulate the HTNB phenotype (confirmed by radio-telemetry measurements). The inner medulla (IM) and residual kidney (RK) were subjected to Western blot analysis and RNA-sequencing with subsequent validation of the most promising genes-candidates.

Results: In wild-type animals, PDE3A mRNA and protein expression were higher in the IM compared to the RK. In PDE3A mutant animals, the IM PDE3A protein level was decreased. Protein levels of various cAMP signalling pathway components were not changed in PDE3A mutants in both IM and RK. However, the phosphorylation level of cAMP response element-binding protein (CREB) was significantly increased in IM in PDE3A mutants. The mRNA levels of 27 genes were changed upon PDE3A mutation in the regulatory region; some of them clustered as mitochondrial or inflammatory response proteins. The PDE3A mutation in the catalytic domain led to more profound changes in mRNA expression profiles.

Conclusions: In summary, our data show that hypertension-inducing mutations of PDE3A have no profound effects on the expression level of cAMP signaling proteins but change the global transcriptional profiles in the kidney. Alterations of the inflammatory cytokine production or mitochondrial metabolism could be involved in the renoprotective effects of PDE3A mutations.

Funding: Government Support - Non-U.S.

PO1829

Cerebrovascular Dysfunction in CKD

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Background: Cerebrovascular dysfunction, characterized by reduced cerebrovascular reactivity, cerebral hypoperfusion, and increased pulsatile flow within the brain precedes the onset of dementia and is linked to cognitive dysfunction. While large-artery vascular dysfunction is prevalent in chronic kidney disease (CKD), cerebrovascular function has not been well characterized to date in moderate-to-severe CKD.

Methods: Using transcranial Doppler, we compared middle cerebral artery (MCA) blood flow-velocity response to hypercapnia (normalized for blood pressure and end-tidal CO_2; a measure of cerebrovascular reactivity) and MCA pulsatility (a measure of cerebrovascular stiffness) in patients with stage 3-4 CKD vs. age-matched healthy controls using an independent samples t-test. We also administered the trail making test (parts A and B) as an index of processing speed and measured carotid-femoral pulse-wave velocity (CFPWV) as an index of aortic stiffness.

Results: Seven participants with CKD (2F, 68±3 yrs [mean±s.e.m.], estimated glomerular filtration rate [eGFR]: 38±5 ml/min/1.73m^2) were compared to 8 healthy controls (1F, 63±2 yrs, eGFR: 83±5 ml/min/1.73m^2). MCA pulsatility index was greater (1.08±0.10 vs. 0.85±0.04 A.U.; $p<0.05$) and normalized MCA blood flow-velocity response to hypercapnia tended to be lower (-6.3±4.0 vs. 11.6±7.3 %; $p=0.06$) in CKD as compared to healthy controls. Trail making part A time was slower (A: 31.8±3.3 vs. 20.2±1.6 sec; $p<0.01$); part B time tended to be slower (longer time to complete): 71.7±13.6 vs. 42.7±6.7 sec; $p=0.07$) and CFPWV was greater (1122±115 vs. 811±88 cm/sec; $p<0.05$) in CKD vs. control. Greater MCA pulsatility index correlated with worse cerebrovascular reactivity ($r = -0.63$, $p=0.01$), greater CFPWV ($r= 0.65$, $p<0.01$), slower trail making part B time ($r =0.59$, $p<0.05$), and lower eGFR ($r = -0.53$, $p=0.09$).

Conclusions: Impaired cerebrovascular function is evident in patients with moderate-to-severe CKD. Increased cerebrovascular stiffness is associated with reduced kidney function, increased aortic stiffness, impaired processing speed, and worse cerebrovascular reactivity.

PO1830

Circadian Clock Provides Beneficial Effects Against Endothelial Dysfunction by Regulating Heme Synthesis and Heme Oxygenase 1 Expression

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Background: The circadian clock is a molecular mechanism that confers 24 hours variations in gene expression and function to regulate number of physiological functions in humans. Chronic circadian clock disruption is associated with vascular stiffness and dysfunction in endothelial signaling and responses. 5-Aminolevulinic acid (ALA) is the common precursor of heme. The iron ion is inserted into PpIX to form heme in the mitochondria and incorporated into hemoproteins. Heme is a ligand of REV-ERBα and REV-ERBβ which modulate circadian rhythms by binding to the ROR region of CLOCK or BMAL1 to suppress the expression of these genes. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence HO-1 which play an important part in the protection of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of HO-1 expression in the knocked down cells. To synchronize circadian rhythms, serum stimulations were performed. Cells were also pre-incubated with or without 1 mM ALA and 0.5 mM sodium ferrous citrate (SFC).

Results: In aorta from Bmal1 KO mice, there was a reduction in HO-1 expression in mice with a dysfunctional circadian rhythm. Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to the regulation of key risk factors for cardiovascular disease. These include HO-1 which is significantly reduced in Bmal1 KO mice. ALA/SFC co-incubation affected the oscillation and phase of core clock genes and led to increase of HO-1. HO-1 levels followed a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating Heme synthesis and HO-1 expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.

PO1831

Bradykinin Reduces Long-Lasting TRPV1-Mediated Inward Currents in Afferent Nonfiring Renal Neurons

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Background: Bradykinin had been reported to be sympathoexcitatory via renal afferent nerves. Hence we tested the hypothesis that bradykinin directly stimulates cultivated renal neurons with afferent axons.

Methods: Dorsal root ganglion neurons (Th11-L2) of rats were investigated in voltage clamp mode to assess inward currents and current clamp mode to assess action potential (AP) generation [neurons classified as tonic (high AP generation upon stimulation), phasic (AP ≤ 5 upon stimulation) or no firing]. Stimulation of TRPV1 receptors by protons (pH 6) with and without the addition of bradykinin (1, 10,100 μM). 111 DRG renal neurons retrogradely stained with DiI for investigation.

Results: Bradykinin (BK) alone did not induce inward currents nor APs. Proton stimulation (pH 6) of TRPV1 significantly augmented long-term inward currents (baseline -0.360±0.09nA vs. -1.39±0.34nA, $p<0.05$, mean±SEM) and increased action potential production in tonic neurons (0 APs/10s vs. 9.57±1.89 APs/10s*, $p<0.05$, mean±SEM). However, the co-stimulation of renal neurons with protons and BK had any effect only in one specific subgroup of renal neurons: it significantly decreased long-lasting currents in non firing neurons (ΔI upon stimulation with 100μM BK&pH6: -0.129±0.02nA, 10μM BK&pH6: -0.119±0.03nA, 1μM BK&pH6: -0.063±0.02 nA versus pH 6: -0.312±0.06nA*, *$p<0.05$, mean±SEM).

Conclusions: Bradykinin was only able to reduce long-lasting, TRPV1 dependent inward currents in non-firing renal neurons. Alterations of inward currents are likely involved in the release of neurogenic proinflammatory peptides (SP, CGRP). Hence, bradykinin might impair the release of neuropetides from intrarenal axons of a specific subgroup of renal afferent neurons.

PO1832

The Impact of rs2254524 LSS Polymorphism on Blood Pressure in a New Mouse Model

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Background: The blood pressure (BP) response to salt intake is associated with hypertension (HTN) and shows great variability among individuals. Endogenous ouabain (EO) is a steroid hormone previously associated with HTN. To dissect EO and HTN link at genetic level, we identified as a propensity factor the missense variation rs2254524 (Val642Leu; V642: CC variant; L642: AA variant) in the Lanosterol Synthase (LSS), a key enzyme in steroid biosynthesis. In patients, the LSS A variant influences the BP and circulating EO level in response to a low salt diet. Moreover, high EO levels were detected in LSS AA kidneys and are associated with a faster decline in GFR in hypertensives. We hypothesized that LSS affects salt-sensitive HTN by regulation of EO biosynthesis.

Methods: We generated a knock-in mouse model carrying the rs2254524 SNP expression in all tissues. We performed all animal procedures on male mice. The Blood Pressure was measured by the tail-cuff system, on 5 consequent days in conscious mice, after appropriate training.

Results: LSS AA mice were viable, healthy, and undistinguishable phenotypically from LSS CC. The LSS transcript and protein levels were slightly reduced in the Adrenal Gland of LSS AA mice at 3 months of age and in the kidney at 6 months of age. At 3 months of age, EO quantification in LSS AA kidney is about 3.3 pmol/g tissue (SD =1.69) compared to 2.6 pmol/g tissue (SD =1.1) in control. At baseline, LSS AA mice did not affect SBP and kidney function at 3, 6, and 9 months of age. Nevertheless, we observed an increasing trend in SBP upon High Salt (4% NaCl) diet administration in AA mice, compared to that fed with Control Salt Diet (0.5% NaCl), at 3 months (Fig. 1).

Conclusions: Our preliminary results show that the LSS AA variant affects BP upon high-salt diet administration at 3 months, but further studies are necessary to deepen the effect of LSS A variant on salt-sensitivity at different ages.

Funding: Government Support - Non-U.S.

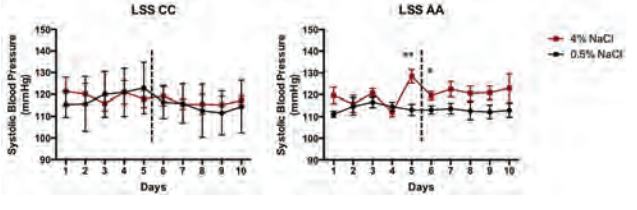

Fig. 1: SBP measurement by the tail-cuff system in LSS CC and LSS AA mice upon 4% and 0.5% NaCl diets administration. The first 5 days are considered as training. Bars indicate average ± SEM. *$P < 0.05$; **$P < 0.01$

PO1833

RNA Sequencing Reveals Induction of Specific Renal Inflammatory Pathways in a Rat Model of Malignant Hypertension

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Background: In malignant hypertension (MH), far more severe kidney injury occurs than in the "benign" form of the disease. The pathogenesis of this peculiar renal injury of malignant hypertension remains incompletely understood. Using a rat model in which some but not all animals develop MH, we performed an unbiased analysis of gene expression by RNA-sequencing to identify transcriptional changes in the kidney specific for malignant hypertension.

Methods: Renovascular hypertension in rats was induced by placing a 0.2 mm clip on the left renal artery (2K1C). Five weeks later, all 2K1C rats had developed hypertension. Rats were then sacrificed, and renal cortical RNA was extracted from the right kidney exposed to high blood pressure. To distinguish MH from non-malignant hypertension (NMH), we considered two factors: weight loss and typical renovascular lesions. Differential gene expression was assessed in three groups: MH, NMH and normotensive, sham operated controls (N=5 per group for RNA sequencing, N between 8 and 14 for other analyses).

Results: Mean blood pressure measured intraarterially was elevated to a similar degree in MH (207±10 mmHg) and NMH (201±4 mmHg) compared to controls (113±3 mmHg, $p<0.05$). 886 genes were exclusively regulated in MH only. Principal component analysis revealed a separated clustering of the three groups. The data pointed to an upregulation of many inflammatory mechanisms in MH including pathways which previously attracted little attention in this setting: Transcripts from all three complement activation pathways were upregulated in MH compared to NMH but not in NMH compared with controls; immunohistochemistry confirmed complement deposition in MH exclusively. The expression of chemokines attracting neutrophil granulocytes as well as actual granulocyte infiltration were increased only in MH rats (CXCL6: 4.1-fold in MH over NMH).

Conclusions: The hypertensive kidney injury in malignant hypertension of 2K1C rats includes a robust expression and deposition of complement components as well as infiltration of neutrophil leukocytes, features which are not observed in the non-malignant course of renovascular hypertension. These pathways may contribute to the specific kidney injury observed in malignant hypertension.

Funding: Government Support - Non-U.S.

PO1834

Toll-Like Receptor 4 (TLR4) an Effector of Renal Inflammation and Sodium (Na) Transport

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Background: Na sensitivity of blood pressure (BP) is risk factor for cardiovascular mortality compared to Na resistant subjects. In addition, constrained cholesterol (chol) efflux is novel predictor for future cardiovascular events. Dysregulation of ABCA1, a chol efflux protein, is implicated in hypertension and kidney disease while ABCA1 ablation in macrophages stimulates TLR4 dependent inflammation. We surmised that tubular ABCA1 depletion similarly enhances TLR4 dependent inflammation in a model of Na sensitivity.

Methods: Transgenic mice ($Tg^{PAX8rtTA;tetO\text{-}Cre/+}$), which express CRE in tubular epithelia when fed doxycycline, were bred with mice expressing floxed ABCA1 to generate mice deficient in tubular ABCA1 (FF). Western blotting was performed on whole kidney protein lysate, renal plasma membrane (PM), and mpkCCD cells. Amiloride sensitive short-circuit current (AIsc) was measured in shear and static exposed mpkCCD cells.

Results: FF mice are phenotypically consistent with Na sensitivity (abstract# 3600350). FF and littermate controls (WT) mice fed a chol enriched diet for 6 weeks, a low Na and a high Na diet for 1 week were euthanized and kidneys extracted. Steady-state protein expression of NLRP3 inflammasome increased in ABCA1 deficient (1.5±0.1; n=7 $p<0.05$) vs. WT kidneys (1.0±0.1; n=5); however, TLR4, a receptor that stimulates NLRP3, was unchanged. Western blot of renal PM showed enhanced TLR4 abundance in FF (1.9±0.3; n=3; $p<0.05$) vs. WT (1.0±0.2; n=3) kidneys. Because Na enriched diets augment urine volume, tubular flow, and, thus fluid shear stress (FSS), the role of TLR4 signaling on FSS mediated Na transport was tested in mpkCCD cells. The AIsc in FSS (0.4 dynes/cm^2) exposed cells was greater (40.8±2.1 μA/cm^2;n=20, $p<0.05$) than in static cells (26.7±1.6 μA/cm^2; n=20) and the FSS induced AIsc was reduced (31.5±2.6 μA/cm^2; n=18, $p<0.05$ vs FSS exposed cells) by 10 μM basolateral TAK242, a TLR4 antagonist. FSS (n=9; 1.6±0.2, $p<0.05$) and 5 μM PSC (n=6; 1.7±0.2, $p<0.05$), an ABCA1 inhibitor, also induced NLRP3 protein abundance compared to static cells (n=9; 1.0±0.1) and (n=5, 1.0±0.1), respectively.

Conclusions: ABCA1 tubular deficiency enhances TLR4 PM localization and activation in kidney to induce NLRP3 while a cell model confirms that FSS and reduced ABCA1 stimulate NLRP3 abundance. TLR4 also regulates FSS-induced ENaC-dependent Na transport.

Funding: Veterans Affairs Support, Private Foundation Support

PO1835

T Lymphocytes in Human Hypertension

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Background: Mouse models have shown that T lymphocytes are required for hypertension (HTN) development and accumulate in the vasculature and kidneys. The role of immune cells, including T lymphocytes, remains poorly understood in patients with HTN. Here, we analyzed immune cells in human kidney tissue samples in patients with HTN.

Methods: Human kidney tissue was obtained from the unaffected portions of 631 tumor nephrectomies and included clinical, histological and follow up data. Tissue was microdissected into glomerular and tubular compartments for RNA-sequencing. *In silico* deconvolution of each kidney sample was performed using the CIBERSORTx method to enumerate relative cell type fractions. Flow cytometry was used for validation analyses using cell type specific antibodies in another set of 58 human kidney tissue samples. Regression analyses were used to determine the associations of renal immune cells and clinical parameters. Linear mixed modeling was used to assess longitudinal data.

Results: CD4 and CD8 T-cells were increased in patients with HTN ($p<0.05$) while T regulatory cells (Tregs) were decreased (0.4% vs. 0.6%, $p=0.022$). In adjusted models, HTN was associated with older age, Black race, diabetes, decreasing eGFR, dendritic cells (DCs) and Tregs and with increasing CD4 T-cells ($p<0.001$). In samples with CKD stages 1-2, older age, lower Tregs and natural killer T-cells and higher CD4 T-cells were associated with HTN, independent of baseline eGFR or the degree of renal fibrosis ($p<0.001$). In our flow cytometry cohort, HTN was also significantly associated with higher CD4 T-cells, lower Tregs and DCs, but also lower CD8 T-cells, independent of eGFR ($p=0.009$). Longitudinal data were available for 149 subjects for an average of three years and showed that older age, lower baseline eGFR and higher Th17 cells were associated with lower eGFR over time ($p<0.001$).

Conclusions: *In silico* deconvolution resolved a variety of renal immune cells and provided complementary information to flow cytometric analyses in kidney tissue. While multiple T-cell populations were increased in the setting of HTN, Tregs were decreased. These findings were independent of eGFR at CKD stages 1-2. Th17 cell expansion predicted faster eGFR decline. Our results highlight an important association between T-cell populations, HTN, kidney disease and kidney function decline.

Funding: NIDDK Support, Commercial Support - Merck, Boehringer Ingelheim

PO1836

Focal Adhesion Kinase: A Major Regulator of Myocardial Failure in CKD

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Background: The focal adhesion pathway is essential in signal communication between the extracellular matrix and the cytoskeleton. Failure of this signaling pathway results in cytoskeletal dysfunction and has been shown to be intricately involved in the progression of ischemic cardiomyopathy. Whether this occurs in CKD-associated cardiomyopathy is currently unknown. In this study, our aim was to investigate the role of focal adhesion kinase (FAK), a central component of the focal adhesion pathway in the failing heart in CKD.

Methods: We performed a cross-sectional cohort study of explanted human heart tissues from hemodialysis-dependent (HD, n=19), hypertension with preserved renal function (HTN, n=10), and healthy control (n=21) donors. Left ventricular (LV) tissues were subjected to RNA sequencing, qPCR, and protein analyses. Mechanistic and interference RNA studies using *in vitro* human ventricular cardiac fibroblast models were also conducted.

Results: Hearts from HD donor exhibited significant myocardial fibrosis ($p<0.01$) compared to HTN and control. HD and HTN hearts had higher heart weights ($p<0.01$) and greater LV wall thickness ($p<0.01$) compared to control hearts. RNA-sequencing revealed that the focal adhesion pathway was one of the most perturbed pathways in HD hearts compared to control. FAK mRNA and protein expression was significantly upregulated ($p<0.05$), and major cytoskeletal proteins associated with the focal adhesion pathway, including β-actin ($p<0.01$), β-tubulin ($p<0.01$), vinculin ($p<0.05$), and vimentin ($p<0.01$) were significantly dysregulated in HD hearts compared to control. Uremic mineral stressors (high phosphate and high calcium) decreased FAK expression as well as β-tubulin ($p<0.05$) and vimentin, and promoted cleavage of FAK and vimentin, *in vitro*. Concurrent FAK siRNA transfection and mineral stress significantly decreased both full-length and cleaved FAK expression ($p<0.05$) and further dysregulated vimentin ($p<0.05$) and vinculin ($p<0.05$) expression, *in vitro*.

Conclusions: FAK and the focal adhesion pathway plays a central role in the development of CKD-associated cardiomyopathy and appears to preserve the dynamic formation of the cytoskeleton in HD hearts. These findings suggest a potential therapeutic role for targeting the focal adhesion pathway in the management of cardiac remodeling in CKD.

PO1837

Dual Action of β2AR-Agonism Confers Protection Against Heart Failure and Renal Dysfunction via Inotropic and Lusitropic Effects and Normalized Cholesterol Homeostasis in a Mouse Model of Alport Syndrome

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Background: *Col4a3*$^{-/-}$Alport mice present a model of heart failure with preserved ejection fraction (HFpEF) secondary to CKD. HFpEF is characteristically unresponsive to pharmacological intervention. Here, we tested the hypothesis that selective β2AR modulation with salbutamol could alleviate symptoms of CKD and simultaneously augment cardiac function. Secondarily, we investigated the mechanism of actions of such β2AR-mediated therapeutics on cardiac and renal functions.

Methods: Alport mice were injected intraperitoneally with salbutamol or DMSO vehicle as a single bolus of 200μg/dose in short-term studies or daily with 100 μg/dose for 2 weeks long-term. Cardiac and renal functions, cAMP levels, *in vivo* renal tubular LDL-C uptake and renal histology were evaluated post-injection.

Results: Short-term, salbutamol improved renal function in parallel with decreased LDLR levels and reduced uptake of LDL-C into renal tubules. Long-term, cardiac diastolic function assessed by isovolumetric relaxation time (IVRT), filling pressures (E/E′), and myocardial performance index, and systolic function reflected by ejection fraction, stroke volume and cardiac output improved significantly in parallel with increased cardiac cAMP. Mechanistically, in the kidney, salbutamol induced IDOL-mediated ubiquitination and subsequent lysosomal degradation of the LDLR via a novel β2AR-mediated, cAMP-independent pathway involving the Rac1/Cdc42 β1PixGEF. β1Pix reversibly sequesters IDOL into a complex with LDLR, thereby blocking the degradation pathway. β2AR stimulation dissipates the complex reactivating IDOL-mediated LDLR degradation thereby re-establishing LDL-C homeostasis and renal function. Using flow cytometry in HEK293T cells, ectopic expression of β1Pix stabilized cell surface LDLR abundance in an IDOL-dependent and PCSK9-independent manner.

Conclusions: β2AR agonism represents a potential treatment strategy to alleviate progression of CKD and heart failure associated with HFpEF phenogroup 3.

Funding: Other NIH Support - NHLBI, Private Foundation Support

PO1838

Phenotyping CKD-Associated Cardiac Fibrosis

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Background: Myocardial fibrosis is a pervasive and progressive complication in CKD patients. Mechanistically, increased collagen cross-linking has been shown to be a critical determinant of tensile strength, stiffness of collagen fibers, and resistance to degradation in ischemic cardiomyopathy, as opposed to increased collagen deposition alone. Whether similar metabolic processes and physiochemical alterations occur in CKD is largely unknown. Herein, we investigated the fibrotic phenotype in CKD-associated cardiomyopathy and the role of disordered mineral stressors.

Methods: Human left ventricular (LV) tissues were collected from hemodialysis (HD; n=13), hypertensive (HTN; n=8), and healthy control (n=12) donors to compare matrix proteins. Mechanistic *in vitro* studies involving treatment of human ventricular cardiac fibroblasts (HCFs) with either 1.8-3.8mM β-glycerophosphate (BGP) or 2.4-5.0mM $CaCl_2$ in media were conducted. Protein expression was assessed by immunoblotting.

Results: We report increased trimeric (400 kDa) collagen I (COL1) in LV tissues from HD and HTN ($p<0.05$) compared to healthy control. Uniquely, monomeric (150 kDa) COL3 was decreased in HD hearts ($p<0.05$) compared to HTN and healthy control. Dimeric (250 kDa) or monomeric COL1 (139 kDa) and other COL3 multimers were not found in any groups. HD and HTN hearts exhibited increased periostin ($p<0.05$) compared to healthy control. There was no significant difference in fibronectin or α-smooth muscle actin (α-SMA) between groups. We next performed dose-dependent studies in HCFs treated with either BGP or $CaCl_2$. 3.8 mM BGP stimulated increased trimeric but not dimeric COL1 ($p<0.05$), and reduced monomeric COL3 ($p<0.01$) synthesis leading to increased total COL1:3 ratio ($p<0.05$), *in vitro*. No other forms of COL1 or COL3 were observed. Additionally, 3.8mM BGP decreased fibronectin expression ($p<0.01$), but did not significantly change periostin or α-SMA expression. At 5 mM $CaCl_2$ treatment, this decreased COL3 ($p<0.01$), fibronectin ($p<0.05$), and periostin ($p<0.05$) expression.

Conclusions: Cardiac fibrosis in hearts from HD patients is characterized by increased trimeric COL1 expression and increased COL1:3 ratio that can be driven by disordered mineral stressors. These changes suggest pathologic cross-linking that can lead to altered mechanical properties and further studies are warranted.

Funding: Other NIH Support - NIH 5K23DK115683

PO1839

Plasma Proteins Associated with eGFR and Incident Cardiovascular Events in the Cardiovascular Health Study Cohort

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Background: Proteomics may help identify mechanisms through which low estimated glomerular filtration rate (eGFR) increases risks of heart failure (HF), myocardial infarction (MI), and cardiovascular (CV) death.

Methods: We utilized an aptamer-based assay to measure 1300 proteins among 3185 older adults in the Cardiovascular Health Study. Proteins associated with eGFR were identified using linear regression models. A Bonferroni-corrected p-value less than $7.6x10^{-8}$ was used to account for multiple testing. Proteins significantly associated with eGFR were tested for associations with incident HF, MI, and CV death using Cox-proportional hazard regression adjusting for demographic and clinical variables. We evaluated whether proteins mediated associations between eGFR and incident CV events.

Results: The mean baseline eGFR was 70 ml/min/1.73m^2 and over a follow-up median of 13 years, there were 1033 incident HF, 555 incident MI, and 963 CV death events. 797 proteins were significantly associated with eGFR. Of these, 52, 0, and 22 proteins were associated with incident HF, MI, and CV death, respectively. All proteins associated with HF and CV death significantly mediated the effects between eGFR and incident CHF and CV death, respectively. The 10 proteins most strongly associated with both HF and CV are shown in the **Table**.

Conclusions: eGFR is associated with a large number of plasma proteins. A subset of these proteins are also associated with incident HF and CV death and may reflect mechanisms through which reduced eGFR increases the risk of these outcomes.

Funding: Other NIH Support - NIH - NHLBI

Protein	Beta (95% CI) corresponding to log2-ISD higher protein concentration for every 10 ml/min/1.73m^2 lower eGFR	HF		CV Death	
		HR (95% CI)	Proportion Mediated [α]	HR (95% CI)	Proportion Mediated [α]
N-terminal pro-BNP	0.13 (0.11, 0.15)	1.61 (1.49, 1.74)	0.56	1.51 (1.40-1.63)	0.54
Growth/differentiation factor 15	0.29 (27.2, 30.8)	1.35 (1.24, 1.46	0.79	1.34 (1.23-1.46)	0.78
Tumor necrosis factor receptor superfamily member 1A	0.43 (0.42, 0.45)	1.36 (1.23, 1.51)	1.00[β]	1.26 (1.13-1.40)	0.89
Macrophage metalloelastase	0.19 (0.17, 0.21)	1.27 (1.18, 1.37)	0.39	1.33 (1.23-1.44)	0.48
Angiopoietin-2	0.18 (0.16, 0.20)	1.24 (1.15-1.33)	0.34	1.29 (1.20-1.39)	0.42
Tumor necrosis factor receptor superfamily member 11B	0.09 (0.08, 0.12)	1.23 (1.14-1.32)	0.18	1.25 (1.18-1.35)	0.20
Endostatin	0.37 (0.35, 0.39)	1.26 (1.16-1.38)	0.83	1.26 (1.13-1.42)	0.81
Insulin-like growth factor-binding protein 7	0.12 (0.10, 0.14)	1.23 (1.16-1.31	0.22	1.18 (1.10-1.26)	0.18
Alpha-1-antitrypsin	0.06 (0.04, 0.08)	1.18 (1.11-1.27)	0.12	1.17 (1.09-1.25)	0.11
Periostin	0.09 (0.07, 0.12)	1.15 (1.08-1.24)	0.13	1.16 (1.09-1.24)	0.14

[α] Proportion by which protein mediates association between eGFR and CV event; all p-values $<1x10^{-15}$

[β]Proportion set to 1.0 (original value >1.0)

PO1840

Characterization of Pendrin in Urinary Extracellular Vesicles in a Rat Model of Aldosterone Excess and in Human Primary Aldosteronism

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Background: Pendrin is a Cl/HCO_3 exchanger selectively present in the intercalated cells of the kidney. Although experimental studies demonstrated that pendrin is involved in the fluid volume regulation and acid/base balance, its role in human hypertension is not fully understood. Here, we investigated the changes in pendrin levels in urinary extracellular vesicles (uEVs) isolated from patients with primary aldosteronism (PA) and in a rat model of PA.

Methods: This study included 30 patients who were diagnosed as having PA in Yokohama Rosai Hospital or in Teikyo University Hospital. The protocol was approved by the institutional review board. In animal experiments, SD rats received continuous infusion of aldosterone after uninephrectomy. Isolation of uEV was performed by the ultracentrifugation method in accordance with the previous report (Fernandez-Llama et al. KI 2010).

Results: Western blot analysis revealed that pendrin is detected in dimeric and monomeric forms in uEVs in humans and in rats. In aldosterone-infused rats, pendrin levels in uEVs were highly correlated with the pendrin abundance in the kidney. We also found significant correlation between abundance in uEVs and that in the kidney for Na-Cl cotransporter and epithelial Na channel in this model. In PA patients, pendrin levels in uEVs were reduced by 49% from the baseline by adrenalectomy or pharmacological MR blockade. Correlation analysis revealed that the magnitude of pendrin reduction after treatment significantly correlated with the baseline aldosterone-renin ratio (ARR), and tended to inversely correlate with serum K^+ levels. Furthermore, a cross-sectional analysis in PA patients confirmed a significant correlation between ARR and pendrin levels in uEVs.

Conclusions: These data are consistent with experimental studies demonstrating the role of pendrin in aldosterone-induced hypertension, and suggest that pendrin analysis in uEVs may also be useful to understand the pathophysiology of human hypertension.

PO1841

The Impact of Calcification on Intraplaque Hemorrhage in Coronary Atherosclerosis from Autopsy Samples: The Hisayama Study

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Background: Vascular calcification is the specific feature of arterial change and is often seen in coronary arteries among patients with chronic kidney disease (CKD) and older subjects. The information whether vascular calcification is associated with intraplaque hemorrhage is scarce. We aim to examine how much area of calcification is the highest risk on plaque vulnerability.

Methods: We examined 375 coronary arteries obtained from autopsy samples of subjects with CKD stages 0 to 5 in a general Japanese population. Arteries were divided into quintiles based on vascular calcification area. The association of calcification area with the presence of intraplaque hemorrhage in coronary arteries was estimated by using a logistic regression analysis.

Results: Calcification lesions were counted in 149 coronary arteries. All calcification lesions were existed in intima. Subjects in the fourth quartile of calcification area had a significantly higher likelihood of intraplaque hemorrhage than those in the lowest quintile after adjusting for confounders (odd ratio [95% confidence interval], 19.93 [1.48-267.71]), whereas subjects in highest quintile did not (7.86 [0.61-101.70]). The calcification area at highest risk for the presence of intraplaque hemorrhage was 2.02 mm^2, and the risk was constant at greater area than this value in the logistic analysis with restricted cubic spline.

Conclusions: The present study suggests that larger vascular calcification is associated significantly with increased risk for intraplaque hemorrhage, subsequently linking to plaque vulnerability. Above a certain amount of calcification area, these increasing trends may no longer be observed.

PO1842

Radiation Exposure and Coronary Atherosclerosis: Differential Effect of the Radiation Site

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Background: Accelerated coronary artery atherosclerosis is a common complication of thoracic radiation therapy as result of unintended direct cardiac radiation. It is unclear however whether specific areas of the heart are more susceptible to the effects of radiation. In this study we hypothesize that accelerated development of atherosclerotic lesions post radiation (RT) is dependent upon differential sensitivity of specific areas of the heart to the effects of RT.

Methods: Male Apolipoprotein E knockout mice on a high fat diet received 16Gy cardiac RT targeted to the whole or partial (apical or basal) region of the heart at 9 or 16 weeks of age(n=5 per group). Atherosclerotic lesions in H&E stained slides and inflammatory infiltrates in the hearts by IHC were assessed 8 weeks following radiation and compared to unirradiated controls.

Results: Our studies show that:(1) Subendocardial atherosclerotic lesions at the base of heart in mice irradiated at 9 weeks of age after basal irradiation are comparable to whole heart irradiation. (2) A greater number of atherosclerotic lesions were present in the basal coronary arteries and basal subendocardial vasculature after irradiation of the cardiac base as compared to unirradiated controls in mice irradiated at 16 weeks of age (Table). (3) Apical or whole heart irradiation had no impact on the development of lesions in the basal region of the hearts of 16 week old mice (Table). (4) IL-6 was significantly increased in the serum of mice 6 hours post basal cardiac irradiation (105.10±17.56 pg/ml) when compared to unirradiated controls (29.85±11.63 pg/ml) demonstrating an early inflammatory response. (5) Infiltration of inflammatory cells (CD45 and CD3) and enhanced expression of endothelial adhesion molecules (CD31) were differentially and locally regulated based upon the site of irradiation.

Conclusions: Our results indicate that the base of the heart is more prone to development of RT induced atherosclerotic lesions likely due to acute and delayed inflammatory responses. Avoiding this area from direct radiation exposure may improve the quality of life for cancer patients receiving thoracic RT.

Field of cardiac irradiation	Number of Atherosclerotic lesions (16 week old mice)			
	Myocardial and Subendocardial vasculature		Major Coronary Arteries	
	Basal lesions	**Apical lesions**	**Basal lesions**	**Apical lesions**
No RT	0.2 ± 0.2	0.6 ± 0.4	9 ± 2.70	1.6±0.92
Whole	5.2 ± 1.74	7 ± 1.51*	17.6 ± 2.11	4.2±1.24
Base	6.66 ± 2.07*	2.16±1.53	29.33 ± 5.48*	8.16±2.3
Apex	4 ± 1.37	6.8 ± 1.06*	11± 3.06	6.2±2.49

* $p < 0.05$ compared to unirradiated mice

PO1843

Correlations of Creatinine with Biomarkers of Tubular Injury and Secretory Function in Patients Admitted with Heart Failure

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Background: Serum creatinine values during hospitalization for decompensated heart failure (ADHF) may not comprehensively capture kidney function. The aim of this pilot study was to evaluate correlations of traditional markers of filtration (serum creatinine) with novel measures of tubular injury and tubular secretion in patients admitted with ADHF.

Methods: Biospecimens were obtained within 24 hours of admission in 61 patients admitted with ADHF at a University of Washington hospital. We measured serum creatinine, urine tubular injury markers (urine NGAL, KIM-1, Il-18 and TIMP2 standardized to urine creatinine) and proximal tubular secretory function ([urine concentration]/[plasma concentration] normalized to U_{Cr}.). We calculated spearman correlations of each kidney measures with each other and admission serum brain natriuretic peptide (BNP).

Results: Serum creatinine poorly correlated to biomarkers of tubular injury (**Table 1**). Higher serum creatinine was significantly correlated with lower clearance of all secretory biomarkers aside from cinnamoylglycine. Admission BNP did not correlate with serum creatinine or injury biomarkers but had a consistent inverse relationship with secretory biomarkers that did not reach statistical significance.

Conclusions: The results from this pilot study demonstrate that serum creatinine poorly correlates with biomarkers of tubular injury and inversely correlates with tubular secretory clearance in patients admitted for ADHF. More research is needed to understand how filtration, tubular injury, and secretory clearance relate to clinical outcomes and response to treatment in patients with ADHF.

Funding: NIDDK Support

		Tubular Injury Biomarkers					Secretory Clearance Biomarkers				
	Serum Creatinine	Urine NGAL	Urine KIM-1	Urine/Plasma KIM-1	IL-18	TIMP2	Cinnamoylglycine	Isovalerylglycine	Kynurenic acid	Pyridoxic acid	Tiglylglycine
Serum Creatinine											
Urine NGAL	-0.16										
Urine KIM-1	0.25	0.14									
Urine/Plasma KIM-1	-0.34*	-0.03	0.29								
IL-18	-0.16	0.23	-0.1	-0.06							
TIMP2	-0.01	-0.02	-0.07	-0.28	0						
Cinnamoylglycine	-0.23	-0.12	-0.09	0.26	-0.44*	-0.17					
Isovalerylglycine	-0.57***	0.03	-0.09	0.04	-0.12	0.1	0.28				
Kynurenic acid	-0.44*	0.18	-0.06	0.22	-0.31	-0.11	0.58***	0.71***			
Pyridoxic acid	-0.46**	-0.05	-0.11	0.29	-0.37*	-0.22	0.56***	0.56***	0.89***		
Tiglylglycine	-0.47**	0.08	-0.13	0.17	-0.28	-0.14	0.68**	0.70***	0.90***	0.93***	
Serum BNP	-0.1	-0.1	0.08	0.09	-0.13	-0.06	-0.2	-0.27	-0.27	-0.28	-0.32

*p<0.05; **p<0.01; ***p<0.001

Table 1: Correlation matrix of biomarkers on admission for ADHF

PO1844

RAAS vs. COVID: Case of an 18-Year-Old with New-Onset Hypertension

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Introduction: It has been increasingly known that SARS-CoV-2 causes an imbalance in the Renin-Angiotensin-Aldosterone System (RAAS). Here we present an interesting case of a young man, who presented with new onset of HTN and elevated renin and aldosterone levels with a h/o COVID-19.

Case Description: An 18-year-old Caucasian man with a remote history of asthma initially presented to his primary care physician with new onset of headaches. He was noted to have an elevated blood pressure, but otherwise a benign physical examination. A workup for secondary HTN revealed an elevated renin (8.7 ng/mL/hr), aldosterone levels (42 ng/dL) and otherwise unremarkable. He was started on Enalapril 5mg daily. A workup including CT and MRI of the brain, were unremarkable. He was referred to nephrology for the new diagnosis of HTN and abnormal renin and aldosterone levels. During the initial renal evaluation, patient was asymptomatic and his BP was well controlled on the Enalapril. Renin and aldosterone levels were repeated, about 8 weeks after the cessation of Enalapril. Patient's blood pressure remained well controlled and didn't require any medications. Since the diagnosis of HTN, the patient maintained a strict low salt diet. He always had good fluid intake. At a follow up visit, patient continued to remain asymptomatic and with good blood pressure control without needing medications. Repeat renin (1.9 ng/mL/hr) and aldosterone (16.8 ng/dL), as well as aldosterone/renin levels were resulted within normal limits. Later patient admitted that he was diagnosed with COVID-19 a month prior to his onset of headaches.

Discussion: SARS-CoV-2, which causes COVID-19, is known to hijack the RAAS cascade and use ACE2 enzyme to make human cell entry. Studies have demonstrated the possible correlation between COVID severity and comorbidities such as HTN (potentially involving the RAAS). Current recommendations are to continue the use of ACE Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) in COVID-19 patients. Our case, not only supports the above findings, but also demonstrates how RAAS is vulnerable to SARS-CoV-2, can manifest with new onset HTN and other complications. It is also interesting to see, how ACEIs and ARBs should be utilized as first line agents for BP control and to improve outcomes. To much relief, the effect on RAAS by the SARS-CoV-2 seems to be transient and short lived.

PO1845

Page Kidney: A Case of Spontaneous Subcapsular Hemorrhage Secondary to Anticoagulation

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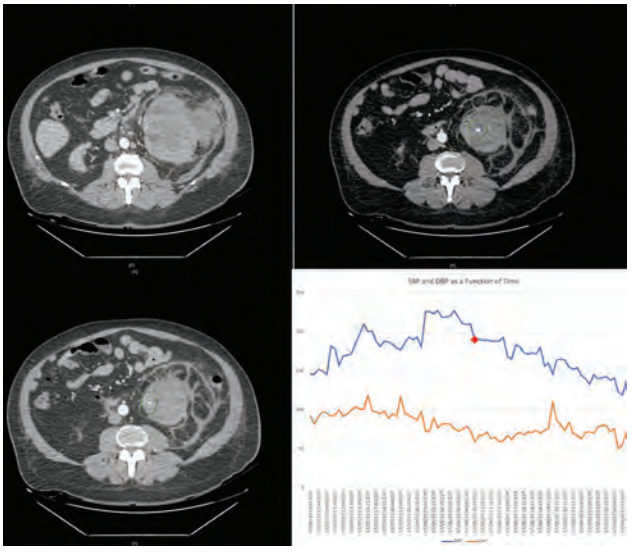
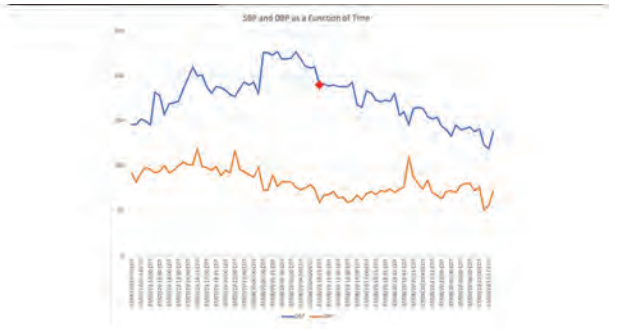
Introduction: Page kidney is a rare condition caused by external compression on the renal parenchyma resulting in hypo-perfusion, activation of the renin-angiotensin-aldosterone system, and secondary hypertension. The etiologies of Page kidney include trauma, iatrogenic, spontaneous hematomas, and extrarenal compression.

Case Description: 52-year-old male with a history of polycystic kidney disease (PCKD) on hemodialysis, atrial fibrillation, and aortic stenosis s/p mechanical valve replacement on Warfarin presented to the hospital for acute left flank pain. Pain was described as severe. On exam, the patient was afebrile and hemodynamically stable. Labs were notable for WBC 11.8, Hgb 7.4, and INR 2.4. CTA demonstrated a large hematoma originating from the left kidney measuring 14.3 x 12.7 cm. There were additional findings concerning for active arterial extravasation and compression of renal parenchyma. Patient was transfused 1 unit of PRBC's and admitted to the intensive care unit. While admitted, he became progressively more hypertensive despite escalating antihypertensive therapy. He ultimately underwent angiography and coil embolization to stop the bleed. Following successful coil embolization, his blood pressure normalized and anti-hypertensive medications were titrated off.

Discussion: Our case is unique in that it is the first case of a spontaneous bleed secondary to anticoagulation in the setting of PCKD. The combination of PCKD in a patient with significant need for ongoing anti-coagulation results in a dramatic increase in incidence of Page kidney.





Graphical Representation of Average Blood Pressures Readings Before and After Intervention

-Red Dot = Coil Embolization

PO1846

Page Kidney and Uncontrolled Hypertension: Rare Complication Post Kidney Biopsy

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Introduction: Page kidney is a rare phenomenon defined as an external compression of the renal parenchyma that can lead to hypertension and acute kidney injury. Compression of the renal parenchyma can occur from the formation of a subcapsular hematoma of traumatic or non-traumatic origin. This phenomenon can be seen as a rare cause of hypertension related to subcapsular hematoma formation following kidney biopsy. We report a case of a 34-year-old-male with chronic kidney disease who developed abdominal pain and uncontrolled hypertension within 24 hours of kidney biopsy, found to have imaging findings consistent with Page kidney as a complication of the procedure.

Case Description: A 34-year-old male patient with a history of HTN, CAD, and stage 3B CKD presented to the ER with left flank pain and hypertensive urgency with SBP > 200 mmHg one day following a native kidney biopsy. He underwent a kidney biopsy for evaluation of sub-nephrotic range proteinuria and unclear etiology of CKD. CT abdomen/pelvis with contrast demonstrated a new 3.5 cm left kidney subcapsular hematoma with perinephric and retroperitoneal extension. Abdominal pain worsened and repeat imaging showed expansion of the hematoma up to 24.5 cm. Before, during, and after kidney biopsy, the patient had well-controlled HTN with SBP range in the 130-140s mmHg. The day following the biopsy, SBP had risen to over 200 mmHg. Given his recent biopsy, significant HTN, and expansion of subcapsular hematoma on imaging, Page kidney was identified as the culprit leading to uncontrolled HTN. He was admitted to the ICU and started on a nicardipine drip with improvement in BP. Interventional radiology was consulted, and the patient underwent a left renal angiogram showing active extravasation at the hematoma site, which was then embolized. The patient achieved adequate BP control and the nicardipine drip was successfully weaned off. He was then transitioned back to his home oral antihypertensives.

Discussion: Page kidney refers to a condition in which there is an external force compressing the kidney which results in decreased kidney perfusion manifesting in a state of ischemia. This activates the RAAS system leading to secondary hypertension. Although many cases have previously been reported, Page kidney remains an uncommon cause, especially over recent years, of uncontrolled secondary hypertension and acute kidney injury.

PO1847

Nonsuppressed Plasma Renin Activity in Primary Aldosteronism with Hypertensive Kidney Disease

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Introduction: Primary aldosteronism (PA) prevalence has been estimated at 4.7–25.5% of all hypertensive patients. Renin aldosterone ratio (ARR) serves as a widely used screening test. Elevated ARR with suppressed plasma renin activity (PRA) is considered a positive screening test which should be followed by confirmatory testing. There are cases when PA is associated with non-suppressed PRA as in our case.

Case Description: A 37-year-old African American female patient with a past medical history of chronic kidney disease stage 4 presented to the hospital with a complaint of severe headache for 2 days associated with nausea and vomiting. Physical exam was remarkable for tachycardia and elevated blood pressure at 190/101 mmHg. Notable labs include low potassium at 3.4 [3.5 – 5.0 mmol/L], elevated creatinine at 4.84 [0.40 – 1.00 mg/dL] with a baseline creatinine of 2.36 mg/dL, urinalysis was positive for proteinuria. Secondary hypertension workup showed unremarkable renal duplex ultrasound, unremarkable thyroid function test, normal free plasma metanephrine, unremarkable urine drug screen. Screening for Cushing's syndrome wasn't performed given there were no supporting clinical manifestations. Plasma aldosterone concentration (PAC) elevated at 64.1 [3.1 – 35.4 ng/dL] with normal PRA at 1.7 ng/mL/hr. Calculated ARR was elevated at 37.7 ng/dL per ng/mL/hour, which raised the suspicion for primary aldosteronism (PA). Saline infusion test (SIT) showed elevated post-infusion PAC at 78.1 ng/dL which confirmed the diagnosis of PA.

Discussion: There are reports in literature that PA is more common than initially thought and has adverse effects on cardiovascular and renal systems independent of hypertension. So early diagnosis and management are highly recommended. The initial finding of non-suppressed PRA despite elevated ARR complicated diagnostic process. Multiple case studies reported non-suppressed PRA in patients with PA, especially when associated with hypertensive kidney disease and arteriosclerosis. In our case, kidney biopsy showed glomerulosclerosis with arteriopathy consistent with hypertensive kidney disease. We suggest focusing on ARR as a reliable screening for PA and not solely depend on the fact that PA is associated with suppressed PRA, especially in these cases. Another important point is to consider lowering ARR cutoff for diagnosis of PA since PRA isn't completely suppressed in these cases.

PO1848

Abiraterone-Induced Mineralocorticoid Excess Despite Concurrent Prednisone in Setting of Drug-Induced Liver Injury(DILI)

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Introduction: Abiraterone, a CYP17A inhibitor used in the treatment of castration-resistant prostate cancer(CRPC), is prescribed with concurrent glucocorticoids(GC) to prevent secondary mineralocorticoid excess(SME). We hereby describe a case of refractory hypokalemia in setting of abiraterone-induced SME despite prophylactic GC.

Case Description: A 70-year-old male with CRPC on abiraterone 1g and prednisone 5mg daily, presented with jaundice, fatigue and hypertension. Workup revealed hyperbilirubinemia, transaminitis and profound hypokalemia.Liver biopsy demonstrated DILI. Abiraterone was thus discontinued. Hypokalemia persisted despite aggressive repletion with up to 320mEq KCl daily. Deoxycorticosterone elevation confirmed abiraterone-induced SME. Increased dosage of prednisone to 40mg daily and addition of eplerenone led to prompt normalization of potassium and blood pressure. Darolutamide was started after DILI resolution for CRPC treatment.

Discussion: Abiraterone's antitumor effect lies in reduction of androgen production by CYP17 inhibition. Excessive deoxycorticosterone/corticosterone accumulation, driven by reactive rise in corticotropin, may manifest as hypokalemia, hypertension or fluid retention. GC coadministration serves to mitigate SME. SME in this case may be explained by:1)Liver injury:Pharmacokinetic studies have shown increased systemic abiraterone exposure in liver impairment up to 3.6 folds, necessitating dose reduction or drug discontinuation. Severe liver impairment causing decreased availability of hepatic 11β-HSD1 may also drive down conversion of prednisone into its active form prednisolone, removing negative feedback to corticotropin.2)Prednisone 5mg BID or dexamethasone 0.5mg daily has shown superiority to prednisone 5mg daily(in this case) for SME prevention, at expense of greater weight gain and insulin resistance. Eplerenone can be used in addition to GC in SME treatment and may be noninferior to GC as steroid sparing preventive option. Spironolactone should be avoided due to its affinity to androgen receptor. It is prudent to monitor for medication adjustment as SME resolves.

Hormones	Reference Values	Results
ACTH *(pg/dl)*	6-76	16 (non-suppressed)
Cortisol *(ng/dl)*	6-23	5.4
Deoxycorticosterone *(ng/dl)*	3.5 – 11.5	42
Renin/Aldosterone *(mcg/dl)*	2- 17	< 2.1
Aldosterone *(ng/dl)*	2-9	8.5
Urine potassium *(mEq)*	< 20	65.6 (**potassium repleted during sampling)*
Urine Creatinine *(mg/dl)*	20 -275	67.6
24 hours urine potassium *(mEq)*	25 – 125	192
Creatinine *(mg/dl)*		0.9 – 1.1 at baseline

PO1849

Characteristics and Outcomes of Cancer Patients with Severe Hyponatremia

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Background: Hyponatremia is the most common electrolyte disorder in cancer patients and associated with poor prognosis in several types of cancer. Severe hyponatremia (serum sodium < 120 mmol/L) is linked to increased hospital length. We conducted this retrospective study to evaluate for clinical and laboratory characteristics of cancer patients with severe hyponatremia.

Methods: Medical records from previous 2 years at Chulabhorn hospital were reviewed. Cancer patients who had serum sodium less than 120 mmol/L were included. Clinical data, including symptoms, causes of hyponatremia, treatments, response to treatments and survival rate, were recorded.

Results: A total of 154 patients with cancer and severe hyponatremia were identified. 147 patients (95.5%) had solid malignancy. Only 7 patients (4.5%) had hematologic malignancy, all of which were lymphoma. The most common solid malignancy was hepatocellular carcinoma (14.9%), followed by lung cancer (14.3%) and pancreatic cancer (10.4%). Interestingly, 36.3% of patients were asymptomatic despite severe hyponatremia. Of 98 patients that were symptomatic, the most common symptom was fatigue (30.5%), followed by nausea/vomiting (26.0%) and alteration of consciousness (19.5%). Seizures were present in only 3 patients (1.9%). The most common cause of hyponatremia was volume depletion (83.8%), which was mostly due to poor intake. Syndrome of inappropriate antidiuresis (SIAD) was the cause of severe hyponatremia in only 7 patients (4.5%). Most of our patients (76.0%) were treated with isotonic saline infusion and 83.8% of which responded with significant improvement in serum sodium level. Hypertonic saline infusion was given in only 27 patients (17.5%). Survival rate at 30 days was 46.1% and survival rate at 90 days was 26.6%.

Conclusions: Our data demonstrated that the most common cause of severe hyponatremia in cancer patients was volume depletion from poor intake, in contrast to SIAD which was suggested by other previous studies. In addition, most patients in our cohort responded to isotonic saline infusion. Fluid restriction and diuretic/aquaretic drug administration, presuming that patients have SIAD, may worsen the serum sodium level in these hypovolemic cancer patients. This study emphasized the importance of clinical evaluation and investigation for cancer patients with severe hyponatremia to achieve the correct diagnosis and provide proper management.

PO1850

Novel Use of Daratumumab for Post-Hematopoietic Cell Transplant Membranous Nephropathy

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Introduction: Membranous nephropathy (MN) is the most common cause of glomerulopathy after hematopoietic cell transplantation (HCT), usually seen with graft versus host disease (GVHD). Although remission frequently occurs upon immunosuppression, 20% of patients fail to respond and may progress to end stage renal disease. Here we report the rapid remission of a treatment resistant patient with daratumumab (Dmab).

Case Description: A 16 year old female 1 year post-HCT for beta thalassemia major was started on ruxolitinib for oral GVHD. Three months later, she developed nephrotic syndrome. Renal biopsy showed MN. Serum and renal tissue were negative for PLA2R antibody. Ruxolitinib was changed to ibrutinib in case MN was medication induced. She was treated with tacrolimus (trough 3 – 8 ng/mL), prednisone, losartan, atorvastatin, and 4 weekly rituximab infusions. Eight months into therapy, she failed to meet criteria for even partial remission. The toxicity of additional steroids and/or cyclophosphamide was undesirable. With 0% CD19 cells, rituximab was not indicated. Thus, plasma cell depletion with Dmab was trialed. Dmab was given at weeks 1, 4, and 17. Her nephrotic syndrome resolved and her serum albumin was greater than 3.0 gm/dL by week 10. She weaned off of steroids and tacrolimus by week 16, at which time she had near-complete remission of her renal disease. Trialed off of losartan week 16 – 17, but protein excretion increased, so it was restarted. Time course and biomarkers of MN are in Figure 1.

Discussion: The mechanism of HCT-associated MN is incompletely understood. Its association with GVHD and often successful treatment with rituximab have implicated direct or indirect humoral activation as potential pathogenic mechanisms. The success of CD38 depletion with Dmab may implicate alloantibody production by resident plasma cells as a driver of refractory disease. Dmab may be a novel therapeutic option for HCT patients who are not responsive to traditional MN therapy.

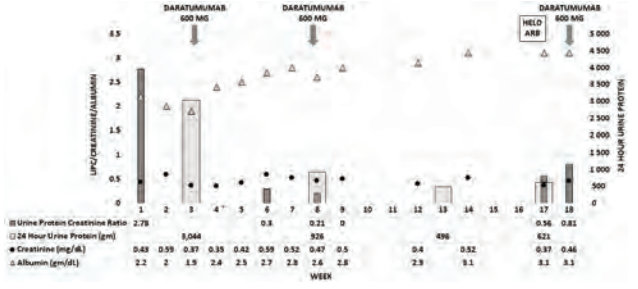

Figure 1: Time course and biomarkers of MN after Dmab. *Urine collection 15 hours

PO1851

M2-Like Macrophages in Injured-Kidney Cortex Promoted Kidney Cancer Progression via the Inhibition of CD8 T Cell Infiltration

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Background: Chronic kidney disease (CKD) affects mortality of the cancer patients, especially kidney cancer. However, the biological mechanism remains unknown. Recently, several studies showed that M2-like macrophages had pro-tumor in the tumor effects as well as pro-fibrotic roll in the injured kidney. We aimed to assess the effect of M2-like macrophages in the injured kidney on kidney cancer progression.

Methods: We injected murine kidney cancer cells on renal subcapsule 14 days after unilateral ischemic reperfusion injury (IRI) or aristolochic acid (AA) administration which were used as an injured kidney model. We evaluated cancer progression 20 days after tumor injection and examined macrophage characteristics and intra-tumor T cell population by flow cytometry. To assess the effect of M2-like macrophages on cancer progression and intra-tumor T cell, we used the adoptive transfer of M2-like macrophages collected from the tumor on IRI-treated kidneys and liposomal clodronate (CL) which removed M2-like macrophages from IRI-treated kidneys. We examined whether the inhibition of T cell infiltration contributed to tumor progression in CL-treated IRI kidneys and sham-treated IRI kidneys by using anti-CD8 or anti-CD4 antibodies.

Results: Kidney cancer on IRI kidneys (IRI-KC) was more progressive than that on sham-operated kidneys (Sham-KC). M2-like macrophages accumulated in the IRI-kidney cortex and IRI-KC. Interestingly, the intra-tumor T cell population decreased in IRI-KC compared to Sham-KC. The same phenomenon was observed in the AA model. T cell function and regulatory T cell infiltration were not different between IRI-KC and Sham-KC. Besides, the adoptive transfer experiment showed that kidney cancer co-injected with M2-like macrophages was more progressive than that with Other-type macrophages and intra-tumor T cell decreased in the M2-like macrophage co-injection group. Contrarily, the CL experiment showed that M2-like macrophage depletion from the IRI-kidney cortex inhibited tumor progression and increased tumor infiltrated CD8 T cell. And CD8 T cell removal after M2-like macrophage depletion abrogated this tumor-inhibiting effect, however, CD4 T cell removal didn't affect tumor progression.

Conclusions: M2-like macrophages in injured kidneys promoted kidney cancer progression through the inhibition of CD8 T cell infiltration.

PO1852

Identifying Patients with CKD Risk at the Time of Partial Nephrectomy

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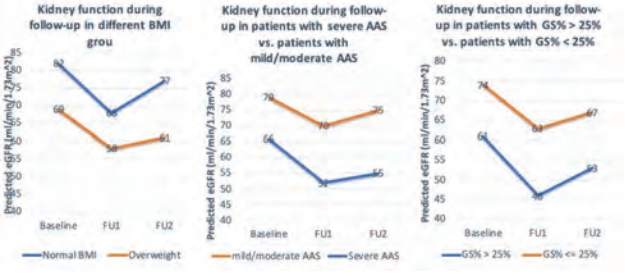
Background: The prevalence of chronic kidney disease is high among kidney neoplasm patients because of the overlapping risk factors. We aim to identify risk factors of eGFR decline in kidney cancer survivors post partial nephrectomy (nx).

Methods: All partial nx patients with neoplasm at Northwell Health were included (2018/7-2020/5, n=187). Clinical and histology parameters, including neoplastic and non-neoplastic pathology, were analyzed. Non-neoplastic assessment includes glomerulosclerosis(GS), interstitial fibrosis and tubular atrophy(IFTA), and a semiquantitative estimate of the severity of arterial and arteriolar sclerosis (AAS). Multivariate linear mixed model was performed. Independent variates included age, sex, hypertension, diabetes, baseline eGFR, tumor diagnosis, proteinuria, GS%, IFTA%, and AAS.

Results: The median follow-up time is 147d. In all patients, independent risk factors of post-nx decreased eGFR were female($p=0.02$), age($p=0.01$), overweight($p<0.001$), eGFR<90 at the time of nephrectomy($p<0.001$), severe AAS($p<0.01$), and prolonged follow-up. In the ones with baseline eGFR≥90(n=61), proteinuria($p<0.001$) and BMI($p<0.001$) were independent risk factors of post-nx decreased eGFR. For every 1 kg/m^2 increase in BMI, there is a 3.3, 3.8, and 3.7ml/min/1.73m^2 decline of eGFR at baseline, within 3 mo post-nx, and longer follow-up. For every 100mg/dl increase in urine protein, there is an 11.4, 17.3, and 19.5ml/min/1.73m^2 decline of eGFR at baseline, within 3 mo post-nx, and longer follow-up. In patients with baseline eGFR<90ml/min/1.73m^2(n=126) longer follow-up, severe AAS($p=0.02$), GS%>25%($p=0.02$) and overweight ($p=0.03$) were independent risk factors of decreased post-nx eGFR. eGFR time trend of patients with and without these risk factors is shown in the figure.

Conclusions: We propose a minimum workup for this population to include eGFR, urinalysis, and non-neoplastic pathology evaluation. The time of kidney cancer treatment may be a unique opportunity for these patients to be identified and directed to early interventions, including nephrology consults and patient education on nutrition and weight control.



PO1853

Development of 3D Renal Cell Carcinoma Organoids and Cancer Invasion Assay

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Background: Recent advances in *in vitro* 3D culture technologies, such as organoids derived from hPSCs, have opened new avenues for development of human disease models. Modeling cancer by utilizing cancer organoids provides advantages as they maintain 3D cell-cell interactions, heterogeneity, microenvironment, and drug response of the sample they originate from. Such preclinical models are essential for more efficient translation of cancer research into novel treatment regimens for patients. 5-year survival rate at advanced stage IV RCC is less than 10%, as RCC is also notorious for resistance to chemotherapy and radiation therapy. Therefore, development of effective tools for better understanding and drug screening for RCC are needed. Kidney cancer organoids and novel assays such as cancer invasion assays can be useful tools to personalize potential therapeutics.

Methods: Primary kidney cancer cell lines were generated from patient biopsy samples. 3D kidney cancer organoids and non-cancer kidney organoids for cancer invasion assay were generated from primary kidney cancer cell lines and hPSCs, respectively, by modifications of our laboratory's prior published kidney organoids techniques. Organoids were characterized by immunostaining. Upon maturation, organoids were added onto the non-cancer kidney organoids and incubated together for the invasion assay with or without treatment with drugs. Frozen sections and imaging were utilized to examine the cancer invasion. Kidney cancer organoids were treated with various drugs to investigate efficacy in reduction or inhibition of the invasion.

Results: RCC cancer organoids showed significantly better expression of kidney cancer markers such as KIM-1, HIF-1α, HIF-2α, and CAIX9 compared to 2D primary RCC cells. Addition of the cancer organoids to normal kidney organoids led to invasion of the cancer organoids into the normal kidney organoids within 3 days. Treatment of the cancer organoids by the receptor tyrosine kinase inhibitor, sunitinib or the histone acetyltransferase inhibitor (A-485) showed reduction in efficacy of cancer invasion.

Conclusions: Development and use of cancer invasion assay for renal cell carcinoma utilizing kidney cancer and normal kidney organoids could lead to better understanding of cancer invasion and provide the capability to screen and profile for identification of potential treatment options in renal cell carcinoma.

Funding: NIDDK Support, Other NIH Support - NCATS, T32

PO1854

Multi-Omics Approach to Uncover Underlying Biology of Low-Risk Clear Cell Renal Cell Carcinoma Patients with Progressive Disease

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Background: Renal Cell Carcinoma (RCC) constitutes approximately 3 % of all cancers and its incidence is rising worldwide, especially in Western countries. In the last two decades, enormous advances have been made in the development and implementation of medical therapies for metastatic ccRCC, however, surgery still represents the only curative option. One of the issues in developing a curative medical therapy lies in the high degree of inter,- and intra tumor heterogeneity. We believe that by applying multi-omics technology to highly specific subgroups and comparing them to closely matched controls we can mitigate the heterogeneity issue and deepen our understanding one step and subgroup at the time.

Methods: We assembled a cohort of ccRCC patients (n=443) and identified all "low-risk" patients which later developed progressing tumours (n=8). Subsequently we performed genome-wide expression profiling, miRNA profiling and proteomics profiling from formalin-fixed samples obtained at initial surgery from these "low-risk" patients and 16 matched patients not progressing to recurrence with metastasis. The patients were matched for Leibovich sore, creatinine, age, sex, tumor size and tumor stage.

Results: Pathway analysis yielded differences between progressive and non-progressive patients in categories such as Molecular Mechanisms of Cancer, B Cell Receptor Signaling in mRNA data and Acute Phase Response Signaling and FXR/RXR Activation in proteomics data. By integrating our three -omics analysis we revealed that acute Phase Response Signaling also plays a role on all three levels. Additionally, we developed a 14-component classifier, drawing from both mRNA, miRNA and protein-based data that reliably differentiated the different subgroups. We further examined the correlations between each of the components and uncovered a dense network of interactions.

Conclusions: Multi-omics methods represent an important tool in furthering our understanding renal cancer biology in the pursuit of medical therapies.

PO1855

TMEM27 Expression and Clinical Characteristics and Survival in Clear Cell Renal Cell Carcinoma

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Background: Transmembrane protein 27 (TMEM27/collectrin), a glycoprotein and homolog of angiotensin-converting enzyme 2 (ACE2), is a regulator of renal amino acid uptake in the proximal tubule and may have a protective role in hypertension. Two previous reports have shown that the absence of TMEM27 expression in clear cell renal cell carcinoma (ccRCC) correlates with poorer cancer-related survival. Here we report our findings of TMEM27 expression in ccRCC and clinical outcomes.

Methods: We conducted a retrospective analysis to identify all cases of ccRCC diagnosed between 2010 and 2015 at the University of Rochester Medical Center. The intensity of TMEM27 immunostaining on tumor tissue was semi-quantitatively graded on a scale of 0, 0.5, 1, 1.5, 2, 2.5, and 3 by a single pathologist, and correlated with tumor characteristics and survival.

Results: There were 321 cases of ccRCC. There was evidence of metastasis at time of nephrectomy in 36 (11.2%), and at the latest follow up in 70 (21.8%), and 82 (25.5%) died as of Spring 2021. TMEM27 staining intensity correlated inversely with various tumor characteristics (Table 1). Kaplan-Meier survival analysis showed worse all-cause mortality for tumors without any TMEM27 staining (0) compared to 0.5 or higher, p = 0.02 by log-rank test.

Conclusions: The absence of TMEM27 expression is associated with more aggressive tumor characteristics and poorer all-cause mortality in ccRCC. TMEM27 may be a useful biomarker to assess cancer prognosis. Further studies are needed to better assess if TMEM27 is protective in RCC.

Table 1: Correlation between TMEM27 Staining and Clinical Characteristics

Clinical Characteristic	r value	p-value
Tumor size	-0.191	<0.001
TNM stage (pTx)	-0.145	<0.01
TNM stage (Nx)	-0.152	NS
Fuhrman grade	-0.187	<0.001
Sarcomatoid rhabdoid present	-0.073	NS
Large vessel venous invasion	-0.113	<0.05
Lymphatic invasion	-0.072	NS
Metastasis at time of nephrectomy	-0.126	<0.05
Metastasis at follow-up	-0.094	NS
Composite	-0.201	<0.001
Composite with death	-0.202	<0.001

NS: Not Significant, TNM: Tumor, Node, Metastasis

PO1856

Role of miR-23b and miR-133a in Apoptosis Control Induced by TRAIL in Lung Adenocarcinoma and Kidney Carcinoma Cell Lines

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Background: Lung and kidney cancer are often diagnosed as advanced disease and frequently become resistant to systemic therapies. Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) binds to TRAIL receptor 1 and 2 (TRAILR1/R2) on the cell surface to stimulate apoptosis, making TRAIL apoptotic pathway a promising target for cancer therapy. Cullin-3 ubiquitination is essential to TRAIL receptors activation. However, resistance to TRAIL is an obstacle to achieve an effective anti-tumoral therapy. One of the mechanisms that lead to TRAIL resistance appears to be dependent on translocation, mediated by clathrin (CLTA), of TRAIL receptors to the nucleus. MicroRNAs (miRs)-23b and -133a may have relevant role in TRAIL resistance.

Methods: A549 and CaKi-2 cell lines and their respective controls (MRC-5 and HK2) were used. mRNA expressions of miR-23b, miR-133a, TRAIL-R1/R2, CUL3, CLTA Apaf-1 and KPNA-1 were estimated by RT-qPCR. MTT assay was used to evaluate the effect of TRAIL-induced cytotoxicity. TRAIL receptors celllular distribution was determined by western blot.

Results: Both cell lines were TRAIL resistant on MTT. TRAIL-R1 and TRAIL-R2 were predominantly located in nuclear compartment of A549 cells. TargetScan showed that miR-23b targets CUL3, Apaf-1 and KPNA-1 and miR-133a targets CLTA. MiR-23b expression was upregulated in A549 and CaKi-2 cells. MiR-23b inhibition upregulated CUL3 expression in A549 cells. In contrast, miR-133a was undetectable in both cell lines. TargetScan was used to determinate potential mRNAs targets for miR-23b and miR-133a.

Conclusions: MiR-23b expression was upregulated in A549 and CaKi-2 cells. However, supposed miR-23a target mRNAs were unchanged suggesting no relationship between miR-23a and those molecules. MiR-23b inhibition upregulated CUL3 expression in A549 cells, which could enhance TRAIL receptors activation and sensivity- this will be investigated in next step. In contrast, miR-133a was undetectable raising the hypothesys of an increased capacity of cells to translocate TRAIL receptors to the nucleus via clathrin and thus be resistant to TRAIL. The possible miR-133a ability to reduce clathrin expression may represent a novel approach for control of TRAIL apoptotic pathway and must be further investigated as a TRAIL sensitizing mechanism.

PO1857

Recapitulating Kidney Angiomyolipoma with Renal Organoids Generated from Tuberous Sclerosis Complex Patient-Derived Induced Pluripotent Stem Cells

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Background: Angiomyolipomas (AMLs) constitute 80% of the renal lesions found in patients with Tuberous Sclerosis Complex. AML can cause kidney failure and lead to premature death due to the formation of vascular aneurysms that are prone to spontaneous bleeding. Key aspects of the pathobiology of AMLs, and most remarkably the cell(s) type(s) and developmental mechanisms that give raise to the lesions, remain unknown. Previous efforts to recapitulate AML experimentally using transgenic mice have failed to produce reliable models of AMLs, precluding our ability to study tumor mechanisms and develop novel therapies.

Methods: We directed the nephric differentiation of a series of TSC patient-derived iPSC lines that included a line carrying a heterozygous microdeletion in the *TSC2* locus (*TSC2*$^{+/-}$), a TALEN-engineered isogenic cell line carrying microdeletions in both *TSC2* alleles (*TSC2*$^{-/-}$) and a cell line in which the original mutation present in the patient was corrected using CRISPR-Cas9 (*TSC2*$^{+/+}$).

Results: We derived renal organoids from isogenic TSC2$^{-/-}$, TSC2$^{+/-}$ and TSC2$^{+/+}$ iPSCs. Flow cytometry analysis of kidney organoids derived from TSC2$^{-/-}$ hiPSCs but not from isogenic TSC2$^{+/-}$ or TSC2$^{+/+}$ hiPSCs were enriched in ACTA2^{+} cells, a percentage of which (~24%) co-expressed melanocyte markers including premelanosome protein (PMEL), melanin A (MLANA) and cathepsin K (CTSK) indicative of a myomelanocytic phenotype that is a hallmark of kidney AMLs. Morphologically, ACTA2^{+} cells found in *TSC2*$^{-/-}$ organoids had a plump myoid morphology that matched the well-characterized morphology of kidney AML cells. Whole transcriptome RNA sequencing (RNA-seq) of *TSC2*$^{+/-}$, *TSC2*$^{+/+}$ and *TSC2*$^{-/-}$ organoids identified *MLANA, PMEL, GPNMB, MITF, CTSK* and *ACTA2* as genes that were exclusively upregulated in *TSC2*$^{-/-}$ organoids, confirming the myomelanocytic phenotype of *TSC2*$^{-/-}$ AML organoids. Hallmark gene sets enriched in expression in *TSC2*$^{-/-}$ renal organoids in each comparison included IL6-JAK-STAT3 signaling, adipogenesis, angiogenesis, fatty acid metabolism, KRAS signaling and estrogen response, as major pathways shared with kidney AMLs.

Conclusions: Collectively, our findings support the notion that AMLs originate from cells of the renal lineage and suggest a central role for *TSC2* loss-of-heterozygosity (LOH) genetic mechanisms in the etiology of AML.

Funding: NIDDK Support

PO1858

Characterization of Wilms Tumor and Human Fetal Kidney Using Spatial Transcriptomics

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Background: Growing evidence links Wilms tumor (WT) to aberrant nephrogenesis. Studies highlighted the genetic complexity of WT, but little is known about the molecular mechanisms that regulate WT development. Using Spatial transcriptomics (ST), which allows analysis of the gene expression based on morphological context, we showed important differences between WT subtypes and defined the interactive gene networks involved in WT development using human fetal kidney (hFK) as reference.

Methods: Using Visium 10x Genomics, we generated spatial maps of gene expression in human fetal kidney (hFK) andfavorable (stage III) and unfavorable (stage I) WTs. Data were analyzed using Space Ranger software v1.0.0, Seurat v3.2, Panther V14, and Loupe Cell Browser and further analyzed against our previously generated bulk/sc-RNA seq data on the same samples.

Results: ST identified specific clusters in hFK that closely recapitulated the developmental stages of normal nephrogenesis (nephrogenic zone, glomeruli, tubules, and stroma). Unfavorable WT and favorable WT clusters showed heterogeneity of the tumor landscape (blastema, epithelium, and stroma and non-renal phenotypes). Blastema in WT favorable vs. WT unfavorable, though histologically identical, presented different transcriptomics profiles. WTs also showed gene expression typical of muscle tissue (or other non-renal phenotypes) rather than mature kidney structures, which correlated with the histologic absence of mature tubules and glomeruli. Comparative RNA-seq analysis identified cells expressing SIX2 and CITED1 as the root cells of the origin of the WT. Unfavorable WT expressed a higher level of CITED1 in blastema foci and higher expression of uncommitted genes and modulation of inductive nephrogenic signals like WNT and FGF. We also identified genes expressed specifically in WT subtypes and performed a preliminary characterization of the immune milieu of WT.

Conclusions: The spatiotemporal mapping combined with different transcriptomic data highlighted the heterogeneity of the WT subtypes confirming uncommitted nephron progenitors as driving the development of WT. We identified genes that may allow for better stratification of WT and potential therapeutic targets for distinct WT subtypes.

Funding: Private Foundation Support

PO1859

Recurrent Renal Cell Carcinoma Post Renal Transplantation

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Introduction: Renal Cell Carcinoma (RCC) can occur in renal transplant recipients (RTR). RCC recurrence post nephrectomy occurs in 20-40% of non-transplant(Tx) patients and in less than 15% of RTR. The median survival for patients with metastasis is 6-12 months with 5 year survival less than 10%. We present 3 RTR who developed recurrent RCC post-Tx.

Case Description: RTR1 was 61 years old and received a deceased donor kidney Tx (DDKTx) for IgA nephropathy. He was induced with thymoglobulin. Immunosuppression(IS) included Mycophenolate Mofetil (MMF), Tacrolimus (FK), and steroids (S). 8 years pre-Tx, a 2.5cm RCC lesion was found in the R native kidney, and he underwent nephrectomy. 1 year later, he developed BK viremia, and IS was changed to Everolimus and S. 2 years post-Tx, RCC metastasis was detected only in the pancreas head and tail. Treatment involved tyrosine kinase inhibitors(TKI) and VEGF inhibitors without resolution; he died within 2 years of RCC recurrence with a functioning allograft. RTR2 was 56 years old and received a DDKTx, secondary to ADPKD. IS involved MMF, Cyclosporine, and S. History was significant for L nephrectomy 3 years pre-Tx for RCC. 1 year later, she had a R nephrectomy for RCC. Both lesions were small and renally limited. 10 years post Tx, she presented with recurrent RCC in the pancreas and thyroid. Treatment involved change in IS to Sirolimus and Azathioprine. No other treatment was taken by the patient. She died 4 years later with a functioning allograft. RTR3 is a 54 year-old who received a living, related renal Tx for CKD stage 5. IS included MMF, FK, and S. 8 years post-Tx, he was diagnosed with an 8cm RCC lesion of the L native kidney and underwent nephrectomy. After a 6 year tumor free interval, RCC recurred only in the lungs and lymph nodes. He received IS reduction and TKI with progression of disease to bone metastasis. His current treatment involves TKI with Denosumab, and he still has a functioning allograft.

Discussion: Our cases demonstrate that RCC recurrence occurs at variable time points post-Tx and can present aggressively in RTR with poor outcomes. We suspect that recurrent disease arises from micrometastatic tumor cells that escape immune surveillance. RTR with a history of RCC prior to Tx should be monitored closely for metastatic recurrence post Tx.

PO1860

Impact of ESKD on Overall and Cancer-Specific Mortality in Patients with Localized Prostate Cancer (PCa): A Retrospective Cohort Study of SEER-Medicare

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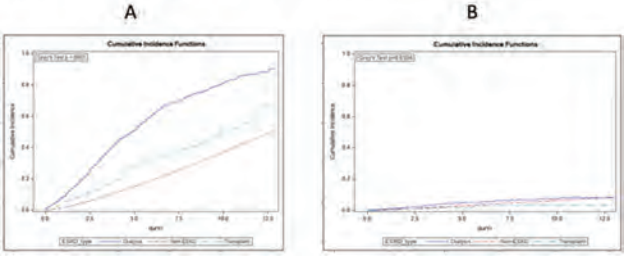
Background: Our objective was to compare overall and PCa specific mortality between ESKD and non-ESKD patients with localized PCa.

Methods: Study participants were male patients, who were diagnosed with localized PCa between January 1st 2004 and September 30, 2015 (last day of International Classification of Diseases-9-Clinical Modification (ICD-9-CM) use) and were 40 years or older at the time of diagnosis. ESKD status, further stratified into dialysis and kidney transplant (KT) was determined using ICD-9-CM codes. Time to death from any cause was modeled using Cox regression and time to PCa specific death using Fine and Gray competing risk model.

Results: At a median follow up of 6.2 years, 3.5 years and 5.0 years for non-ESKD (N=186,482), dialysis (N=970) and KT (N=413), overall mortality rates were 1.8%, 8.5%, and 4.8% at 1-year, 7.7%, 31.5% and 13.5% at 3-years and 15.2%, 50.8% and 27.9% at 5-years respectively (P-Value: <0.001), Figure 1. In multivariate model, dialysis status was associated with 2.9 times higher hazard of death (HR: $_{2.6}2.9_{3.1}$) and transplant status was associated with 2 times higher hazard of death (HR: $_{1.7}2.0_{2.4}$) compared to non-ESKD group. Rates of PCa specific mortality were 0.4%, 1.1%, and 0.7% at 1-year, 1.6%, 3.1%, and 1.5% at 3-years and 3%, 4.8%, and 2.2% at 5-years for non-ESKD, dialysis, and transplant groups respectively (P-value: 0.04). In multivariate model, dialysis status and transplant status were associated with similar risks for PCa specific death to non-ESKD group, Figure 2.

Conclusions: ESKD patients have excess relative overall mortality but similar PCa specific mortality compared to non-ESKD patients with localized PCa.

Figure 1: Cumulative incidences for overall (A) and prostate cancer specific mortality (B), stratified by ESKD status.



Cumulative Incidence Curves

Table 1: Associations of Overall Mortality and Prostate Cancer Specific Mortality with ESKD (dialysis and KT), Localized PCa (2004-2015)

Model	Outcome	Parameter	Hazard Ratio	95% Confidence Interval	P Value
Univariate	Overall Mortality	Dialysis	4.141	3.818, 4.492	<.0001
		Transplant	1.645	1.398, 1.937	<.0001
	Cancer Specific Mortality	Dialysis	1.278	0.978, 1.669	0.0720
		Transplant	0.601	0.333, 1.084	0.0907
Age Adjusted	Overall Mortality	Dialysis	5.020	4.626, 5.448	<.0001
		Transplant	2.249	1.909, 2.648	<.0001
	Cancer Specific Mortality	Dialysis	1.455	1.110, 1.906	0.0066
		Transplant	0.792	0.437, 1.435	0.4416
Multivariate	Overall Mortality	Dialysis	2.851	2.622, 3.099	<.0001
		Transplant	1.995	1.694, 2.351	<.0001
	Cancer Specific Mortality	Dialysis	1.036	0.781, 1.373	0.8066
		Transplant	0.933	0.510, 1.707	0.8215

Hazard Ratios for Mortality

PO1861

Case of Spontaneous Tumor Lysis Syndrome in Metastatic Prostate Cancer

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Introduction: Tumor lysis syndrome has been described in hematological malignancies mainly where there is a large tumor burden that lyse in relatively short period of time causing a large burden of metabolites that causes AKI. In this case, we will present a case of spontaneous tumor lysis syndrome caused by widespread metastatic cancer prostate which is an unusual cancer to cause such syndrome. That metastasis was mainly to the bone marrow causing a picture of pancytopenia, which also raises the possibility that the tumor lysis syndrome could be due to the breakdown of the cells of the bone marrow rather than the lysis of the prostate cancer cells.

Case Description: 65-year-old male patient presented with altered mental status upper GI bleed, hyperkalemia of 6.2, severe acidosis with bicarbonate of 7 and AKI with a creatinine of 7.32 and BUN of 181, calcium 9.3, phosphorus 7.4, uric acid 41.5, bilirubin of 2.9 and LDH was high at 789, alkaline phosphatase was 345, patient had severe anemia with hemoglobin of 2.6, white count 12,600 and thrombocytopenia with platelet count of 6000. urine analysis showed uric acid crystals. flow cytometry analysis of peripheral blood did not reveal a clonal population of cells or expanded population of blasts. CT scan chest abdomen pelvis suggested diffuse osseous lytic and blastic metastatic lesions. Serum immuno-electrophoresis was negative. PSA level of more than 1400.

Discussion: The severe AKI along with the significant elevated serum uric acid level, and presence of uric acid crystals in the urine sediment, made it highly likely the diagnosis of TLS. The presence of diffuse osseous lesions and a PSA above the level that can be measured were consistent with metastatic prostate cancer as the underlying malignancy. No history of treatment was obtained. TLS in solid malignancies is extremely rare, especially without anti-neoplastic therapy. In this case, the presence of severe anemia and thrombocytopenia were highly suspicious for bone marrow invasion, and possible contributor to TLS. Regretfully, a bone marrow biopsy couldn't be obtained before patient expired. Conclusion: TLS can be caused by solid cancers like prostate cancer if it is widely metastasized. Bone marrow extension with lysis of bone marrow cells maybe a contributing factor.

PO1862

Overlooked and Unanticipated: Life-Threatening Hypocalcemia due to Denosumab in a Patient with Prostate Cancer

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Introduction: Denosumab is a monoclonal antibody that inhibits osteoclast-mediated bone resorption by binding to receptor activator of NF-κB ligand, which is upregulated by tumor cells. Despite FDA warning, insidious and severe onset hypocalcemia is a malignant and overlooked complication in patients with advanced CKD.

Case Description: A 77-year-old man with a history of prostate cancer and CKD stage 4 presented to the ED with tremors and numbness in both arms along with perioral dysesthesias. In addition to furosemide and metoprolol, he received his first dose of denosumab 2 weeks prior to presentation, indicated for bone metastasis. Physical examination was remarkable for the Chvostek sign and delayed reflexes in the upper and lower extremities. Lab results were as follows: Na 136 mEq/L, K 4.4 mEq/L, HCO3: 6.4 mEq/L, Cr: 4.8 mg/dL, PO4: 6.1 mg/dL, Ca: 4.8 mg/dL, Mg: 2.6 mg/dL & albumin: 3.5 g/dL. Further studies showed: 25-OH vitamin D: 6.5 (<25 ng/mL), iPTH: 988 (10-55 pg/mL), C-telopeptide: 167 (40-465 pg/mL), ALKP: 243 (44-147 iU/L). Urine calcium-to-creatinine ratio was 0.04, suggestive of minimal calcium excretion. ECG showed prolonged QTc. Given the clinical evidence of severe hypocalcemia and ECG changes, the patient was started on peripheral calcium infusion with hourly iCa2+ measurements to maintain iCa >1 mmol/L and reversal of QTc prolongation. Concomitantly, the patient was treated with calcium carbonate 2500 mg TID, ergocalciferol 50,000 units weekly, and calcitriol 0.5 mcg BID. After 72 hours, his ionized calcium levels stabilized with aggressive oral therapy only. Serum calcium at discharge was 8.2 mg/dL and remained low in the range of 7.5-8.9 for the following 8 weeks.

Discussion: Denosumab has a prolonged elimination half-life (up to 32 days) and therefore, it can induce severe & relapsing hypocalcemia, especially in patients with low vitamin D stores. While patients with creatinine clearance <30 mL/min have been found to be prone to adverse effects, no dose modification has been considered for this therapy. Close monitoring within 14 days after the administration of denosumab and prophylactic therapy with oral calcium and vitamin D could be anticipated in this population.

PO1863

Impact of CKD on the Nutritional Status of Patients with Cancer

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Background: Cancer patients routinely live with impaired nutritional status and other comorbidities. There are few prospective data on the impact of chronic kidney disease (CKD) on the nutritional aspects of patients with cancer.

Methods: Patients with solid cancer, admitted for treatment at a cancer hospital in Brazil (Instituto do Câncer do Estado de São Paulo) were prospectively evaluated between April2015 and October2017. Patients underwent a nutritional evaluation including subjective global assessment produced by the patient(PG-SGA), anthropometry(Arm Muscle Area-AMB, weight, height) and electrical bioimpedance(BIA). Sarcopenia was defined as a fat-free mass index(BIA) ≤17.4kg /m² for men and ≤15kg/m² for women. Measurement of the glomerular filtration rate was determined through plasma clearance of ^{51}Cr-EDTA (mGFR). CKD was classified according to the KDIGOguidelines based on mGFR indexed for body surface area.

Results: Six hundred and ninety-six pts were enrolled. Patients were 60(51-67) years, 51.9% male. The most common cancer sites were breast(26.3%), prostate(20%), and gastrointestinal(12.2%). A total of 14.7% had metastatic disease, 94.9% ECOG 0or1. Median mGFR was 81.1(66.7-94.6), with 55.7%, 32.8% and 11.5% presenting mGFR G1, G2 and G3, respectively. When compared to patients with mGFR G1, patients with mGFR G2 and G3 had a higher frequency of malnutrition by PG-SGA and BMI, and a higher proportion of muscle deficit according to AMB. In addition, fat free mass deficit, sarcopenia and lower phase angle values were more frequently observed in mGFR G2 and G3 according to the BIA data(Table1).

Conclusions: In patients with cancer admitted for treatment lower mGFR was associated with worse nutritional status. Therefore, nutritional monitoring in conjunction with the oncology, nephrology and nutritional team is necessary.

Table 1: Association of the Glomerular filtration rate (GRF) according to the KDIGO classification and the clinical oncological and nutritional characteristics

Caracteristics	Overall (696)	G1* (388)	G2** (228)	G3*** (80)	p
Malnutrition PG-SGA****	93 (13.4%)	38 (9.8%)a	35 (15.4%)b	20 (25%)b	<0.001
Anthropometry					
BMI***** (Kg/m²)	27.32 (24.36-30.9)	27.7 (24.84-31.57)	26.99 (23.96-29.74)	26.44 (23.71-30.63)	0,010
Low weight	59 (8.5%)	19 (4.9%)a	26 (11.4%)b	14 (17.5%)b	<0.001
Eutrophy	226 (32.5%)	109 (28.1%)a	90 (39.5%)b	27 (33.8%)b	
Overweight	195 (28%)	119 (30.7%)a	60 (26.3%)a	16 (20%)a	
Obesity	216 (31%)	141 (36.3%)a	52 (22.8%)b	23 (28.7%)b	
Muscular area of the arm (cm²)	41 (33-49)	42 (33-50)	39 (32-45.7)	39.5 (32-48.7)	0,007
Reserve low / muscle deficit	68 (9.8%)	27 (7.0%)a	29 (12.7%)b	12 (15.0%)b	<0.001
Electrical Bioimpedance					
Fat free mass (Kg)	48.4 (41.4-57.77)	67.4 (59.6-74.5)	68.4 (59-73.4)	68 (53.9-73.2)	0,008
Deficit fat free mass	113 (16.2%)	52 (13.4%)a	43 (18.9%)b	18 (22.5%)b	0.017
Sarcopenia	110 (15.9%)	41 (10.6%)a	46 (20.2%)b	23 (28.7%)b	<0.001
Phase angle	5.9 (5.2-6.5)	6.1 (5.6-6.7)	5.7 (5.0-6.2)	5.0 (4.5-5.8)	<0.001
< Percentile 5	138 (19.8%)	62 (16%)a	56 (24.6%)b	20 (25%)a,b	0,017

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PO1864

The Impact of a Nutritional-Nephrological Combined Approach (NNCA) on the Metabolic Profile and Perceived Quality of Life of CKD Patients

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Background: Nutritional therapy (NT) based on controlled protein intake represents a cornerstone in the management of CKD. However the international guidelines do not precisely define an adequate protein intake for onco-nephrological patients. Aim of our study is to investigate the impact of a low-normal protein diet on metabolic profile and quality of life in CKD pts affected (CS) or not (CT) by urological non-metastatic malignancies treated with a NNCA.

Methods: 103 pts were enrolled in the Urological Department at San Raffaele hospital between 2018 and 2020, screened for absence of malnutrition and administered a conventional CKD protein-controlled diet (0,7-1 g/Kg/die, 30-35 kcal/ Kg/die) including aproteic foods. Anthropometrical outcomes, lab test exams and clinical variables were examined at baseline and after 6 months. To evaluate the impact of the NNCA on perceived quality of life, a QoL-Short Form36 (SF36) questionnaire were administered to pts.

Results: The combined treatment produced eGFR and urea parameter improvements (49% of pts improved eGFR, 65% uremia) without negatively altering the anthropometrical outcomes. The nutritional status was preserved in both groups and all pts had an improvement in **BMI** (CS: 2.8 kg/h²; CT: 1.3 kg/h²) **PA°** (CS: 2.8%; CT: 1.3%), **BCM/h²** (CS: 1.31; CT: 0.38) and **FFM/h²** (CS: 0.1; CT: 2) and a decrease of **WC** (CS: -1.3cm; CT: -1,65cm), and **ECW/ICW** (CS: 0.02; CT: 0.03). The SF36 questionnaire highlighted a good perceived quality of life in subjects treated with the NNCA, even if social activities were negatively affected.

Conclusions: Our study suggests that low-normal protein high calories diet ameliorates the nephrological scenario, the metabolic complications and the nutritional perspective in uro-oncological CKD pts. Following NNCA, perceived quality of life has been pushed towards high scores and does not appear to be influenced by physical health and emotional status. Harsh clinical monitoring and food choice limitations may have increased the perception of the pathological condition, thereby increasing the sense of responsibility in adhering to the NT. All this improves the physical health, but also demotivates pts and worsens their social attitudes.

PO1865

A Rare Case of Calcitriol-Mediated Hypercalcemia in Metastatic Gastrointestinal Stromal Tumor (GIST)

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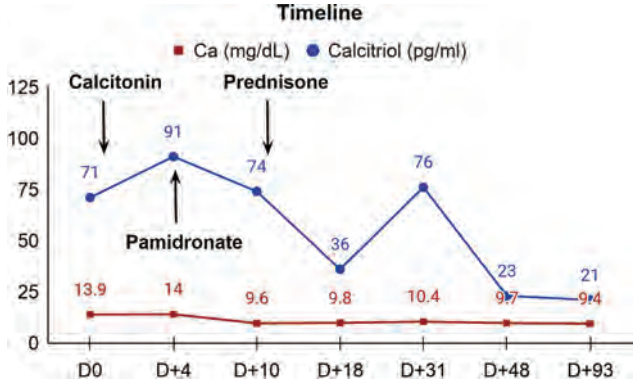
Introduction: Hypercalcemia accompanies 10-30% of malignancies. Calcitriol production accounts for <1% cases, usually with lymphoma, but has been reported with solid tumors.

Case Description: A 62 year old male with GIST with liver involvement was admitted for an elevated calcium (Ca) of 13.9 mg/dL & AKI with creatinine (Cr) 2.2 mg/dL. Diagnosed with GIST 3 years prior, he was treated with imatinib & an investigational mitogen-activated protein kinase enzyme inhibitor. Due to disease progression, he was switched to sunitinib 1 week prior to admission and endorsed taking 100,000 IU of OTC vitamin D tablets daily for perceived immunologic benefits. Further workup showed bland urinalysis & fractional sodium excretion of 2.6%. Renal sonogram was normal. AKI was ascribed to hypercalcemia-mediated vasoconstriction & renal blood flow reduction. He had an ionized Calcium 6.6 mg/dL (nl: 4.8-5.3 mg/dL), appropriately low PTH & PTHrP 0.9 pmol/L (nl ≤4.2 pmol/L). The 25(OH) vitamin D was reported at >156 ng/mL, then quantified at 240 ng/mL. Calcitriol was elevated at 71 pg/mL (nl: 18-64 pg/nL). Etiology of hypercalcemia was thought to be from excess vitamin D intake. Cr & Ca improved with hydration, calcitonin & pamidronate. He was readmitted with recurrent hypercalcemia, persistently high 25(OH) vitamin D & calcitriol. Suspected

to be tumor-mediated, prednisone was added to suppress conversion of 25(OH) vitamin D to calcitriol. Over a 3-week prednisone taper, Ca, Cr, 25(OH) vitamin D, calcitriol normalized.

Discussion: In kidneys, 1 alpha hydroxylase converts 25(OH) vitamin D to calcitriol causing Ca retention. This occurs autonomously in lymphomas & granulomatous diseases causing hypercalcemia. Our case is unique as it (a) describes calcitriol mediated hypercalcemia associated with GIST, (b) highlights that hypercalcemia in malignancy can be multifactorial & in our case was from excess vitamin D intake & elevated calcitriol levels.



Timeline of Events

PO1866

Kidney Pathology Findings in Patients with AKI Associated with Tyrosine Kinase Inhibitors

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Background: Tyrosine kinase inhibitors (TKIs) are widely used targeted cancer therapy as they play a critical role in the modulation of growth factor signaling. Nephrotoxicity associated with TKIs can lead to interruption of therapy. However, the literature on the kidney pathology associated with TKIs nephrotoxicity is limited. Here, we present our center observation of tubular and glomerular lesions attributed to possible TKIs.

Methods: We retrospectively reviewed all cancer patients from 2018 to 2020 who we were treated with TKIs and underwent a kidney biopsy at the University of Texas MDACC.

Results: We identified 13 cancer patients treated with Sunitinib, Cabozantinib, Lenvatinib, Regorafenib, Erlotinib, Osimertinib and Ibrutinib between 2018-2020 and developed acute kidney injury (AKI) attributed to possible TKI nephrotoxicity. The median age was 70 (range, 43 to 80) and the median time to develop AKI was 4 months (range, 1 to 58 months) of starting TKI. AKI was severe (stage ≥3) in 6 patients, among which 4 required hemodialysis. Most of the patients had bland urine (7 out of 13) and proteinuria was observed only in 6 patients. Thrombotic microangiopathy (TMA) was the most common pathological finding followed by acute tubular injury (ATI) as they were observed in 5 and 4 patients, respectively. One patient had proliferative glomerulonephritis, one patient had chronic lymphocytic leukemia infiltration, and one patient had no active lesion. TKIs were discontinued in nine patients, and nine patients had partial kidney recovery. Five patients had disease progression and died within 4 months of AKI.

Conclusions: Our case series has demonstrated that kidney limited TMA and ATI were common pathology findings in patients with suspected TKI nephrotoxicity. Nonetheless, half of patients with TMA were on concurrent checkpoint inhibitor therapy with TKI and half of the patients with ATI had associated sepsis diagnosis. The mechanism is likely multifactorial and possibly related to mTOR and VGEF inhibition leading to endothelial injury, and inhibition of the downstream signaling pathway of MAPK/ERK1/2 leading to ATI. Urine analysis was not predictive of the kidney pathology. Treating nephrotoxicity by discontinuation of the offending TKI was associated with partial kidney recovery, however patients had poor overall prognosis.

PO1867

Renal Pathology in Cancer Patients in a New Era of Treatments

Mónica Bolufer,[1] Clara García-Carro,[2] Maria Jose Soler.[1] On behalf of the GLOSEN/ONCONEFROLOGÍA. *[1]Vall Hebron, Barcelona, Spain; [2]Hospital Clinico San Carlos, Madrid, Spain.*

Background: Classically patients with metastatic cancer were not submitted to invasive procedures because of their short life expectancy. Kidney biopsy(KB) is an especially useful diagnostic and prognostic tool in these patients when they develop kidney injury. The aim of our study is to assess clinical and histological characteristics of patients with active solid organ malignancy that underwent KB in a multicenter cohort

Methods: We performed a multicenter collaborative study. Clinical, demographical and histological date from patients with an active neoplasia or in active cancer treatment who underwent KB were collected. We studied the follow-up of the patients in terms of renal function and survival.

Results: 124 patients with cancer who underwent KB during the study period from 11 hospitals were included.63.7% men, mean age 67(SD ±10.28) years old. The indications of KB were acute renal failure (56.6%), proteinuria (20.2%) and exacerbation of CKD (15.3%). At the time of the KB, 30.6% patients presented diabetes and 63.7% high blood pressure. Malignancies: lung (30.6%), intestinal (27.4%), melanoma (7.3%) and genitourinary(17.7%), with 44.3% metastatic cancer Oncoespecific treatment:35.5% received chemotherapy, 31.4% immunotherapy (of which 26.3% received more than 1 checkpoint inhibitor), 24.2% specific therapies and 3.2% conservative treatment Baseline renal function before KB,16.1% presented Cr>1.5mg/dL. At the time of KB, mean Cr 2.54mg/dL ([1,7-3,9 (IQ 25-75)], urine protein/Cr ratio 895mg/g[275-2610(IQ 25-75)] and 53.2% hematuria KB diagnosis:35.5% acute interstitial nephritis (AIN), acute tubular necrosis(8.9%) and IgA nephropathy(8.1%).65% of patients received corticosteroids for an average of 4.8 months[SD ± 3,9].20.2% required kidney replacement therapy and 36.3% presented Cr>1.5mg/dL at 3 months. Average follow-up 16.23[5.5-32,8(IQ 25-75)] months and 37.9% died at the end of follow-up Metastatic cancer at the moment of KB was identified as an independent risk factor for mortality (p=0.012)

Conclusions: Currently, AIN is the first cause of kidney injury in biopsied patients with active cancer. This is followed by thrombotic microangiopathy, membranous nephropathy and IgA among others. KB in this group of patients provides valuable diagnostic and prognostic information. More studies are needed to expand the consensus in the diagnosis and treatment of oncological patients with renal injury

PO1868

Treatment of PLA2R-Negative Membranous Nephropathy in the Setting of Immune Checkpoint Inhibitor and Renal Cell Carcinoma

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Introduction: Systemic therapy of renal cell cancer (RCC) has undergone major changes over the past decade with the development of targeted therapies such as tyrosine kinase inhibitors (TKIs) and biologic therapies such as immune checkpoint inhibitors (ICIs). Familiarization of the unique nephrotoxicity associated with each treatment is necessary to optimize renal outcomes and cancer care.

Case Description: 57-year-old male with metastatic RCC s/p left nephrectomy progressed after being treated for 16 weeks with the TKI axitinib in combination with pembrolizumab, an ICI targeting PD-1. He subsequently progressed after a 14-week course with second-line cabozatinib (TKI) and was initiated on third-line levatinib (TKI) plus everolimus (mTOR inhibitor) two months prior to presenting with severe diarrhea. Labs were notable for creatinine (Cr) of 2.28 mg/dL (baseline 0.96 mg/dL). CT revealed suspicion for colitis and decreased tumor size of his metastatic disease. Further work-up revealed: 2.87 g on 24 h urine protein, negative anti-GBM and ANCA antibodies, and normal complements. Renal ultrasound showed a hypertrophic right kidney measuring 14 cm in length without obstruction. Due to the broad AKI differential, steroids were empirically started for possible immune-mediated disease, and biopsy was obtained. Pathology revealed membranous nephropathy (MN) with mesangial deposits, PLA2R and THSD7A were negative. With worsening renal function (Cr 3.87 mg/dL) and risk for progression to dialysis, treatment with rituximab (1 g IV D1 and D14) was initiated. Follow-up labs at one month showed Cr 1.50 mg/dL and the patient was restarted on levatinib and everolimus with continued durable response.

Discussion: While TKIs may induce TMA and mTOR inhibitors have been associated with proteinuria and ATN, our patient revealed a unique presentation of secondary MN that was likely induced by his relatively recent ICI therapy. MN can also present as a paraneoplastic lesion, but it is rarely associated with RCC and the presentation did not correlate with his improved CT scan. Given his deteriorating kidney function, treatment with rituximab was fortunately successful and allowed for continued treatment with durable cancer response.

PO1869

Primary Adrenal Insufficiency Secondary to Immune Checkpoint Inhibitors

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Introduction: ICI's are humanized or human immunoglobulin antibodies. Administration of a monoclonal antibody that interrupts the interaction between PD-L1 and PD-L2 and the T-cell PD-1receptor allows tumor-infiltrating lymphocytes (activated T cells) to aggressively identify and destroy cancer cells. However, Use of ICIs can result in toxicity called immune-related adverse events (IrAEs). We present a case of a 55 year old male with history of metastatic malignant melanoma who presented with ICI induced adrenal insufficiency.

Case Description: 55-year-old male PMH of HTN, COPD, Hypothyroidism, metastatic malignant melanoma was recently started Nivolumab presented to the ED with altered mental status and confusion. Laboratory values were notable for hypoglycemic (46mg/dl), hyponatremia (124mmol/l) and borderline High K (5mmol/l), serum osmolality 256 mosm/kg and urine osmolality 538 Mosm/kg. He was initially treated with IV dextrose. Serum cortisol and ACTH were checked to rule out adrenal insufficiency

as etiology for above laboratory abnormalities and history of treatments with ICI (nivolumab). while awaiting these lab results, patient was started on fluid restriction and salt tablets for management of hyponatremia based on available labs at that point which pointed to hypotonic hyponatremia with high urine osmolality pointing to ADH release and goal for correction for sodium level maintained 6-8 Meq for 24hours. Both serum early morning cortisol and ACTH levels were reported to be low with values of 1.4ug/dl and 3.5pg/ml respectively. Patient was subsequently started on IV fluids and IV Hydrocortisone 100 Q8H. Serum sodium level improved at an appropriate rate during the course of hospitalization and serum sodium at the time of discharge was in safe range (136mmol/l). Other peripheral hormones including prolactin, GH, TSH, LH and FSH which were normal. MRI Brain was done to rule out Hypophysitis which revealed normal sella.

Discussion: Long-term follow-up of endocrine irAEs suggests that on occasions thyroid function may recover, but that dysfunction of the corticosteroid and gonadal axis is likely to be permanent. Patients should be informed of the potential adverse events prior to initiation of immune checkpoint inhibitors. Laboratory findings similar to our patient should raise concern for adrenal insufficiency to allow timely diagnosis and management and thus prevent morbidity and mortality.

PO1870

Immune Checkpoint Inhibitors Associated Distal RTA with and Without AKI

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Introduction: As immune checkpoint inhibitors (ICPI) gain popularity as a widely used anti-cancer therapy, unique immune-related adverse events (irAE) are being associated with their use. Hereby, we present two cases that link ICPI therapy to distal RTA, one with and one without AKI.

Case Description: A 73-year-old male with urothelial cancer on pembrolizumab was evaluated for AKI and acidosis. After 5 doses of ICPI therapy, he was noted to have a serum creatinine of 1.8mg/dl (normal baseline) and a serum CO2 of 20mmol/L. Over the next few days, the serum C02 further decreased to 11mmol/L and serum potassium declined to 3.0mmol/L. Further workup revealed a urine pH of 6.5 with a positive urine anion gap. He was diagnosed with likely ICPI-induced AIN with distal RTA and initiated on sodium bicarbonate, potassium citrate, and prednisone 60mg/day. His ICPI was held. After 2 weeks of treatment, his serum creatinine returned to 1.2mg/dl and serum C02 to 22mmol/L. A 46-year-old female was diagnosed with metastatic lung cancer and squamous cell cancer of the right tonsil for which she was initially treated with Carboplatin/Paclitaxol/Pembrolizumab followed by maintenance Pembrolizumab. Almost 3 months after being initiated on ICPI, she was noted to have normal gap metabolic acidosis that gradually worsened to serum CO2 of 15mmol/L along with serum potassium of 2.4meq/L and serum creatinine of 0.6 mg/dl. Further workup showed a urine anion gap of +26, urine osmolar gap of 80, urine pH of 6.0. 24-hour urine citrate was undetectable. Diagnosis of distal RTA secondary to pembrolizumab was made and therapy was held. Steroids were not initiated, as the kidney biopsy, performed within 2 months of holding the therapy, did not reveal any tubulitis or cellular infiltrates. She is being treated with potassium citrate with normalization of acidosis and hypokalemia.

Discussion: We describe two cases of distal RTA presenting as immune related adverse events associated with use of ICPI. AKI presence is not necessary. Prompt recognition and treatment can lead to quick recovery. It has been postulated that a difference in the expression of PD-L1 among the tubular epithelial cells is responsible for isolated distal RTA

PO1871

Immune Checkpoint Inhibitor-Associated Electrolyte Disorders: Query of the FDA Adverse Event Reporting System

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Background: Electrolyte disorders with immune checkpoint inhibitors(ICI) therapy are not well characterized. Single center studies have noted hyponatremia as the most common electrolyte disorder associated with ICI.

Methods: We performed a revised more recent query of the FAERS database with a more detailed look at electrolyte disorders only (search terms: hyponatremia, hypernatremia, hypokalemia, hypercalcemia, hypocalcemia, hypophosphatemia, hypomagnesemia, acidosis, hyperphosphatemia and renal tubular acidosis) from 2011-2021.

Results: A total of 2556 cases of electrolytes disorders were reported to the FAERS system. The most commonly reported abnormality is hyponatremia (53.7%), followed by hypokalemia (18.71%), hypercalcemia (9.65%), hyperkalemia (5.56%) and hypocalcemia at 4.68%. The remaining abnormalities were <4%. In all three groups of the agents (CTLA4 inhibitors, PD and PDL1 inhibitors), the trend remained similar. Most events were reported at a median age of 64 in all 3 groups analyzed. Among reported events, proportions of events in male were statistically more significant ($p<0.01$) than females in all 3 drug groups. Nivolumab (n=1130) and ipilumumab (n=684) had the highest number of patients reported with electrolyte disorders. Hyponatremia persisted as the most common abnormality in each specific drug as well. Hypokalemia and hypercalcemia were faily common. Hyperphosphatemia, hypernatremia, hypophosphatemia along with acidosis made up the least number of cases reported.

Conclusions: Electrolyte disorders are an under-recognized cause of ICI therapy. Hyponatremia, hypokalemia and hypercalcemia seem to be the three most commonly reported events with these classes of drugs.

Medication Group	Reaction	Male (N=1461) n (%)	Female (N=921) n (%)	Missing (N=174) n (%)	Overall (N=2556) n (%)
CTLA-4 Inhibitor(m=684)	Hyponatraemia	216 (31.58)	120 (17.54)	27 (3.95)	363 (53.07)
	Hypokalaemia	55 (8.04)	58 (8.48)	15 (2.19)	128 (18.71)
	Hypercalcaemia	35 (5.12)	25 (3.65)	6 (0.88)	66 (9.65)
	Hyperkalaemia	23 (3.36)	14 (2.05)	1 (0.15)	38 (5.56)
	Hypocalcaemia	19 (2.78)	11 (1.61)	2 (0.29)	32 (4.68)
	Hypophosphataemia	9 (1.32)	9 (1.32)	5 (0.73)	23 (3.36)
	Hypomagnesaemia	7 (1.02)	6 (0.88)	4 (0.58)	17 (2.49)
	Acidosis	7 (1.02)	4 (0.58)	2 (0.29)	13 (1.90)
	Hypernatraemia	1 (0.15)	1 (0.15)	0 (0.00)	2 (0.29)
	Hyperphosphataemia	0 (0.00)	1 (0.15)	0 (0.00)	1 (0.15)
	Renal Tubular Acidosis	0 (0.00)	0 (0.00)	1 (0.15)	1 (0.15)
PD-1 Inhibitor(m=1539)	Hyponatraemia	352 (22.87)	210 (13.65)	37 (2.40)	599 (38.92)
	Hypokalaemia	118 (7.67)	132 (8.58)	21 (1.36)	271 (17.61)
	Hypercalcaemia	157 (10.20)	68 (4.42)	9 (0.58)	234 (15.20)
	Hyperkalaemia	126 (8.19)	47 (3.05)	8 (0.52)	181 (11.76)
	Hypocalcaemia	55 (3.57)	23 (1.49)	4 (0.26)	82 (5.33)
	Hypomagnesaemia	22 (1.43)	27 (1.75)	8 (0.52)	57 (3.70)
	Renal Tubular Acidosis	31 (2.01)	5 (0.32)	4 (0.26)	40 (2.60)
	Acidosis	17 (1.10)	12 (0.78)	1 (0.06)	30 (1.95)
	Hypophosphataemia	13 (0.84)	8 (0.52)	2 (0.13)	23 (1.49)
	Hypernatraemia	14 (0.91)	2 (0.13)	2 (0.13)	18 (1.17)
	Hyperphosphataemia	0 (0.00)	2 (0.13)	2 (0.13)	4 (0.26)
PD-L1 Inhibitors(m=333)	Hyponatraemia	82 (24.62)	54 (16.22)	8 (2.40)	144 (43.24)
	Hypokalaemia	36 (10.81)	42 (12.61)	3 (0.90)	81 (24.32)
	Hypercalcaemia	18 (5.41)	13 (3.90)	1 (0.30)	32 (9.61)
	Hyperkalaemia	21 (6.31)	6 (1.80)	1 (0.30)	28 (8.41)
	Hypocalcaemia	11 (3.30)	6 (1.80)	0 (0.00)	17 (5.11)
	Hypomagnesaemia	7 (2.10)	9 (2.70)	0 (0.00)	16 (4.80)
	Hypophosphataemia	6 (1.80)	4 (1.20)	0 (0.00)	10 (3.00)
	Acidosis	2 (0.60)	2 (0.60)	0 (0.00)	4 (1.20)
	Hypernatraemia	1 (0.30)	0 (0.00)	0 (0.00)	1 (0.30)

Review of the Food and Drug Administration Adverse Event Reporting System database for adverse events related to electrolytes by gender by different medication classes.

PO1872

Immune-Checkpoint Inhibitor Use in Patients with ESKD

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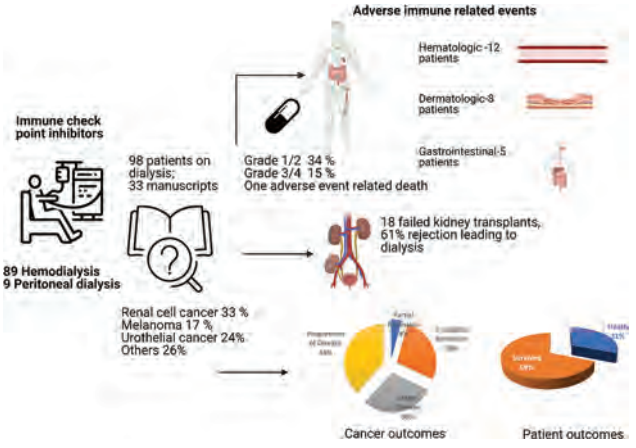
Background: As use of immune check point inhibitor(ICI) therapy becomes increasingly widespread across different types of cancer, their use in patients receiving dialysis is likely to increase.

Methods: We performed a structured search of the MEDLINE and EMBASE databases from inception to February 2021. We sought to identify case reports, case series, observational studies and clinical trials which described the use of ICI therapy for cancer in patients receiving dialysis [either hemodialysis (HD) or peritoneal dialysis (PD)]. For each included study, we performed a standardized patient-level data abstraction using pre-specified parameters of interest: patient demographics, cancer diagnosis, ICI treatment characteristics, dialysis modality, immune-related adverse events (irAE), cancer outcomes and survival.

Results: 136 citations for title and abstract screening were noted. Of these 33 met criteria for inclusion. 98 cases with patient-level data were included. Analysis of the reported cases in the literature demonstrates similar incidence of immune-related adverse events in patients with ESKD receiving dialysis as compared to the general population (49%). Grade 3 and 4 adverse events had been seen in fifteen patients (16%). Cancer remission (complete and partial) was seen in close to 30% of patients. Stable disease was seen in 28% and progression of disease in approximately 36% of patients. One-third of the patients died. Urothelial and RCC represented approximately half of all treated cancers, and accounted for approximately 50% of all deaths reported (**Figure**). Eighteen of the reported dialysis patients had prior kidney transplant. Of these, 11 (61%) initiated dialysis after ICI-related rejection of their kidney allograft.

Conclusions: ICI is well tolerated in ESKD patients. Additional data in the dialysis population with use of ICI, and involvement in prospective studies, is needed to better assess outcomes, particularly within specific cancer types.



PO1873

Methotrexate-Induced AKI: Incidence, Risk Factors, and Recovery

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Background: Data on short and long term renal outcomes after high dose methotrexate (HD MTX) in large adult cohorts using a standardized definition of AKI is lacking. This is a report on the incidence of AKI after HD MTX, renal outcomes when HD MTX is continued after AKI, and long term renal function in patients who survived beyond 5 years after Risk factors for AKI following HD MTX were also examined.

Methods: In this single center retrospective case control study, all adult patients (>18 years) who had received HD MTX (defined as >1g/m^2) from 2003 – 2013 were analyzed. AKI was identified by a ≥1.5x increase in baseline serum creatinine (Cr) within 4 days after HD MTX. We have collected age at first HD MTX, race, cancer, baseline and all Cr values after HD MTX, and cumulative dose (CD) of MTX. Univariable and multivariable logistic regression models were performed with AKI as the dependent variables. Overall survival for patients that had received HD MTX was presented in a Kalpan-Meier analysis.

Results: In a cohort of 865 patients, 32.1% developed AKI. Patients who developed AKI had a lower baseline Cr (0.7 ±0.2 vs 0.9 ± 0.2; p<0.001), a higher eGFR (95.1 ± 21.8 vs 90.0 ± 22.0; p<0.001) and received a higher CD (25,750 (14100 – 35000) vs 20,000 (9425 – 34,300); p<0.01). There was no statistical difference in overall survival among patients who developed AKI (p=0.13) (Figure 1) and those who continued to receive HD MTX after AKI (p=0.32) (Figure 2). Recovery from AKI to within 20% of baseline Cr was associated with a higher probability of survival (p<0.001).

Conclusions: Despite its relatively common incidence in adult patients receiving HD MTX, AKI does not affect overall survival and should not be a barrier to further administration of chemotherapy.

Figure 1

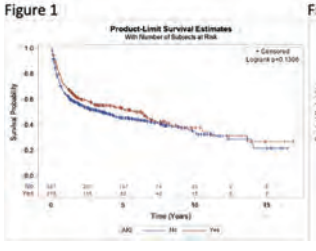
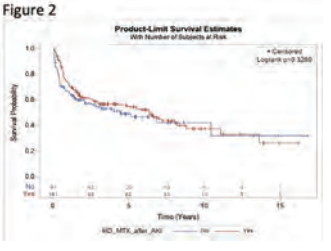


Figure 2



PO1874

Proximal Tubule Dysfunction and Hemophagocytic Lymphohistiocytosis (HLH) Following Use of Novel Immune Checkpoint Inhibitor

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Introduction: Bintrafusp alfa is a bifunctional fusion protein that inhibits transforming growth factor β (TGF-β) and programmed death ligand 1 (PD-L1) currently being studied for treatment of various cancers. Reported adverse effects include rash and hypothyroidism. We present a patient with renal proximal tubule dysfunction manifested by multiple electrolyte derangements after receiving bintrafusp alfa.

Case Description: A 62 year-old male with squamous cell carcinoma of the head and neck refractory to chemotherapy, radiation and proton therapy was admitted for dysphagia, fever and hypotension two weeks after starting experimental immunotherapy with bintrafusp, NHS/IL-12, and PDS101. He developed hypokalemia requiring high dose supplementation, hypophosphatemia, hyponatremia, hypocalcemia, hypoalbuminemia and non-nephrotic range proteinuria. Other labs showed pancytopenia, elevated transaminases, thyroid stimulating hormone, inflammatory markers and anti-glomerular basement membrane antibodies. Work up showed renal potassium, phosphorus and sodium wasting with glomerular filtration rate (GFR) above 75 mL/min. Respiratory distress and hemoptysis concerning for diffuse alveolar hemorrhage led to ICU transfer. Kidney biopsy showed no glomerular injury, linear basement membrane fluorescence, glomerulosclerosis, interstitial fibrosis or immune complex-deposits. Proximal tubules were focally dilated, suggestive of tubular injury. HLH was subsequently diagnosed and treatment with steroids and intravenous immune globulin was followed by electrolyte normalization and improved clinical status.

Discussion: Immune checkpoint inhibitors are increasingly used for cancer treatment. These medications carry risk of immune-related adverse effects. While secondary HLH has been reported with use of immune checkpoint inhibitors, cases are few and renal involvement even rarer. To date there have been no documented cases of secondary HLH with profound electrolyte derangements but normal GFR after receiving bintrafusp alfa. Awareness of these adverse events is necessary as these medications see more widespread use. *The views expressed are those of the authors and do not necessarily reflect the official policy the Department of Defense or the U.S. government.*

PO1875

Utility of Liquid Chromatography in Monitoring Methotrexate Levels After Glucarpidase for Methotrexate Toxicity

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Introduction: Methotrexate (MTX) is an anti-metabolite with a 1,000-fold affinity for dihydrofolate reductase, competitively inhibiting the reduction of dihydrofolate to tetrahydrofolate that is needed for DNA/RNA and protein synthesis. High-dose MTX is defined as a dose higher than 500 mg/m^2 and results in acute kidney injury in 2-12% of patients. Values above 10 μM at 24 h post-infusion confer a high risk for toxicity.

Case Description: A 61 y/o male with newly diagnosed primary CNS diffuse B cell lymphoma was admitted for De Angelis regimen which included MTX 3,500 mg/m^2. His creatinine increased from 0.9 to 3.1 mg/dL despite concurrent hydration, urinary alkalinization, and leucovorin. MTX level was 89 at 24 h, confirming MTX toxicity. He then received a single dose of glucarpidase 50 U/kg IV. Plasma MTX levels remained high at 44, 41, and 14 on post-glucarpidase days 1, 2, and 3. In contrast, high-performance liquid chromatography (HPLC) measurement of MTX was below 0.05 on post-glucarpidase day 2, showing efficacy of glucarpidase in lowering MTX levels.

Discussion: After high-dose MTX, serum levels must be monitored to determine when to administer leucovorin and glucarpidase, a recombinant carboxypeptidase-G2 that cleaves MTX to inactive metabolites. Intrarenal MTX crystallization can 1) obstruct the tubules, 2) damage the tubular epithelium, and 3) vasoconstrict the afferent arterioles. Because volume depletion and acidic urine are major risk factors for AKI, hyperhydration and urine alkalinization are mandatory during high-dose MTX treatment. Early intervention with the combination of leucovorin and glucarpidase is highly effective in patients who develop kidney dysfunction. A single dose of glucarpidase 50 U/kg IV reduces plasma MTX concentration by >97% within 15 mins. Liquid chromatographic measurement of MTX is recommended within 48 hours of glucarpidase administration, as the MTX metabolites 7-hydroxymethotrexate and 4-deoxy-4-amino N10 methylpteroic acid (DAMPA) cross react with standard immunoassays and falsely elevate the level. In our patient, the serum MTX levels were still elevated by immunoassay, while they were undetectable by liquid chromatography. We recommend using HPLC when available to confirm the lowering of MTX by glucarpidase.

PO1876

Cerebral Salt Wasting Caused by High-Dose Methotrexate

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Introduction: Severe acute hyponatremia is a rare complication of high-dose methotrexate (HDMTX) use.

Case Description: We present an interesting case of a 54 year-old man with relapsed diffuse large B-cell lymphoma with central nervous system (CNS) involvement who received a chemotherapy regimen including HDMTX. He received a single dose of 7.2 g of intravenous HDMTX. Baseline serum sodium (Na) was 140 mmol/L. Within 48 hours serum Na dropped to 120 mmol/L and patient developed mild headache and confusion. Laboratory evaluation revealed a urine Na 245 mmol/L, fractional excretion of sodium (FeNa) 2.5%, urine potassium 47 mmol/L and urine osmolality 561 mOsm/kg. Serum tests showed Na 120 mmol/L, chloride 81 mmol/L, osmolality 245 mOsm/kg, uric acid 2.5 mg/dL, TSH 0.6 uIU/mL, cortisol level 15 microg/dL, creatinine 0.6 mg/dL and a low serum ADH level (<0.8 pg/mL). Rest of serum electrolytes were within normal limits. Patient was polyuric and soon became hypotensive and tachycardic. He was treated with a combination of 3% hypertonic saline and oral loop diuretics with subsequent improvement in symptoms, increase in serum sodium and reduced natriuresis.

Discussion: We hypothesize a case of cerebral salt wasting due to the toxic neurologic effect of HDMTX in a vulnerable patient with an underlying CNS tumor. HDMTX has been associated with toxicity to neurosecretory aspects of the cerebrum which may lead to activation of CNS natriuretic peptides which are thought to be responsible for fluid regulation. There are multiple literature reports about cases of subarachnoid hemorrhage, strokes or seizures who developed hyponatremia originally thought to be due to SIADH, but then attributed to stimulation of CNS natriuretic peptides. We did not measure a serum B-type natriuretic peptide (BNP) in our patient, however serum ADH level was low. BNP was initially called brain natriuretic peptide because it was first found in brain tissue.

However, BNP is produced primarily by myocardial cells of the left ventricle in response to stretch. The primary natriuretic peptides of the CNS are thought to be C-type natriuretic peptide and D-type natriuretic peptide, which have been shown to induce natriuresis leading to hyponatremia and suppressed ADH levels, as was possibly seen in our patient. We report this case to allow clinicians to be aware of this possible occurrence.

PO1877

Cisplatin-Induced AKI Cancer Mouse Model Refinement

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Background: Cisplatin (CIS), a common chemotherapeutic, causes acute kidney injury (AKI) in up to one-third of patients. Traditional mouse models use healthy mice and a single, lethal dose of CIS (20-30 mg/kg). This model does not accurately reflect the clinical use of CIS where cancer patients receive 25-100 mg/m^2 once every 3-4 weeks. There is a need for a multi-dose mouse cancer model of CIS-AKI that more closely reflects CIS clinical use.

Methods: C57BL/6 male mice (8 weeks old; n=45) were injected in the right flank with murine lung cancer cells (CMT167; 0-1,500,00 cells). Subcutaneous solid tumors were allowed to grow for ~2 weeks until digital caliper measurement confirmed they were ≥50 mm^3. Mice were then dosed with CIS (0, 12.5, 15 mg/kg) or vehicle (saline) 1x/week for up to 4 weeks. Mice were evaluated for outcomes of general health (body weight), survival, cancer progression (tumor volume), and kidney injury (SCr, BUN, KIM-1). Assessments were performed ≥1x/week until sacrifice after 1-4 weeks of CIS treatment. Analyses for differences from baseline to sacrifice based on both cancer cells injected and CIS dose were assessed by 2-way ANOVA with a Tukey-Kramer post-hoc test. $p<0.05$ was considered statistically significant.

Results: Groups injected with >1 million CMT167 cells experienced the greatest decline in survival due to rapid tumor growth and ulceration (0% at 8 d). Cancer-free mice treated with CIS also experienced poor survival due to dehydration and weight loss (60% at 15 d). Mice injected with 50,000 CMT167 cells had the best survival (100% at 13 d). Body weight was significantly decreased as CIS dose increased ($p=1.9*10^{-8}$) and increased as number of CMT167 cells increased ($p=5.5*10^{-8}$). Tumor volume was significantly increased as number of CMT167 cells increased ($p=5.1*10^{-5}$) and somewhat decreased as CIS dose increased (p=0.092). CIS dose did not significantly impact BUN or SCr levels but an increase in KIM-1 was somewhat associated with an increased CIS dose (p=0.105; 12.5 vs 15 mg/kg CIS p=0.191). There were no significant differences in body weight, tumor volume, or survival between the 12.5 and 15 mg/kg CIS treated mice.

Conclusions: The results indicate that the ideal CMT167 mouse cancer model of CIS-AKI should use 50,000 CMT167 cells and 15 mg/kg CIS. This model can be used to better understand CIS-AKI and to test potential protective compounds.

Funding: Other NIH Support - NIGMS

PO1878

Renal Outcomes in High-Dose Cisplatin in Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A New and Interesting Perspective

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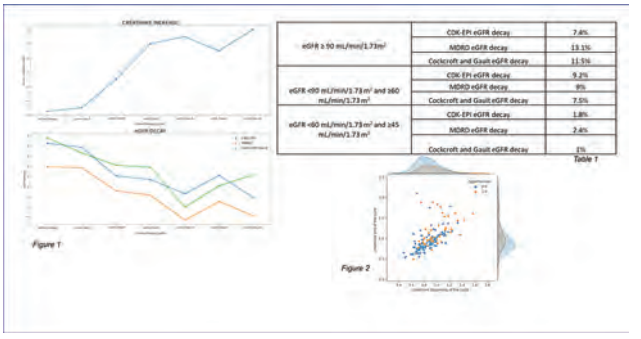
Background: Three-weekly high-dose cisplatin (100 mg/m2) concomitant to radiotherapy represents the standard of care with a curative intent in most of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). Nevertheless, cisplatin is known as a particularly nephrotoxic drug especially at the cumulative dose of 200 mg/m2 or more. Aim of this study was to investigate the incidence of AKI in patients with LA-SCCHN during and after treatment with high-dose cisplatin-based CRT to identify risk factors for cisplatin-induced AKI.

Methods: A consecutive cohort of 82 patients treated with cisplatin cumulative dose >=200mg/m2 concomitant to radiotherapy, was enrolled in a tertiary single Hospital between 2019 and 2020. Serum creatinine, hemoglobin, lymphocytes and eGFR formulas (CKD-EPI, MDRD, Cockcroft-Gault) were detected at baseline and after each cycle of chemotherapy. AKI and CKD onset were determined according to K-DIGO criteria. Tumor clinical stage as well as comorbidities were also included. Bayesian linear regression was used to evaluate the impact of the clinical and pathological features on eGFR decay through cycles.

Results: At baseline, 57% of pts were CKD I stage, 37% CKD II stage, 6,1 % CKD III stage A-B. Medium decay of eGFR from the baseline to the end of 3 cycle is reported in table 1 showing CKD different stages. The marked decay appears in day 10 during cycle 2 (Figure 1). Performing a bayesian linear regression over cycles, hypertension showed a remarkable impact on the eGFR decay through the therapy over time (Figure 2). However, the AKI incidence was very low in all CKD classes; 2,4% in 1 cycle, 4,8% in 2 cycle and 2,4% in 3 cycle.

Conclusions: Surprisingly, from these data high dose of cisplatin seems feasible in different CKD stages with very low rate of renal toxicity events and AKI-CKD onset.



PO1879

Double Hit: A Case of Chromogranin A-Mediated Proximal Tubulopathy That Progressed to Full-Blown Fanconi Syndrome After Treatment with Everolimus

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Introduction: Hypophosphatemia is an independent risk factor for poor patient outcomes. We present a rare case of hypophosphatemia from a complication of a neuroendocrine tumor (NET) and the treatment for it.

Case Description: A 54-year-old female with metastatic NET presented with dyspnea. Patient had Pneumonia which was treated but a comprehensive electrolyte panel revealed profound hypophosphatemia (phosphorous levels < 1mg /dl). Initial suspicion was that poor nutritional status may be the underlying etiology, however despite aggressive intravenous phosphate supplementation, the hypophosphatemia was resistant. Workup revealed obvious evidence of Fanconi syndrome. Patient had profound glucosuria with normal serum glucose. 24 hours urine phosphorous excretion was markedly elevated at 900 mg. Vitamin D level was borderline low but activated (1,25-vitamin D) levels were markedly low at 1.8 pg/ml. PTH levels were only mildly elevated at 120 pg/ml. A deeper investigation into her course found that patient was diagnosed with a NET 8 months prior to this presentation and had evidence of mild glucosuria with mild-moderate hypophosphatemia at that time. Chromogranin A levels from her NET were substantially elevated at that time. Serial urine analyses during the course of her disease were reviewed, and it was evident that the glucosuria became markedly worse after the patient was started on everolimus therapy. We concluded that hypophosphatemia in this patient is from chromogranin A mediated proximal tubulopathy that developed to full blown Fanconi Syndrome after everolimus. We changed phosphorous supplementation to oral only and recommended holding everolimus provided it was appropriate from an oncological standpoint. Follow up of the patient in 4 weeks off everolimus showed continued improvement in phosphorous levels.

Discussion: Both chromogranin-A and mtor inhibitors have shown to cause acute tubular injury in proximal tubules. Our case is unique in the sense that it presented as severe hypophosphatemia from Fanconi syndrome secondary to two uncommon culprit agents that acted in a sequential manner to worsen the proximal tubulopathy. Based on this case we recommend that in NET patients with high chromogranin A levels, we check for signs of proximal tubulopathy before starting mtor inhibitor therapy.

PO1880

Renal Function Outcomes in Metastatic Non-Small-Cell Lung Carcinoma Patients Treated with First-Line Therapy: An Unexpected Scenario

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Background: Immune checkpoint inhibitors (ICIs) and platinum-based chemotherapy (CT) are possible options for the palliative treatment of metastatic non-small cell lung cancer (NSCLC). Recently, CT in combination with immune- checkpoint inhibitors has become the treatment of choice for this setting of patients(pts). Aim of our study was to compare the nephrotoxic effect of both ICIs and CT in a cohort of metastatic NSCLC pts.

Methods: A consecutive cohort of 292 pts treated in first-line for NSLCL with immunotherapy or CT was enrolled in a multicentric trial between 2018-2021. eGFR (using CKD-EPI formula 2009) was detected at baseline and after each cycle of therapy to determine AKI and CKD onset according to K-DIGO criteria. Comparison between numerical variables was performed using linear regressions between groups using Kruskal-Wallis rank sum test for numerical variables and Pearson's Chi square test for categorical variables.

Results: Clinical and pathological characteristics are reported in table 1. In terms of eGFR decay and CKD onset during the treatment cycle, no significative differences were observed (Figure 1). The same behaviour happened with AKI incidence over cycles (p=0.3) (Figure 2). Further analysis including clinical variables lead to the same results, suggesting that the nephrotoxicity of CT and immunotherapy could be considered overlap and not negligible.

Conclusions: Our study surprisingly highlights that both cisplatin/carboplatin-based CT and immunotherapy display a similar incidence of AKI and eGFR decay over time in NSLCC metastatic patients

PO1881

AKI with BRAF and MEK Inhibitors May Not Be a Class Effect

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Introduction: BRAF tyrosine kinase inhibitors are used in the treatment of BRAF mutant metastatic melanoma. Simultaneous MEK inhibition has been shown to have better response rates and fewer side effects. Renal toxicity has been reported with these agents which can include AIN, ATN and Fanconi syndrome. We report a case of AKI due to biopsy proven AIN from BRAF and MEK inhibitor vemurafenib and cobimetinib

Case Description: This is a 64-year-old woman with diabetes mellitus type 2, stage IV melanoma with BRAF V600E mutation and baseline serum creatinine (SCr) of 0.8 (0.6-1.1) mg/dL. She has been treated with multiple chemotherapy regimens and immunotherapy (last dose of immunotherapy 28 months prior to presentation). Patient received reduced dose dabrafenib and trametinib until 8 months prior to presentation but stopped due to development of fever and AKI (SCr 1.7mg/dL). She was started on vemurafenib 480 mg BID every other day and cobimetinib 40mg every other day 6 ½ months before presentation. Two months later the vemurafenib dose was increased to 960mg BID but patient was noted to have AKI with SCr of 4.5 mg/dl and vemurafenib and cobimetinib were stopped. Her blood pressure was elevated to 154/70 mmHg. Urinalysis showed protein of 100 mg/dL, 0-3 RBC/HPF and 0-6 WBC/HPF. SCr improved to 2.2 mg/dL but remained elevated and renal consult was obtained with subsequent kidney biopsy. It showed active, subacute, and chronic interstitial nephritis with extensive tubular atrophy. Patient was treated with prednisone 50 mg daily and was tapered down to 10 mg daily over two months. Repeat CT scan showed new peritoneal nodules and she was started on a new BRAF/ MEK combination of encorafenib and binimetinib. She is currently tolerating these medications with SCr stable at 1.5mg/dl.

Discussion: BRAF and MEK inhibitors are associated with AKI secondary to ATN and AIN. In the above case, the patient developed AIN with vemurafenib and cobimetinib which were discontinued resulting in significant improvement in kidney function. Due to progression of disease she was started on encorafenib and binimetinib which she is tolerating well. This case demonstrates that renal toxicity from BRAF and MEK inhibitor may not be a class effect and may also be dose dependent. It may be possible to consider a dose reduction or switch to another medication in the same class if renal toxicity is noted.

PO1882

Acute Proteinuric Renal Failure in a Lung Cancer Patient Treated with Poziotinib: First Case Described in the Literature

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Introduction: The therapeutic approach to non-small cell lung cancer (NSCLC) has changed significantly in recent years: genomic drivers have enabled the development of new molecularly targeted therapies. The improvements obtained in the survival of these patients, the adverse events related to these novel treatments should not be forgotten. Poziotinib is a new generation tyrosine kinase inhibitor which has been recently registered for the treatment of patients with EGFR/HER2 exon 20 insertion mutation.

Case Description: In 2017, a 58-year-old woman was diagnosed with a pT2, N2, M0, G2 NSCLC for which she was surgically treated with lobectomy and lymphadenectomy, followed by adjuvant CT; and after metastatic relapse, further CT until July 2020. Upon progression, she started Poziotinib. She was referred to us due to the occurrence of hypomagnesemia, hypokalemia and proteinuria (2.8 g/24 h), despite a normal renal function., The objective examination and blood tests were all normal, and the patient did not report any symptom. Due to a quick worsening of renal function (sCr 2 mg/dl), and in particular of proteinuria (3.3 g/24 h), Poziotinib was stopped and dexamethasone 4 mg/day was started. Examinations for glomerulopathies were not diriment; a renal biopsy was performed in order to guide therapeutic decisions. The histological picture showed incomplete glomerular sclerosis (5/15 glomeruli), outbreaks of tubulointerstitial sclero-atrophy, as well as interstitial inflammatory lymphoplasmacytic infiltrate; immunofluorescence was negative for all antisera, while electron microscopy is presently still in progress. Following the discontinuation of Poziotinib, a progressive improvement of AKI and a reduction of proteinuria (1.3 g/24 h) was observed, allowing to hold the drug accountable, in the absence of any other risk factor, for the renal AE observed. From a histological viewpoint, nephroangiosclerosis was documented, but steroidal therapy may have hidden peculiar glomerular lesions. Poziotinib wasn't resumed.

Discussion: This is the very first case of renal toxicity from Poziotinib treatment reported so far. Cases like this highlight the need for both a nephro-oncological evaluation as well as for dedicated paths to perform rapid renal biopsies in order to characterize these events and improve their management.

PO1883

Enfortumab Vedotin-Induced Diabetic Ketoacidosis and AKI: A Case Report

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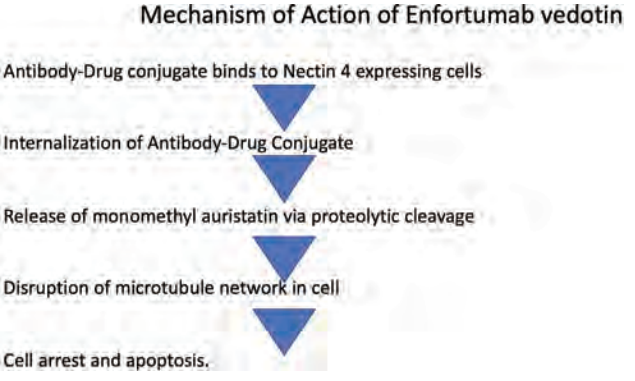
Introduction: Enfortumab vedotin is a novel antineoplastic agent in the management of advanced urolthelial cancers. While hyperglycemia has been reported, diabetic ketoacidosis and AKI are rare.

Case Description: A 69-year-old male with history of metastatic urothelial cancer (treated with carboplatin/gemcitabine and Nivolumab) and CKD who presented to hospital one week after receiving Enfortumab with Diabetic Ketoacidosis (DKA) and AKI with Cr of 3.6mg/dL (Baseline 1.8mg/dL). Urine microscopy revealed granular casts consistent with tubular injury. Patient remained hyperglycemic despite titrating dose of IV regular insulin and subsequently developed shock, toxic epidermal necrolysis, and worsening renal failure with anuria requiring continuous renal replacement therapy. Despite maximal support, patient passed away.

Discussion: Enfortumab vedotin comprises antinectin-4 antibody and a microtubule-disrupting agent monomethyl auristatin E (MMAE). The drug binds to Nectin-4, expressed on tumor cells, with high affinity, which induces the internalization of MMAE and leads to subsequent cell apoptosis through impaired cell division. Dermatologic toxicity occurs from drug binding to Nectin-4 expressed on normal skin cells. AKI was reported in 1% of patients of the phase 2 trial but not in the phase 3 trial. Nectin-4 protein is expressed and can be stained in renal tubular epithelial cells. While DKA may have contributed to our patient's tubular injury, direct tubular toxicity may be possible and requires further research. Physicians prescribing Enfortumab vedotin should be aware of this potential side effect.



PO1884

An Elevated Serum Creatinine in a Patient Receiving Palbociclib

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Introduction: Serum Creatinine (SCr) is the most widely used parameter in clinical practice to estimate glomerular filtration rate (GFR). Various drugs have been reported to cause a reversible and transient elevation in SCr without a true reduction in overall kidney function

Case Description: A 66-year-old woman with a past medical history of metastatic right breast poorly differentiated invasive ductal carcinoma, hormone receptor-positive, and HER2 negative. Who received treatment with fulvestrant and palbociclib, the dose of Palbociclibwas was 100mg orally a day. Presented for evaluation of elevated serum creatinine with decreased eGFR. On initial evaluation sCr was 1.6mg/dl, blood urea nitrogen of 21mg/dl, eGFR of 33ml/min/1.73m^2, her baseline eGFR was ranging from 42 to 52 ml/min/1.73m^2 in the past one year. An estimated glomerular filtration rate by cystatin C was performed and showed a value of 47ml/min with a cystatin-C level of 1.36mg/dl, which was at her baseline kidney function for the past year.

Discussion: Creatinine is freely filtered by the glomerulus and actively secreted by the proximal tubule from the peritubular capillaries, which accounts for 10-40% of creatinine clearance. The organic cation transporter 2 (OTC2), multidrug and toxin extrusion protein (MATE) 1 and MATE2-K, are the solute carrier transporters in the kidney that mediate this active tubular secretion. Clinical studies of abemaciclib, another selective inhibitor of CDK 4/6, have shown a reversible increase in creatinine of about 15-40% over baseline of patients with cancer and healthy subjects. This effect has been seen in about 25% of patients treated with abemaciclib however none of the clinical trials on palbociclib have

reported an increase in serum creatinine. In our case, the difference between eGFR by cystatin C and by serum creatinine demonstrated not a true decrease in kidney function. We have attributed these events to inhibition of the tubular secretion of creatinine by palbociclib and decided to continue treatment with palbociclib. Physicians should be aware that patients undergoing therapy with palbociclib require monitoring of kidney function and an increase in serum creatinine from baseline, might represent an inhibitory effect of the secretion of creatinine and not an actual decrease in kidney function.

PO1885

A Case of IgA Nephropathy in the Setting of Sezary Syndrome and Mogamulizumab

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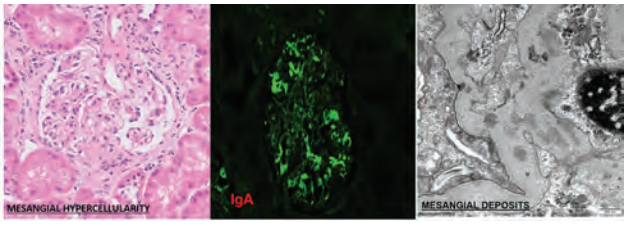
Introduction: IgA Nephropathy (IgAN) is an autoimmune disease with complex pathogenesis. Sezary syndrome (SS) is a leukemic subtype of cutaneous T cell lymphoma (CTCL). A rare association has previously been reported between IgAN and CTCL. Mogamulizumab (MG) is a monoclonal antibody drug targeting C-C chemokine receptor type 4 (CCR4) and is used in the treatment of CTCL and SS. MG has been associated with drug eruptions and systemic immune-mediated adverse events.

Case Description: A 63 year-old woman with SS was treated with MG. Her skin symptoms improved and circulating Sezary cells cleared. Due to a cutaneous drug eruption, the frequency of MG administration was reduced to monthly after cycle 7. Labs prior to cycle 19 demonstrated serum creatinine (Cr) 1.77 mg/dL from a prior baseline ~0.9-1.0 mg/dL. She received intravenous fluids but Cr worsened to 3.97 mg/dL. Urinalysis (UA) revealed more than 20 red blood cells (RBCs) per high powered field (HPF). 24 hour urine protein to creatinine ratio (UPCR) was 2.03 g/g. Serologies and complements were normal except double stranded DNA which was 12 IU/mL (normal <4 IU/mL). Kidney biopsy demonstrated mesangial immune complex deposition with IgA, IgG, and C3 predominance consistent with IgAN (Oxford M1E0S1T1C0). Prednisone was initiated at 1 mg/kg/day and tapered over 6 months. MG was stopped. After 6 months Cr had improved to 1.10 mg/dL. UA showed 3-5 RBCs per HPF with UPCR of 0.122 g/g. Her SS remained well controlled without systemic therapy.

Discussion: This case reinforces the association between IgAN and CTCL which has been described in prior case series. In patients with CTCL, altered T cell populations and a dysregulated immune response may contribute to the pathogenesis of IgAN. Complicating this case is the use of MG which can deplete normal CCR4-expressing regulatory T cells by inducing antibody-dependent cellular cytotoxicity. MG is associated with cutaneous granulomatous drug eruptions in which alterations in T cell populations have been implicated. Systemic autoimmune complications outside of the kidneys have also been reported. The possibility that MG could play a role in IgAN should be considered.



PO1886

Filgrastim-Induced Crescentic Glomerulonephritis

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is caused by deposition of monoclonal immunoglobulins in the glomeruli. It is one of renal disorders included in the spectrum of monoclonal gammopathy of renal significance (MGRS). IgG3 with kappa light chain is the most common type. Autologous stem cell transplantation (SCT) provides a durable remission and better renal outcomes. Granulocyte colony stimulating factor (GCSF) is a recombinant glycoprotein used for mobilization of bone marrow in SCT. GCSF has been implicated as a cause of crescentic transformation of an acute glomerulonephritis in one prior case with a monoclonal deposits in a kidney transplant patient. In this case, we report the clinical and pathologic findings of GCSF induced exacerbation and crescentic transformation of pre-existing PGNMID with successful treatment and SCT.

Case Description: A 48-year-old male with recent diagnosis of MGRS presenting as MPGN and monoclonal IgG Kappa with C3 deposits on biopsy and treated with Velcade, cyclophosphamide and dexamethasone with a plan for SCT. Patient was admitted after acute increase in creatinine from 2.87 m/dl to 6.6mg/dl with hematuria and proteinuria after receiving GCSF during stem cell mobilization. Timing of acute renal injury correlated with increase in WBC after GCSF injections with a peak of 69 K/ul. Repeat kidney biopsy was significant for crescentic membranoproliferative (62% crescents) glomerulonephritis with monoclonal IgG/Kappa deposits. Patient received 5 sessions of plasmapheresis, one dose of renally adjusted IV Cytoxan, and pulse steroids followed with a taper. After a month he undergone an Autologous SCT (creatinine at baseline1.6mg/dl). His kidney function continued to improve and after 16 months post SCT his creatinine is at 1.4mg/dl.

Discussion: GCSF enhances neutrophils activation in large counts and induces its endothelial activation. In the presence of pre-existing renal pathology, MGRS and MPGN with IgG kappa and C3 deposits in this case, the localized immunoglobin and complement deposits in the glomeruli can attract activated neutrophils leading to its infiltration and degranulation in the glomerular microenvironment, and resulting in rupture of glomeruli basement membrane and formation of crescent. Therefore, GCSF induced kidney injury should be suspected due to its potential risk for exacerbating pre-existing glomerulonephritis.

PO1887

Creatinine-Cystatin C Ratio and Mortality in Cancer Patients: A Retrospective Cohort Study

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Background: Muscle wasting is prevalent in cancer patients, and early recognition of this phenomenon is important for risk stratification. Recent studies have suggested that the creatinine-cystatin C ratio may correlate with muscle mass in several patient populations. The association between creatinine-cystatin C ratio and survival was assessed in cancer patients.

Methods: A total of 3,060 patients who were evaluated for serum creatinine and cystatin C levels at the time of cancer diagnosis were included. The primary outcome was 6-month mortality. The 1-year mortality, and length of intensive care unit (ICU) and hospital stay were also evaluated.

Results: The mean age was 61.6±13.5 years, and 1,409 patients (46.0%) were female. The median creatinine and cystatin C levels were 0.9 (interquartile range [IQR], 0.6-1.3) mg/dL and 1.0 (IQR, 0.8-1.5) mg/L, respectively, with a creatinine-cystatin C ratio range of 0.12-12.54. In the multivariate Cox analysis, an increase in the creatinine-cystatin C ratio was associated with a significant decrease in the 6-month mortality (per 1 creatinine-cystatin C ratio, hazard ratio [HR] 0.35; 95% confidence interval [CI], 0.28-0.44). When stratified into quartiles, the risk of 6-month mortality was significantly lower in the highest quartile (HR 0.30; 95% CI, 0.24-0.37) than in the lowest quartile. Analysis of 1-year mortality outcomes revealed similar findings. The highest quartile was also associated with shorter length of ICU and hospital stay (both $P<0.001$). These associations were independent of confounding factors.

Conclusions: The creatinine-cystatin C ratio at the time of cancer diagnosis significantly associates with survival and hospitalization in cancer patients.

Fig. 1

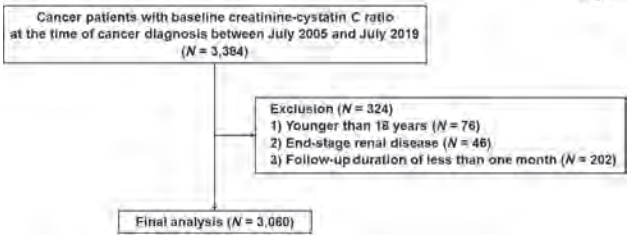
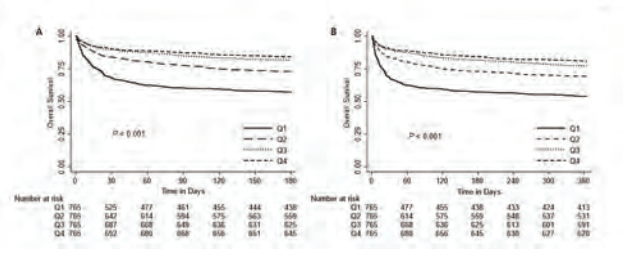


Fig. 2



PO1888

Comparison of Kidney Volume-Based Methodology to Glomerular Filtration Rate Estimating Equations to Predict Measured Glomerular Filtration Rate in Cancer Patients

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Background: Total kidney volume (TKV) has been associated with both measured glomerular filtration rate (mGFR) and with equations recommended to estimate GFR (eGFR) in clinical practice. However, there is scarce data comparing measurement of TKV to eGFR equations as predictors of mGFR, particularly in the oncology setting.

Methods: We enrolled 181 cancer patients treated at an academic tertiary cancer hospital in Brazil (Instituto do Câncer do Estado de São Paulo), who had undergone abdominal imaging and measurement of GFR by plasma clearance of 51Cr-EDTA within 60 days. eGFR was determined based on the CKD-EPI equation using Scr (eGFRcr) and Scr combined with Scys (eGFRcr-cys). eGFR and mGFR were non indexed for body surface area. Total kidney volume (TKV) was measured using a semi-automatic segmentation program, excluding non-functional tissues. The correlations between mGFR and TKV as well as mGFR and eGFR were calculated using the Pearson correlation coefficient. Linear regression models for mGFR having TKV and eGFR equations as predictors were built.

Results: Patients were 55 (14.0) y, 50.3% male. Most common cancer sites were breast (22.7%), male genital (21.8%) and gastrointestinal (20.9%). ECOG levels 0/1 corresponded to 95% of patients. Mean (SD) Body mass index was 27.18 (5.18). Mean (SD) mGFR, eGFRcr and eGFRcr-cys were 84.8(27.23), 90.4 (24.9), and 83.8 (25.9), ml/min, respectively. Mean (SD) TKV for both kidneys was 302.2 (77.9) cm3. PCC for mGFR-TKV, mGFR-eGFRcr and mGFR-eGFRcr-cys were 0.76, 0.78 and 0.85, respectively. TKV improved the coefficient of determination of the linear regression models when added to both eGFRcr and eGFRcr-cys, in overall and assessed subgroups (Table 1).

Conclusions: In conclusion, our results suggest that measurement of TKV is a reliable predictor of mGFR in cancer patients with the potential to be incorporated to the current eGFR equations used in clinical practice.

Table 1: Linear regression models for measured glomerular filtration rate

	Predictors															
	eGFRcr				eGFRcr + TKV				eGFRcr-cys				eGFRcr-cys + TKV			
Population	I	B1	B2	R^2	I	B1	B2	R^2	I	B1	B2	R^2	I	B1	B2	R^2
Overall (n=189)	9.91	0.8	--	0.62	31.2	0.51	9.91	0.73	58.12	0.64	--	0.75	-8.78	0.62	0.12	0.88
Sex																
Male (n=94)	10.88	0.79	--	0.63	-12.17	0.46	0.16	0.73	6.42	0.89	--	0.75	-12.22	0.63	0.12	0.84
Female (=95)	8.05	0.79	--	0.59	-13.03	0.55	0.14	0.70	13.35	0.78	--	0.72	-4.4	0.69	0.11	0.78
Age (y)																
≥65 (n=57)	4.3	0.84	--	0.62	-19.8	0.59	-0.15	0.73	5.66	0.90	--	0.75	-15.45	0.69	0.12	0.88
<65 (n=132)	12.08	0.74	--	0.51	-2.8	0.41	0.12	0.66	10.31	0.83	--	0.68	-4.27	0.57	0.12	0.74
Diabetes																
Yes (n=25)	3.47	0.90	--	0.71	-19.26	5.16	0.15	0.80	5.16	0.94	--	0.84	-9.11	0.71	0.09	0.86
No (n=164)	10.15	0.78	--	0.60	-9.60	0.49	0.15	0.70	9.42	0.84	--	0.71	-8.40	0.60	0.12	0.78
BMI (Kg/m²)																
<24 (n=61)	5.81	0.76	--	0.65	-6.34	0.63	0.08	0.65	10.81	0.76	--	0.69	-2.34	0.63	0.08	0.72
24 to <30 (74)	13.46	0.75	--	0.53	-14.12	0.50	0.16	0.62	12.37	0.80	--	0.72	-9.37	0.55	0.11	0.76
≥30 (n=54)	21.18	0.74	--	0.59	-4.65	0.38	0.17	0.72	16.34	0.83	--	0.72	-3.67	0.54	0.13	0.79

mGFR is the outcome. eGFRcr, eGFRcr-cys and TKV are the predictors. mGFR: measured glomerular filtration rate; eGFR: estimated glomerular filtration rate is based on CKD-EPI equation, being eGFRcr based on serum creatinine level and eGFRcr-cys being eGFR based on both serum creatinine and serum cystatin C levels. CKD-EPI equation. BSA: body surface area, BMI: body mass index, CKD: chronic kidney disease. TKV: total kidney volume. I: intercept. B1 beta coefficient for eGFR equation. B2: beta coefficient for TKV. R^2: coefficient of determination, represents the proportion of the variance for a dependent variable that's explained by the predictors. eGFR and mGFR were assessed in mL/min/1.73m² values.

PO1889

Modifications of Renal Function in Cancer Patients Undergoing Repeated and Frequent Administrations of Iodinated Contrast Medium (CM): A Multicentric Retrospective Study from Italy

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Background: Contrast-enhanced computed tomography (CECT) is the imaging of choice for the diagnosis, staging, and follow-up of cancer patients, not to take into account its role to evaluate response to oncological treatments; in fact, it has been estimated that 47% of all CECTs are prescribed by Oncologists. Comorbidities, nephrotoxic concomitant medications, as well as chronic dehydration from different causes (nausea and vomiting, diarrhea, etc …) expose cancer patients to a higher risk of developing acute kidney injury (AKI) from CM. Risk factors, definition (PC-AKI vs CI-AKI) and preventive measures have been recently reconsidered, ultimately downsizing the incidence of this adverse event.

Methods: Aim of this study was to retrospectively assess the effects on renal function of repeated CM administrations in 407 oncological patients on active treatment, collected from 5 Italian oncology departments; patients should have undergone at least 3 CECT (on the average 3.5) within a single year (Fig I).

Results: According to our study, neither significant differences in eGFR values (calculated with the CKD-EPI formula) between the baseline and the different post-CECT timepoints, nor AKI cases (defined according to the RIFLE criteria), were recorded.

Conclusions: Repeated CM administrations in cancer patients did not lead to a worsening of renal function, confirming that CI-AKI has a significantly lower incidence than previously thought. Notably, 80% of the patients examined were found to be at low-risk, highlighting some kind of reluctance of Medical Oncologists and Radiologists to perform CECTs in these patients. On the contrary, the administration of CM could, and should, be freely used, in cancer patients, even in those at a higher risk.

Age	>65	183 (45%)
	<65	224 (55%)
Sex	Male	228 (56%)
	Females	179 (44%)
Heart disease	Yes	79 (20%)
	No	274 (67%)
	Unknown	54 (13%)
Nephrectomy	Yes	171 (42%)
	No	236 (58%)
Diabetes	Yes	73 (18%)
	No	313 (77%)
	Unknown	21 (5%)
Hypertension	Yes	195 (48%)
	No	196 (48%)
	Unknown	16 (4%)
Kidney failure	Stages I and II	281 (69%)
	Stadio iiia	85 (21%)
	Stadio iiib	33 (8%)
	Stage IV	8 (2%)
	Stage V	0 (0%)
Type of tumor	Genitourinary	199 (49%)
	Gastro-intestinal	57 (14%)
	Lung	45 (11%)
	Head-neck	3 (0,8%)
	Cute	16 (4%)
	Udder	41(10%)
	Other	46 (11,2%)
Type of oncology therapy	Cytotoxic chemotherapy	175 (43%)
	Drugs with molecular target	134 (33%)
	Immunotherapy	142 (35%)
	Hormone therapy	16 (4%)

PO1890

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits: Searching for the Underlying Clone

Vincent Javaugue,[1,2] Virginie Pascal,[3] Sébastien Bender,[2] Jean-Michel Goujon,[1] Guy Touchard,[1] Christophe Sirac,[2] Frank Bridoux.[1,2] Centre national de référence amylose AL et autres maladies par dépôts d'Ig monoclonales *[1]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [2]Centre National de la Recherche Scientifique, Limoges, France; [3]Centre Hospitalier Universitaire de Limoges, Limoges, France*.

Background: The pathophysiological mechanisms of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) are still largely unknown. Only 30% of PGNMID cases have a detectable circulating monoclonal immunoglobulin (Ig) and a bone marrow corresponding clone.

Methods: We reviewed a French cohort of PGNMID with particular focus on hematological characteristics. A high-throughput sequencing assay from bone marrow and/or blood mRNA encoding immunoglobulins (RACE-RepSeq) was used to detect the underlying clone.

Results: Seventy-one patients (M/F ratio=1.6, median age 59 years) were included. At diagnosis, 73% had renal insufficiency (median serum creatinine=1.7 mg/dL). All patients had proteinuria, with nephrotic syndrome in 59% and microscopic hematuria in 85% of cases. No patient had extra-renal manifestations. By light microscopy, kidney biopsy revealed membranoproliferative glomerulonephritis (74%), mesangial glomerulonephritis (14%) or membranous glomerulonephritis (12%). By immunofluorescence (IF), deposits stained for IgG in 55 cases (mostly IgG3κ), IgM in 7 cases, IgA in 4 cases or light chain (LC) only in 5 cases. Serum and/or urine immunofixation was positive in 26 cases (37%). An underlying clone was found in 21 cases (30%) using bone marrow or blood flow cytometry analysis. The clonal detection rate was particularly low in IgG3κ-PGNMID (9%). The nature of the clone differed with PGNMID subtype: lymphoplasmacytic in IgM-PGNMID, and plasmacytic in IgA/LC-PGNMID. RACE-RepSeq analysis failed to detect a bone marrow or blood clone in 18/26 cases (IgG3κ-PGNMID, n=17; IgGAκ-PGNMID, n=1). IF analysis of kidney samples using anti-Vκ antibodies showed positive staining for Vκ1, Vκ2, Vκ3 and Vκ4 in 3/3 tested IgG3k-PGNMID patients without a detectable clone, whereas deposits stained only for Vκ2 in one IgG1k-PGNMID patient who had a bone marrow Vκ2 clone by RACE-RepSeq analysis.

Conclusions: These results suggest that PGNMID is a heterogeneous medical condition and that some cases might involve oligoclonal production of nephrotoxic Ig restricted to the IgG3k isotype. Such cases should no longer be classified as MGRS.

PO1891

Rituximab-Associated Flare of Cryoglobulinemic Vasculitis

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Background: Patients with cryoglobulinemic vasculitis (CV) can develop disease flare after rituximab administration. The pathogenesis is hypothesized to be from immune complex deposition in the microvasculature, wherein the immune complex consists of the involved cryoglobulin and an antigenic portion of rituximab. Our objective was to describe the prevalence, clinical characteristics, predisposing factors, and outcomes of rituximab-associated flare of CV.

Methods: We conducted a retrospective study in a tertiary referral center. We defined disease flare as any clinical deterioration within two weeks following rituximab administration, including onset of new organ involvement or worsening of the underlying CV not clearly explained by disease progression alone - with or without laboratory evidence.

Results: Among 64 patients with known CV who received rituximab therapy in our center, 14 (22%) developed disease flare. Median age was 67.5 years. Seven patients (50%) had type II CV while the other half had either type I (n=6) or type III (n=1). Twelve patients (86%) had IgM-mediated CV flare. Twelve patients (86%) had an underlying B-cell lymphoproliferative disorder as the cause of their CV. CV flare occurred after a median time of 5.5 days (range: 2-8 days). The organ systems most involved were the skin (n=10), kidneys (n=5), and peripheral nerves (n=3). Nearly all patients received treatment directed against their underlying diseases, including chemotherapy, corticosteroids, and/or plasmapheresis during the flare. Patients who developed flare were more likely to have B-cell lymphoproliferative disorder as the underlying etiology of their CV (p=0.03), had lower creatinine levels prior to rituximab treatment (0.8 vs. 1.05 mg/dL, p=0.01), and eventually received more treatments with plasmapheresis together with rituximab (p=0.03). Eight patients (57%) died after a median time of 27 months.

Conclusions: In our study, the prevalence of rituximab-associated flare of CV is 22%, and it can occur in all types of CV. Flares tend to arise about two days (less than one week) after rituximab administration and are more likely to happen in patients with an underlying B-cell lymphoproliferative disorder. These flares do not indicate failure of response to treatment. Clinicians should be cognizant of its existence and have a high index of suspicion for this phenomenon.

PO1892

Membranous-Like Glomerulopathy with Masked Monoclonal IgG Deposits

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Introduction: Membranous-like glomerulopathy with masked monoclonal IgG deposits (MGMID) is a recently described entity characterized by a membranous pattern of injury with monoclonal IgG-kappa restriction, unmasked by pronase digestion on formalin-fixed paraffin-embedded (FFPE) tissue by immunofluorescence microscopy (IF). Retrospective pathology and chart review was performed within a large health system in the USA between 2019-2021 identifying 5 patients.

Case Description: All 5 patients were Caucasian females with median age 17 years (range 12-48). On presentation, 4 patients had elevated urine protein to creatinine ratio (UPC), 3 had microscopic hematuria, and 1 patient had an eGFR <90ml/min/1.73m^2. Of note, 1 patient presented post-partum. Serologic workup revealed positive antinuclear antibody (ANA) in 1 patient (see table) who had a known history of juvenile idiopathic arthritis. Kidney biopsy revealed a membranous pattern of glomerular injury in all patients, with global glomerulosclerosis from 0-31%, segmental glomerulosclerosis from 2-7%, and interstitial fibrosis and tubular atrophy from 2-50%. Electron microscopy revealed subepithelial/intramembranous deposits without substructural organization. Finely granular capillary wall reactivity for C3 was noted on routine IF on frozen sections. On FFPE after pronase digestion, all cases revealed glomerular capillary wall staining for gamma-1 (4 cases) or gamma-3 (1 case) and kappa light chains; lambda light chains were negative. Extensive hematologic workup was negative for monoclonal bands or lymphoproliferative processes. All patients were treated with angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy, and 2 patients were also treated with Rituximab. Four patients had an improvement in UPC. None of the patients required kidney replacement therapy.

Discussion: MGMID is a peculiar entity with monoclonal IgG glomerular deposits primarily affecting young Caucasian females, without obvious correlation to monoclonal lymphoproliferative disorder. Treatment with ACEi or ARB +/- Rituximab improved UPC in most patients in this case series. Better understanding of this entity is important to guide therapy.

Table. Demographics, serologic workup, treatment, and post-treatment results for patient with MGMID

Patient	age	creat	upc	hematuria	ANA	dsDNA	low C3	low C4	ANCA	RF	SFLC	bone marrow	treatment (tx)	post-tx creat	post-tx upc
1	12	0.34	1.17	+	+	-	-	+	-	-	TNP	TNP	ACEi	0.6	0.43
2	17	0.99	1.7	-	-	-	-	-	-	TNP	TNP	TNP	ACEi/ARB	0.85	0.5
3	17	0.77	1.1	+	-	-	-	-	Ind	-	TNP	TNP	ACEi	0.77	0.2
4	26	0.78	5.5	+	-	-	-	-	-	+κ	-		ACEi/Ritux	0.93	2.7
5	48	1.80	0.1	-	-	-	-	-	-	TNP	+κ	-	ACEi/Ritux	1.47	0.6

Abbreviations: creat, serum creatinine; upc, urine protein to creatinine ratio; ANA, antinuclear antibody; dsDNA, anti-double stranded DNA antibody; ANCA, anticytoplasmic nuclear antibody; RF, rheumatoid factor; SFLC, serum free light chains; +, positive; -, negative; Ind, indeterminate; TNP, test not performed; κ, kappa; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ritux, rituximab.

PO1893

Thrombotic Microangiopathy, Its Clinical Characteristics, Etiologies, and Outcomes: A Case Series of 33 Patients

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Background: Thrombotic Microangiopathy (TMA), is a pathologic pattern of injury that has a variable presentation and etiologies. Here we present a case series of 33 patients from our academic center with biopsy proven TMA, describe their clinical characteristics and compare the differences between drug- induced TMA and other causes of TMA (Table 1)

Methods: We collected data on clinical characteristics, detailed biopsy findings, etiologies and treatment details for 33 patients at our institution with biopsy proven diagnosis of TMA

Results: The average age of the patients who had a kidney biopsy diagnosis of TMA was 49.18 years. 13/33 patients were African-American. Upon initial assessment, 29/33 patients had acute kidney injury, 9/33 had malignant hypertension (BP> 180/120 on presentation), and 15/33 had MAHA. In those in which a cause was able to be determined, 12/33 had drug induced TMA with the most common medication being VEGF inhibitors & Tyrosine kinase inhibitors with anti-VEGF properties (8/12). Three patients had TMA secondary to calcineurin inhibitors and one patient had cocaine induced TMA. 3/33 had complement mediated TMA, diagnosed by confirming activation of the alternative complement cascade. In patients with drug induced TMA, 6/12 patients had improved proteinuria and kidney function after withdrawl of the drug, 3 remained dialysis dependent and 2 were transitioned to home hospice. In the drug induced TMA category, 33% patients were dialysis dependent on discharge from the hospital as opposed to 43% in the non-drug induced TMA category.

Conclusions: Every patient with biopsy proven TMA should undergo a thorough history including medication use and work up, so optimal management can be initiated. In our series, 50% of the patients with drug induced TMA improved after withdrawl of the culprit medication.

Categories	Drug Induced TMA (N=12)	Non-Drug Induced TMA (N=21)
Age		
Mean (SD)	52.5 (14.22)	46.7 (20.56)
Gender - n (%)		
Male	5 (41.67)	10 (47.62)
Female	7 (58.33)	11 (52.38)
Ethnicity - n (%)		
White	3 (25.00)	8 (38.10)
African American	5 (41.67)	8 (38.10)
Asian	2 (16.67)	2 (9.52)
Jewish	1 (8.33)	1 (4.76)
Other	0	1 (4.76)
Unknown	1 (8.33)	1 (4.76)
Malignant Hypertension - n (%)		
Yes	3 (25.00)	6 (28.57)
No	9 (75.00)	14 (66.67)
Unknown	0	1 (4.76)
Microangiopathic Hemolytic Anemia - n (%)		
Yes	6 (50.00)	9 (42.86)
No	5(41.67)	11 (52.38)
Unknown	1 (8.33)	1 (4.76)
Dialysis Dependent - n (%)		
Yes	4 (33.33)	9 (42.86)
No	8 (66.67)	12 (57.14)

PO1894

TAFRO: A New Cause for Thrombotic Microangiopathy Mimicking Atypical Hemolytic Uremic Syndrome Successfully Treated with Anakinra and Eculizumab

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Introduction: arTAFRO is syndrome of Castleman's disase with : thrombocytopenia, anasarca, myelofibrosis, AKI & organomegaly. We present a 17 yr old girl with abdominal lymph nodes who rapidly developed anasarca, splenomegaly, AKI requiring dialysis, & respiratory failure requiring mechanical ventilation. After a lymph node bx 2 months later showed multicentric Castelman's, plasma cell variant, we realized she early on had TAFRO.

Case Description: She rapidly developed ansarca, an 18 cm spleen, & abdominal nodes to 1.9 cm. Bacterial cultures, spinal tap, viral resp panel, mono, HIV, HVV-8 levels were normal (NL). Hg dropped to 6.7 gm/dl without hemolyisis, platelets 57,000 & WBC,15,500. CRP was 32.5 & sed rate 130. Oliguria ensued & creatinine rose to 3.6 mg/dl. Urinalysis had +1 protein, +3 blood with granular casts. ANA, ASO, streptozyme, myeloperoxidae, proetinase -3, serum immunofixation, anti-phospholipid abs, IgG subclasses, anti-mitochondrial & smooth muscle abs, HLA-B27, ADAMSTS-13 levels & abs were NL. IL-2R levels were markedly high at 12,340 pg/ml as were IL-18, 930 pg/ml, CXCL9 107 pg/ml but Il-6 was only 11.3 pg/ml. Bone marrow showed inceased megakaryocytes & no hemophagocytosis. aHUS testing was negative for all geneitc causes & no abs were found to any complements(C) but both, C3, 65 mg/dl & C4, 4 mg/dl were low & the membrane attack complex C5-C9, markedly elevated at > 50 mg/dl. Renal bx showed endothelial swelling & thrombotic micoangioapathy (TM) confirmed on EM with negative IF. 3 pulses of solumedrol daily, dialysis, 2 plasmaphareses before the aHUS panel returned were started along with 2 doses of Anakinra, an anti-IL-1 drug, 4mg/kg sub q separated by 3 days & 1 dose of Eclizumab, 1200 mg iv. She rapidly improved, was extubated & was discharged off dialysis with a NL creatinine & no edema.

Discussion: We conclude: 1). TAFRO can mimic aHUS & present with markedly elevated IL-2R levels rather than IL-6 levels which can fix complement by the classsic pathway leading to high membrane attack complexes adding to capillary leak, anasarca and TM. 2) An Anti IL-1 drug, Anakinra, & a drug inhibiting C5 cleavage to C5a & C5b, Eclizumab can be combined to successfully treat TAFRO 3) TAFRO must now be added to all reviews and textbooks as a new cause for TM & AKI with classic complement pathway activation.

PO1895

Large Abdominal Mass: An Unusual Presentation of Multiple Myeloma

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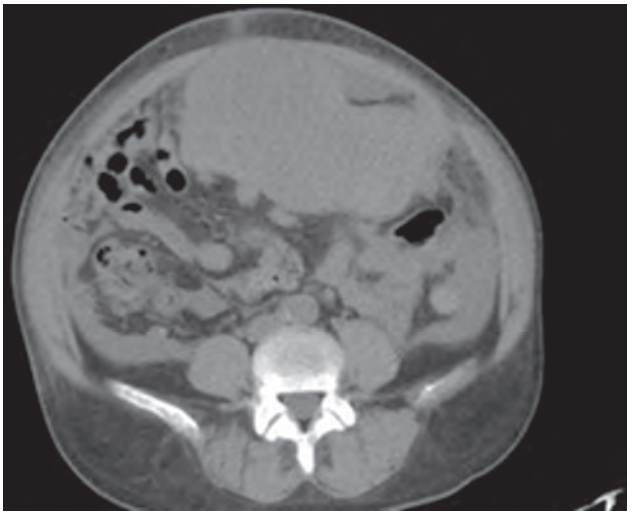
Introduction: Extramedullary Soft Tissue Mass (ESTM) is an infrequent presentation of Multiple Myeloma. We present a unique case of Multiple Myeloma with very large bulky tumor masses.

Case Description: A 69 year old AA female presented with severe abdominal distention. CT Scan showed a 17 x 10 x 10 cm mass originating in the retroperitoneal region, a 12.5 cm mass in the pelvis and a 4.3 x 2.7 cm mass in the liver as shown in the image. Further testing showed anemia and renal failure. Biopsy of the mass revealed multiple myeloma, driving a monoclonal IgG lambda clone. FISH panel was positive for 17P/TP53 deletion which is very unfavorable. Patient was treated initially with dexamethasone/cyclophosphamide/Velcade and later with Daratumumab/Carfilzomib/dexamethasone without any response and remained on dialysis ultimately succumbing within 6 weeks of diagnosis.

Discussion: Initial Extramedullary Soft Tissue Mass (ESTM) manifestations in Multiple Myeloma occur in about 3% of the cases. In a large majority (93.5%) these lesions are solitary. Our patient had large, multiple masses with high tumor burden and unfavorable cytogenetic signature. She did not respond to therapy despite utilization of aggressive regimens. This is a very unique presentation of myeloma and with the unfavorable characteristics, had a dismal prognosis despite aggressive therapy.



CT Abd showing ESTM

PO1896

Fibrillary Glomerulonephritis and Graft vs. Host Disease

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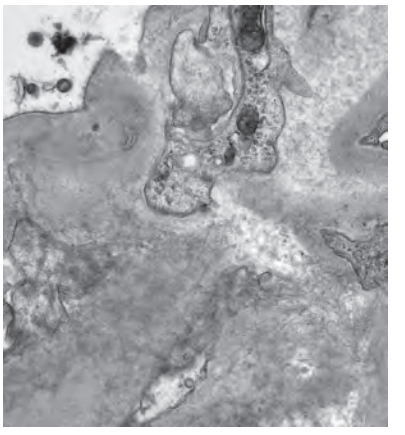
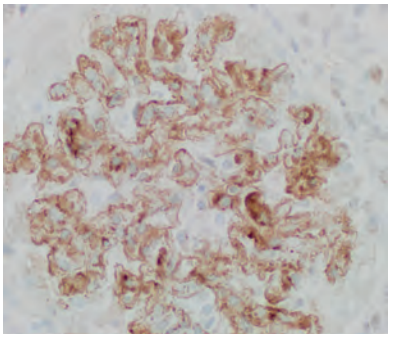
Introduction: Fibrillary Glomerulonephritis (FGN) is rare and seen in 1% of kidney biopsies. Etiology is unkown. It is associated with malignancy, monoclonal gammopathy, autoimmune disorders and infections. There has not been FGN case reported in a pt with Graft Versus Host Disease (GVHD). We present a case AKI sec to FGN with h/o Acute Lymphocytic Leukemia, status post Allogeneic Stem Cell Transplant complicated by Gastrointestinal GVHD.

Case Description: 67 yo African American female with DM, HTN, ALL s/p ASCT in remission, recently diagnosed with GI GVHD, presented with nausea, vomiting & diarrhea. Vitals: BP 140/70, Temp 37°C, HR 109. Exam showed 3+ LEs edema. Labs: Cr 3.5 mg/dL, baseline of 1.1mg/dL. Urinalysis showed hematuria and14.6g/g protein. Histology showed C3 crescentric GN. DNAJB9 stain returned positive and EM findings confirmed FGN. Patient recieved Soulmedrol, followed by Rituximab and then Cyclophosphamide. She was dialysis dependent within 6 mos of diagnosis.

Discussion: FGN may have an undescribed association with GVHD. It is understudied because of rarity. It can present with AKI and kidney Bx is needed for diagnosis and to guide treatment. The trigger to get biopsy was the unexplained protein & blood in urine. Cr stabilized intially. However, earlier diagnosis and treatment could have delayed progression to ESRD.



Fibrils in mesangial matrix



DNAJB9 staining

PO1897

Recurrent Fibrillary Glomerulonephritis Secondary to Chronic Lymphocytic Leukemia: A Rare Case of Treatment Success

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Introduction: Fibrillary GN is a rare form of glomerular disease characterized by the random deposition of small (20nm) fibrils in the mesangium and capillary walls of the glomerulus. There is a recognized association with hepatitis C, malignancy and autoimmune conditions. It is poorly responsive to treatment and up to half of the patients reach ESRD by six years. We present a case of Fibrillary GN secondary to CLL with complete remission after receiving Bendamustine and Rituximab and a subsequent relapse treated with Ibrutinib with good renal recovery.

Case Description: A 69-year-old male presented in 2014 with a pathological spinal fracture and was subsequently found to have CLL. He had normal renal function and no proteinuria at the time of diagnosis and his CLL was managed conservatively. In 2016 he developed nephrotic syndrome (ACR >1000) with a significant decline in renal function to an eGFR of 18ml/min. He underwent a renal biopsy which showed an MPGN pattern of injury with fibrils on electron microscopy suggesting fibrillary glomerulonephritis. He received Bendamustine and Rituximab for CLL and went into complete remission of his nephrotic syndrome and improvement in renal function to eGFR of 57ml/min.

He remained in remission for four years. In 2020 he had relapse of his nephrotic syndrome and eGFR dropped to 17ml/min. Further imaging suggested progression of the CLL. He had a further renal biopsy which again confirmed recurrent Fibrillary GN. He was started on the Tyrosine kinase inhibitor (TKI) Ibrutinib in December 2020 and within 3 months his renal function had improved to an eGFR of 33ml/min and reduction in proteinuria.

Discussion: TKIs have mostly been linked with kidney injury secondary to the potential deleterious effects on the renal endothelium. This is the first reported case of the use of a TKI as a treatment for Fibrillary GN secondary to CLL. In addition, there is scarcity of experience with relapse of Fibrillary GN as it is usually a progressive disease and with little prospect of recovery. This case highlights the following: If there is an identifiable cause driving Fibrillary GN, treatment can be associated with remission of proteinuria and improvement in renal function. Monitoring of the underlying disease is important as recurrence can result in subsequent relapse of nephrotic syndrome. TKIs used with caution can be beneficial in the setting of MGRS.

PO1898

Ruxolitinib for Graft vs. Host Disease-Associated Nephrotic Syndrome: A Case Report

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Introduction: Graft-versus-host disease (GVHD) is a serious complication of allogenic stem cell transplant in which donor T-cells attack the host antigens. We report a case in which ruxolitinib successfully treated GVHD-related nephrotic syndrome.

Case Description: A 48-years-old male known to have myelodysplastic syndrome (MDS) was referred for evaluation of proteinuria. He was diagnosed with MDS four years prior. Since his disease was persistent with azacitidine, he received allogenic stem cell transplant (SCT) about a year after the MDS diagnosis and he achieved complete remission. However, the post-transplant course was complicated by chronic GVHD which manifested mainly as non-specific interstitial pneumonia (NSIP) about three and a half-year post-transplant. NSIP was treated with high-dose oral steroid therapy, which was tapered down to a maintenance dose of 10 mg daily, and Mycophenolate Mofetil. During his course of GVHD, he had persistent mild proteinuria (UPCR less than 1 g/g of creatinine) without active urine sediment. This proteinuria was noted initially prior to NSIP diagnosis, improved while on high-dose prednisone but progressively worsened after the prednisone was tapered to 10 mg once daily. The proteinuria peaked at 2.4 g/g of creatinine with hypoalbuminemia of 2.6 g/dL at which point it was investigated with a renal biopsy. Renal biopsy showed Membranous Nephropathy with negative staining for anti-PLA2R antibody. The patient was started on ruxolitinib at a dose of 10 mg twice a day. Subsequent follow-up showed drastic reduction in proteinuria. UPCR (g/g of creatinine) of 0.96, 0.4 and 0.09 was noted at 1,2- and 5-months post-therapy initiation respectively.

Discussion: Nephrotic syndrome is a rare manifestation of GVHD with membranous nephropathy histology seen in almost two thirds of patients. Traditionally treated with high-dose steroid with variable efficacy, we decided against it due to the patient-reported adverse effects from prior high-dose steroid therapy. Recent studies such as REACH2 and REACH3 trials have demonstrated that ruxolitinib, a selective Janus Kinase (JAK) 1 and 2 inhibitor, has superior efficacy than other second-line therapy options available. Hence, ruxolitinib can be considered in GVHD-associated Nephrotic syndrome especially if a steroid-sparing approach is needed.

PO1899

Clonal Hematopoiesis of Indeterminate Potential Is Associated with Worse Kidney Function and Anemia in a Cohort of Patients with Advanced CKD

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an inflammatory premalignant disorder resulting from acquired genetic mutations in hematopoietic stem cells. CHIP is common in aging populations and associated with cardiovascular morbidity and overall mortality, but its role in chronic kidney disease (CKD) has not been investigated.

Methods: We performed targeted sequencing to detect CHIP mutations in a cohort of 87 adults with advanced CKD (eGFR < 60 ml/min/1.73m2). Kidney function, hematologic, and mineral bone disease parameters were assessed cross-sectionally at baseline, and a total of 2,091 creatinine measurements and 3,382 hemoglobin measurements were retrospectively collected over the following 12-year period.

Results: At baseline, 20 of 87 (23%) cohort participants had CHIP detected. Those with CHIP had lower baseline eGFR (22.3 ± 2.5 vs. 28.2 ± 1.4 ml/min/1.73 m2, P = 0.04) in age- and sex-adjusted regression models. Individuals with CHIP had a 2.5–fold increased risk of a 50% decline in eGFR or ESKD in a Cox proportional hazard model adjusted for age and sex (95% confidence interval, 1.3–4.7). Further, those with CHIP had lower hemoglobin at baseline (11.6 ± 0.3 vs. 12.8 ± 0.2 g/dL, P = 0.0003) and throughout the follow-up period despite a greater use of erythropoiesis-stimulating agents. Mean cell volume was associated with variant allele fraction, suggesting CHIP may contribute to defective erythropoiesis in CKD.

Conclusions: CHIP was associated with lower eGFR, progression of CKD, and anemia in individuals with advanced CKD. Further assessment of the direction of causality between CHIP and CKD and validation in additional cohorts is required.

Funding: Private Foundation Support

PO1900

Case of C3 Glomerulopathy in a Patient with Mesothelioma

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Introduction: C3 glomerulopathy has been described in autoimmune diseases and in monoclonal gammopathy caused by plasma cells and B-cell lineage cells malignancies. There have been no reports of C3 glomerulopathy that is associated with mesothelioma. We report here a case of C3 glomerulonephritis was diagnosed in patient with pulmonary mesothelioma.

Case Description: 84-year-old male patient presented with shortness of breath with fluid overload and vasculitic rash in the lower extremities, elevated BUN and creatinine and potassium of 5.7. Patient has been diagnosed with resectable pulmonary mesothelioma two months prior to his presentation and had received only one treatment of immune check inhibitor (Nivolumab plus Ipilimumab) one day prior to admission. Work up was done and showed AKI, proteinuria and hematuria, but negative work up for autoimmune disease or paraproteinemia or an infectious etiology. Decision was made to proceed with kidney biopsy which showed C3-dominant immune-complex mediated glomerulonephritis affecting about 35% of glomeruli with segmental crescent formation in about 5% of the glomeruli, diffuse acute tubular injury and minimal interstitial fibrosis and tubular atrophy.

Discussion: C3 glomerulopathy has been associated with autoimmune diseases and hematological malignancies and is related to uncontrolled activation of the alternative complement pathway, however solid tumors like mesothelioma may also trigger an immune mechanism that would lead to C3 glomerulopathy. We will discuss the possibility that the C3 glomerulopathy was due to or in association with the recent diagnosis of mesothelioma, also I will discuss the possible mechanisms of this association.

PO1901

NELL-1 Membranous Nephropathy Associated with Diffuse Reactive Lymphadenopathy

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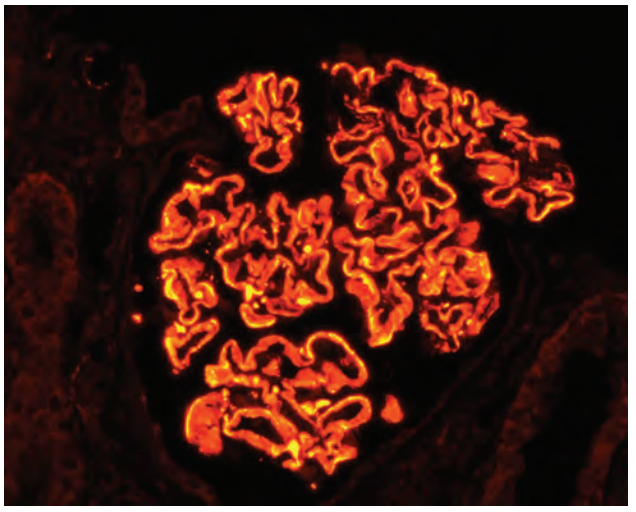
Introduction: We present a case of neural epidermal growth factor like-1 (NELL-1) MN associated with diffuse lymphadenopathy without evidence of malignancy or autoimmune disease.

Case Description: A 53-year-old woman with a BRCA 1 mutation presented with nephrotic syndrome. Diffuse lymphadenopathy was found on examination. Laboratory evaluation revealed serum albumin of 1.9 mg/dl, creatinine of 0.4 mg/dl, and UPCR 13.5 g/g. Urine microscopy showed protein (4+), and bland urine sediment. Serum PLA2R antibody was negative. Four excisional lymph node biopsies were performed, all of which revealed reactive hyperplasia without evidence of hematological malignancy. Flow cytometry and a bone marrow biopsy were negative. Serology for ANA, CRP, ESR, C3, C4, EBV, HIV, and Hepatitis B, and C were all negative. Renal pathology revealed diffuse, fine pinholes along the glomerular basement membranes using a Jones sliver stain. By immunofluorescence (IF), glomeruli showed diffuse, global finely granular capillary loop staining for IgG (3+), C3 (1-2+), and stained equally for κ and λ light chains. An IF stain for NELL-1 showed diffuse granular staining capillary loops (3+) while immunohistochemical stains for PLA2R and EXT2 were essentially negative. The ultrastructural evaluation revealed numerous, confluent subepithelial electron-dense deposits along with severe foot process effacement.

Discussion: NELL-1 associated MN was recently discovered as a distinct type of MN. In one series, 33 % of NELL-1 MN associated with malignancies, which is more often than the other known types of MN. The constellation of findings in this case with NELL-1 MN associated with reactive diffuse lymphadenopathy without evidence of malignancy or autoimmune disease is a rare presentation. Therefore, this case adds to the existing literature on NELL-1 associated MN, which helps to raise the awareness of this novel clinical presentation.



NELL-1 granular capillary loops staining

PO1902

Nephrotic Syndrome as a Paraneoplastic Entity

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Background: Association between nephrotic syndrome (NS) and cancer is known but it has been barely studied. Membranous nephropathy (MN) has been identified as a paraneoplastic disease. Incidence of cancer at the time of biopsy of MN is 10-20%. Rates in other glomerulopathies are limited. Concomitant malignancy is associated with poor outcome in NS: cancer therapy is a priority and immunosuppression for NS should be restricted. There is no consensus for cancer screening in patients with NS, with or without known risk factors. Aim: To establish the incidence of cancer in a cohort of patients with NS onset & to analyze clinical & histologic characteristics, type and risk factors for cancer.

Methods: All patients with NS at one hospital in Madrid between 1/2013-12/2019 and all patients with NS at one hospital in Barcelona between 1/2018- 6/2020 were included. Demographical, clinical and laboratory data were recorded. Patients who presented cancer 1 year before or 2 years after NS onset were identified. A logistic regression model was performed to identify risk factors for cancer.

Results: 114 patients presented with NS during the study periods. 57% men, mean age 57.3±17.3. 60% presented high blood pressure, 36% DM2, 7% HIV, and 6% hepatitis C. 44.7% reported smoking, and 13.1% alcohol consumption. More frequent histologic diagnosis: diabetic nephropathy (17.5%), MN (14.9%), minimal change disease (7.9%), membranoproliferative glomerulonephritis (7.9%). 8 patients presented anti phospholipase A2 receptor antibodies. 17.5% patients presented cancer: 12 patients 1 year before the NS onset (10 solid organ, 2 haematological cancer), and 8 patients 2 years after NS onset (3 solid organ, 5 haematological cancer). Patients with cancer were older (72.3±10.3 vs 53.2±17.1, p<0.0001). No differences in smoking, viral infections, renal function, proteinuria or glomerulopathy. Multivariate analysis showed age as the only risk factor for cancer (OR 1.122, IC 95% 1.050-1.1980; p=0.0007).

Conclusions: In our cohort, 17.5 % patients with NS presented also concomitant cancer. Age was the only risk factor for neoplasia. No association between cancer and gender, type of glomerulopathy, or known risk factors for neoplasia as alcohol, tobacco or viral infection was found.

PO1903

Complement Activation in a Mouse Model of Cisplatin-Induced Renal Interstitial Fibrosis

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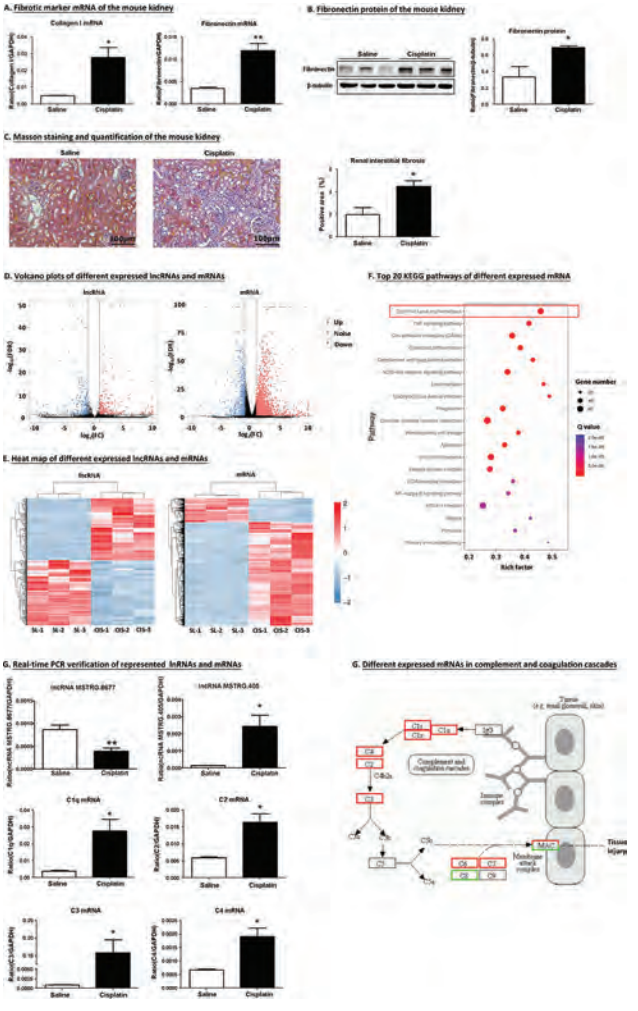
Background: Cisplatin is widely used for tumor chemotherapy. Renal interstitial fibrosis and chronic renal failure could be induced by periodic use of cisplatin. The mechanism of cisplatin induced renal interstitial fibrosis needs to be clarified.

Methods: In cisplatin group, male C57BL/6 mice were intraperitoneal injected with cisplatin(10mg/kg) on day 0, 7 and 21, and killed on day 28. In control group, mice were intraperitoneal injected with saline and killed at the same timepoint as cisplatin group. The kidney tissue was collected for RNA Illumina high-throughput sequencing, real-time PCR, western blot and masson staining.

Results: Through real-time PCR, western blot and masson staining, successful establishment of a mouse model with cisplatin induced renal interstitial fibrosis was confirmed. Through RNA high-throughput sequencing, 387 long noncoding RNAs(lncRNAs) and 2427 mRNAs were differently expressed between cisplatin group and control group. The expression of lncRNA MSTRG.8677 and lncRNA MSTRG.405 were verified by real-time PCR with the same tendency as RNA sequencing. Complement C3 was found to be at the top among the different expressed mRNAs by RNA sequencing. Several terms related to immunity were found to be within the top 20 terms through GO enrichment analysis of different expressed mRNAs. Systemic lupus erythematous pathway(ko05322,Q=3.4e-17), including the complement cascade pathway, was found to be the top pathway through KEGG enrichment analysis of different expressed mRNAs. The mRNA expression of C3, C1q, C2 and C4 were found to upregulated remarkably in cisplatin group by RNA sequencing and verified by real-time PCR.

Conclusions: Renal interstitial fibrosis could be induced by intraperitoneal injection of cisplatin periodically in mice, with complement cascade pathway activation in the diseased kidney.

Funding: Other NIH Support - National Natural Science Foundation of China(No.81800595)



PO1904

Changes in Humoral Biomarkers (Klotho) in Patients with Haematological Tumors Undergoing Chemotherapy and Allogeneic Bone Marrow Transplantation Developing AKI

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Background: Acute kidney injury (AKI) is a complication in patients with hematological cancers after chemotherapy (CT) receiving allogeneic bone marrow transplant. It increases the morbidity and mortality rate associated with the procedure. Some urinary/plasma biomarkers (Klotho) have been evaluated as predictors of AKI development after cardiac surgery showing high prognostic value

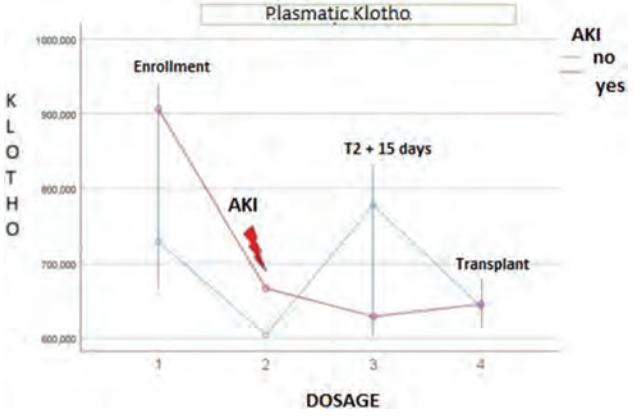
Methods: Our work is investigating the role and association of these determinants as early markers of susceptibility to AKI during CT, and predictors of CKD. So far, we have enrolled 13 leukemic patients who are candidates for induction CT and subsequent bone marrow transplantation. All the patients carried out sampling for renal function at each

cycle and at the same time plasma and urine were collected. Klotho plasma levels were measured in 4 phases diagnosis (t1); onset of AKI/2 months from diagnosis in patients without damage (t2); 15 days after t2 (t3); bone marrow tx (t4)

Results: We measured Klotho levels in 13 patients. The subjects are respectively 9 M and 4 F, mean age 49 years, all with normal renal function (mean creatinine 0.81 mg/dl) at diagnosis. The mean number of chemotherapy courses was 3.2. 7 patients developed stage I AKI according to AKIN criteria. No differences in anthropometric parameters were observed between the two groups. In subjects with development of renal damage, the average time of development was 2 months from diagnosis. While plasma Kl decreases in a similar way in the first CT in the two groups, in no-AKI group the filtrate return normal before the next cycle. The restoration of normal kidney function is not observed in the Aki group (MANOVA p <0.006)

Conclusions: This trend allows us to hypothesize that Kl is an indication of incomplete recovery of renal (tubular?) function before the next CT cycle, predisposing to the development of kidney disease

Funding: Private Foundation Support



PO1905

Systemic Amyloidosis Presenting as Progressive Dysphagia, Hypercalcemia, and Proteinuria

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Introduction: Systemic amyloidosis consists of several disorders whereby amyloid fibrils deposit in the extracellular tissue of multiple organs and as such, is associated with a wide spectrum of disease leading to significant morbidity and mortality. The severity and clinical manifestations of systemic amyloidosis is highly dependent on the site of amyloid fibril deposition.

Case Description: We present a 75-year-old male with no medical history who presented with dysphagia and epigastric abdominal pain. Lab work revealed moderate hypercalcemia and acute kidney injury (AKI) with urinalysis significant for >500mg/dL of protein. He received intravenous fluid resuscitation with improvement in renal function and temporary resolution of hypercalcemia. His AKI and hypercalcemia were attributed to volume depletion and possible milk-alkali syndrome due to consumption of calcium carbonate. After discharge however, he continued to have persistent sub-nephrotic range proteinuria, mild hypercalcemia and progressive renal insufficiency. UPEP and serum free light chain analysis revealed elevated kappa light chains. A kidney biopsy showed glomeruli with mesangial expansion as well as Congo red positive staining of glomeruli, interstitium, and vessels. Electron microscopy showed mesangial deposition of fibrillary material consistent with AL kappa light chain renal amyloidosis. Prior to follow up with Hematology, he was re-hospitalized for AKI, acute liver injury concerning for hepatic amyloidosis and progressive dysphagia likely due to gastrointestinal involvement. Therapy was initiated with bortezomib and dexamethasone; however, no significant kidney recovery was observed, and he remained dependent on dialysis. Due to rapid clinical decline, additional chemotherapy was not offered, and he was transitioned to comfort care.

Discussion: This patient presented with dysphagia, persistent hypercalcemia, renal insufficiency and proteinuria highlighting the clinical variability of systemic amyloidosis. As such, systemic amyloidosis, a rare infiltrative disorder, requires a high level of clinical suspicion in order to reach an early diagnosis and prevent long-term complications and mortality associated with advanced, multi-organ involvement. In addition, it is crucial to exclude coexisting multiple myeloma in patients presenting with hypercalcemia, renal insufficiency and AL amyloidosis.

PO1906

Will the Real Creatinine Please Stand Up? Elevated Creatinine in a Patient with Smoldering Myeloma

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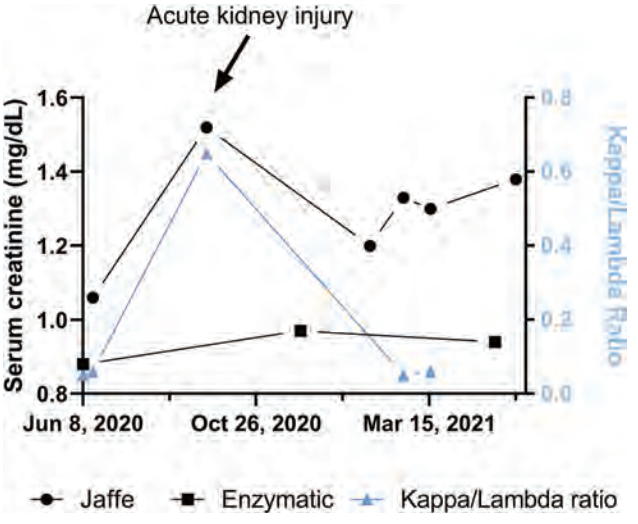
Introduction: Monoclonal gammopathies cause altered kidney function by a variety of mechanisms. The assessment of patients with monoclonal proteins is further complicated by non-physiologic alterations in laboratory assays, including the assessment of serum creatinine, as reported in this case of a patient with smoldering myeloma.

Case Description: A 47 yo woman with a history of mixed connective tissue disease, hypertension, and IgG lambda light chain smoldering myeloma was referred for evaluation of creatinine of 1.6 mg/dL. Her medications were acebutolol, furosemide, hydrochlorothiazide and aspirin. Examination revealed BP 129/86, HR 60 without notable physical findings. Her laboratory evaluation was significant for a creatinine of 0.88 mg/dL, BUN of 10 mg/dL, albumin of 4.6 g/dL and total protein of 9.0 g/dL, with an M-spike of 1 g/dL. Her urine protein-creatinine ratio was 0.47 g/g creatinine. Over the next year, creatinine at her primary oncologist ranged from 1.2-1.3 mg/dL (except for a single episode of acute kidney injury), while in the nephrology clinic the creatinine was 0.8-0.9 mg/dL. Further investigation determined that the external lab used a picric acid-based creatinine assay, while creatinine from the nephrology clinic was measured using an enzymatic method.

Discussion: Monoclonal proteins have previously been reported to interfere with creatinine assays, primarily in patients with Waldenstrom's macroglobulinemia. We report here a patient with a monoclonal IgG lambda paraprotein interfering with a Jaffe-based creatinine assay leading to pseudohypercreatininemia. Both nephrologists and oncologists should be aware of this phenomenon in the care of patients with all types of paraproteinemias, so that alternative means of kidney function assessment (such as measurement of cystatin c) can be employed when creatinine assays are unreliable.



Serum creatinine and kappa/lambda free light chain ratios

PO1907

A Unique Case of Light Chain Proximal Tubulopathy

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Introduction: Light chain proximal tubulopathy (LCPT), a rare form of monoclonal gammopathy of renal significance (MGRS), is characterized by the accumulation of monotypic light chains within proximal tubular cells. LCPT may present in multiple ways, including acute kidney injury, chronic kidney disease (CKD), Fanconi's syndrome, and proteinuria. We present a case of LCPT, presenting with CKD and non-nephrotic range proteinuria (NNRP).

Case Description: A 62 year old Caucasian male with a past medical history of IgM kappa light chain monoclonal gammopathy of undetermined significance (MGUS) presented for evaluation of CKD. Serum creatinine at the time of initial presentation was 1.4 mg%, which correlated with an estimated GFR of 54. No other electrolyte derangements were present. Urinalysis was negative for glycosuria, pyuria, or hematuria with unremarkable urine microscopy. He had NNRP on spot quantification of approximately 400 mg/g creatinine and 32 mg/g of this proteinuria was albuminuria. There was no history of hypertension or diabetes, and he denied NSAID use. He was taking no medications felt to cause chronic interstitial nephritis. Renal ultrasound was unremarkable, and 24 hour ambulatory blood pressure monitoring documented normal BP levels, on no medications. At follow up, the patient's creatinine fluctuated between 1.4-1.6 mg%, and his proteinuria between 400-600 mg/g creatinine. Renal biopsy was pursued because there was no apparent cause to explain his CKD. Biopsy revealed numerous kappa light chain crystalline structures within proximal tubular epithelial cells by immunofluorescence staining of paraffin sections, after pronase-digestion. There was no other evidence of multiple myeloma or Waldenstrom's macroglobulinemia on prior bone marrow biopsy. He subsequently began therapy with bendamustine and rituximab.

Discussion: We present a case of LCPT manifesting as CKD G3a A1-2. The case was indolent in nature, but was confirmed on renal biopsy using paraffin digestion to prove monoclonality of the crystalline deposits. This led to the diagnosis of a MGRS, and necessitated initiation of chemotherapeutic agents. LCPT is a rare manifestation of MGRS, and might not have been recognized in this case if suspicion had not been high, and biopsy had not been pursued.

PO1908

Deceiving Schistocytes

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Introduction: Myelodysplastic syndrome (MDS) is a clone bone marrow disorder characterized by dyshematopoiesis, which may manifest as cytopenias and non-immune hemolytic anemia. Schistocytes are commonly associated with causes of microangiopathic hemolytic anemia (MAHA), however, schistocytosis with a high reticulocyte count in the peripheral blood smear is a rare and unusual manifestation of MDS.

Case Description: We report the case of a 63-year-old male who presented with complaints of asthenia, fatigue and malaise for the past 3 months. His previous medical history included a past of heavy smoking, arterial hypertension and grade 3 chronic kidney disease (CKD) developed after nephrectomy due to urothelial carcinoma in 2012. He also had in situ papillary urothelial carcinoma of the bladder in 2016, with a course of intra-vesical mitomycin. Vital signs were normal and physical examination was unremarkable. Blood work revealed macrocytic anemia (hemoglobin 7.2g/dL; MGV 101fL) and thrombocytopenia (77.000/μL) and peripheral blood smear demonstrated 16% schistocytes, with normal coagulation tests, lactate dehydrogenase and haptoglobin. Coombs test was negative. Renal function was stable and there was no evidence of hematoproteinuria. Inflammatory markers were negative. A diagnosis of microangiopathic anemia was assumed and the patient was started on daily plasmapheresis and steroids, while further investigation was under way. Folate and cobalamin levels were normal, anti-nuclear antibodies and HIV, hepatitis B and C serologies were negative and full-body CT scan did not show signs of occult malignancy. Levels of C3 and C4 were also within the normal range. ADAMTS-13 activity was 21%. No clinical or analytical improvement was noted after 6 sessions of plasmapheresis (platelet count nadir of 38.000/μL and persistence of schistocytosis). Bone marrow biopsy was performed and a diagnosis of refractory anemia with excess blasts was made.

Discussion: Hemolytic anemia is a common occurrence in patients with hematologic malignancies, particularly acute and chronic myeloid leukemia, but are rarely observed in MDS, with only a few cases reported in the literature. This case highlights the importance of considering a diagnosis of MDS in patients presenting with refractory cytopenias and MAHA.

PO1909

Granulomatous Interstitial Nephritis Secondary to Chronic Lymphocytic Leukemia

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Introduction: Granulomatous interstitial nephritis (GIN) is a rare disorder defined by histological interstitial nephritis and interstitial granulomas. Common association includes medications, sarcoidosis, and infections. We present a less common case of GIN secondary to chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Case Description: A 57 year old male with benign prostatic hypertrophy presented in early 2020 with leukopenia, lymphadenopathy, and sicca symptoms. A lymph node biopsy in March 2020 revealed non caseating granulomatous lymphadenitis diagnosed as sarcoidosis without clear pulmonary involvement and treated with steroids. His creatinine (Cr) was 0.83 mg/dL, calcium 9.5 mg/dL, white blood cell count of 2600, hemoglobin 12.6 g/dL, platelet count of 322,000, lactate dehydrogenase 1094 U/L, uric acid 8.3 mg/dL, negative SS-A/SS-B, negative Epstein Barr Virus, angiotensin converting enzyme 70 U/L, and a normal urinalysis. In August 2020, his Cr rose to 4.24 mg/dL, with urine studies notable for 1+ protein and rare eosinophils. He had negative hepatitis B, hepatitis C, ANA, MPO, and PR3. His free kappa/lambda ratio was 1.89 (normal) and negative serum protein electrophoresis. PET/CT showed non-FDG avid diffuse lymphadenopathy. Renal biopsy revealed mesangial hypercellularity, severe interstitial inflammation, a lymphocyte predominant infiltrate with CD 20 positive B cells and non-caseating granulomas with eosinophils. He was diagnosed with GIN with atypical B cell lymphoid infiltrate. His prednisone dose was increased and he underwent a bone marrow biopsy revealing a CD5+ B cell lymphoproliferative disorder, consistent with Stage 4 CLL/SLL. Cytogenetics revealed trisomy 12 with significant bone marrow involvement, indicating an intermediate prognosis. He is being treated with Obinutuzumab and venetoclax with improvement in his Cr to 2.19 mg/dL.

Discussion: Our case report recapitulates findings from a prior case series in 2015. Search of University of Pittsburgh Pathology database from 2010-2020 yielded no patient with a diagnosis of GIN secondary to CLL. Our patient had partial renal recovery with steroids, obinutuzumab, and venetoclax indicating the efficacy of this regimen compared to rituximab, cyclophosphamide, and steroids. Our case highlights a rare entity of GIN that maybe underdiagnosed in patients with CLL.

PO1910

A Case of Oncogenic Osteomalacia with Urinary Phosphate Wasting Masked by AKI

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Introduction: Hypophosphatemia in patients with oncogenic osteomalacia (OO) is due to excess production of fibroblast growth factor 23 (FGF-23) causing urinary phosphate wasting. However, in patients with coexisting acute kidney injury (AKI), hypophosphatemia may normalize as the AKI worsens potentially masking renal phosphate wasting. In-appropriately low or normal phosphorous levels in patients with AKI should prompt further work up to identify potential renal phosphate wasting.

Case Description: 36-year-old morbidly obese woman presented with right-sided abdominal pain and fatigue for 2 weeks. Initial laboratory evaluation revealed AKI (Cr 2.1 mg/dL, baseline 1.2) that failed IV fluid therapy prompting nephrology consultation. Other labs included urine protein creatinine ratio 0.2 g/g, alkaline phosphate (895 U/L), mild hyperbilirubinemia (1.8 mg/dL), mild hypercalcemia (corrected Ca 11 mg/dL), hypophosphatemia (1.8 mg/dL), low vitamin D (28 ng/mL), normal PTH (19 pg/mL), normal PTHrP (2.2 pmol/L) and low normal calcitriol (28 pg/ml). Kidney ultrasound was normal. Liver ultrasound revealed an ill-defined mass not seen in CT scan. FGF-23 levels were sent due to suspicion of OO and returned very high at 12,715 RU/ml. Patient was readmitted to the hospital for accelerated work up to identify the source of FGF-23. Repeat labs on admission showed Cr of 2.2 mg/dL, normal phosphorous 3.2 mg/dL and bilirubin 12 mg/dL. Random liver biopsy showed tumor cells positive for CD56 and Ki-67, with a proliferation rate of 80% indicating high grade metastatic neuro endocrine tumor. Localization of primary tumor was unsuccessful. Oncology was consulted and chemotherapy was entertained, but the patient rapidly deteriorated and opted for comfort measures.

Discussion: Reduced phosphate excretion in patients with AKI leads to hyperphosphatemia, stimulating FGF-23 production to facilitate phosphaturia. However, when AKI is associated with inappropriately low or normal phosphate levels, renal phosphate wasting from other causes should be suspected. Fractional excretion of phosphate might also be falsely low as the decreased eGFR can potentially hinder phosphate excretion. Early detection and accelerated work up could potentially lead to early diagnosis and appropriate treatment.

PO1911

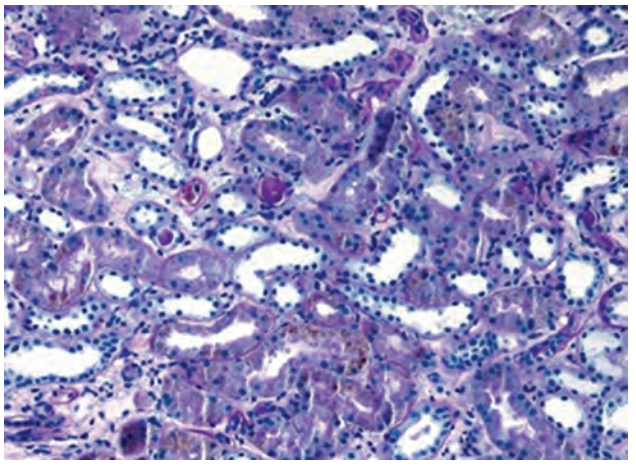
Lysozyme Nephropathy: A Rare Yet Treatable Cause of AKI in Chronic Myelomonocytic Leukemia

Andrew Donati, Anushree C. Shirali. *Yale University School of Medicine, New Haven, CT*.

Introduction: Lysozyme is a small lytic enzyme with bactericidal properties synthesized by monocytes that is freely filtered by the glomerulus. It can be produced in large quantities by neoplastic cells of monocytic lineage resulting in nephrotic range proteinuria (lysozymuria). Lysozyme can accumulate in proximal tubular cells thereby causing toxic injury resulting in tubular cell injury.

Case Description: A 69 year old woman was referred to nephrology clinic for evaluation of elevated serum Cr. Her past medical history included Type-2 Diabetes Mellitus, Hypertension, Hyperlipidemia, JAK2/V617F-positive Polycythemia Vera, Chronic Myelomonocytic Leukemia, bilateral renal angiomyolipomas and gout. Physical exam was unremarkable. Lab data were notable for creatinine (Cr) 1.7 mg/dL (baseline 1.2), Calcium 11.1 mg/dL, Uric acid 7.7 mg/dL, WBC 65.1 x 1000/uL (ANC 40.4; Monocytes 14.3), Hemoglobin 11.6 g/dL and Platelets 141 x 1000/uL. Electrolytes, liver function tests, and viral hepatitis serologies were within normal limits. Urinalysis was unremarkable. Urine albumin/Cr ratio was 79.4 mg/g of creatinine. A kidney biopsy was performed. Light microscopy revealed focal acute tubular injury and PAS-positive cytoplasmic granules. Electron microscopy revealed electron dense aggregates in the cytoplasm of the proximal tubular cells. Serum lysozyme was > 60 mcg/mL (reference range 5-11 mcg/mL). A diagnosis of lysozyme-induced nephropathy (LyN) was made. Repeat bone marrow biopsy revealed myeloid neoplasm with 13% blasts. She started treatment with Decitabine/Cedazuridine and her WBC improved to < 10 1 x 1000/uL and her Cr improved to 1.2 mg/dL.

Discussion: This case demonstrates an uncommon and often under-recognized cause of acute tubular injury in patients with chronic myelomonocytic leukemia. Lysozyme-induced nephropathy can be reversed with targeted therapy.



Light microscopy revealed focal acute tubular injury and PAS-positive cytoplasmic granules (PAS stain).

PO1912

Lymphomatous Infiltration of the Kidney in a Patient with Waldenstrom Macroglobulinemia

Prasanth Ravipati, Lihong Bu, Zohar Sachs, Patrick H. Nachman. *University of Minnesota Twin Cities, Minneapolis, MN.*

Introduction: Kidney disease can be an initial presentation or a chronic manifestation of plasma cell dyscrasias. The aim of this case report is to illuminate a rare presentation of kidney disease driven by lymphomatous infiltration of the kidney in a patient with Waldenstrom's Macroglobulinemia (WM).

Case Description: A 70 year old female with an 8 year history of WM (IgM, kappa) was referred for declining renal function. Four months prior to presentation, she had stable WM disease activity and was without symptoms of worsening disease burden. In November of 2020, she was hospitalized with SARS-CoV-2 infection with respiratory failure and acute kidney injury (AKI). Her serum creatinine (sCr) peaked at 3.7 mg/dL from a baseline of 0.9 mg/dL, but recovered to a sCr of 1.1 mg/dL by the time of discharge. Two months after discharge, her renal function began to decline prompting nephrology referral. Her sCr had risen to 1.9 mg/dL and she had new onset proteinuria of 1.5 g/day. A kidney biopsy showed lymphomatous infiltration of the tubulointerstitium without glomerular involvement. Immunofluorescence microscopy showed strong IgM and kappa stain but minimal lambda stain. Immunohistochemistry showed heavy interstitial staining for CD20 + B cells, and the presence of CD138 + plasma cells. Treatment with rituximab and bendamustine resulted in an improvement in renal function (sCr 1.4 mg/dL).

Discussion: WM is an uncommon hematologic malignancy, and extramedullary involvement is rare. Only 7% of a cohort of patients with WM who underwent kidney biopsy had lymphomatous infiltration of the kidney [Higgins et al., CJASN 2018]. In our case, the differential diagnosis was broad given the patient's modest proteinuria and kidney dysfunction in the context of recent AKI and hospitalization. Considerations included paraprotein related disease, medication related interstitial nephritis, or possibly an undefined sequela of SARS-CoV-2 infection. This case emphasizes the importance of surveillance for kidney dysfunction in patients with plasma cell dyscrasias, even if patients appear to have stable lymphoproliferative disease. Additionally, the effects of SARS-CoV-2 infection in patients with indolent lymphomas is unknown, but it is noteworthy that our patient developed lymphomatous kidney involvement after initial recovery of AKI in the setting of SARS-CoV-2 infection.

PO1913

Beware of the "B": Type B Lactic Acidosis and Atypical Renal Interstitial Infiltrate

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Introduction: Lactic acid is an endogenous substrate for gluconeogenesis produced by muscle and other tissues. Lactate is the anion of lactic acid and is a source of base though Kreb's cycle. Lactic acid levels can increase due to impaired oxygen delivery (type A) or impaired oxygen utilization by cells (Type B). Here we describe a patient with an unusual presentation of lactic acidosis, and atypical renal interstitial infiltrate.

Case Description: A 32-year-old female with a history of chemotherapy and allogeneic bone marrow transplant in 2018 due to pre-B cell acute lymphoblastic leukemia (ALL) presented with concerns of sepsis due to suspected appendicitis and abnormal labs (pH 7.2, anion gap of 23, bicarbonate level of 10 mmol/L). Her lactate persistently ranged from 10-14 mmol/L despite antibiotics and bicarbonate containing fluids. Additionally, labs were consistent with acute kidney injury (Creatinine (Cr) 1.8 mg/dL from a baseline of 0.8 mg/dL). A kidney biopsy was performed given unexplained rise in Cr and enlarged kidneys (14 cm on renal ultrasound) which was suggestive of significant interstitial nephritis and tubulitis. Further immunohistochemical stains ordered due to suspicion of ALL reoccurrence, showed a mixture of CD3 and CD20-positive lymphocytes as well as CD68-positive cells. The atypical interstitial infiltrate was positive for CD10, CD45, CD79A, TDT, and PAX-5, consistent with B-cell leukemia. Flow cytometry and bone marrow biopsy confirmed the relapse of pre B-cell ALL. The patient was treated with steroids and blinatumomab, resulting in improvement in kidney function and resolution of lactic acidosis.

Discussion: Although our patient had lactic acidosis and AKI in the setting of presumed sepsis, a common clinical presentation, she had a completely different diagnosis. Her persistent lactic acidosis and atypical interstitial infiltrate led to the diagnosis of relapsed ALL with kidney involvement. Malignancy causes Type B lactic acidosis due to increased tumor cells' metabolism, overexpression of cellular glycolytic enzymes, mitochondrial dysfunction, thiamine, and riboflavin deficiency. Tumor cells have a high rate of glucose uptake and preferential production of lactate, even in the presence of oxygen, known as "Warburg effect." Type B lactic acidosis from malignancy overall portends a poor prognosis. The goal of therapy is to target the underlying malignancy.

PO1914

A Case of Hemophagocytic Lymphohistiocytosis (HLH) due to Large B Cell Lymphoma with infiltration in the kidneys

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Introduction: Secondary HLH is a life-threatening manifestation of certain malignancies and prompt diagnosis is essential in preventing poor outcomes. Kidney involvement in Large B cell lymphoma is under-reported and diagnosis can be challenging in the absence of abnormal kidney function.

Case Description: A 55-year-old male with no significant history was admitted to our facility with worsening mental status. He had 2 prior hospitalizations at an outside facility where he was treated with steroids for a presumed auto-immune CNS syndrome and partial improvement in symptoms. Vitals signs were normal on arrival and he was non-verbal on exam with right sided weakness. Lumbar puncture was negative for infection or malignant cells on analysis. MRI brain showed contrast enhancing lesions. Hospital course was complicated by persistent fevers, a rise in Serum creatinine (Scr) to 1.5md/dl on day 4 of admission in addition to new worsening thrombocytopenia and evidence of ongoing hemolytic anemia. Urinalysis revealed hematuria, no proteinuria, few WBCs but no active sediment. Other lab parameters were relevant for LDH of 3000, Ferritin >3000, TG of 1171 and soluble IL-2 receptor level elevated at >33,000. Patient met clinical criteria for HLH with concerns over a thrombotic microangiopathy (TMA) related to HLH and therefore a kidney biopsy was performed which revealed a diffuse atypical lymphocytic interstitial infiltrate, consistent with large B-cell lymphoma. No evidence of TMA was seen. A bone marrow biopsy performed at the same time, confirmed diffuse large B cell lymphoma with pleomorphic features and extensive involvement. A diagnosis of HLH secondary to Large B-Cell Lymphoma with infiltration to the bone marrow & kidneys was made. The patient's clinical condition deteriorated, and continuous form of renal replacement therapy was started in ICU. Chemotherapy was initiated, however he remained critically ill with worsening lactic acidosis, multi-organ failure and ultimately expired from cardiopulmonary arrest.

Discussion: Malignancy associated HLH is a challenging diagnosis which is often misdiagnosed. Diffuse large B cell lymphoma infiltrating the kidney confers a poor prognosis and this case illustrates the utility of a kidney biopsy in early diagnosis of a diffuse lymphoproliferative disorder which can improve patient outcomes

PO1915

A Unique Case of Paraneoplastic Lupus Nephritis Biopsy Finding in a Patient with Head and Neck Cancer

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Introduction: Rheumatic disease can be one of manifestations of paraneoplastic syndrome. We present a case of supraglottic squamous cell carcinoma (SCC) associated nephrotic syndrome and kidney biopsy suggestive of lupus-like changes.

Case Description: 56-year-old male with past medical history of hypertension, opioid abuse (on methadone) and an active smoker was admitted to the hospital for evaluation of painful neck swelling which he first noticed four days prior to admission. Examination was remarkable for lower extremity edema and left neck mass. Nephrology was consulted for evaluation of nephrotic syndrome. Significant laboratory workup revealed spot urine protein/creatinine ratio of 19 grams, serum albumin 2.2 g/dl and a normal serum creatinine 0.9 mg/dl. Serological workup for proteinuria including phospholipase A2 receptor antibody (PLA2R Ab) was negative. Biopsy of the neck mass was suggestive of supraglottic squamous cell carcinoma, subsequently treated with carboplatin and radiotherapy. A kidney biopsy was done for further evaluation. While there were no glomerular changes on light microscopy, immunofluorescence (IF) showed full house capillary staining (IgG, IgM, IgA, C3, C1q, kappa and lambda light chains). Also, enhanced glomerular staining for PLA2R was seen. Electron microscopy revealed sub epithelial deposits. Given lupus like finding on IF, serologies were tested and were negative. Given absence of systemic symptoms of lupus, negative serologies and negative PLA2R Ab, presumed diagnosis of membranous glomerulonephritis secondary from malignancy was made. He was treated conservatively with diuretics, angiotensin convertase inhibitor and anticoagulation for thromboembolism prevention. Proteinuria improved with above treatment, however patient expired due to tumor complications and metastasis.

Discussion: Paraneoplastic systemic lupus erythematous has been reported in patients with solid tumors. Proposed hypothesis is tumor driven breakdown of self-tolerance antigens, which causes generation of auto antibodies. Auto immune disease usually precedes the diagnosis of malignancy and patients develop symptoms later. Our

case is unique, although biopsy was indicative of lupus nephritis, patient had no clinical or laboratory finding for lupus. Nephrologist and oncologist should be aware of this rare clinical association for appropriate diagnosis and management

PO1916

Light Chain Deposition Disease (LCDD) in the Setting of Smoldering Myeloma (SM)

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Introduction: Only 50-60% of patients with LCDD meet the criteria for multiple myeloma (MM). SM, a proliferative plasma cell disorder is a precursor for active symptomatic MM. As LCDD is rare, there is limited data for the treatment of LCDD in the setting of SM.

Case Description: A 49-year-old female was found to have proteinuria and microscopic hematuria during a routine workup. Further evaluation showed proteinuria of 4.0 g/day, serum creatinine of 1.3 mg/dL, kappa light chain (KLC) 94.7 mg/dL, lambda light chain (LLC) 1.57 mg/dL, kappa-Lambda ratio (K/L) 60.24, Hemoglobin 12.8 g/d, Calcium 9.26 mg/dl. Kidney biopsy showed nodular mesangial expansion with mild hypercellularity. Moderate tubular atrophy and interstitial fibrosis. Immunofluorescence showed strong kappa staining of mesangium, glomerular, and tubular basement membrane (TBM) with negative lambda staining. Electron microscopy showed the presence of subendothelial, mesangial, and TBM electron dense deposits. Findings were considered to be consistent with kappa associated LCDD. Bone marrow biopsy showed monoclonal plasma cell population in the bone marrow (5% by flow cytometry and 10-15% by CD138 stain) consistent with smoldering myeloma. FISH was abnormal for monosomy of 13 and 11;14 translocation. The skeletal survey was negative for any lytic lesions. She was treated with Bortezomib/Dexamethasone/Cyclophosphamide based regimen weekly for 8 weeks which resulted in a decrease in KLC to 1.45 mg/dl, LLC to 1.0 g/dl, and K/L ratio to 1.45 with negative serum immunofixation. 24-hour urine protein improved to 2.6 g/d. Serum creatinine remained stable at 1.3 mg/dl. Bone marrow biopsy after chemotherapy showed residual plasma cell myeloma involving 5% of the marrow cells. She underwent high dose melphalan followed by Autologous Stem Cell Transplantation (HDM/ASCT). Follow-up labs six years later confirmed successful treatment with serum creatinine improving to 1.02 mg/dl, 24hr-urine protein 484mg/d without microscopic hematuria. SPEP and UPEP remain negative.

Discussion: We report a case of successfully treated LCDD with high dose chemotherapy followed by HDM/ASCT in the setting of smoldering myeloma with six years of follow-up. Patients with LCDD in smoldering myeloma may benefit from high dose chemotherapy along with HDM/ASCT and it should be considered a treatment option.

PO1917

Delayed Thrombotic Microangiopathy Post Bone Marrow Transplant, an Atypical Presentation: A Case Report

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Introduction: Thrombotic Microangiopathy (TMA) is a potentially lethal complication of Bone Marrow Transplantation (BMT). We report a case of delayed TMA post-BMT which was successfully treated with Rituximab.

Case Description: A 53-year-old male known to have hepatosplenic gamma-delta T-cell lymphoma (HSTCL) was referred for evaluation of worsening creatinine. He was diagnosed with HSTLC 6 years ago that was refractory to multiple therapies, and ultimately, two years later, he received Double Unit Cord Blood (dUCB) transplantation with good response and minimal residual disease. Despite receiving tacrolimus and mycophenolate mofetil (MMF) for prophylaxis of Graft versus Host Disease (GVHD), he developed mild popular rash consistent with Grade I GHVD skin and recurrent pneumonitis concerning for lung GHVD which responded to steroids. The tacrolimus and MMF were discontinued and steroids were gradually tapered off. Eight months post-transplant, serum creatinine (sCr) started to gradually increase from a baseline of 1.0 mg/dL. We were consulted eighteen months post-dUCB when sCr reached 1.8 mg/dL. Additional evaluation showed mild proteinuria (UPCR 0.77 g/g of creatinine), no active urine sediment, low haptoglobin (< 30 mg/dL) and worsening thrombocytopenia (105 THO/μL). A renal biopsy showed glomeruli with variable capillary wall thickening and double contours, moderate fibrosis of 40-50%, negative immunofluorescence for complement and immunoglobulin, and the electron microscopy showed subendothelial expansion and endothelial swelling. These findings were compatible with chronic TMA lesion concerning for renal GVHD. The patient was treated with weekly Rituximab 375 mg/m^2 for a total of 4 doses with stabilization of sCr and normalization for hemolysis labs, including normalization of platelet count.

Discussion: TMA is a well described complication post-BMT with multifactorial etiology (medication, GVHD, radiation, etc.) with early onset within the first 30-45 days after transplantation, and the mortality rate is approximately 30-80%. Our patient had the unusual delayed presentation post-BMT (after 18 months). Although historically not the first line, several case reports have been published showing use of Rituximab, an anti-CD20 monoclonal antibody, with positive response.

PO1918

A Rare Case of Monoclonal Gammopathy of Renal Significance

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Introduction: Monoclonal gammapathy of renal significance represents a group of disorders in which monoclonal immunoglobulin secreted by a non malignant or premalignant B cell or plasma cell clone causes renal damage. These disorders do not meet diagnostic criteria for multiple myeloma or lymphoproliferative disorder.

Case Description: 64 year old female with hx of hypertension, presented to ED for worsening lower extremity edema, dyspnea. She was admitted for CHF exaceration. Admission creatnine was 2.0 (prior baseline 1.0). She developed resistence to diuretics with worsening renal failure requriing dialysis. She had 6.0 grams of proteinuria. Kidney biopsy showed ATN, and findings consistent with PGNMIG with IG3k. She had spep/upep/free light chains ratio which were all normal. Bone marrow biopsy was normal. Since no clone had been identified to guide treatment, plan made to treat her with bortexumib, cytoxan and dexamethasone.

Discussion: -PGNMIG is a monclonal gamopathy which resembles immune complex GN - Most comman pattern seen in PGNMIG is IG3k (this is more nephritogenic and has ability to activate compliment cascade causing inflammatory damage. Majority of the patient with PGNMID do not have clone identified. In such patients treatment is empiric with bortexumib/cytoxan/dexamethasone or rituximab.

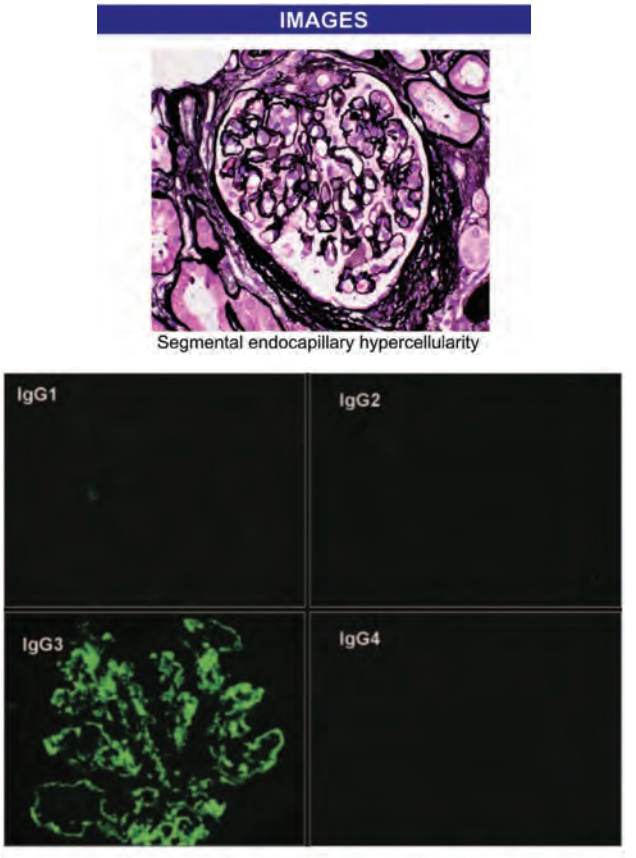

Figure 5. On IF staining for IgG subtypes, there is strong glomerular positivity for IgG3 with negative staining for IgG1, IgG2, and IgG4. Magnification, ×400.

PO1919

Review of Onconephrology Cases: An Insight from the Middle East

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Background: Onconephrology is a new subspecialty of nephrology and its data was sparse from the middle east. We have collected data of cancer patients admitted to a tertiary care center and referred to the department of Nephrology to recognize the most common preventable causes of AKI and their outcome in this patient population

Methods: We conducted a retrospective observational study of 39 admitted cancer patients referred to the department of Nephrology between November 2020 and March 2021.

Results: In our study 69% were males, 31% were females. Tumors were;prostate cancer(n=6), bladder cancer (n=5), RCC (n=5), HCC(n=4) and Colon cancer (n=3), breast cancer (n=3), unknown primary (n=2), (n=1) were SCC, tongue, ovary, thyroid, endometrial cancerand laryngeal cancer, additioanlly B cell lymphoma (n=1)and multiple myeloma (n=4). Background history of CKD was present in, 38% (n=15) of the cohort. CKD stage 3 was the most prevalent (n=10). 1 patient had ESRD and maintained on dialysis and 2 patients had undergone a kidney transplant. Recurrent AKIs were most common (n=6), followed by nephrectomy (n=4) and hypertension (n=4), other included diabetes mellitus, urinary tract obstruction, atrophic kidneys, and multiple myeloma. Causes of AKI were Sepsis 30%, hypovolemia 12%, urinary tract infection 10.2%, drug-induced AKI 10% & Hypercalcemia 7.6%.Less common causes were hemorrhagic shock and IV iodinated contrast exposure. Only 33% of the study population was actively receiving oncotherapy at the time of admission. Amongst the cohort, 48% were oliguric and the rest were non-oliguric. A total of 16 patients, received renal replacement therapy during admission; CRRT was done in 10/16 patients, 5/16 patients received conventional hemodialysis and 1 patient received both modalities. Amongst the patients requiring CRRT, the survival rate was 21%, and for patients who received hemodialysis, the survival rate was 50%.41% of the patients died during the admission; 62% of the deaths were deemed secondary to underlying cancer and the remaining 38% were attributed to other causes; the most common being sepsis.

Conclusions: Our study reiterates the importance of prevention of AKI by early recognition and prompt management of risk factors. This study prompts the need for quality improvement initiatives aiming at improving the outcomes of such patients at all tertiary care centers

PO1920

Pseudohyperkalemia Leading to Pseudohyponatremia in Severe Leukocytosis

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Introduction: Electrolyte abnormalities are common in oncologic malignancies. However spurious derangements are rarer. Here we present a case of coexisting reverse pseudohyperkalemia and pseudohypoanatremia in chronic lymphocytic leukemia.

Case Description: An 84 year old male was diagnosed with chronic lymphocytic leukemia after presenting with weight loss and fevers. Labs showed a WBC of 760 K/mcl, Plasma sodium was 133 Meq/L, plasma potassium 8.8 Meq/L, BUN 15mg/dl, Creatinine 2.8 mg/dl and a GFR of 20 ml/min. Urine analysis showed 100 mg/dl of protein, 300 mg/dl of glucose and small blood. Urine sodium of 82 meq/L and osmolality of 444 mosmol/kg with serum osmolality of 300 mosmol/kg. EKG did not show any hyperkalemic changes. He received insulin, dextrose and kayexalate. Repeat plasma potassium was 10.7 Meq/L. Given high suspicion for reverse pseudohyperkalemia due to leukocytosis, serum labs were sent. Serum potassium was 4.2 Meq/L and serum sodium 134 Meq/L with a concurrent plasma Potassium of >9.0 Meq/L and plasma sodium of 127 Meq/L. The WBC count remained elevated at 693.2 K/mcl. The serum sodium is measured at our institution with direct ion-specific electrode method making derangements from hyperlipidemia and hyperproteinemia unlikely. Treatment was started with methylprednisolone and Rituximab for CLL. The WBC count trended down from 693 to 339.5 K/mcl. Serum potassium remained stable (3.7-4.9) as well as serum sodium (138-141) with concurrent plasma values decreasing in disparity from potassium >9Meq/L to 4.9 Meq/L and sodium 127 Meq/L to 139 Meq/L as the WBC count decreased.

Discussion: This case portrays a challenging case of reverse pseudohyperkalemia and pseudohyponatremia in severe lymphocytosis. While the phenomenon of pseudohyperkalemia in leukemia/lymphomas is established, reverse pseudohyperkalemia where plasma potassium is falsely elevated compared to normal serum levels is lesser known. Furthermore, no mechanism has been established for pseudohyponatremia in plasma samples compared to serum samples in leukocytosis however it was postulated that sodium levels decrease reciprocally to potassium due to potassium release from the leukocytes. Hence in cases of reverse pseudohyperkalemia serum samples are preferred over plasma samples. Parameters need to be established to avoid treatment of spurious electrolyte disorders to avoid treatments resulting in hypokalemia and hypernatremia.

PO1921

Light Chain Proximal Tubulopathy Without Fanconi Syndrome as the Sole Presenting Feature of Multiple Myeloma

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Introduction: Light chain proximal tubulopathy (LCPT) is a rare pattern of immunoglobulin-related renal injury that occurs in the setting of dysproteinemias. Classic disease associations for LCPT are multiple myeloma, monoclonal gammopathy of renal significance, and other hematolymphoid neoplasms. The key LCPT pathologic feature is the accumulation of monoclonal light chains within the cytoplasm of proximal tubule (PT) cells with resultant clinical PT defects, proteinuria, and renal dysfunction.

Case Description: A 64-year-old male with prostatic adenocarcinoma presented for evaluation of incidentally discovered proteinuria (3.852 g/g creatinine) and stage two chronic kidney disease. Initial evaluation was significant for a kappa/lambda ratio of 474.79, serum M-spike of 0.9 g/dL, and urine M-spike of 1.082 g/dL. Urine immunofixation electrophoresis revealed 94.1% Bence-Jones protein (1.629 g/24h) comprising monoclonal IgG, kappa type. Other laboratory features of myeloma (hypercalcemia, anemia) were absent. Renal biopsy revealed monoclonal kappa light chain crystal inclusions in the cytoplasm of PT epithelial cells. Glomeruli show no significant histologic or ultrastructural abnormalities. Despite the severe histopathologic dysfunction, no clinical features of Fanconi Syndrome were present, including a negative work up for renal tubular acidosis as well as no renal wasting of phosphorous, amino acids, glucose, uric acid, or potassium. PET scan revealed diffuse marrow infiltrating disease with multiple lytic osseous lesions, and the patient was referred to oncology to begin chemotherapy.

Discussion: LCPT continues to be a rare pattern of kidney injury with significant variability in presentation based largely on the composition of the light chains. The toxicity of kappa light chains results from their ability to form crystals, which resist lysosomal proteolysis. Although our patient had extensive crystalline inclusions and significant evidence of tubular injury, no clinical evidence of proximal tubulopathy was evident with proteinuria as the sole presenting feature of diffuse myeloma. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

PO1922

Monoclonal Gammopathy of Renal Significance: Not Reserved for the Elderly

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Introduction: Monoclonal gammopathy of renal significance (MGRS) is defined by renal involvement of monoclonal immunoglobulins in the absence of other organ involvement. MGRS includes a wide variety of renal lesions. It is particularly important to distinguish MGRS from monoclonal gammopathy of undetermined significance (MGUS), as early treatment improves renal survival.

Case Description: 36F with a history of pre-eclampsia, stage II chronic kidney disease, and hypertension well-controlled on valsartan 320 mg and metoprolol succinate 100 mg, presented 2 years postpartum with worsening hypertension and proteinuria. Initial urinalysis was positive for 3+ proteinuria and 2+ blood, with dysmorphic RBCs on sediment. Urine protein to creatinine ratio (UPC) was 1574 mg/g Cr. ANA and ANCA were negative, and complements were normal. Her creatinine rose from 1.2mg/dL to 1.8mg/dL over the next two years, and proteinuria rose to 4.7 g/d. Renal biopsy confirmed IgG kappa monoclonal immunoglobulin deposition disease, with large subepithelial deposits and moderate tubular injury, with 20% global and segmental glomerulosclerosis, 10% interstitial fibrosis and tubular atrophy, and moderate vascular sclerosis. Serum and urine immunofixation and serum free light chain ratio were normal. Bone marrow biopsy was also negative, confirming the diagnosis of MGRS. She was treated with dexamethasone and bortezomib for a year, followed by lenalidomide, with stabilization of her renal function and proteinuria for over 3 years. Her creatinine is 2.4mg/dL and UPC is 354mg/g Cr. She has been off therapy for 4 months with no change.

Discussion: There has been historical resistance to treat MGRS, as it does not meet criteria for a proliferative disorder and chemotherapy toxicity is of concern. However, it is associated with progression to CKD/ESRD without treatment. Treatment depends on renal pathology and clone type, and may include proteasome inhibitors, alkylating agents, or immunomodulators. Certain forms of MGRS, such as AL amyloidosis, may benefit from autologous hematopoietic stem cell transplantation due to its high rate of recurrence. Her young age is an unusual feature of MGRS. This case highlights the need for renal biopsy in patients with worsening proteinuria and renal function out of proportion to hypertension, and the role of chemotherapy in MGRS to change the trajectory of disease.

PO1923

Variable Expression of Eighteen Common Housekeeping Genes in Human Non-Cancerous Kidney Biopsies

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Background: Housekeeping, or reference genes (RGs) are, by definition, loci with stable expression profiles that are widely use as internal controls to normalize mRNA levels. However, due to specific events, such as pathological changes, or technical procedures, their expression might be altered, failing to fulfil critical normalization pre-requisites.

Methods: To identify RG genes suitable as internal controls in human non-cancerous kidney tissue, we selected 18 RG candidates based on previous data and screen them in 30 expression datasets (>800 patients), including our own, publicly available or provided by independent groups. Datasets included specimens from patients with hypertensive and diabetic nephropathy, Fabry disease, focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, and minimal change disease. We examined both microdissected and whole section-based datasets. Expression variability of 4 candidate genes (*YWHAZ*, *SLC4A1AP*, and *ACTB*) was further examined by qPCR in biopsies from patients with hypertensive nephropathy (n=11) and healthy controls (n=5).

Results: Only *YWHAZ* gene expression remained stable in all datasets whereas SLC4A1AP was stable in all but one Fabry dataset. All other RGs were differentially expressed in at least 2 datasets, and in 4.5 datasets on average. No differences in *YWHAZ*, *SLC4A1AP*, *RPS13* and *ACTB* gene expression between hypertensive and control biopsies were detected by qPCR.

Conclusions: Although RGs suitable to all techniques and tissues are unlikely to exist, our data suggest that in non-cancerous kidney biopsies expression of *YWHAZ* and *SLC4AIAP* genes is stable and suitable for normalization purposes.

PO1924

Comparison of Proteomic Methods in Evaluating Biomarker-AKI Associations in Cardiac Surgery Patients

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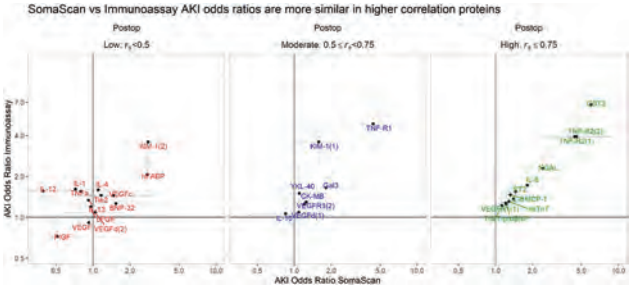
Background: Although immunoassays are the most widely used protein measurement method, aptamer-based methods such as the SomaScan platform can quantify up to 7,000 proteins per sample, creating new opportunities for unbiased discovery.

Methods: In a substudy of the TRIBE-AKI cohort, preop and postop plasma samples from 294 patients with previous immunoassay measurements were analyzed using the SomaScan platform. Inter-platform Spearman correlations (r_s) and AKI associations were compared across 30 preop and 34 postop immunoassay-aptamer pairs. Possible factors contributing to inter-platform differences were tested for association with inter-platform correlation, including target protein, experimental, immunoassay, and aptamer characteristics.

Results: The median r_s was 0.54 (IQR 0.34-0.83) in postop samples and 0.41 (IQR 0.21-0.69) in preop samples. We observed a strong association between r_s and biomarker molarity, with Spearman correlation 0.64 preop and 0.53 postop. No strong associations with other factors were found, including %CVs of both platforms and storage time. We observed significant immunoassay-AKI associations for 13 proteins preop and 24 postop, and SomaScan-AKI associations for 8 proteins preop and 12 postop. All significant AKI associations as measured by SomaScan were also significant as measured by immunoassay. AKI odds ratios were significantly different (P <0.05) between platforms in 4 (14%) pairs, none of which had r_s >0.50.

Conclusions: Although similar AKI associations were observed overall, biomarkers with high physiological concentrations tended to have the best inter-platform operability. Aptamer assays provide unprecedented coverage, excellent precision, and promise for disease associations, but interpretation of results should keep in mind a broad range of correlations with immunoassays.

Funding: NIDDK Support



PO1925

Performance of Creatinine-Based Equations to Estimate Glomerular Filtration Rate in the Context of Drug Dosage Adaptation

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Background: The 1976 Cockcroft-Gault (CG) creatinine-based equation is still used to estimate GFR (eGFR) for dose adaptation of drugs excreted by glomerular filtration although it estimates creatinine clearance. It was developed based on non-standardized creatinine assays and is not recommended by any nephrology guidelines. Incorrect eGFR may lead to hazardous over- or underdosing. We aimed to compare the performance of CG with modern equations based on standardized creatinine assays.

Methods: In a cross-sectional analysis CG was validated against measured GFR (mGFR; using various tracer methods) in 15,479 participants and compared with the Modification-of-Diet-in-Renal-Diseases (MDRD), Chronic-Kidney-Disease-Epidemiology (CKD-EPI), Lund-Malmö-Revised (LMR), and European-Kidney-Function-Consortium (EKFC) equations. Validation focused on bias, imprecision and accuracy (percentage of estimates within ±30% of mGFR, P30), overall and stratified for mGFR, age and body mass index intervals at mGFR <60 mL/min, as well as classification in mGFR stages.

Results: The CG equation performed worse than the other equations, overall and in mGFR, age and BMI subgroups in terms of bias (systematic overestimation), imprecision and accuracy (P30 overall for CG/MDRD/CKD-EPI/LMR/EKFC 73.6%/81.0%/82.4%/87.5%/86.9%) except for patients ≥65 years where bias and P30 were similar to MDRD and CKD-EPI, but worse than LMR and EKFC. At BMI [18.5-25[kg/m^2, all equations performed similarly and at BMI<18.5kg/m^2 CG and LMR had the best results though all equations had poor P30-accuracy (CG/LMR 58.7%/57.2%). At BMI≥25kg/m^2, bias of CG increased with increasing BMI (+19.3mL/min at BMI≥40kg/m^2). The four more recent equations also classified mGFR stages better than CG.

Conclusions: The CG equation exhibited worse performance to estimate GFR overall and in analyses stratified for GFR, age, and BMI. CG was inferior to correctly classify the patients in the mGFR staging compared to more recent creatinine-based equations.

PO1926

Human Kidney Mimetic Tissue Using Endogenous Lipids and Metabolites as Standards for Quantification and Quality Control

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Background: Mass spectrometry imagine (MSI) determines the spatial localization of molecular species directly from the sample and has been heralded in tissue analysis. However, majority of studies have not been quantitative and reproducible. The presentation of a quantified tissue distribution has distinct benefits over the common approach of quantifying the tissue homogenate especially if tissue distribution is heterogeneous, making overcoming this limitation a top priority.

Methods: An improved mimetic tissue mold has been developed. Briefly, human kidney tissue was cut into small pieces and spiked with a normalization standard (lyso-PAF), an antioxidant, and a phospholipase A2 (PLA2) inhibitor to protect endogenous lipids and metabolites from the most common degradation. Lipidomic and metabolomic analyses of this mimetic tissue were performed, and the absolute amounts of various compounds were measured and used as standards for side by side MSI analysis of any tissue sample of interest. Since stabilizers are used, the quantitative data of the mimetic tissue are reliable and can be used as quality control (QC) tracers to tissue samples during storage and shipment.

Results: Mimetic tissue molds were prepared by spiking stable isotope labeled compounds at different concentrations layer by layer for validation. Initial validation experiments found that: a) MSI can detect the concentration differences with acceptable linearity, accuracy, and repeatability; b) Spiking of high concentrations affects the endogenous signals; c) It's not practicable to spike each compound for its quantification due to signal suppression, high material and labor consumption; d) Using endogenous amounts as reference standards is a suitable approach. To use the homogenized mimetic tissue as a spatial quantitative and QC standard, the endogenous amounts of lipids and metabolites were measured with bulk omics. More than 200 lipids, 25 amino acids, and numinous organic acids were quantified.

Conclusions: Quantifying endogenous lipids and metabolites using bulk methods as MSI quantification standards is innovative in the field. The similarity of tissue matrix and targeting compounds between mimetic and sample tissues can provide more meaningful and reliable results.

Funding: NIDDK Support

PO1927

Comparison of Aptamer-Based and Antibody-Based Assays for Protein Quantification in CKD

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Background: Novel aptamer-based technologies can identify over 7000 analytes per sample, offering a high-throughput alternative to traditional immunoassays in biomarker discovery. However, the specificity for distinct proteins has not been thoroughly studied in the context of chronic kidney disease (CKD).

Methods: We aimed to validate the use of SOMAscan, an aptamer-based technology, for the quantification of 8 immune activation biomarkers and cystatin C in 498 participants from the African American Study of Kidney Disease and Hypertension (AASK) using immunoassays as the gold standard.

Results: Six biomarkers (IL-8, TNFRSF1B, cystatin C, TNFRSF1A, IL-6 and suPAR) had moderate-to-high correlations (Pearson r=0.22 to 0.94, Spearman r_s=0.30 to 0.98,) between SOMAscan and immunoassay measurements and three (IFN-γ, IL-10 and TNF-α) were uncorrelated (r=-0.03 to 0.10, r_s=-0.03 to 0.06). Of those with moderate-to-high correlations, TNFRSF1B, cystatin C, TNFRSF1A, and suPAR were negatively correlated with iothalamate-measured GFR and associated with higher risk of ESKD. All 6 biomarkers with moderate-to-high correlations were associated with increased risk of mortality. On average, immunoassay measurements were more strongly associated with adverse outcomes than their SOMAscan counterparts (Figure).

Conclusions: SOMAscan is an efficient and relatively reliable technique for the quantification of biomarkers in the setting of CKD and for the detection of potential associations with clinical outcomes. Targeted immunoassays of candidate proteins may provide additional prognostic information.

Funding: NIDDK Support

	Correlations between assays		Correlations with mGFR	Associations with ESKD			Associations with Mortality		
	r	r_s	*r*	HR	P	LRT P*	HR	P	LRT P*
IL-8									
Immunoassay			0.06	0.89 (0.75-1.06)	0.18	0.84	**1.41 (1.20-1.65)**	**<0.001**	**0.005**
SOMAscan	**0.94**	**0.95**	0.09	0.87 (0.72-1.05)	0.15	0.51	**1.31 (1.13-1.53)**	**0.001**	0.08
SUR					*0.51*			***0.004***	
TNFRSF1B (#1)									
Immunoassay			**-0.66**	**2.77 (2.34-3.27)**	**<0.001**	**0.003**	**1.58 (1.31-1.90)**	**<0.001**	0.26
SOMAscan	**0.93**	**0.93**	**-0.71**	**2.59 (2.21-3.04)**	**<0.001**	0.12	**1.54 (1.28-1.84)**	**<0.001**	0.52
SUR					*0.09*			*0.56*	
TNFRSF1B (#2)									
Immunoassay			**-0.66**	**2.77 (2.34-3.27)**	**<0.001**	**<0.001**	**1.58 (1.31-1.90)**	**<0.001**	0.11
SOMAscan	**0.92**	**0.92**	**-0.70**	**2.37 (2.05-2.73)**	**<0.001**	0.76	**1.50 (1.26-1.79)**	**<0.001**	0.74
SUR					***<0.001***			*0.28*	
Cystatin C									
Immunoassay			**-0.79**	**3.08 (2.57-3.69)**	**<0.001**	**<0.001**	**1.52 (1.26-1.84)**	**<0.001**	0.94
SOMAscan	**0.89**	**0.89**	**-0.76**	**2.64 (2.22-3.14)**	**<0.001**	0.84	**1.63 (1.35-1.98)**	**<0.001**	**0.01**
SUR					***0.01***			*0.19*	
TNFRSF1A									
Immunoassay			**-0.76**	**3.43 (2.87-4.10)**	**<0.001**	**<0.001**	**1.51 (1.25-1.82)**	**<0.001**	**0.002**
SOMAscan	**0.85**	**0.85**	**-0.72**	**2.81 (2.38-3.32)**	**<0.001**	0.08	**1.34 (1.12-1.60)**	**0.001**	0.32
SUR					***0.03***			***0.02***	
IL-6									
Immunoassay			0.03	0.97 (0.83 – 1.13)	0.69	0.70	**1.23 (1.05-1.46)**	**0.01**	**0.02**
SOMAscan	**0.22**	**0.33**	-0.08	0.99 (0.87-1.13)	0.91	0.98	1.02 (0.85-1.22)	0.85	0.69
SUR					*0.79*			*0.08*	
suPAR									
Immunoassay			**-0.34**	**1.80 (1.52-2.13)**	**<0.001**	**<0.001**	**1.55 (1.27-1.89)**	**<0.001**	**<0.001**
SOMAscan	**0.23**	**0.30**	**-0.17**	1.19 (1.00-1.42)	0.05	0.57	**1.39 (1.09-1.77)**	**0.007**	**0.04**
SUR					***0.001***			*0.43*	
IFN-γ									
Immunoassay			-0.03	1.11 (0.96-1.27)	0.15	0.17	1.11 (0.92-1.34)	0.30	0.25
SOMAscan	0.07	0.06	0.05	1.01 (0.87-1.18)	0.86	0.97	0.87 (0.71-1.07)	0.19	0.14
SUR					*0.33*			*0.07*	
IL-10									
Immunoassay			0.02	**1.20 (1.06-1.36)**	**0.01**	**0.01**	1.19 (1.00-1.42)	0.06	0.06
SOMAscan	0.10	-0.03	-0.06	1.03 (0.89-1.20)	0.68	0.75	0.98 (0.82-1.18)	0.85	0.73
SUR					*0.09*			*0.15*	
TNF-α (#1)									
Immunoassay			**-0.30**	**1.46 (1.27-1.68)**	**<0.001**	**<0.001**	**1.71 (1.42-2.06)**	**<0.001**	**<0.001**
SOMAscan	0.02	-0.03	-0.11	1.11 (0.95-1.28)	0.19	0.31	1.09 (0.92-1.29)	0.29	0.39
SUR					***0.01***			***0.001***	
TNF-α (#2)									
Immunoassay			**-0.30**	**1.46 (1.27-1.68)**	**<0.001**	**<0.001**	**1.71 (1.42-2.06)**	**<0.001**	**<0.001**
SOMAscan	-0.03	-0.01	0.19	0.83 (0.69-1.00)	0.05	0.05	0.82 (0.65-1.02)	0.07	0.05
SUR					***<0.001***			***<0.001***	

Figure 1. Analysis Results. Person and Spearman correlation coefficients of protein levels measured via traditional immunoassays vs. SOMAscan. Pearson correlation coefficients of protein levels (as measured by traditional immunoassay vs. SOMAscan) with mGFR. Adjusted hazard ratios (HR) for biomarker levels with incident ESKD and mortality. Models were adjusted for sex, age, and randomized treatment groups. Seemingly unrelated regression (*SUR*) p-values were used to compare the strength of the association between biomarkers measured via immunoassay vs. SOMAscan and ESKD and all-cause mortality. *P-values for the likelihood ratio test (LRT) compare a predictive model using both assays vs. a single assay alone for each protein. In this instance, the LRT P-value for 'immunoassay' indicates whether the additional use of immunoassay provides any additional prognostic information after SOMAscan analysis and vice versa. Statistically significant findings in bold.

PO1928

Prescribed Sodium Bicarbonate and Incident CKD in US Veterans

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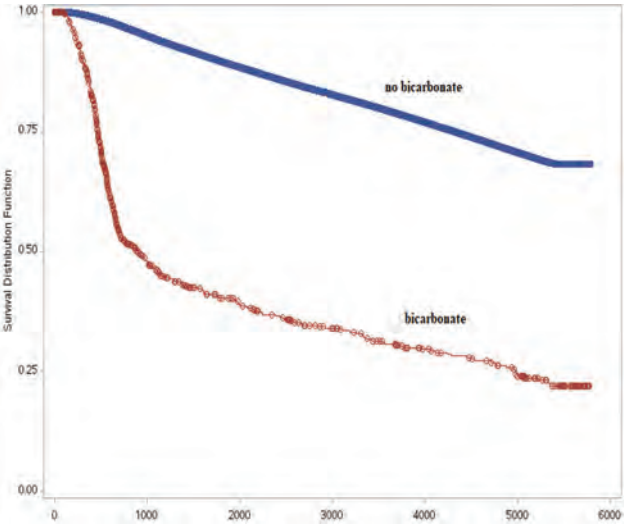
Background: Sodium bicarbonate is prescribed for a variety of medical conditions including treatment of hypobicarbonatemia that may happen in the setting of metabolic acidosis or due to other pathologies. Hypobicarbonatemia is usually observed with chronic kidney disease (CKD) when eGFR < 60 mL/min/1/73 m2 and is uncommon without established CKD (eGFR > 60 mL/min.). It is not known whether incident sodium bicarbonate prescription in patients with normal kidney function is associated with adverse outcomes including de novo chronic kidney disease, which we sought to examine in a large national cohort of Veterans.

Methods: In 2,524,842 US Veterans with normal baseline eGFR (≥60 ml/min/1.73m2) and available data on albuminuria in 2004-2006, we examined the association of de novo prescription of bicarbonate medications during the baseline period with incident CKD over 14 years. Associations were examined in hazard models adjusted for demographics, major comorbidities, baseline eGFR, and albuminuria category.

Results: We identified 759 Veterans who were incident bicarbonate users. Overall, patients were a mean 61±14 years old, 7% female, 16% Black, and 5% Hispanic. Bicarbonate users were more likely to be male, Black, smokers, with higher frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, diabetes, and cardiovascular comorbidities. They also were more likely to have albuminuria. Bicarbonate medication users had a 4.8-fold higher risk of incident CKD (HR: 4.81, 95%CI: 4.38, 5.27).

Conclusions: Veterans with eGFR ≥60 ml/min/1,73m2 who were prescribed sodium bicarbonate exhibited nearly five times greater likelihood of incident CKD. Whether bicarbonate therapy is a surrogate of disease condition with higher risk of CKD or whether it causes CKD directly remains to be examined in additional studies.

Funding: Clinical Revenue Support



PO1929

LRP2-Facilitated Regulation of Mitochondrial Metabolism by Extracellular Cues: Important Roles for Signal Peptides' Leucines in Protein-Protein Interactions and Signaling

Qingtian Li,[1] Michael Holliday,[1,2] Jenny S. Pan,[1,2] Li Tan,[3,1] Jeffery Li,[1] David Sheikh-Hamad.[1,2] *[1]Baylor College of Medicine, Houston, TX; [2]Michael E DeBakey VA Medical Center, Houston, TX; [3]Sichuan University West China Medical Center, Chengdu, China.*

Background: Stanniocalcin 1 (STC1), a mitochondrial intracrine activates mitochondrial anti-oxidant defenses. LRP2/megalin shuttles STC1 to the mitochondria through retrograde early endosome-to-Golgi- and Rab32, and LRP2 KO impairs mitochondrial respiration and glycolysis.

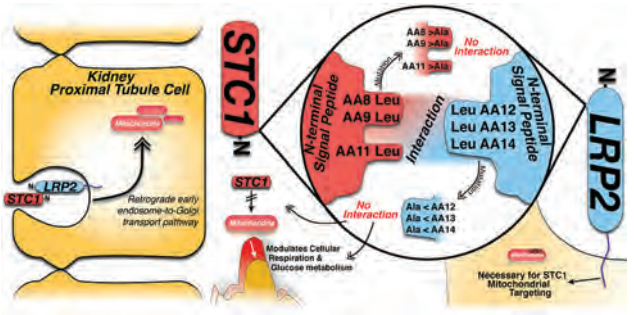
Methods: We determined STC1-LRP2 interaction domains using HA- and FLAG-tagged fragments of STC1 and LRP2, respectively, co-expressed in HEK293T cells.

Results: The trans-membrane domain of LRP2 is required for trafficking to the mitochondria. STC1-FLAG expressed in LRP2 KO cells fails to reach the mitochondria; thus, mitochondrial STC1 is extracellularly-derived via LRP2-mediated trafficking. Tri-leucines L12-14 in LRP2's signal peptide interact with STC1's signal peptide. Mutant LRP2 (L12-L14 -> A12-14) does not bind STC1, while hSTC1 lacking signal peptide or Leucines L8/9/11 does not bind LRP2. Using Seahorse analyzer, STC1 fails to induce

respiration or glycolysis in megalin KO MEF expressing mutant LRP2, while mutant hSTC1 (L8/L9/L11 -> A8/A9/A11) fails to reach the mitochondria or induce respiration and glycolysis in WT MEF.

Conclusions: Our data suggest direct regulation of mitochondrial metabolism by extracellular cues and reveal an important role for signal peptides and their leucines in protein-protein interactions and signaling.

Funding: Veterans Affairs Support



Graphic abstract

PO1930

Hypertriglyceridemia-Related Lipid Profiles Affect Glomerulosclerosis in IgA Nephropathy

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Background: Dyslipidemia, is one of the common complications of renal failure. There are many clinical factors that affect IgAN prognosis or histopathology. However, there are only few studies that analysis focused on the histopathologic features between IgA nephropathy with hypertriglyceridemia and related lipid profiles. We evaluate histopathologic features in IgAN between HyperTG group compared to normal TG group

Methods: Study Design This study is a cross-sectional study of a multi-center cohort that underwent kidney biopsy at 8 university hospitals affiliated with the College of Medicine Catholic University between January 2015 and May 2020 were diagnosed with IgAN. A total of 480 patients were enrolled in final cohort. Patient were divided into 2 groups that group 1; <150mg/dL, group 2; ≥150mg/dL. **Statistical Analysis** Logistic regression analyses were performed to estimate the odds ratios (ORs). To define high grade of global and segmental glomerulosclerosis ≥25% define as high grade glomerulosclerosis and <25% define as low grade glomerulosclerosis. Grades 2-4 of MME, MCP were defined as high grade.

Results: Association between serum TG and histopathologic parameters Multivariable linear regression analysis showed that the that percent of GS, SS and CA, MME, MCP scores were positively associated with TG levels. Table 4 shows that HyperTG group showed more higher risk for global and segmental sclerosis after adjusting clinical and labaratory variables.

Conclusions: In conclusion, HyperTG is associated with glomerular sclerosis and mesangial proliferation. Also, HyperTG is independently relevant risk factor for global and segmental sclerosis.

	TG							
	Univariable				Multivariable			
	β	t	r^2	p	β	t	r^2	p
Global sclerosis	0.187	4.128	0.035	<0.001	0.173	3.544	0.060	<0.001
Segmental sclerosis	0.174	3.850	0.029	<0.001	0.149	2.995	0.107	0.003
Capsular adhesion	0.161	3.480	0.024	0.001	0.129	2.643	0.094	0.009
Mesangial matrix expansion	0.115	2.525	0.011	0.012	0.109	2.329	0.024	0.034
Mesangial cell proliferation	0.117	2.564	0.012	0.011	0.139	2.825	0.017	0.005
Endocapillary proliferation	0.030	0.645	0.001	0.598	-	-	-	-
Monocyte infiltration	0.004	0.086	0.000	0.931	-	-	-	-
Neutrophil infiltration	0.076	1.654	0.004	0.099	-	-	-	-
Interstitial Fibrosis	0.054	1.182	0.001	0.238	-	-	-	-
Tubular Atrophy	0.057	1.233	0.001	0.218	-	-	-	-
Arterial intimal hyalinosis	0.002	0.043	0.000	0.965	-	-	-	-
IgA Mesangial Deposit	0.012	0.264	0.000	0.792	-	-	-	-
C3 Mesangial Deposit	0.036	0.784	0.001	0.433	-	-	-	-
C4d Mesangial Deposit	0.000	<0.010	0.000	0.992	-	-	-	-

Multivariable analysis was adjusted for each histologic parameter and clinical parameters, including age, sex, Systolic BP, BMI, haemoglobin, uric acid, glucose, ALT, eGFR, spot urine P/Cr, HDL-C, LDL-C, total cholesterol, and serum IgA levels.

Table 3 Linear regression for TG and the histopathologic parameters

	Crude	p	Model 1	p	Model 2	p	Model 3	p
Global sclerosis								
Group1	Ref.		Ref.		Ref.		Ref.	
Group2	1.715(1.131-2.601)	0.011	1.701(1.122-2.579)	0.012	1.695(1.055-2.723)	0.029	1.791(1.111-2.887)	0.017
Segmental sclerosis								
Group1	Ref.		Ref.		Ref.		Ref.	
Group2	2.382(1.525-4.282)	<0.001	2.366(1.316-4.253)	0.004	2.334(1.213-4.492)	0.011	2.310(1.200-4.446)	0.012
Mesangial matrix expansion								
Group1	Ref.		Ref.		Ref.		Ref.	
Group2	1.689(0.998-2.859)	0.051	1.703(1.006-2.882)	0.047	1.586(0.907-2.774)	0.106	1.563(0.893-2.737)	0.118
Mesangial cell proliferation								
Group1	Ref.		Ref.		Ref.			
Group2	1.587(0.952-2.646)	0.076	1.600 (0.960-2.668)	0.072	1.409(0.818-2.428)	0.216	1.303(0.745-2.281)	0.353

Model 1: adjusted for age, sex, systolic BP

Model 2: adjusted for Model 1+ glucose, ALT, HDL-C, Total cholesterol, uric acid, UPCR

Model 3: adjusted for Model 2 + eGFR, BMI

Table 4 Logistic regression for TG groups and histopathologic parameters

PO1931

Percutaneous Kidney Biopsy in Outpatient Setting: Can I Go Home Now?

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Background: Kidney biopsies are a key diagnostic tool in renal dysfunction; however, complications ranging from bleeding to hematoma requiring embolization can occur. There is conflicting evidence on how long to keep patients post-biopsy. Some studies show 100% of serious complications occur within 8 hours, while others show that one-third can occur after 8 hours. Shorter observation periods prevent unnecessary testing and help reduce healthcare costs. Our study aims to assess if patients can be safely discharged with a six hour observation period post-biopsy.

Methods: Single-center retrospective Quality Improvement (QI) study of patients undergoing outpatient percutaneous native kidney biopsy over last 5 years (n=177) divided into 2 groups: -Group A: Same-day discharge after -Group B: 23-hour observation after US-guided biopsy by Urology Outcomes compared included timing of hemoglobin (Hb) drop post-procedure, readmission rates, need for transfusions, imaging or interventions.

Results: Of 177 patients, 75 (42.3%) were in Group A and 102 (57.6%) in Group B. Drop in Hb and post-biopsy complications were not significantly different between the groups. Three patients had bleeding complications, two of which required transfusion (Table). All three patients with bleeding complications had >10% Hb drop within first 6 hours post-biopsy. No readmissions related to biopsy occurred.

Conclusions: There were no major complications in either group. This QI study suggests that the majority of asymptomatic patients can be safely discharged at 6 hrs post-biopsy if Hb is stable. This could help reduce healthcare costs and burden to patients. This is a limited single center study: further larger studies are needed to confirm this.

Bleeding Complications Post-Kidney Biopsy									
Patient #	SBP Prior to Biopsy	Hb up to 1 month prior	Hb <6 hrs post-biopsy (% decrease from prior)	Hb 18-20 hrs post-biopsy	Symptoms	Imaging findings	Transfusion (units of pRBC)	Procedures Needed	Length of Stay in days (LOS)
#1 (Group A)	140-159	12	9 (↓25%)	9.1	Flank pain on side of biopsy, hematuria	Perinephric hematoma	None	Bladder irrigation and bedside clot retrieval	5
#2 (Group B)	140-159	9.9	8.2 (↓17%)	6.6	None	Perinephric hematoma	1unit	None	2
#3 (Group B)	<140	8.2	7.1 (↓13%)	6.7	None	Retro -peritoneal hemorrhage	2units	None	2

Bleeding Complications Post-Kidney Biopsy

PO1932

Does Obtaining an Extra Biobank Sample Increase the Risk of Post-Kidney Biopsy Complications? A Single-Center Experience

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Background: Kidney biopsy(KB) is the "gold standard" for nephropathies diagnosis and it has a low rate of complications. Obtaining material for KB biobank requires the extraction of extra renal cylinder. The objectives of study are to analyze the characteristics of a cohort of patients with KB, the safety and show whether obtaining extra renal cylinder is associated with an increased risk of complications.

Methods: Observational and prospective study of KBs performed in our center during 2019 and 2020. We started a collection of KB samples to biobank at 2019. In patients who accepted, instead of two cylinders, three cylinders were obtained during the procedure. Clinical and laboratory data of patients were reviewed. Risk factors for complications, including the number of cylinders obtained, was also assessed.

Results: 221 patients in whom we performed a KB at our hospital were included in the biobank. 8 patients(3.6%) underwent trans-jugular renal biopsy, which we have excluded. Of the remaining 213, 126(59.2%) were men, the mean age 56.8(± 16.9) years, 122(57.3%) patients had hypertension, 46(23%) were diabetics, 14(6.5%) were under anticoagulant treatment and 35(16.4%) under antiplatelet treatment. The mean creatinine was 2.22(±1.9) mg/dl, protein/creatinine urine ratio 1119.6[448.3-2957.9]mg/gr, the hemoglobin pre-KB was 12.1(± 2.3) g/dL, 254380(± 8873) platelets, INR 0.98(± 0.09), prothrombin time 11.8(± 1.16) seconds. 69.5%(n=148) of patients 3 renal cylinders were obtained, 27.2%(n=58) 2 cylinders and in 3.3% (=7) one cylinder. Minor complications were observed in 13.6%(n=29) and major complications in 3.3%(n=7). We observed that patients with complications in KB were younger(p=0.034), had less weight(p=0.022), more transfusions(p=0.003), more platelets(p=0.038), a lower PT(p=0.05) and 1 cylinder was obtained in the KB with more frequency(p=0.012). In a multivariate regression logistic analysis PT (OR:1.497,p=0.042), transfusions(OR:5.38,p=0.032) and 1 cylinder obtained(OR:7.258,p=0.032) were identified as a risk factors of KB complications.

Conclusions: KB is a procedure with a low complication rate. Obtaining three KB cylinders for biobank has not shown an increase in the rate of complications, which in concordance with previous published studies remains low.

PO1933

Assessment of Glomerular Number in Fresh Renal Tissue and Renal Pathological Specimens

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Background: On-site evaluation of fresh renal tissue at the time of renal biopsy is useful. However, some cases present poor correlation in glomerular number between fresh renal tissue and renal pathological specimens.

Methods: To examine the usefulness of on-site evaluation, the correlation between glomerular number in fresh renal tissue and renal pathological specimens, and associated factors disturbing the evaluation were investigated via a retrospective cross-sectional observational study.

Results: In the included 129 cases, there was a significant positive correlation between glomerular number in fresh renal tissue and renal pathological specimens. The median ratio of glomerular number (renal pathological specimen/fresh renal tissue) was 0.74 (0.48–0.97). According to this ratio, all cases were divided into three groups: a reasonable estimation group (65 cases), underestimation group (32 cases), and overestimation group (32 cases). Comparing the reasonable estimation group with the underestimation group, significant differences were detected in the extent of interstitial fibrosis and tubular atrophy (IFTA) and in the extent of interstitial inflammation. Logistic regression analyses also demonstrated that IFTA and interstitial inflammation were significantly associated with underestimation.

Conclusions: In conclusion, glomerular number counted by on-site evaluation of fresh renal tissue estimated the actual number of glomeruli in the renal pathological specimen, suggesting clinical benefit. Since tubulointerstitial lesions, such as IFTA and/or interstitial inflammation, may make it difficult to recognize glomeruli in fresh renal tissue, the possibility of underestimation of results for cases with possible severe tubulointerstitial lesions should be considered.

PO1934

Variability in Estimates of Nephron Number from Biopsy

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Background: Nephron number may predict kidney health and functional capacity. It is unknown whether biopsies can be used to predict glomerular number (Nglom) in individuals, or how many subjects are required to detect differences between populations. We investigated the accuracy and precision of Nglom measured from biopsy.

Methods: We examined 6 human kidneys, rejected for transplant. We performed 8-10 needle biopsies. We used this and cortical volume to estimate Nglom. We simulated 210-227 "virtual biopsies" (VB) from 3D cationized ferritin- enhanced MRI (CFE-MRI), in 4-5 clusters of 12-18 VBs in bottom, upper, and middle poles (Fig. 1Ai).

Results: Nglom estimated from single needle biopsy had up to 70% error depending upon where it originated (Fig. 1Bi). Nglom estimated from needle and VB varied consistently by ~ 50% (Fig. 1Biv), and there was no preferred biopsy location for accurate estimates of Nglom. The maximum variability in mean Nglom within clusters of closely packed virtual biopsies was 11-56% (Fig. 1Biv). Based on statistical analysis, > 200 physical biopsies are required to be 95% certain the estimated Nglom is within +/- 20% of true Nglom.

Conclusions: A single biopsy is not sufficient to predict Nglom in the individual kidney, but this work provides the required number of subjects required to detect differences in Nglom between populations.

Funding: NIDDK Support

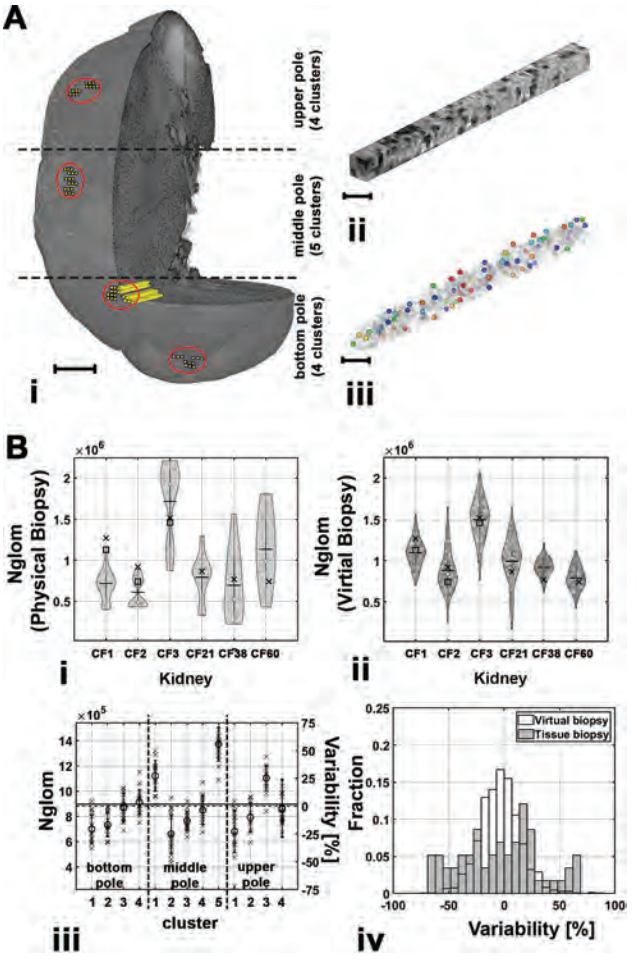

Figure 1. (A) "Virtual biopsy" from 3D CFE-MRI. (i) 3D visualization of single VB with (ii) CF-labeled (black dots) and (iii) segmented glomeruli (spheres). Scale =1 mm. (B) Distribution of Nglom from (i) physical and (ii) virtual biopsies (VB). (iii) The mean Nglom±SD within the clusters of VB. (iv) Variability in Nglom.

PO1935

Epidemiology of Medical Kidney Disease in the Southwestern United States, 1989-2018

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Background: Kidney biopsy is the main source of epidemiological information for kidney disease. However, large-scale epidemiological studies for glomerular disease (GD) in the US are very limited, and there are no such studies for non-glomerular disease (non-GD). Here, we describe 30-year temporal and demographic trends in GDs and non-GDs in the southwestern US between 1989 and 2018.

Methods: In this retrospective study, all kidney biopsy data at Pathology, Cedars-Sinai Medical Center (CSMC), Los Angeles, CA, between 1989 and 2018 were reviewed. We analyzed the most common 26 GDs and the most common 9 non-GDs. The frequencies of GD and non-GD subtypes and the temporal trends in each disease subtype within demographic subgroup were our primary and secondary outcomes. In addition, the frequency distribution of each disease category was evaluated across age categories stratified by sex and race.

Results: Among 48,068 patients (mean age =50.3 ± 19.3 y.o.; 52.0% men; 55.5% white; 18.4% Latino; 11.1% black; 9.8% Asian; 5.2% others), GD and non-GD composed 83.4% and 16.6% of all biopsies, respectively. In GDs, the frequency of diabetic glomerulosclerosis increased over the three decades (8.4%, 12.2%, and 22.0% of diagnoses; *P* for trend <0.003). The frequency of FSGS, lupus nephritis, immune complex-glomerulonephritis (GN), membranous nephropathy, and minimal change disease declined substantially over time. On the other hand, IgAN and ANCA/pauci-immune GN remained stable. In non-GDs, nephrosclerosis was the most frequent in study period. However, acute tubular necrosis/injury slightly increased over time and became the most common subtype in the latest 10 years. These temporal trends were largely preserved within all demographic subgroups, although cross-sectional frequency distributions differed according to age, sex, and race.

Conclusions: We reported the largest epidemiological study of medical kidney disease in the US. The relative renal biopsy frequencies of many GDs and non-GDs showed significant changes over the three decades in the southwestern US. Temporal

trends were consistently observed within all major demographic groups. We provided evidence that changes in demographics (age, sex, and race) contributed minimally to these findings, suggesting that environmental and lifestyle changes contribute to them.

PO1936

Pathology Core Scoring Parameters and Reproducibility in the CureGN Study

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Background: CureGN is an NIH-funded multi-center, prospective, observational cohort study of patients with minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), or IgA nephropathy from 66 international sites with 2500 enrolled participants. The large scale of CureGN requires a practical systematic approach to pathologic scoring that can be applied consistently across a large number of cases and multiple scoring pathologists. The method reflects common pathology practices, generating data for assignment to currently used disease classifications and use in future studies utilizing conventional parameters. The objective of this analysis was to determine and evaluate the pathology scoring reproducibility.

Methods: The CureGN Core Scoring Workgroup established definitions of multiple glomerular, tubular, interstitial and vascular lesions evaluated semi-quantitatively, as observed by light, immunofluorescence, and electron microscopy (EM). All cases with complete pathology data as of April 2019 were randomly assigned for scoring of whole slide and EM images to one of eleven pathologists; a random subset of >10% were scored by a second pathologist. Reproducibility was assessed using Gwet's AC1 statistic.

Results: Of 797 biopsy specimens (141 MCD, 186 FSGS, 205 MN, 265 IgA) scored by at least one pathologist, 94 were scored twice (12%). Of 60 pathology features, 46 (77%) demonstrated excellent reproducibility (Gwet's AC1>0.8), and 12 (20%) had good reproducibility (Gwet's AC1>0.6). Mesangial hypercellularity scored as absent, focal or diffuse had moderate reproducibility (AC1=0.58), but scored as absent vs present had AC1=0.71. The percent glomeruli scored as having no lesions had fair reproducibility (AC1=0.34).

Conclusions: The majority of pathologic features scored showed excellent reproducibility, supporting the hypothesis that these features can be scored consistently by multiple pathologists. Future studies will include correlation of these histopathologic features with clinical and demographic characteristics at the time of biopsy and eventually disease biomarkers and clinical outcomes.

Funding: NIDDK Support

PO1937

Dysmorphic Lysosomes, Pathognomonic of Chronic Interstitial Nephritis in Agricultural Communities (CINAC)

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Background: The etiology and pathogenesis of CINAC are unknown. Two hypotheses have been put forward. Dysmorphic lysosomes (DL) were described as pathognomonic however some argue that DL are non-specific findings. Therefore, we did an observational study of electron microscopic (EM) findings in CINAC comparing to published cases.

Methods: Sixteen patients from Central America, suspected of CINAC clinically underwent kidney biopsy (KB). Demographic characteristics, blood and urine analysis data were collected. Renal histology was studied using light (LM), immunofluorescence (IF), and electron microscopy (EM). We reviewed the literature in PubMed using the following search terms (a). "Chronic Interstitial Nephritis + Electron Microscopy + Kidney" and identified 8 relevant cases (Group A) (b). "Dysmorphic Lysosomes, Electron Microscopy" found 14 cases that described the EM findings (Group C).

Results: Of the 8 patients in group A, who had CIN, only 2had DL on EM. One patient had Calcineurin Inhibitors (CNI) and one patient from Sri Lanka had chronic kidney disease of unknown origin, which is also considered as CINAC. In patient who had CNI, the DL had irregular edges unlike the smooth rounded DL of varying sizes noted in all CINAC patients. In the control group, C, the patients who had DL, were 14 but the DLs were present in organs other than kidneys. The two patients had DL in the kidneys, one was Fabry's disease, and the other was Light chain Proximal tubulopathy (LCPT). In Fabry's disease, the DL were lamellated. In LCPT the DL were rectangular due to the characteristics of the lambda proteins.

Conclusions: Dysmorphic Lysosomes may occur in multiple disorders, however, in young persons with agricultural exposure, non-nephrotic proteinuria, presence of tubular inflammation, presence of smooth rounded clusters of DL are pathognomonic. Morphology of the DL is dictated by the contents of the lysosomes as in the case of LCPT; further, evaluation is recommended.

	CIN-GrA	CINAC-GrB	DL-GrC	Total
DL-Kidney Positive	2	16	2	
DL-Kidney Negative	6	0	12	
	8	16	14	28

The Chi-square statistic is 21.3929. The p-value is 000023.

DL= Dysmorphic Lymphocytes.

GrA: CIN, GrB: CINAC, GrC: Have dysmorphic lymphocytes.

PO1938

Reduction of Globotriaosylceramide Inclusions in Renal Peritubular Capillaries in Patients with Fabry Disease Following Treatment with Pegunigalsidase Alfa

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Background: Fabry disease (FD) is a rare genetic disorder characterized by reduced activity of the lysosomal enzyme α-galactosidase A (α-Gal A), leading to accumulation of sphingolipids such as globotriaosylceramide (Gb_3) and globotriaosylsphingosine ($lysoGb_3$), and organ dysfunction. Gb_3 inclusions form in various renal cell types and Gb_3 clearance from renal peritubular capillaries (PTCs) has been used as a surrogate endpoint in trials of approved FD therapies. The objective of this analysis was to quantify the reduced burden of Gb_3 inclusions in PTCs in patients with FD participating in a phase 1/2 trial of pegunigalsidase alfa (recombinant α-Gal A) enzyme replacement therapy.

Methods: In a phase 1/2 dose-ranging study (NCT01678898), 18 adults with FD received 0.2 mg/kg, 1.0 mg/kg, or 2.0 mg/kg of pegunigalsidase alfa by intravenous infusion every 2 weeks for up to 12 months. Kidney biopsies were taken at baseline and after 6 months of treatment. Levels of Gb_3 inclusions in renal PTCs were determined using the Barisoni Lipid Inclusions Scoring System (BLISS) protocol (Barisoni L et al. Arch Pathol Lab Med. 2012;136:816–824).

Results: Of 14 evaluable patients with available kidney biopsies at baseline and 6 months, 12 patients (85.7%) had ≥20% reduction, 11 patients (78.6%) had ≥50% reduction, and 3 patients (21.4%) had ≥90% reduction in Gb_3 inclusions. In the analysis (n=13; excluding 1 male patient due to minimal renal involvement), the mean BLISS score 6 months from baseline was lowered for all doses (reduced by 75.5%, 86.5%, and 39.5% in the 0.2 mg/kg, 1.0 mg/kg, and 2.0 mg/kg treatment groups, respectively). The magnitude of reduction of Gb_3 inclusions was greater in males (n=7; reduction: 85.0%) vs females (n=6; reduction: 47.7%). Overall, mean BLISS score was reduced from 4.23 at baseline to 0.83 at 6 months (67.8% ± 8.9%). Reduction in Gb_3 inclusions at 6 months was correlated with a reduction in plasma $lysoGb_3$ at 12 months (R=0.905).

Conclusions: Results from this phase 1/2 study demonstrated that pegunigalsidase alfa reached the affected tissue and effectively reduced the number of Gb_3 inclusions in renal PTCs at 6 months in adults with FD.

PO1939

Patients with Active Mantle Cell Lymphoma May Present with Monoclonal, Polyclonal, or C3-Dominant Glomerulonephritides, Which Respond to Lymphoma-Directed Therapy

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Background: There are limited reports on kidney biopsy findings in patients with mantle cell lymphoma (MCL).

Methods: We initiated a multi-institutional, retrospective review of kidney biopsy findings from patients with active and treated MCL.

Results: Twenty-nine patients (31 biopsies) with MCL and kidney biopsies were identified, with a median age of 66 (range 48-87), 76% of whom were men. Nineteen patients had active MCL at the time of biopsy, 13 of which (68%) presented with acute kidney injury, proteinuria and/or hematuria, and biopsy findings attributable to lymphoma (Table); 6 (32%) had findings not readily attributable to MCL. Of the former, 10 (77%) had immune complex (IC) disease including proliferative glomerulonephritis with monotypic Ig deposits (PGNMID, 2), C3 dominant GN (3), PLA2R-negative membranous (MN, 3), and/or tubular basement membrane deposits (2). Lymphomatous infiltration was present in 6, 3 with coincident IC lesions. Four with available follow-up were treated for MCL, all with remission of GN (1 PGNMID, 2 C3 dominant GN, 1 MN). Ten patients were biopsied while MCL was in remission; these findings were attributed to various underlying diseases.

Conclusions: In patients with active MCL who undergo kidney biopsy, 68% had kidney biopsy findings attributable to lymphoma. Diverse immune complex diseases were seen in ~50%, including monoclonal, polyclonal, and C3 dominant GN patterns, and nearly 1/3rd had lymphomatous infiltration. Limited follow-up suggests these IC lesions respond to MCL-directed therapy.

Case	Age Sex	Bx indication	Kidney bx diagnosis	Light microscopy	IF	EM deposit location	Follow-up
1	66F	AKI, nephrotic proteinuria, hematuria	PGNMID	MPGN with diffuse crescents	IgG3 kappa (2+), C3 (3+), C1q (2-3+)	Mes, subendo	MCL treated, GN in remission at 5 months
2	65M	AKI, nephrotic syndrome, hematuria	PGNMID	Mesangial, endocapillary proliferative; focal crescents	IgG3 kappa (3+), C3 (3+), C1q (2-3+)	Mes, subendo, rare subepi	Unknown
3	61M	AKI, nephrotic proteinuria, hematuria	C3 dominant GN, lymphoma infiltration	Mesangial proliferative	C3 (4+), IgG (2+), k (2+), l (2+), C1q (1-2+)	Mes	MCL treated, GN in remission at 28 months
4A &B	68M	AKI, proteinuria, hematuria	C3 dominant GN	Mesangial proliferative	C3 (3+), C1q (tr-1+)	Mes, rare subepi	Persisted on repeat bx at 5mo, then MCL treated and GN in remission at 7 years
5	87M	AKI, subnephrotic proteinuria, hematuria	C3 dominant GN, AIN	Mesangial proliferative, mild AIN	C3 (2-3+), C1q (2+), IgG (tr-1+)	Mes, parames	Unknown
6	73M	Progressive CKD subnephrotic proteinuria	MPGN, lymphoma infiltration	MPGN	No gloms available	Mes, subendo, few subepi	Unknown
7	66M	Nephrotic syndrome	Membranous GN, THSD7A+	membranous	IgG (4+), k (2+), l (3+), C3 (3+)	Global subepi, rare mes	Unknown
8	59F	Nephrotic syndrome	Membranous GN, PLA2R-	membranous	IgG (3+), k (2+), l (3+), C3 (3+)	Irregularly distributed subepi	MCL treated, GN in remission at 4.5 years
9	69M	Progressive CKD, subnephrotic proteinuria	Membranous, segmental, TBM deposits, lymphoma infiltration	membranous	IgG (2+), k, l, C3, C1q (all 1-2+), with chunky TBM deposits	Subepi, subend, mes, TBM	Unknown
10	77M	AKI	TBM deposits, ATN	ATN, normal glomeruli	Coarse TBM staining for IgG, k, l, C3	Fine granular TBM	Unknown
11	76M	AKI, hx lupus	Lymphoma infiltration, mild lupus	Mesangial proliferative, duplicated GBM	IgG, IgM, k, l, C3, C1q (all 1+)	Mes, subendo, rare TRI	Unknown
12	72F	AKI	Lymphoma infiltration, arterionephrosclerosis	Normal glomeruli	Negative	Negative	Unknown
13	74M	AKI (autopsy)	Lymphoma infiltration, diabetic nephropathy	Nodular mesangial sclerosis	Not performed	Not performed	(autopsy)

PO1940

Anti-Brush Border Antibody Disease with Nephrotic Syndrome: A Clinicopathologic Analysis of Five Cases

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Background: Anti-brush border antibody(ABBA)disease is a recently described etiology of acute kidney injury and progressive renal tubular injury that mainly affects the older patients. ABBA is characterized by the presence of circulating autoantibodies to the proximal tubular brush border protein LRP2(megalin)and IgG immune complex deposits along the basement membrane of proximal tubules. In the present study, we report 5 cases of ABBA that all presented as nephrotic proteinuria.

Methods: We retrospectively screened for ABBA disease through our renal biopsy cohort from January 2018 to May 2021. The anti-brush border antibody disease was diagnosed based on the presence of ABBA in the serum, showing positive ABBA on a kidney section by indirect immunofluorescence with patient's serum, and kidney histology. Histology of the biopsies and clinical data were analyzed.

Results: Five cases with ABBA disease were identified, out of 0.1% total biopsies. Mean age was 41 years (29-54) with a M:F ratio of 1:4. At biopsy, all had nephrotic syndrome with proteinuria (12.1 g/24h, 3.8-27 g/24h). Only one patient presented with acute kidney injury. Serologies, including ANA, dsDNA, ANCA, anti-GBM were negative. C3 and C4 levels were normal. Neither acute tubular injury nor intensive Interstitial inflammation were found in all these biopsies. Proximal tubular brush border and glomerular basement membranes stained positive for IgG in all cases, and 3 cases also have positive deposits in some segments of TBM. Staining for IgG subclass showed that IgG1 was positive, while IgG2, IgG3 and IgG4 were not detected. Interestingly, we found light chain monotype of lambda in two patients. Electron microscopy showed diffuse podocyte foot process effacement in all cases. All patients received prednisone plus cyclophosphamide therapy and achieved complete recovery after 2 months (range: 1-3) (Table 1).

Conclusions: We report 5 cases of anti-ABBA disease with nephrotic syndrome recovered after treatment with prednisone and cyclophosphamide. The mechanism of podocyte injury in anti-ABBA disease requires additional studies.

Table 1 Clinical characteristics and pathologic findings at presentation

	#1	#2	#3	#4	#5
Age/Sex	29/F	34/F	54/M	34/F	54/F
24h-Urine protein(g/d)	3.8	13.7	11.9	27	4.2
Serum albumin(g/l)	13.5	18	20	24.1	26
Serum Cr(mg/dl)	0.5	1.1	1.8	0.8	0.8
Interstitial inflammation	None	None	Focal#	None	None
Deposit in proximal tubular brush border	Y	Y	Y	Y	Y
Deposit in TBM	Y	Y	Y	N	N
Deposit in glomeruli	Y	Y	Y	Y	Y
IgG subclass	IgG1	IgG1	IgG1	IgG1	IgG1
Light chain monotype	N	N	N	lambda restrict	lambda restrict
Podocyte foot process effacement	diffuse	diffuse	diffuse	diffuse	diffuse

Focal, <50% of cortical surface area

PO1941

Time-Course Kidney Injury in Mice Remnant Kidney Model Fed by High-Protein Diet

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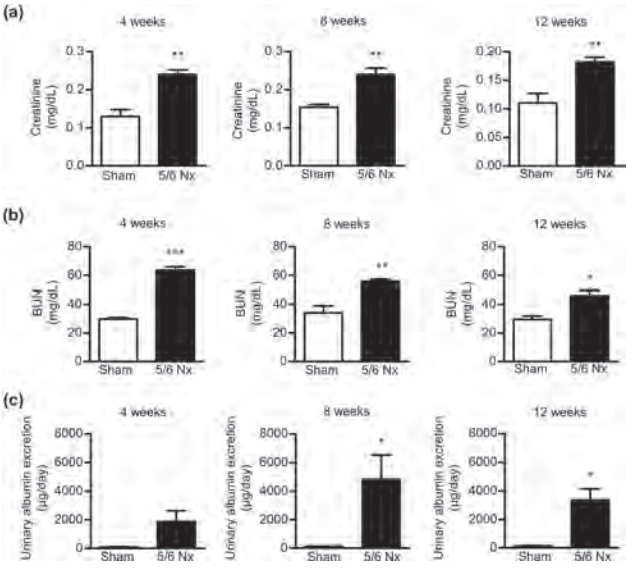
Background: Numerous animal models of CKD have been developed, but mice are relatively resistant to kidney injury. The remnant kidney model mimics progressive renal failure, and widely used in CKD research. The present study was performed to evaluate the effects of combined high-protein diet (HPD) loading and 5/6 nephrectomy (Nx) in a susceptible strain of mice (129/Sv).

Methods: Male 8–11-week-old 129/Sv mice underwent 5/6 Nx or sham surgery, then 2 weeks later were switched to an HPD, and cardiovascular parameters, kidney function, and renal histology were assessed after 4, 8, or 12 weeks.

Results: The 5/6 Nx group showed blood pressure elevation, cardiac hypertrophy, renal function decline, severe albuminuria, and glomerular hypertrophy. However, the glomerulosclerosis by 5/6 Nx was very mild and there was only modest tubulointerstitial inflammation and fibrosis in the 5/6 Nx group, even after 12 weeks of HPD loading. Furthermore, the sham group showed no histological changes.

Conclusions: Thus, an HPD alone is insufficient to cause renal pathology, and a combination of 5/6 Nx and HPD loading induces mild renal pathology.



PO1942

Neutralizing Antibodies in Preventing Polyomavirus Nephropathy: Lessons from the Mouse

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Background: Definitive polyomavirus nephropathy (PyVN) affects kidney transplants and impacts allograft function and survival. Data suggest that neutralizing PyV strain specific antibodies can attenuate and possibly even prevent disease. Here we report observations from the mouse on the protective role of anti-PyV antibodies.

Methods: Six breeding mice had been exposed to murine PyV (MUPyV). They had developed a robust IgG response while lacking definitive PyVN and only showing minor qPCR evidence of intra organ MUPyV. Newborns of exposed breeders were split: group 1 (n=23) was injected at birth with MuPyV; group 2 (n=19) was not injected. Group 3 (n=24) was born to unexposed breeders and injected with MUPyV at birth. Tissue, plasma, and urine were analyzed at various time-points (0,1,2,3,6, and 10 weeks) by light microscopy, immunohistochemistry, qPCR, and MuPyV antibody titer testing. The nonparametric Wilcoxon Rank Sums test was used for p-value comparisons

Results: Newborns from exposed breeders had IgG titers between 160-640, no IgM, and only subclinical minor molecular evidence of intra organ MUPyV by qPCR. During 10 weeks of follow up, groups 1 and 2 both cleared MuPyV. By week 10, MUPyV was largely undetectable in the setting of significantly reduced IgG titers (0-40; no IgM). Prior to clearance, both groups displayed a mild transient increase in IgG titers (up to 2560; no IgM) at weeks 2 and 3. MUPyV clearance occurred earlier in group 2 with significantly lower qPCR reads in kidney and spleen noted on week 2 ($P<0.03$). There was no MUPyV induced organ injury. In contrast, group 3 showed persistently high intra organ qPCR reads starting post MUPyV injection on day 0 and lasting through week 10 ($p<0.05$ compared to groups 1/2). Histologically apparent viral tissue injury was first noticeable at week 1 and persisted thereafter. IgG and IgM levels remained undetectable until week 2, when they began to slowly rise. By week 10, IgG titers had risen significantly (up to 20480) while IgM titers had decreased to 0

Conclusions: Preexisting neutralizing antibodies protect from PyVN and facilitate clearance of subclinical MUPyV. In contrast, established MUPyV induced disease/injury is unaffected by neutralizing antibodies. This data can help with developing preventative treatment strategies in man.

PO1943

Renal Failure of the Non-Crisis Variety in Scleroderma

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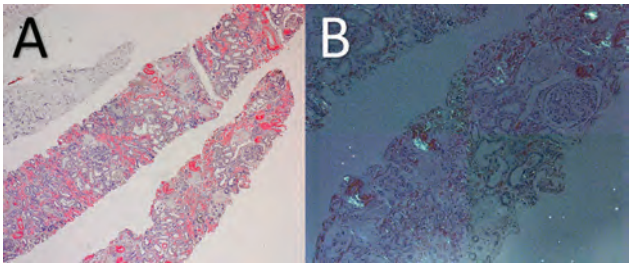
Introduction: Renal disease from systemic sclerosis (SS) classically presents as scleroderma renal crisis (SRC). In contrast, amyloidosis in SS is rare.

Case Description: A 73-year-old woman with untreated limited SS for >20 years (with ANA 1:160 centromere pattern, negative Scl-70, sclerodactyly, perioral scleroderma, telangiectasias, Raynaud's, and mild pulmonary hypertension), CKD with baseline creatinine of (Cr) ~1.5 mg/dL, Barrett's esophagus, and recent right below-knee amputation (for chronic wound osteomyelitis and invasive squamous cell carcinoma) is readmitted 2 weeks later for a pseudomonal stump infection. She develops AKI (Cr peak of 6) requiring HD. Renal biopsy reveals amyloidosis [figure]. Immunofluorescence and immunohistochemistry are negative for deposition of kappa, lambda, AA, or leukocyte chemotactic factor 2 (LECT2), but subsequent liquid chromatography-tandem mass spectrometry (LC-TMS) is positive for LECT2.

Discussion: SRC occurs in 5-10% of SS cases but is no longer the primary cause of death in SS with the advent of ACE inhibitors (ACEi). Unlike other autoimmune diseases, amyloidosis, especially renal amyloidosis, is rare in SS. While recovery from dialysis can occur in SRC with ongoing ACEi therapy, AA amyloidosis requiring dialysis carries a poor renal prognosis. LECT2 is a recently discovered amyloid protein that can deposit in multiple organs, with the most significant clinical feature of LECT2 amyloidosis (ALECT2) being slowly progressive renal failure. The pathogenesis is poorly understood. Diagnosis is by renal biopsy, with advanced methods like LC-TMS often needed for LECT2 detection. Though the reason is unclear, ALECT2 seems to have a predilection for Mexican Americans and Native Americans and is likely underdiagnosed in the Southwest U.S. However, it is not usually associated with autoimmune disease, with this being the first known case of ALECT2 occurring in the context of SS.



Biopsy shows amyloid deposits, primarily in the cortical interstitium and vessels, by Congo red stain [A] with green birefringence under polarized light [B], with global sclerosis of 22/35 glomeruli and 50% interstitial fibrosis.

PO1944

Amyloid of Another Kind: The Unexpected Fat Pad Biopsy

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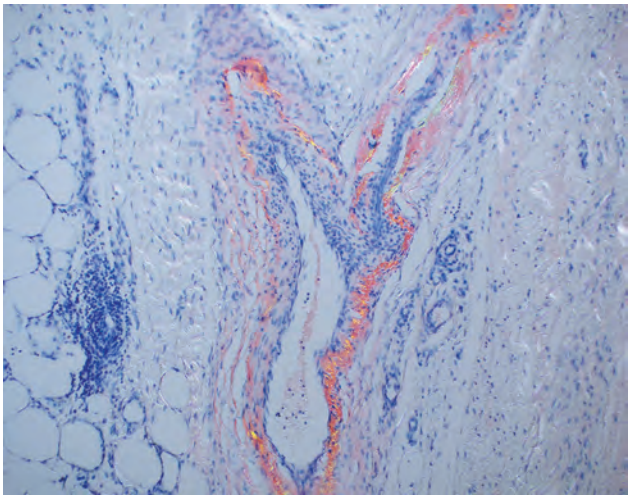
Introduction: Insulin-type amyloidosis is a rare phenomenon in which subcutaneous masses develop at the site of repetitive insulin injections. Here we discuss a patient in which insulin-type amyloid did not present with a subcutaneous mass and instead was diagnosed during the workup for systemic amyloidosis.

Case Description: A 52 year old male with a history of insulin dependent diabetes and stage 3 CKD was evaluated for nephrotic-range proteinuria. He endorsed weight gain, peripheral edema and dyspnea. Physical exam revealed anasarca. He reported a history of amyloidosis in his father. Due to the combination of proteinuria, anasarca and positive family history, a workup for systemic amyloidosis was initiated. Initial serum and urine electrophoresis were non-diagnostic. Urine protein to creatinine ratio was 2610 mg/g. Kappa and lambda ratios were unremarkable. After a rheumatologic workup including ANA, c-ANCA and p-ANCA was negative, an abdominal fat pad biopsy was performed. The fat pad biopsy revealed deep dermal granulomatous vasculitis and vessel damage with extravasated blood. A Congo Red stain showed apple green birefringence on polarization. The site of the fat pad biopsy had no gross abnormalities such as hard masses or skin irregularities. Amyloid typing by liquid chromatography was positive for insulin-type amyloidosis.

Discussion: This case demonstrates a novel clinical and histologic presentation of insulin-type amyloid. By our research, this is the second case report that has discovered insulin type amyloid during the diagnostic workup for systemic amyloid. This finding suggests that a fat pad biopsy be avoided at insulin injection sites. If a patient with insulin dependence has a positive fat pad biopsy we suggest confirmation of the specific amyloid type in order to rule out insulin type amyloidosis.



Congo Red stain showing apple-green birefringence

PO1945

Simultaneous Light-Chain Proximal Tubulopathy (with Crystals), Myeloma Casts Nephropathy, and Intratubular Amyloidosis in a Patient with Monoclonal Gammopathy of Renal Significance

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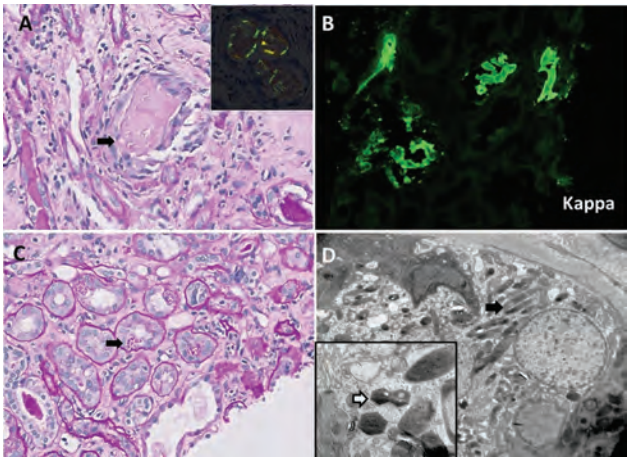
Introduction: Monoclonal gammopathy of renal significance (MGRS) is an important complication of monoclonal disease in the kidney with a spectrum of histological changes involving glomerular and tubulointersitial compartments. While MGRS is usually present as a single pathological entity, a combined two or more pathology features in a single patient is rarely reported.

Case Description: A 67 year old male admitted to the hospital for nausea and vomiting in association with AKI (creatinine 9.06 mg/dL), severe anemia (hemoglobin 6.4 g/dL) and hypercalcemia. Urinalysis showed 4-10 RBCs and proteinuria of 30 mg/dL. SPEP detected a monoclonal IgG kappa light chain. The patient received 2 units of blood transfusion pending further study and hematology consult. Kidney biopsy showed a few thick angulated atypical casts in the distal tubules that show positive birefringent apple green staining by Congo red (Fig 1 A&B). By immunofluorescence, the casts are positive for kappa light chain with negative lambda (Fig 1 C&D). In addition, few proximal tubules show rounds or needle-shape intracytoplasmic structures (Fig 2 A&B). Ultrastructural examination demonstrates intracytoplasmic needles, rod, rhomboid or hexagonal crystals (Fig 2 C&D).

Discussion: The pathophysiological features of MGRS are distinctive, yet it can occur simultaneously in one patient. A throughout pathology and clinical assessment is essential in order to guide the treatment.



A. Atypical cast with sharp edges surrounded by epithelial cells of distal tubules (PAS). Congo red-positive intratubular casts (inset)

B. Intratubular casts are positive for Kappa light chain (Direct Immunofluorescent)

C. Renal cortex shows intracytoplasmic magenta-colored structures (arrow) in proximal tubules (PAS)

D. Ultrastructural images of proximal tubular cells show rod and rhomboid intracytoplasmic crystals (black arrow) and hexagonal and oval-shape crystal (white arrow/inset) (transmission EM)

PO1946

Insidious Granulomatous Interstitial Nephritis (GIN) in a Patient with a History of Diffuse Large B Cell Lymphoma (DLBCL)

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Introduction: GIN has diverse etiology as infections, vasculitis, sarcoidosis, and lymphoma. These diseases can occur in the same patient, making diagnosis and treatment decisions challenging. Here, we report a case of GIN with a fever that developed after a long period since the complete remission (CR) of DLBCL.

Case Description: A 46-year-old man was admitted to our hospital with malaise, dyspnea, and severe renal failure (RF). Twenty years before the admission, he was diagnosed with DLBCL. After 4 years of treatments, he achieved CR. Thirteen years after CR, he presented to our hospital with a persistent fever. At this time, impaired renal function (serum [s] Cr 1.8 mg/dL) was noted. FDG-PET CT showed uptake in the enlarged lymph nodes (LN) around the pancreas and in both kidneys. Biopsy of the LN revealed multiple epithelioid granulomas and no evidence of recurrence of DLBCL, and his fever was resolved spontaneously. Two years later, he was admitted due to advanced RF (sCr 11.8 mg/dL), and hemodialysis (HD) was initiated. Both kidneys were atrophic on CT scan, whereas they still showed intense uptake on Ga scintigraphy. The renal biopsy showed diffuse GIN, but recurrence of DLBCL, sarcoidosis, and vasculitis was denied. Examinations for Tuberculosis (TB) were only positive for the interferon-gamma release assays (IGRAs) and negative for renal stains, systemic cultures, and image studies for lung TB. Anti-TB therapy was administered for his persistent fever that recurred after hospitalization. After the initiation of the anti-TB treatment, his fever gradually resolved, and he has been well, although he cannot withdraw HD.

Discussion: The course of our case suggests that the GIN was induced by TB infection, although our patient did not show typical features of systemic TB except for positive IGRAs. There has been an increase in the number of cases of TB infection diagnosed following GIN, which is presented not with the typical features of classical renal TB but with a more insidious form (Oliveria et al., Clin Kidney J 2017). These cases are often diagnosed later and may associate with a poor prognosis. Our case suggests that anti-TB therapy should be considered for patients with IGRAs-positive GIN after excluding other etiologies of GIN, even without the other diagnostic evidence of systemic TB.

PO1947

Severe Vasculitis Masquerading as Guillain-Barre Syndrome

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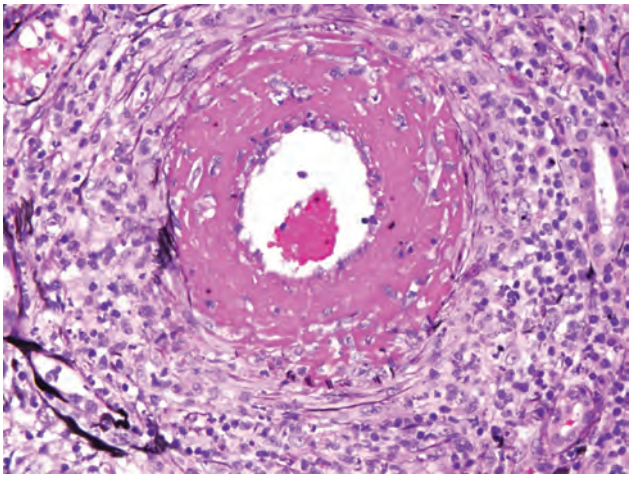
Introduction: Polyarteritis nodosa (PAN) is a rare ANCA-negative, necrotizing arteritis affecting small-medium arteries. Due to rarity of the disease, studies are limited. We present a case of PAN with missed diagnosis at presentation and complicated treatment course.

Case Description: 75-year-old man with hypertension diagnosed 10 months ago presented to outside hospital with bilateral lower extremity ascending numbness and weakness, and arthralgia. Lumbar puncture was inconclusive. He was treated for Guillain-Barre syndrome with IVIG with some improvement. Two months later, he presented to our hospital with localized petechial rash, oliguria, lower extremity edema, right foot drop, marked weakness, and acute kidney injury (creatinine (Cr) 4.09mg/dL). He had hematuria, subnephrotic range proteinuria, high inflammatory markers, and low complements. Renal biopsy revealed necrotizing medium vessel arteritis, consistent with PAN. He was started on steroids and oral cyclophosphamide (CYC) with rapid, dramatic improvement in neurologic symptoms. Unfortunately, a month later, he developed acute hypoxia with worsening multifocal opacities despite adequate diuresis and infectious work-up, including negative bronchoalveolar lavage. Pneumonitis from CYC toxicity was diagnosed. Hypoxia resolved with steroids and replacing CYC with mycophenolate mofetil (MMF). Cr improved to 2.2mg/dL with continued improvement in neuromuscular symptoms.

Discussion: This is a rare presentation of vasculitis causing severe AKI, debilitating peripheral neuropathy and weakness. Neurologic and renal manifestations improved rapidly with treatment. Development of CYC-induced pneumonitis leading to transition to MMF for induction is a rare complication, resulting in rare, but effective treatment. Lastly, development of new onset hypertension in the 8th decade of life warrants work-up for secondary etiologies.



Transmural fibrinoid necrosis of medium-sized renal artery with surrounding inflammatory cells

PO1948

Myoglobin Deposition in the Proximal Tubular Cells in a Patient with Dermatomyositis and Nonglomerular Proteinuria

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Introduction: Dermatomyositis (DM) is a rare inflammatory myopathy characterized by proximal muscle weakness and skin lesions. Clinical manifestations of DM can involve any organ, including the kidneys. Although renal manifestations are rare, the literature describes cases of DM associated with mesangial proliferative glomerulonephritis, minimal change disease, Ig-A nephropathy, and acute tubular necrosis due to myoglobinuria. We report a rare case of DM with a predominant nonglomerular (NG) proteinuria, with kidney biopsy showing myoglobin deposition in the proximal tubules.

Case Description: A 38-year-old man presented with complaints of gradually worsening proximal muscle weakness and violaceous skin rash. Laboratory studies revealed an elevated creatinine phosphokinase (CPK) level of 8,250 IU/, 3+ hematuria with RBC 0-2, serum creatinine of 0.9 mg/dL, 24-hour urine test showed 1.8 g protein with 343 mg of albumin. The ANA titer was 1:1280, dsDNA was negative. A renal biopsy was done, and it showed acute tubular injury with increased proximal tubular cytoplasmic myoglobin staining with no myoglobin casts. There was no evidence of lupus nephritis. After corticosteroid therapy, Hydroxychloroquine, Mycophenolate Mofetil, and later Rituximab; his CPK level, proteinuria, and clinical symptoms have all steadily improved. This case demonstrates an atypical presentation of DM manifested by NG overflow proteinuria.

Discussion: The main renal manifestations of polymyositis are acute kidney injury related to rhabdomyolysis and glomerulonephritis. Our case highlights a rare presentation of NG proteinuria with preserved renal function. The proteinuria likely resulted from myoglobin and impaired absorption of protein by the proximal tubular cells due to pathologic myoglobin deposition. There was no other evidence of proximal tubule impairment such as hypophosphatemia or glucosuria. In a study at Nephropath, looking at five hundred eighty kidney biopsies with myoglobin stain, most of the cases had myoglobin casts, with only 12 % of them having myoglobin deposition in the proximal tubular cells.

PO1949

A Case of Asymptomatic Juxtaglomerular Cell Tumor (JGCT)

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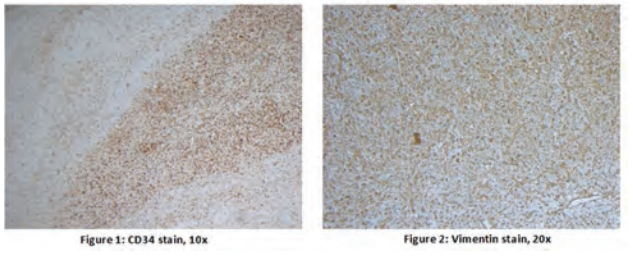
Introduction: JGCT/ reninoma is an extremely rare benign neoplasm of kidneys typically manifesting as hypertension and hypokalemia secondary to renin secreting tumor cells. We present a case of JGCT presenting as an asymptomatic renal mass.

Case Description: A 61-year-old male of with diabetes mellitus, hypertension (>15 years duration, well-controlled with Losartan 100mg daily) presented with right upper quadrant abdominal pain. Computed tomography scan of abdomen /pelvis with intravenous contrast revealed cholelithiasis without cholecystitis and an incidental 3cm mass at the mid-pole of the left kidney without renal vascular involvement. Kidney ultrasound 5 years prior did not show any renal mass. Spot urinalysis showed no hematuria and proteinuria was 96 mg/g (normal < 150 mg/g). Baseline serum creatinine was 1.3-1.4 mg/dl (normal 0.7-1.3 mg/dl). 24-hour urine creatinine clearance was normal. Given the high suspicion for a malignancy, the patient underwent recommended left radical nephrectomy. Kidney mass biopsy diagnosed JGCT. Light microscopy showed well circumscribed tumor with glomoid appearance with sheets of uniform round- to-polygonal cell with clear to eosinophilic cytoplasm. In addition, there were focal endocrine-like, markedly atypical hyperchromatic nuclei occasionally scattered throughout the tumor. Immunohistochemical stains demonstrated diffuse positivity in tumor cells for CD34 (Figure 1), CD117 and vimentin (Figure 2). Patient sustained a slight rise in creatinine post nephrectomy as expected and he continued to require only one anti-hypertensive medication. Patient remained in remission with stable kidney function without recurrence of tumor at 2 years follow-up.

Discussion: JGCT can present as hypertension and hypokalemia. Our patient had optimal blood pressure control on monotherapy. Losartan may have masked the associated hypokalemia. Nephrectomy (partial or radical) is curative and is the recommended treatment.



CD 34 stain and vimentin stain kidney mass pathology images

PO1950

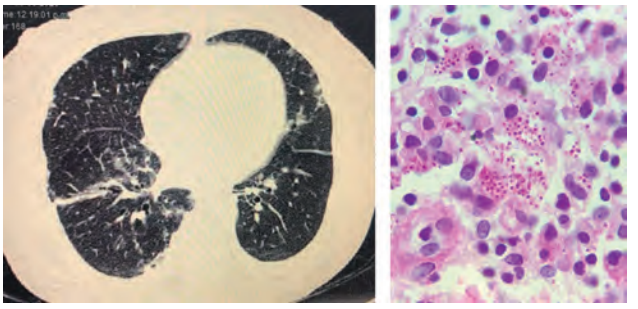
Disseminated Histoplasmosis Mimicking Crohn Disease in Kidney Transplant Recipient

Victor H. Gomez Johnson, Belen Martinez-Vazquez, Octavio R. Garcia-Flores, Francisco Rodríguez. *Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico.*

Introduction: Fungal infections can occur after a kidney transplant due to the use of immunosuppressants. Histoplasmosis is an endemic infection in Mexico and it's pulmonary phase is very common. The risk of complications is high, so an early diagnosis should ideally be made with a biopsy of the affected tissue. We report the case of a kidney transplant recipient with chronic diarrhea associated with disseminated histoplasmosis simulating Chron's disease.

Case Description: A 50-year-old woman with history of CKD of unknown etiology underwent living donor kidney transplant. She received induction with basiliximab and maintenance therapy based on azathioprine, prednisone and cyclosporine. Six years after transplantation, the calcineurin inhibitor was discontinued due to toxicity documented by biopsy and continued with Sirolimus and mycophenolate mofetil. One year after transplantation, she was evaluated for fever and pulmonary nodules, without detecting infectious etiology. One year later, she presented diarrhea and based on the presence of colonic ulcers, Chron's disease was suspected and treatment with mesalazine was started. Due to the persistence of diarrhea, a second colonoscopy was performed establishing the diagnosis of histoplasmosis by means of biopsies of the colonic mucosa and with urinary antigen. Amphotericin B treatment was initiated and 2 weeks later urinary antigen was negative and renal function returned to baseline. Itraconazole-based maintenance therapy was chosen.

Discussion: Acute pulmonary histoplasmosis is caused by inhaling spores and it tends to be a self-limited disease. Disseminated histoplasmosis is common in immunocompromised patients. Gastrointestinal involvement is clinically manifested in 20% of cases, although urinary antigen has a 95% specificity, histopathological identification with PAS(+) and Giemsa(-) stains, remains the ideal test, as they showed submucosal and lamina propia macrophage invasion at the intestinal tissue. Chronic diarrhea can be a manifestation of systemic fungal infection in kidney transplant recipients.



PO1951

Improving the Identification of AKI in the Neonatal ICU: Three Centers' Experiences

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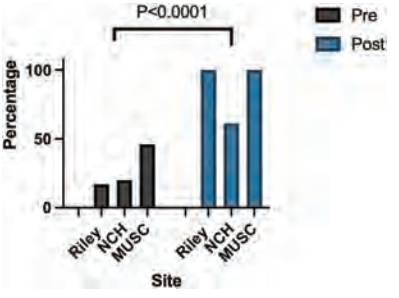
Background: Acute kidney injury (AKI) is common in neonates. Despite its high prevalence, neonatal AKI is diagnosed in <30% of affected neonates. Neonates with AKI are at increased risk for repeated episodes of AKI and CKD. Without an AKI diagnosis, neonates may not be identified for long-term follow up, reducing early identification of CKD and limiting opportunities to slow disease progression.

Methods: In this retrospective cohort study of 3 academic Neonatal Intensive Care Units (NICUs), we evaluated the impact of local standardized approaches implemented to improve neonatal AKI identification. Each center implemented different standardization practices, ranging from automated nephrology consult to neonatology identification based on creatinine. Patients were divided into two groups: 6 months prior to (Cohort 1) and 6 months following (Cohort 2) standardization. We compared AKI incidence and identification, nephrology consultation and nephrology follow-up.

Results: In total, 1887 infants were included. Neonatal AKI identification improved in all three NICUs following protocol implementation (26% to 85%, $p<0.0001$). Each center also saw increases in nephrology consultation (15% to 83%, $p<0.0001$) and nephrology follow-up (7% to 73%, $p<0.0001$). Notably, AKI incidence decreased significantly (21% to 12%, $p<0.0001$).

Conclusions: Multiple strategies can be successfully operationalized to improve neonatal AKI identification. While different in approach, each strategy resulted in increased AKI identification and nephrology involvement. We also report a decrease in AKI rates. This study emphasizes the importance of local standardized approaches to improve AKI identification in the NICU. Further collaborative work by nephrologists and neonatologists is needed to improve identification and follow-up of AKI.



AKI identification rates between Cohorts 1 and 2

PO1952

Diuretic Use, Comorbidity, and Length of Stay in Pediatric AKI

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Background: Acute kidney injury (AKI) and fluid overload (FO) both have well known negative effects on morbidity and mortality in many populations. The combination of AKI and FO is associated with synergistically worse outcomes in critically ill children. Diuretic use in management of AKI and FO has been studied in adults with widely varied outcomes ranging from improved mortality to no significant change to increased comorbidity such as prolonged mechanical ventilation. Therefore utility of diuretics remains unclear, and their use in pediatric patients with AKI has not been characterized.

Methods: The Pediatric Hospital Information System (PHIS) database was queried for patients with diagnosis of AKI from January 2015 to December 2019 with admission LOS <15 days. Those <1 or >18 years of age were excluded. ICD codes were used to discern complex chronic conditions (CCCs) as well as acute comorbidities. Daily medication exposure was used to determine diuretic use. LOS in both the ICU and the inpatient floor was assessed. CCCs of interest were chronic kidney disease (CKD), kidney transplant, and heart failure. Measured comorbidities included: shock, mechanical ventilation, hypoxemia, fluid overload, ascites, edema, and oligoanuria. Numeric data were summarized as medians and IQRs and categorical data as frequency and percent. Associations between diuretic use and comorbidity was assessed by Wilcoxon's rank-sum test and Fisher's exact test. Length of stay was then assessed by longitudinal regression.

Results: There were 5490 encounters for analysis with diuretic use in 951. Demographics were similar between groups. Those with CKD or heart failure were more likely to receive diuretics, while those with kidney transplant status were less likely to receive diuretics. LOS was 1.67 days longer in those who received diuretics despite adjustment for age, gender, and illness severity including CCCs. All acute comorbidities were increased in those who received diuretics.

Conclusions: Children with underlying CCCs were more likely to receive diuretics and to have longer LOS. Comorbidities and LOS were also increased in children with AKI who received diuretics regardless of disease severity. This is clinically important as diuretic use may be a corollary for worse outcomes and increased costs. Due to database limitations, temporal association is unknown and further study is needed.

PO1953

The Association of Diuretic Therapy with Fluid Balance and AKI in Hospitalized Preterm Neonates

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Background: Fluid homeostasis is essential in critically ill preterm neonates because fluid overload is associated with poor outcomes including need for mechanical ventilation, bronchopulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). Acute kidney injury (AKI) is a common comorbidity in preterm neonates. Diuretics are often used to enhance urinary output (UOP) in AKI- associated oliguria and to achieve negative fluid balance (FB).

Methods: Retrospective study of preterm neonates < 37 weeks gestational age (GA) who received diuretics during the first 14 postnatal days in a single level IV NICU (05/2014- 05/2020). We analyzed FB, UOP, and Scr levels on and off diuretics over first 14 days. We studied prevalence of AKI.

Results: 191 preterm neonates met inclusion criteria. By day 8, 50% of patients were treated with diuretics. After adjusting for birthweight and time after birth, there was a statistically significant decrease in weights while on diuretics with a mean difference of 10g. Peak median FB was +58 mL on postnatal day 8. Mean FB difference on and off diuretic therapy was -35 mL. There was smaller difference in FB between those on or off diuretics in younger GA patients compared to older GA patients (Figure 1). UOP increased by 0.6 mL/kg/h and Scr by 0.2mg/dL while on diuretics compared to no diuretic therapy (Table 1). AKI occurred in 9% and 19% of patients based on an increase in Scr of ≥ 0.3 mg/dL or UOP < 1ml/kg/h for 24 hours respectively. In patients who met AKI criteria, oliguria was noted while off diuretics and increased Scr while on diuretics.

Conclusions: In hospitalized preterm neonates, treatment with diuretics was associated with improved UOP and negative fluid balance. SCr increased while on diuretic therapy. Further studies should analyze the effects of diuretics as mediated by FB and AKI on development of BPD and NEC.

Distribution of weight, FB, UOP and Scr in preterm neonates on and off diuretic therapy

	On diuretics	Off diuretics	Difference on and off diuretics
Weight (g)	1523	1537	-10
Mean FB (mL)	31	66	-35
Mean UOP (mL/kg/h)	3.2	3.8	0.6
Mean Scr (mg/dL)	1.1	0.9	0.2

PO1954

Neonatal AKI Is Associated with Impaired Renal Function at 24 Months of Age

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Background: Neonatal acute kidney injury (nAKI) is common, occurring in up to 30% of neonatal intensive care admissions. However, there are currently no guidelines for nephrologic evaluation after the neonatal period. Our objective was to determine the incidence of renal dysfunction at 24-months of age and to identify associated risk factors following nAKI.

Methods: Retrospective single-center cohort study of infants with nAKI (defined as rise in creatinine (Cr) ≥ 0.3, abnormal initial Cr for gestational age, or abnormal rate of Cr decline) seen in pediatric nephrology clinic at 24-months. Abnormal estimated glomerular filtration rate (eGFR) (< 90 ml/min/1.73m^2), hypertension (BP ≥ 95th%ile), proteinuria (TP/Cr > 0.5), and renal length (≥ the 95th or ≤ the 5th %ile) were correlated with high risk NICU events and exposures. Data was obtained by chart review. eGFR was calculated using cystatin C and creatinine separately, using the CKID cystatin C and the revised Schwartz equations, respectively. Data was analyzed using t-tests, Wilcoxon Rank Sum Test, or Chi-square as appropriate.

Results: 36/42 infants with history of nAKI referred to nephrology had a 24-month visit. 20 of 36 subjects (55.5%) had at least one renal abnormality, with 14 (39%) having eGFR < 90 ml/min/1.73m^2 by cystatin C, 7/36 (19.4%) had proteinuria, 3/36 (8.3%) had hypertension, and 4/36 (11.1%) had abnormal renal length. 1/15 subjects with reduced GFR by cystatin C also had a reduced GFR by serum creatinine. Subjects with renal dysfunction at 24 months had a neonatal history of more vasopressors exposure days (mean, 4.5 vs 0.25, p = 0.002), more total diuretic days (mean 122 vs 51 p=0.03), were more likely to be taking a diuretic at discharge (n=11 vs n=3, p= 0.026), or to be of extremely low birth weight (ELBW < 1000 gm) (n=14 vs n=4, p= 0.007) compared to those without renal dysfunction.

Conclusions: The majority of children with nAKI had evidence of renal dysfunction at 24-month of age. Serum Cystatin C was more sensitive at identifying kidney dysfunction than creatinine alone. All children with nAKI should be referred for renal follow-up with a particular focus on children who were ELBW, required vasopressors, or had prolonged diuretic use in the neonatal period.

PO1955

Kidney Outcomes Among Extremely Preterm Born Adolescents with Neonatal AKI

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Background: Infants born preterm are at increased risk for neonatal acute kidney injury (nAKI). AKI increases the risk for CKD long term however, long term kidney outcomes among preterm born survivors of nAKI are not well known. The aim of the study is to evaluate associations between nAKI and microalbuminuria, elevated blood pressure (BP), and reduced kidney mass in adolescents born extremely preterm.

Methods: We obtained 2 manual BPs, a random urinalysis, and kidney ultrasound on adolecents of the University of North Carolina ELGAN (Extremely Low Gestational Age Newborn) cohort between 2017-2019. We retrospectively obtained serum creatinine (SCr) studies from the initial neonatal intensive care unit hospitalization between 2002-2004. We defined nAKI by neonatal KDIGO guidelines.

Results: Of the 31 participants born <28 weeks gestation, mean age was 15.2 years and 58% were overweight/obese. 32% of adolescents had elevated BP, 13% had reduced kidney mass, and 13% microalbuminuria. 52% of the adolescents had a history of nAKI. 81% experienced Stage 1 AKI, 19% had Stage 2 AKI, and no participants experienced Stage 3 AKI. Those with nAKI had lower birth weight, lower APGAR scores, more mechanical ventilator days, lower urine output, greater vasopressor exposure, greater indomethacin exposure, less methylxanthine exposure, greater # of serum SCr measurements, and more days in the hospital. During adolescence, those with nAKI had lower frequency of elevated BP and microalbuminuria but greater frequency of reduced kidney mass(Table 1).

Conclusions: Adolescents with a history of nAKI were more frequently exposed to nephrotoxic factors and had more indicators of severe illness in early life. However, nAKI was not significantly associated with elevated BP, microalbuminuria, or kidney mass in this sample of adolescents born extremely preterm. Further follow up is needed to better characterize manifestation of CKD in adolescents after nAKI.

Table 1

	With Neonatal AKI (n=16)	Without Neonatal AKI (n=15)
Birth characteristics collected 2002–2004		
Gestational Age at Birth (weeks), mean(SD)	25.4 (±0.9)	26.1 (±1.1)
Birth Weight (grams), mean(SD)	776.6 (±184.3)	790 (±176.6)
APGAR 1 minute, md(IQR)	2.5 (2,5)	6 (3,7)
APGAR 5 minute, md(IQR)	5.5 (5,7)	8 (7,9)
Mechanical Ventilator Days, md (IQR)	27.5 (16,28)	8 (3,25)
Urine Output (ml/kg/hr), md (IQR) δ	1.0 (0.4, 1.6)	1.8 (1.5, 2.6)
Use of Vasopressors in first 14 days of life, n(%)	12 (75)	6 (40)
Indomethacin exposure in first 28 days, n(%)	10 (62.5)	5 (33.3)
# of Methylxanthine doses in first 28 days, md (IQR)	3.5 (0, 9.5)	17 (10, 25)
Age at initial AKI (days), md (IQR)	7 (2.5, 11)	----
# of AKI episodes, mean(SD)	1 (1, 1.5)	----
Total # of serum creatinines measured, md (IQR)	17.5 (12, 21.5)	11 (8,13)
Discharge serum creatinine, mean(SD)	0.35 (±0.17)	0.47 (±0.23)
Duration of NICU Course (weeks), mean(SD)	15.1 (±7.7)	9.9 (±5.9)
Ancillary 15-Year Old Kidney Study Visit Characteristics Collected 2017-2019		
Age (years), med (IQR)	15.1 (±0.2)	15.3 (±0.4)
Males, n(%)	9 (56.3)	10 (66.7)
BMI >85th percentile, n(%)	9 (56.3)	9 (60)
Elevated Blood Pressure (>120/80mmHg), n(%)	3 (18.8)	7 (46.7)
Systolic Blood Pressure (mmHg), mean(SD)	114.1 (±8.3)	115.7 (±8.8)
Diastolic Blood Pressure (mmHg), mean(SD)	63.8 (±6.9)	72.1 (±8.2)
Renal Hypoplasia**, n(%)	3 (18.8)	1 (6.7)
Total kidney volume/body surface area, mean(SD)	125.9 (±23.1)	136 (±34.5)
Microalbuminuria (>30µg/g), n(%)	1 (6.3)	3 (20)
Urine Albumin/Creatinine (µg/g), md(IQR)	6.6(4.3, 11.8)	12.5 (5.4,26.4)
Composite Kidney Outcome, n(%)	10 (62.5)	5 (33.3)

δUrine output in the first 12 hours of life;

**Renal hypoplasia defined by body surface area related total kidney volume below the 10th percentile of normative TKV/BSA [1, 2]

PO1956

Prediction Model of CKD at the Age of One Year Following Prenatal Severe Urinary Tract Dilatation

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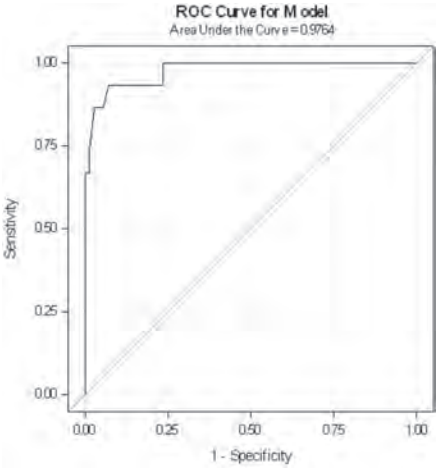
Background: Early childhood chronic kidney disease (CKD) has a wide spectrum of health and developmental implications. Renal replacement therapy may be needed during childhood. Prenatal counselling regarding future renal outcome in cases presenting prenataly with severe urinary tract dilatation (UTD) is challenging. We aimed to create a prenatal ultrasound model for the prediction of early childhood CKD following fetal severe UTD.

Methods: A retrospective cohort study was conducted in a national referral centre. Fetuses diagnosed with severe UTD and maintained follow up comprised the study group. The main outcome was CKD at the age of one year. Logistic regression analysis was used to identify prognostic prenatal ultrasound variables for the renal outcome. Analysis of Maximum Likelihood Estimates was performed to create a multivariable predictive model.

Results: 87 fetuses comprised the study group. 15 cases (17.2%) developed CKD by the age of one year. In all, renal dysfunction and renal dysplasia were diagnosed at birth. Post-natal diagnoses were lower urinary tract obstruction in 5 cases, vesical-ureteral reflux in 10 cases. Bilateral hydronephrosis, abnormal bladder, hydroureter, calyceal dilatation, and abnormal parenchyma, were all significantly related to CKD at the age of one year. A combination of prenatal ultrasound variables yielded a model with a discriminatory ability of c=0.976.

Conclusions: A prediction model incorporating prenatal ultrasound features can discriminate between a normal and an impaired renal outcome at the age of one year. These sonographic features are related to the extent of renal dysplasia and to the remaining functioning nephron mass. Data presented may be used to develop more effective risk assessments and customized parent counseling.



PO1957

Association of Antenatal Corticosteroids with Later Kidney Function in Adolescents Born Preterm with Very Low Birth Weight

Whitney N. Floyd, Andrew M. South. *Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Antenatal corticosteroids (ANCS) are given to pregnant women who are at risk of preterm delivery to accelerate fetal lung development. While studies in sheep suggest that ANCS program deleterious effects on renal development leading to higher blood pressure (BP) and worse kidney function, the persistent effects of ANCS exposure on the long-term health of at-risk individuals remains undescribed. We investigated the association of ANCS with BP and kidney function in adolescents born preterm and hypothesized that ANCS are associated with worse BP and kidney function.

Methods: This was a long-term prospective birth cohort of 175 14-year-old adolescents born preterm with very low birth weight (VLBW, <1500 g). We measured manual BP, serum creatinine, and first-morning urine albumin-to-creatinine ratio (ACR), defined high BP as ≥120/80 mmHg and albuminuria as ACR >30 mg/g, and calculated the estimated glomerular filtration rate (eGFR). We used generalized linear models to estimate the association of ANCS with the outcomes.

Results: The cohort consisted of 58% non-Black participants, 55% female participants, and 53% were exposed to ANCS. Among all participants, mean systolic BP was 106.4 mmHg, 13% had high BP, median eGFR was 124.9 ml/min/1.73 m^2 (n=123), and 7% had albuminuria (n=134). In unadjusted analyses, ANCS was not associated with high BP (RR 1.08 mmHg, 95% CI 0.49–2.37), eGFR (β 3.74 ml/min/1.73 m^2, 95% CI -6.74 to 14.22), or albuminuria (RR 1.31, 95% CI 0.34–5.01).

Conclusions: Our research findings indicate that ANCS exposure was not associated with compromised kidney function or worse BP in adolescents born preterm with VLBW. Future analyses will include adjusting for potentially confounding factors in multivariable models and continuing to assess participants' long-term BP and kidney function.

PO1958

Predictors of Renal Function in Pediatric Liver Transplant Recipients

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Background: Impaired kidney function is a well-recognized complication following liver transplant (LT). In adult LT recipients, the cumulative incidence of renal insufficiency is as high as 10% in 10 years. The burden of kidney dysfunction is thought to be higher in pediatric LT recipients due to longer exposure to nephrotoxic agents & longer lifespan. The aim of this study is to identify predictors of renal function decline in pediatric LT recipients.

Methods: This is a retrospective study of pediatric LT recipients between June 2008 to November 2014. Clinical and biochemical characteristics and eGFR were obtained at baseline, 6, 12, 24, and 60 months. CKD was defined as an eGFR <90 ml/min/1.73 m2 for a least 3 months post-LT. A Multivariable Cox Proportional Hazards model was created to determine predictors of progression to CKD post-LT.

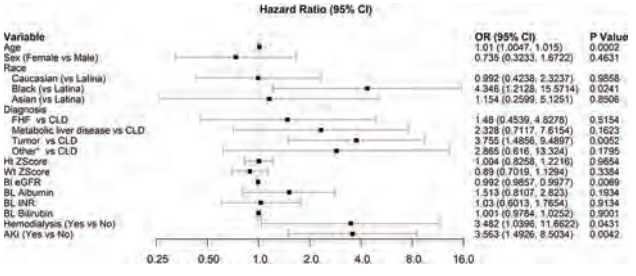
Results: Table 1 shows the baseline characteristics of patients with CKD post-LT compared to those who did not. In bivariate analysis, age, African American race, tumor diagnosis, baseline eGFR, pre-transplant HD and AKI were associated with progression

to CKD (Figure 1). In multivariable analysis, factors associated with increased risk of progression to CKD included: older age at LT (HR 1.012, p<0.001), tumor diagnosis (HR 3.602, p=0.0126) and lower baseline eGFR (HR 0.986, p=0.0014).

Conclusions: In our study we found that risk factors for CKD include: older age at the time of LT, lower baseline eGFR and tumor diagnosis. Further studies are underway to evaluate the role of Tacrolimus in the progression to CKD post LT

Funding: Other NIH Support - This research was supported by NIH National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881

Variable	CKD n=26	No CKD n=67	p
Age at LT, months, median (IQR)	86.2 (43.0-154.8)	19.4 (10.4-64.4)	0.001
Follow-up time in months, median (IQR)	58.6(25.9-60.7)	59.9(59-61.3)	0.061
Sex, n (%)			0.152
Male	20 (76.9%)	41 (61.2%)	
Female	6 (23.1 %)	26 (38.8%)	
Race, n (%)			0.381
Hispanic	11 (44%)	36 (53.7%)	
Caucasian	9 (36%)	24 (35.8%)	
African American	3 (12%)	2 (3%)	
Asian	2 (8%)	5 (7.5%)	
Primary Diagnosis, n (%)			0.031
Cholestatic liver disease	8 (30.8%)	39 (58.2%)	
Fulminant hepatic failure	4 (15.4%)	11 (16.4%)	
Metabolic liver disease	4 (15.4%)	8 (11.9%)	
Tumor	9 (34.6%)	6 (9%)	
Other	1 (3.9%)	3 (4.5%)	
Patient status at LT, n (%)			0.159
Home	12 (46.2%)	40 (59.7%)	
Ward	5 (19.2%)	16 (23.9%)	
ICU	9 (34.6%)	11 (16.4%)	
BL Height Z Score, mean ±SD	1.33 +/- 1.8	-1.34 +/- 1.8	0.780
BL Weight Z Score, mean ±SD	-0.8 +/-1.9	-0.31 +/-1.3	0.550
BL Creatinine, median (IQR)	0.4(0.3-0.6)	0.3 (0.2-0.3)	<0.0001
BL eGFR, median (IQR)	137.2 (97.5-151)	162 (126.5-238)	0.015
BL albumin, mean ±SD	3.5 (3.2-4.2)	3.4 (3.1-3.9)	0.182
BL INR, median (IQR)	1.2 (1.1-1.7)	1.3(1.2-2.2)	0.261
BL bilirubin, median (IQR)	1.8 (0.3-32.6)	11.3(1.1-24.1)	0.408
Hemodialysis Pre-LT, n (%) Yes			0.311*
No	2 (7.7%)	2 (3%)	
	24 (92.3%)	65 (97%)	



PO1959

Clinical Evaluation of Membrane Therapeutic Plasma Exchange Using Prismaflex Machines and Fresh Frozen Plasma in Pediatric Patients

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Background: Previous studies have shown that membrane-based therapeutic plasma exchange (m-TPE) can be an effective method. The availability of a TPE 2000 filter membrane set with Prismaflex machines provides added advantage to perform TPE along with continuous renal replacement therapy (CRRT). The extracorporeal volume of this filter at 125 ml is lower than centrifugation-based apheresis systems. There is very little data on the efficacy and complications of this procedure in small children. Fresh frozen plasma (FFP) has a high citrate content (20 mmol/L). There may be the risk of significant hypocalcemia using FFP as replacements.

Methods: We performed a retrospective analysis of children who underwent m-TPE using the TPE 2000 filter membrane set with Prismaflex machines at our center during last year. We included children who required heparin, or bivalirudin as anticoagulation, and FFP as replacements. Given the minimum blood flow requirements of 100 ml/min, we only performed this procedure with children < 10 kg who were on ECMO. To prevent hypocalcemia, we administered calcium chloride drip with starting dose of 20 mg/kg/hour before initiation of TPE. We adjusted the calcium chloride drip based on the ionized calcium monitoring scale. Additional calcium boluses were given for hypocalcemia persisting after drip adjustment to a maximal rate of 50 mg/kg/hr.

Results: We included eight children in the analysis who required both CRRT and TPE. The age range was 23 days-15 years (median: 2 years). On average, we performed 3.1 treatments per patient with a mean treatment time of 175 minutes. In 2/8 patients, bivalirudin was used. Common complications included hypocalcemia requiring additional calcium bolus (2/8), high transmembrane pressure (TMP) (1/8), and hemodynamic instability (1/8). There was no significant correlation between age and dose of calcium drip required (p-value: 0.433); and ECMO and requirement of additional calcium boluses (p-value: 0.107). There was a significant improvement in inflammatory markers (D-dimer, CRP, IL6) and bilirubin level post-pheresis treatment.

Conclusions: The TPE procedure using Prismaflex may be a practical option for children undergoing CRRT, but further studies are required to assess its use in children with weights less than 20 kg. Most children tolerated the procedure well in our study. Hypocalcemia is a critical complication with this procedure.

PO1960

Comparison of Nafamostat Mesylate and Regional Citrate Anticoagulation in Pediatric CRRT Anticoagulation

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Background: Regional Citrate Anticoagulation (RCA) is the preferred CRRT anticoagulation strategy for children in the US. Nafamostat Mesilate (NM), a synthetic serine protease, has been used widely for CRRT anticoagulation (ACG) in Japan and Korea. While NM is considered safe and effective, there is a paucity of evidence in pediatric CRRT. We compare the safety and efficacy of NM to RCA for pediatric CRRT.

Methods: Using one pediatric hospital in Japan and one in the US, medical records of patients (pts) <21 years of age on CRRT between 2016-2019 were reviewed, excluding pts receiving CRRT with ECMO. Pt demographics, CRRT characteristics, and outcomes were compared between RCA and NM groups. Filter life (FL), defined as the number of hours a single CRRT filter was in use, was the primary outcome. Safety is assessed by bleeding complications.

Results: 76 pts (248 filters) received RCA and 89 pts (226 filters) received NM. Baseline characteristics are shown Table 1. RCA pts were older and received higher Qb. Median FL (hours) did not differ by ACG type (RCA: 35 [16,67] *vs.* NM: 38 [22,68]. The lack of difference in FL between groups persisted when controlling for pt age and CRRT Qb.

Conclusions: RCA and NM are safe and appear to be equally effective ACG for children receiving CRRT. A prospective randomized trial is required to validate these findings.

Patient Demographics/Outcome	RCA(N=76)	NM (N=89)	p-value
Age [yrs: median (IQR)]	8 (1.8-16)	1.3 (0.6-5)	<0.001
Most common disease	Kidney (55.3%)	Liver disease (27.0%)	<0.001
systemic bleeding, n (%)	7 (9.2)	4 (4.5)	0.334
Filter Data	RCA (N=248)	NM (N=226)	p-value
FL [hours: median (IQR)]	34.9 (16.4-66.5)	37.7 (21.7-69.4)	0.646
Mode of CRRT	CVVHDF (96.4%)	CVVHDF (38.9%) CVVHD (42.9%)	<0.001
Qb[ml/min: median (IQR)]	100 (60-150)	50 (30-70)	<0.001

PO1961

NT-ProBNP a Potential Biomarker for Assessing Volume Status of Patients Receiving CRRT

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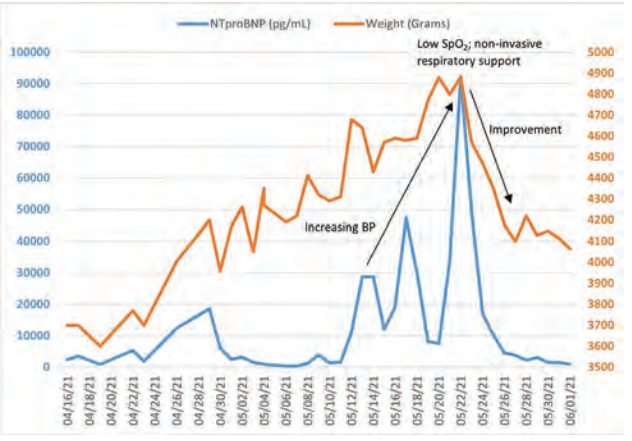
Introduction: Fluid overload is a significant risk factor for morbidity and mortality in patients receiving CRRT. Records of fluid balance, clinical signs of fluid overload (weight, peripheral edema), hemodynamic parameters (tachycardia, blood pressure), filling pressure (CVP), bioelectrical impedance, and radiological studies (CXR, IVC diameter) are the clinical tools that are commonly utilized to help assess volume status, each of which has their own limitations. The aminoterminal fragment of B-type natriuretic peptides (NTproBNP), a biologically inert molecule with half-life of 60-120 min produced from left ventricular myocardium, is well established as a good diagnostic and prognostic indicator of heart failure. Our previous observation of a correlation of NTproBNP with volume status in an infant without cardiac disease who received CRRT led us to use NTproBNP as a surrogate marker of volume status in a newborn currently receiving prolonged CRRT.

Case Description: NTproBNP levels were measured at least twice a week in a 4-month-old anephric (status post bilateral nephrectomy for ARPKD) infant receiving CRRT (clearance 30 – 35 mL/kg/hr). NTproBNP levels were correlated with weight (used as surrogate for volume status), and clinical evidence of cardiorespiratory compromise.

Over a period of 47 continuous days on CRRT, 40 NTproBNP values were obtained. The weights ranged from 3.60 kg to 4.88 kg, while the NTproBNP values ranged from 396 to 92,300 pg/mL. There was a significant correlation between patient weight and NTproBNP levels ($r = 0.57$; $p < 0.001$) which helped guide the patient's fluid management. The relationship between patient weight, NTproBNP level and clinical status is shown in the figure.

Discussion: NTproBNP may be able to be used as a reliable complementary marker for volume status in a select (without underlying cardiac disease) group of pediatric patients receiving prolonged CRRT. Further study is required to validate the findings in a cohort of patients.



PO1962

Prophylactic PD Catheter Placement for Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass: Systematic Review with Meta-Analysis

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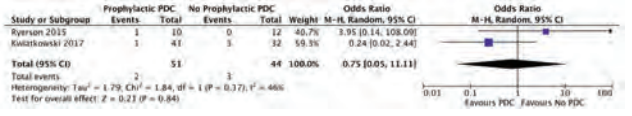
Background: Infants undergoing cardiopulmonary bypass (CPB) are at high risk of fluid overload, requiring peritoneal dialysis (PD). This systematic review evaluates whether prophylactic PD catheter (PDC) insertion at the time of cardiac surgery improves post-operative outcomes.

Methods: Comprehensive literature search was completed Oct-2020. We identified studies that compared children ≤18 years undergoing cardiac surgery with CPB and receiving prophylactic PDC (inserted intraoperatively *or* ≤24 hours postoperatively) *vs.* children who do not undergo prophylactic PDC placement. Data was extracted on population characteristics; perioperative variables; and short-term postoperative outcomes, including time to negative fluid balance (FB); presence and degree of fluid overload; duration of inotropic support and mechanical ventilation; hospital length of stay; and mortality.

Results: Out of 1067 studies, 208 underwent full-text review for eligibility, and 15 were included: 4 randomized controlled trials; 9 cohort studies; and 2 case-control studies. Intervention was prophylactic PDC insertion with passive peritoneal drainage in 6; PD in 7; and passive peritoneal drainage *or* PD in 2. The comparator group typically received furosemide. Baseline characteristics were heterogeneous for the included studies with respect to age, weight, and illness severity. Surgical procedures performed were also variable within and between studies. Time to negative FB and prevention of fluid overload showed mixed results with some studies favoring prophylactic PDC and others showing no difference. Pooled unadjusted OR for in-hospital mortality was 0.75 (95% CI: 0.05-11.11) (Figure 1). No studies reported serious PDC-related complications. Risk of bias was high in most studies, due to higher illness severity in the intervention groups, small sample size, and observational nature of studies.

Conclusions: Prophylactic PDC insertion is relatively safe in children undergoing cardiac surgery with CPB. Some studies have shown prophylactic PDC improves post-operative outcomes, including time to negative FB and in-hospital mortality; others have shown no difference.



PO1963

Iodine-Induced Hypothyroidism in Pediatric Patients Receiving Peritoneal Dialysis: Is Risk Mitigation Possible?

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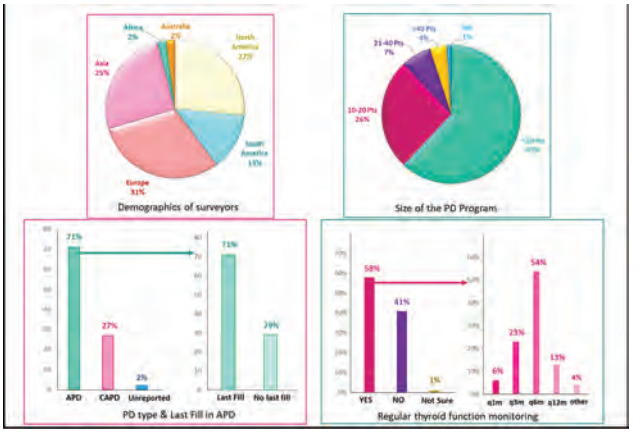
Background: Children with end-stage kidney disease who receive chronic peritoneal dialysis (PD) are at increased risk for thyroid dysfunction. Iodine-induced hypothyroidism (IIH) from exposure to iodine-containing agents is poorly appreciated, particularly in infants and small children.

Methods: An international survey was conducted to better understand current practices pertaining to iodine exposure and the frequency of IIH in patients receiving PD, and to assess awareness of this issue amongst pediatric nephrologists.

Results: 89 centers responded to the survey. Hypothyroidism in PD patients was diagnosed in 64% of responding centers, although only 1/3 of centers suspected/diagnosed IIH. Etiologies of IIH included exposure to povidone-iodine containing PD caps (53%), cleaning solutions with iodine (37%), and iodinated contrast (10%). While the majority of centers (58%) routinely evaluate thyroid function, only 34% aim to limit iodine exposure by avoidance of iodine-containing cleaning solutions (73%) and contrast agents (33%), monitoring of initial PD drain volume (30%), and use of a non-iodine PD cap (23%). Of centers not routinely evaluating for or utilizing methods to prevent IIH, 81% reported being unaware of the risk.

Conclusions: Hypothyroidism is diagnosed in a substantial percentage of pediatric PD programs. Education pertaining to the risk of IIH associated with iodine exposure may decrease the incidence.



			N
PD patients with Hypothyroid?	Yes		57
	No		32
Age group of Hypothyroid pts	<2y		35
	2-5 y		30
	>5y		28
Suspected or diagnosed Iodine induced Hypothyroidism?	Yes		19
Cause of Iodine induced hypothyroidism	Iodine contrast used for imaging		2
	Cleaning solutions containing iodine		7
	PD cap containing iodine		10
	Unknown		2
What specimen(s) was/were checked for Iodine levels	Blood		12
	Urine		2
	PDF		1
	Unsure		7
what were the average initial drain volume(s) at the beginning of PD treatments	<60 mL		6
	60-150 mL		4
	>150 mL		7
	Unsure		6
Were you able to decrease/ halt Iodine exposure in any or all your patients	Yes	Avoided iodine exposure from contrast used for imaging studies	7
	16	Changed to non-Iodine containing cleaning solutions	7
		Increased last fill volumes to enhance initial drain in patients receiving APD	4
		Use of non-Iodine containing PD transfer set cap	3
		Other- Parent removes initial 5 ml drain from transfer set	1
		Other- Alert to possibility so set up arrangements adjusted	1
Why Not?		Suspected but not confirmed	1
		Just treated Hypothyroidism	1
		Only Iodine caps are available	1
Did any of your patients receive oral thyroid supplementation (Levothyroxine?) – N=19	yes		12
	No		4
	Unsure		4
Were you able to D/C Levothyroxine in any or all your patients after Iodine exposure was discontinued? N-12	Yes		7
	No		5

Precautions taken to prevent Iodine induced hypothyroidism		N
Any other measures taken to prevent Iodine induced Hypothyroidism apart from TFTs?	Yes	30
	No	59
No (N=59)- why not?	Unaware of risk	48
	Underestimated risk	1
	Unaware of helpful measures	3
	Did not see Iodine induced Hypothy	3
	Most pts has HYPERthyroidism	1
	Watch TFTs	1
	Not answered	2
Yes (N=30): what precautions	Avoidance of iodine containing cleaning solutions	22
	Monitoring of initial drain volumes in patients receiving APD	9
	Avoidance of contrast use in radiology studies	10
	Use of a non-iodine containing PD transfer set cap	7

PO1964

Factors Associated with High-Cost Hospitalizations for Hemodialysis Catheter-Associated Blood Stream Infections in Children

Heather L. Wasik,[1] Alicia Neu,[2] Bradley A. Warady,[3] Brendan Crawford,[5] Troy Richardson,[6] Heidi G. De Souza,[6] Diana Cardwell,[4] Rebecca Ruebner.[2] The Standardized Care to Improve Outcomes in Pediatric End Stage Kidney Disease (SCOPE) collaborative *[1]State University of New York Upstate Medical University, Syracuse, NY; [2]Johns Hopkins University, Baltimore, MD; [3]Children's Mercy Hospitals and Clinics, Kansas City, MO; [4]Children's Health Children's Medical Center Dallas, Dallas, TX; [5]University of Arkansas for Medical Sciences, Little Rock, AR; [6]Children's Hospital Association, Overland Park, KS.*

Background: Hospitalizations of adults for hemodialysis catheter-associated blood stream infections (HD-BSI) lead to high costs. No studies have evaluated hospitalization costs for HD-BSI in children or identified factors associated with high-costs.

Methods: The Standardized Care to Improve Outcomes in Pediatric End-Stage Kidney Disease (SCOPE) collaborative database was used to identify HD-BSI. SCOPE database linked to the Pediatric Health Information Systems (PHIS) database which provided hospitalization billing data. High-cost hospitalization defined as cost above 50th percentile in our study population. Multivariable logistic regression used to assess the relationship between high-cost hospitalization and patient and clinical characteristics.

Results: The median(IQR) LOS for HD-BSI hospitalization was 5(3-10) days. The median(IQR) cost for HD-BSI hospitalization was $18,375($11,584-$36,266). Cost for each service line was higher in high-cost group(p<0.001)(Figure 1). High-cost HD-BSI hospitalization was associated with ICU stay, LOS, need for catheter replacement/rewiring(Table 1). ICU stay (aOR=4.84, 95% CI 1.66-14.08, p=0.004) and need for catheter procedure (aOR 6.29, 95% CI 2.76-14.35, p<0.001) remained associated with high-cost hospitalization in a multivariable model.

Conclusions: Hospitalizations of children for HD-BSI lead to high costs. Efforts to prevent HD-BSI may reduce the costs of caring for children on hemodialysis.

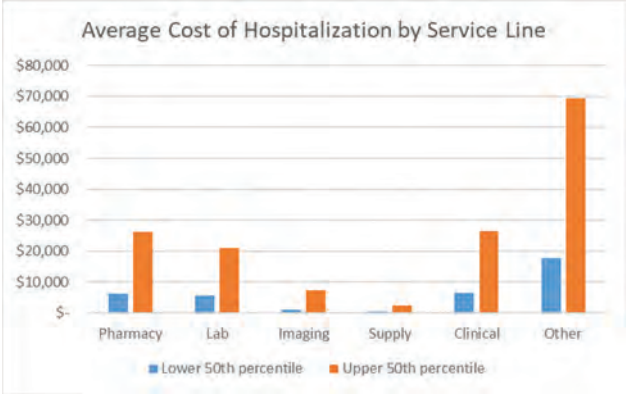


Figure 1

	Lower 50th percentile Cost (n=80)	Upper 50th percentile Cost (n=80)	p-value
Age, n (%)			0.4
0-5 years	53 (33.1)	30 (37.5)	
6-12 years	25 (31.3)	24 (30.0)	
≥13 years	25 (31.3)	33 (41.3)	
Race/ethnicity, n (%)			0.2
Non-Hispanic White	30 (37.5)	21 (26.3)	
Non-Hispanic Black	25 (31.3)	38 (47.5)	
Hispanic	18 (22.5)	13 (16.3)	
Other/Missing	7 (8.8)	8 (10.0)	
Female, n (%)	34 (42.5)	35 (43.8)	0.9
ESRD cause, n (%)			0.211
CAKUT	43 (53.8)	30 (37.5)	
Glomerular	12 (15.0)	19 (23.8)	
Other	25 (31.3)	31 (38.8)	
Causative organism, n (%)			0.7
Gram Positive	44 (55.0)	42 (52.5)	
Gram Negative	34 (42.5)	32 (40.0)	
Fungal	0 (0.0)	1 (1.3)	
Other	2 (2.6)	5 (6.3)	
ICU stay, n (%)	7 (8.8)	21 (26.3)	0.004
Length of stay (days), median (IQR)	3.0 (2.0,4.0)	10.0 (7.0,14.0)	<0.001
Catheter replaced/rewired, n (%)	12 (13.8)	37 (32.5)	0.01

Table 1

PO1965

Hemoglobin and Mortality Across Race Among Children Who Transitioned to Dialysis Therapy: An Analysis of CEFDIM and USRDS Data

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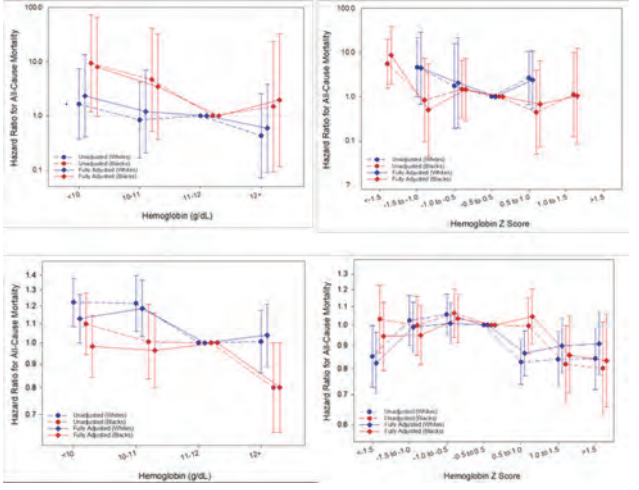
Background: Low hemoglobin (Hgb) is a strong predictor for mortality in adult dialysis patients, and children on dialysis experience optimal Hgb levels less frequently than adults. Racial disparities have also been identified in pediatric dialysis patients, with Blacks experiencing unfavorable clinical outcomes and poor access compared to Whites. However, there is less literature examining the impact of race on the association of Hgb with mortality among pediatric patients on dialysis.

Methods: We retrospectively studied two cohorts of children (age <21) using data from a large dialysis organization (CEFDIM) and a national data system (USRDS). CEFDIM (n=1069) were followed from 2006-2011, while USRDS (n=26,254) were followed from 1995-2016. The association between Hgb and mortality was observed using Cox regression analyses stratified by race, categorizing Hgb by g/dL as well as z scores (ref: Hgb 11-12g/dL, z scores -0.5 to 0.5). Covariates considered in the models included age, sex, BMI, albumin, comorbidities, and dialysis modality type.

Results: Among Black CEFDIM patients, Hgb <10g/dL was associated with increased mortality (7.9 [0.97,65.27]), as was Hgb z scores <-1.5 (8.62 [1.92,38.77]). Among White CEFDIM patients, these associations were null, and no deaths occurred for z scores <-1.5. Among Black USRDS patients, Hgb above 12 g/dL appears to be protective (0.83 [0.65,1.06]), which was not a protective range for White patients. Meanwhile z scores <-1.5 were significantly protective among White patients (0.82 [0.70,0.96]), but not among Black patients (0.94 [0.79,1.13]).

Conclusions: In children undergoing dialysis, protective Hgb target ranges appear to differ by race, with White children experiencing lower mortality risk from extremely low values and Black children receiving protection from high values.



PO1966

Children on Chronic Hemodialysis Before the First Year of Age: A Three-Year Survival Analysis

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Background: Peritoneal dialysis is the method of choice for infants who need renal replacement therapy (RRT). However, when it is not possible to perform it or becomes ineffective, hemodialysis is a feasible method in young children. There are few reports on the survival rate of children undergoing hemodialysis in the first year of life. The goal of this study was to determine the mortality rate and its risk factors in children starting hemodialysis during their first year of life.

Methods: We performed a retrospective cohort study, based on data from a reference Dialysis Center in São Paulo city. Data from 47 (8 females) children who underwent chronic hemodialysis before the first year of age were analyzed. Survival was characterized using Kaplan-Meier methods and log-rank tests, followed by a multivariable Cox regression model.

Results: The median weight on the first hemodialysis session was 4.3 Kg (IQR=3.4 to 5.3), while median age was 4.1 months (IQR=2.3 to 6.0), with 21 children younger than 1 month, and only one older than 6 months. Patients were categorized according to the etiology of Chronic Kidney Disease (CKD), congenital anomalies of the kidneys and urinary tract (53.2%) was the most prevalent cause, followed by congenital renal dysplasia (23.4%), autosomal recessive polycystic kidney disease (8.5%), and other etiologies (14.9%). The survival rates were 93%, 75%, and 64% at 1, 2, and 3 years, respectively. Only cardiovascular comorbidity was significantly associated with the

death outcome (HR=5.7, 95%CI=1.7 – 19.6, p=0.006). Anuria had a significant impact on survival only in univariate analysis. Parameters such as gender, age at hemodialysis onset, ethnicity, early dialysis, etiology of CKD had no impact on survival.

Conclusions: Our retrospective cohort gathers an expressive number of children with this rare and severe condition of early onset of hemodialysis, with a uniform follow-up of all individuals We observed satisfactory survival rates among children who started hemodialysis in their first year of life, comparable to the standards of the international pediatric dialysis centers. Hemodialysis became a safe method in young children until the performance of kidney transplantation.

PO1967

The Cost-Effectiveness of Blood Product Irradiation in Pediatric Hemodialysis Patients Awaiting Kidney Transplant

Kyle Merrill. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Pediatric patients diagnosed with end-stage kidney disease often initiate hemodialysis prior to kidney transplantation. Development of anti-HLA antibodies reduces the organ pool for that patient. Blood products are one known cause of allosensitization, or the development of anti-HLA antibodies. Gamma-irradiation of blood products may decrease this possibility. Patients with less anti-HLA antibodies have higher rates of kidney transplantation. Therefore, a cost-effectiveness analysis of whether to irradite blood products for hemodialysis patients and the chance of successful kidney transplantation was performed.

Methods: A Markov model was utilized in this analysis. The model started with the choice to irradiate blood or not prior to entering the Markov. To simplify the model, it was assumed that transfusion with a non-irradiated blood product will result in a cPRA of 30% and irradiation decreased this to 10%. Patients only received one blood product exposure. After kidney transplant, it was asusmed there was no graft failure and return to dialysis. Mortality rates were calculated based on age-specific mortality tables along with the annual excess mortality for each state of the patient.

Results: The irradiate strategy dominates in the base case and is both cheaper at $985,749 (versus $1,049,614) and more effective at 13.00 quality adjusted life years (versus 12.81) when compared to the choice of non-irradiation. A one-way sensitivity analysis was completed on the relative transplant rate and showed that a rate of 1.0006x was the breakpoint where irradiate dominates non-irradiate. A one-way analysis on the cost of blood product irradiation found that even if irradiation costed 100x the base case, it was still the dominating chioce. The last one-way sensitivity analysis noted that as the monthly cost increased from $0 to $10,000 per month, that until the monthly cost was around $3,700, then the more cost-effective choice was to not irradiate, but at any cost higher than $3,750, then the choice to irradiate dominate non-irradiation.

Conclusions: Blood product irradiation was found to be more cost effective. Even with a slight increase in transplant rate, irradiate remained the more cost-effective choice. The cost of irradiation does not affect the choice to irradiate but if hemodialysis were cheaper, the choice to not irradiate was more cost-effective.

PO1968

Partial Extracorporeal Circuit Blood Primes Are Safe and Do Not Decrease Hematocrit in Small Children

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Background: Partial blood primes (PBP) for extracorporeal therapies have the potential to decrease unique number of blood unit exposures in children when compared to full blood primes (FBP). Pediatric patients (pts) receive a blood prime when the extracorporeal circuit volume (ECV) exceeds 10-15% of their total blood volume (TBV). FBP use packed red blood cells (PRBC; Hct 60%) for the entire ECV while PBP utilize a standardized approach for less PRBC volume per circuit, allowing the same unit to be used for 3-12 treatments depending on ECV. We aimed to show that PBP does not result in more hemodilution or need for transfusions compared to FBP.

Methods: Data from pts receiving continuous kidney replacement therapy (CKRT) or intermittent therapies (INT), including hemodialysis, plasma exchange and aquapheresis, with FBP were collected retrospectively whereas data from PBP were collected prospectively beginning 8/2019 after a change in local practice. The primary outcomes were 1) pre- and post- treatment hematocrit (Hct) and 2) number of transfusions required between FBP and PBP.

Results: 14 pts (median 8.9kg; IQR 6.6, 12) across 42 CKRT filters and 26 pts (9.3kg; 3.4, 14) with 226 INT between 11/2018 and 1/2021 were analyzed. 11 CKRT filters were PBP (26%) and 11 INT pts received PBP (42%). Although pts receiving PBP had lower pre-procedure HCT (29.4% v 33.1%, p=0.03), there was no difference in change of Hct over time between PBP and FBP (p=0.9). Mean (SD) Hct and percent change are shown in Table 1. PRBC transfusion rate did not differ between PBP and FBP (31.8% vs. 26.1%, p=0.4). We estimate the use of PBP saved 4 PRBC units of exposure in CKRT and 29 units of exposure in INT.

Conclusions: The use of PBP does not result in hemodilution compared to FBP, nor does it result in the need for more transfusions. PBP is a safe alternative to FBP, it improves blood product stewardship and has the potential to reduce sensitization in children with ESKD or at risk for CKD, which may facilitate kidney transplant.

Table 1. Hct Levels and Change by Blood Prime Type (all values mean (SD))

	Pre-Treatment Hct (%)		Post-Treatment Hct (%)		Percent Change		
	FBP	PBP	FBP	PBP	FBP	PBP	p-value
CKRT	33.0 (6.3)	28.1 (6.1)	33.9 (6.8)	30.1 (5.7)	3.2 (12.6)	10.1 (23.4)	0.3
INT	33.2 (6.5)	30.7 (4.0)	35.7 (5.7)	31.3 (4.5)	10.9 (26.9)	3.3 (16.0)	0.5

PO1969

Readmission After Pediatric Kidney Transplantation: A Multicenter Cohort Study

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Background: The burden of readmission within one year after pediatric kidney transplant (PKTx) is poorly described, with only one single center study describing rates of readmission as high as 79%. We aimed to examine the epidemiology of readmission after PKTx in a national U.S. cohort.

Methods: We linked the Scientific Registry of Transplant Recipients (SRTR) and the Pediatric Health Information System (PHIS) database, a group of over 50 U.S. pediatric medical centers, to identify PKTx recipients <21 years old who received a kidney-only transplant from 2002-2018 and were discharged from the transplant hospitalization with a functioning graft. We characterized the epidemiology of patient demographic, clinical and transplant factors associated with the initial transplant hospitalization and readmission. We also examined risk factors for readmission within a year using multivariable Cox proportional hazard modeling.

Results: We identified 4,566 patients with a median age of 13 years, 46% had CAKUT and 45% were white, non-Hispanic. Within a year, 3,136 (69%) were readmitted. Factors associated with increased hazard of readmission were age <6 years, black race, public insurance, centers with <15 transplants/year and initial transplant admission >10 days. Transplant admission <5 days was associated with decreased hazard of readmission in the first year.

Conclusions: Over two-thirds PKTx recipients were readmitted within a year post-transplant. Readmission was associated with younger age, black race, public insurance, initial transplant hospitalization and transplant center volume. Future studies to identify modifiable risk factors associated with readmission are planned. Our findings can help improve care models to reduce healthcare utilization and cost.

Funding: NIDDK Support

Table 1: Factors associated with re-hospitalization in the first year

	Adjusted HR (95%CI)
Age at Transplant	
<6	**1.27 (1.12-1.43)***
6-10	Ref
11-17	1.01 (0.91-1.12)
18-21	1.11 (0.96-1.30)
Race	
White, non-Hispanic	Ref
White Hispanic	1.06 (0.96-1.17)
Black	**1.31 (1.01-1.26)***
Other	1.17 (0.99-1.37)
Insurance Type	
Private	Ref
Public	**1.22 (1.03-1.23)***
Other	0.74 (0.46-1.17)
Center Volume (transplants/year)	
<5	**1.19 (1.04-1.37)***
5-9	**1.26 (1.12-1.42)***
10-15	**1.16 (1.04-1.31)***
>15	Ref
Initial Transplant Hospitalization Days	
<5	**0.75 (0.61-0.92)***
5-10	Ref
10-14	**1.30 (1.18-1.43)***
>14	**1.66 (1.50-1.84)***

*p<0.05

PO1970

Encouraging Outcomes from Using a Small-Donor Single Graft in Pediatric Kidney Transplantation

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Background: The use of small pediatric kidneys as single for transplantation is controversial, due to the potential risk for graft thrombosis and insufficient nephron mass.

Methods: Aiming to test the benefits of transplanting these kidneys, 375 children who underwent kidney transplantation in a single center were evaluated: 49 (13.1%) received a single graft from a small pediatric donor (≤15Kg, SPD group), 244 (65.1%) from a bigger pediatric donor (>15Kg, BPD group) and 82 (21.9%) from adult living donors (group ALD).

Results: Groups had similar baseline main characteristics. After 5 years of follow-up, children from SPD group were comparable to children from BPD and ALD in patient survival (94, 96, and 98%, p=0.423); graft survival (89, 88, and 93%, p=0.426); the frequency of acute rejection (p=0.998); the incidence of post-transplant lymphoproliferative disease (p=0.671); the rates of vascular thrombosis (p=0.846); and the necessity for post-transplant surgical intervention prior to discharge (p=0.905). The longitudinal evolution of eGFR was not uniform among groups. The 3 groups presented a decrease in the eGFR, but the slope of the curve was steeper in ALD children. At 5 years, the eGFR of ALD group was 10 ml/min/1.73m² inferior to the others. At that time, the eGFR from SPD group was statistically similar to the BPD (p=0.952).

Conclusions: In a specialized transplant center, the use of small single pediatric donor kidneys is as successful as bigger pediatric donors or adult living donors in transplants after 5 years of follow-up.

PO1971

Clinical Characteristics of Recurrent Focal Segmental Glomerulosclerosis (rFSGS) After Kidney Transplant (KTx) Through Computable Phenotypic Algorithm Analyses of Multicenter Data

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Background: Primary FSGS, a glomerular disease, has a high rate of progression to end stage kidney failure and varying rates of recurrence after KTx. Treatment effects are hard to determine, requiring both large multicenter populations and granular site level data.

Methods: Using the PEDSnet research network of >11 million records, we refined a published computational phenotype (Denburg et al 2019) for a pediatric nephrotic glomerular disorders cohort to identify patients with evidence of KTx. Standardized chart review was used to identify patients with FSGS and rFSGS (urine protein/creatinine ratio > 2.0 mg/mg post-KTx).

Results: In PEDSnet v4.0 data from 1/2009-11/2020 across 6 centers, 4380 patients met criteria for glomerular disorders and 1994 among those were identified as nephrotic. 220 had evidence for KTx. In charts reviewed to-date for these 220 patients, 89/133 had non-genetic FSGS, and 71 received a KTx after 2009. rFSGS was identified in 29/71 patients, mostly early after KTx (Fig. Panel A). Demographic characteristics of those with FSGS (n=89) and rFSGS (n=29) are shown in the Table. After rFSGS, plasmapheresis (n=26) or rituximab (n=24) were the most common treatments used, remission was complete in 14/29 (48%), and partial in another 6. Allograft loss occurred in 7 patients, not significantly worse than in those without recurrence (Fig. Panel B).

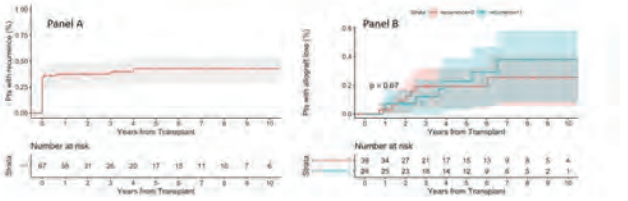
Conclusions: PEDSnet can identify and characterize patients with rare diseases such as rFSGS to create robust databases to compare clinical efficacy of treatments, and for recruitment into clinical trials.

Table:

Characteristic	FSGS (N = 89)	rFSGS (N = 29)
Sex: Female	44 (49.4%)	12 (41.4%)
Race: White	50 (56.2%)	16 (55.2%)
Race: Black or African-American	21 (23.6%)	<11 (<37.9%)
Ethnicity: Hispanic or Latino	11 (12.4%)	<11 (<37.9%)
Follow-up (years)	11.2 (7.3, 14.4)	9.9 (7.9, 15.0)
Age at transplant (years)	13.4 (10.0, 16.8)	13.1 (0.5, 16.7)

All continuous data as median (25th percentile, 75th percentile); categorical data as N (%)

Figure:



PO1972

Prevalence and Progression of Pediatric CKD in a Large National Cohort

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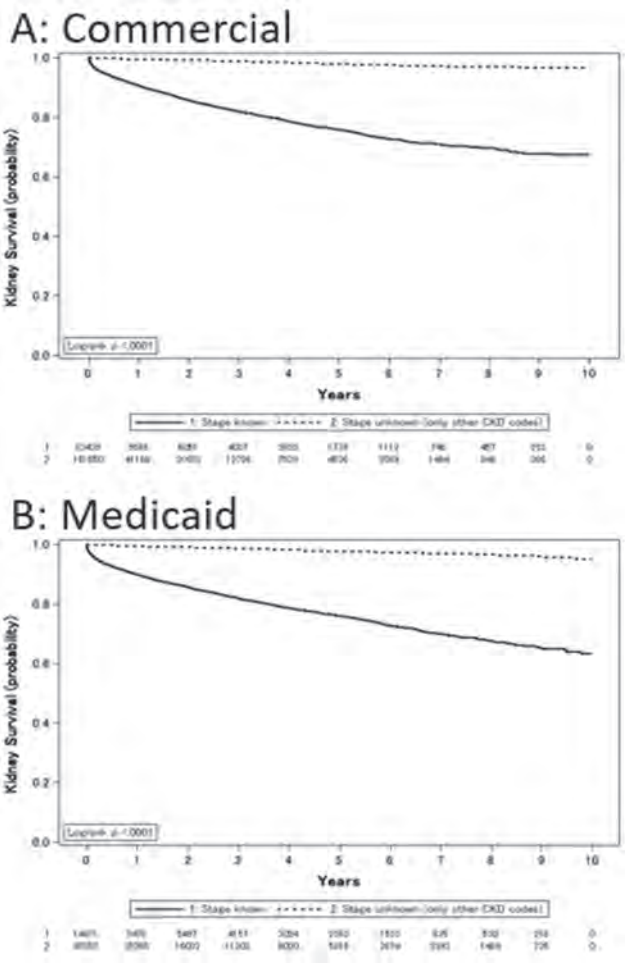
Background: National prevalence and disease progression for pre-ESKD chronic kidney disease in children (pCKD) are not well described.

Methods: Data for children <19 years of age were extracted from the IBM MarketScan commercial and Medicaid databases for the years 2009-2018. pCKD prevalence estimates were calculated using stage-specific ICD-CM diagnosis codes (585 and N18) and additional established qualifying pCKD codes. Survival curves were created to estimate the probability of reaching ESKD, stratified by type of CKD code utilized (stage-specific vs other codes).

Results: We identified children <19 years with commercial insurance (n=42,051,432) and Medicaid (n=13,610,450) over the 10-year period. Among these children, we found 197,318 with pCKD among those with commercial insurance (47 per 10,000) and 101,361 among those with Medicaid (74 per 10,000). pCKD stage-specific diagnoses were infrequently reported (commercial insurance:12%; Medicaid: 14%). Among the children with pCKD, 30% with commercial and 35% with Medicaid had multiple years of follow-up. Survival curves over the 10-year study period showed the majority of the progression to ESKD was among those with stage-specific pCKD (Figure).

Conclusions: In a large national cohort, 298,679 children with pCKD were identified over 10 years, with higher period prevalence in Medicaid-insured children. Stage-specific information was available for a small proportion of children, but when present was associated with a higher probability of reaching ESKD. This data suggests that children with conventional, staged CKD codes are more likely to have rapid progression while other codes that qualify for pCKD may capture children with kidney disease that are slower to progress.

Funding: Other NIH Support - NCATS, Private Foundation Support



Probability of Kidney Survival Stratified by Type of Diagnostic Code

PO1973

Narrow Range of Plant-Protein Intake in the CKiD Cohort Does Not Demonstrate Changes in Estimated GFR

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Background: Vegetable or plant-based sources of protein may confer health benefits in children with progressive kidney disease. There is currently a knowledge gap in understanding the effect of different proportions of vegetable-based proteins on CKD progression in children.

Methods: The CKiD study is a multicenter, observational cohort of children with CKD. The Child Harvard Service Food Frequency Questionnaire (HSFFQ) was used to assess dietary intake. The proportion of vegetable protein (VP%) was defined as the fraction of plant protein to total protein intake. Statistical analysis used a mixed model with random intercept and slope to determine the effect on log-transformed changes in estimated GFR.

Results: This dataset included 2000 records on 631 subjects with a baseline eGFR from 30 to 90 mL/min/1.73m^2 calculated using CKiD Creatinine–Cystatin C 2012 formula. Across all dichotomized groups of children (sex, African American race, Hispanic ethnicity, etiology of CKD, hypertension, anemia, hyperkalemia, hyperphosphatemia, acidosis, BMI < 95th percentile) the median VP% was 32-35% regardless of group. Longitudinal mixed model analysis did not show any effect on eGFR due to changes in VP%.

Conclusions: Children with chronic kidney disease obtain about a third of their protein intake from plant or vegetable-based sources. More than 90% children in the CKiD cohort had a VP% that was less than 50% of total protein intake. Due to the narrow homogeneity of dietary patterns, there was no effect on the change in eGFR with changes in VP%.

Funding: NIDDK Support, Private Foundation Support

Figure: Distribution of Vegetable Protein Percent in the CKiD Cohort at Baseline

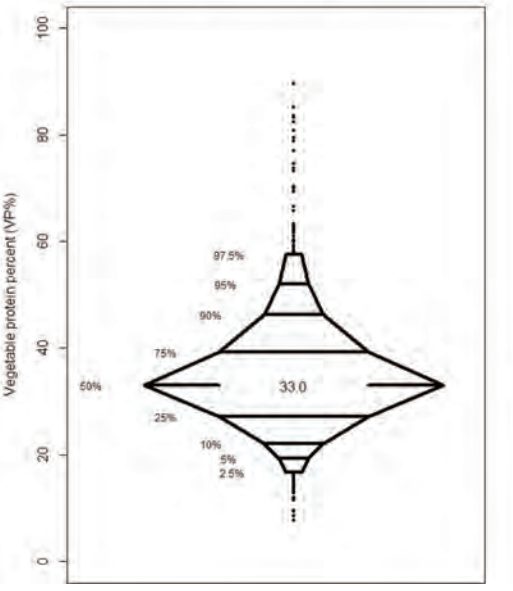

Table 1: Effect of VP% on eGFR

Predictor	Estimate (95% CI) (log scale)	Estimate (95% CI) (% scale)	p-value
VP% at baseline, per 5%	-0.007 (-0.025, 0.011)	-0.7% (-2.4%, +1.1%)	0.44
Change in VP% from baseline, per 5%	0.000 (-0.005, 0.005)	0.0% (-0.5%, +0.5%)	0.99
Age at baseline, per year	-0.003 (-0.012, 0.005)	-0.3% (-1.2%, +0.5%)	0.45
Years from baseline	-0.062 (-0.070, -0.053)	-6.0% (-6.8%, -5.2%)	<0.0001
Male sex	0.016 (-0.050, 0.083)	+1.7% (-4.9%, +8.6%)	0.63
AA race	0.111 (0.026, 0.196)	+11.8% (+2.7%, +21.7%)	0.01
Hispanic ethnicity	-0.079 (-0.178, 0.019)	-7.6% (-16.3%, +2.0%)	0.12
HH Income > $36k/year	0.057 (-0.014, 0.128)	+5.8% (-1.4%, +13.6%)	0.12
Glomerular etiology	0.142 (0.064, 0.220)	+15.2% (+6.6%, +24.6%)	0.0004
Total protein intake, g/kg	0.005 (-0.005, 0.015)	+0.5% (-0.5%, +1.5%)	0.31

PO1974

Diagnosis-Specific Combination of Cystatin C- and Creatinine-Based eGFR

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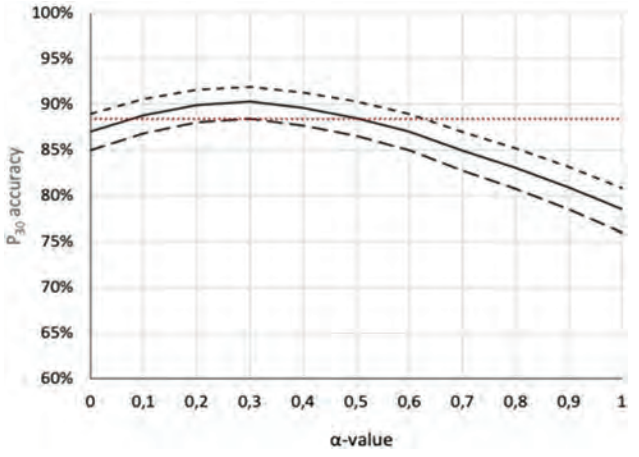
Background: The arithmetic mean of a creatinine- and a cystatin C-based GFR estimation (eGFR) has higher accuracy than either of the two. Smaller studies indicate that the relative contribution of the creatinine- and the cystatin C-based equation should be adapted based on underlying diagnosis.

Methods: Retrospective analysis of 1712 plasma clearance GFR measurements from four pediatric nephrology centers. eGFR was calculated using the height-based Full Age Spectrum equation using creatinine (FAS-creat) and the FAS-cys equation for cystatin C. α describes the contribution of FAS-creat, (1-α) the contribution of FAS-cys. 2/3 of the cohort (mean age 11.8 years, mGFR 93.8 ml/min/1.73m^2) was used to determine the α-values yielding the highest P_{30} accuracy globally (FAS_α) and in diagnosis subgroups. These α-values were validated in the remaining 1/3 of the cohort assessing accuracy, bias and precision.

Results: Globally, the optimal α-value was 0.3 [95% CI 0.2 – 0.4, Figure]. Lower α-values were determined for spina bifida (0), glomerulonephritis (0.2), and liver disease (0.25), while CAKUT, kidney transplantation and tubulointerstitial disease had α-values between 0.35 and 0.55. Accuracy of $FAS_{0.3}$ in the validation cohort was 90.2%, which was significantly higher than accuracy of the arithmetic mean (87.4%, p<0.05). Using the diagnosis-specific α-values rather than $FAS_{0.3}$ improved bias (+2.5 vs +1.3 ml/min/1.73m^2, $p < 0.01$) and precision (14.1 vs 13.8 ml/min/1.73m^2, $p < 0.05$), while accuracy was unchanged. Only in children with spina bifida, a clinically relevant improvement was observed when using the diagnosis-specific α-value.

Conclusions: For calculation of the weighted mean, a fixed mix of 30% FAS-creat and 70% FAS-cys is optimal and yields very high accuracy overall. A disease-specific adaption (i.e. 100% cystatin C eGFR) is clinically relevant only for patients with spina bifida.



PO1975

The Optimal Equation of Estimated Glomerular Filtration Rates for Pediatric CKD Patients in Transition from Adolescent to Adult: Results from KNOW-PedCKD

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Background: Estimated glomerular filtration rate (eGFR) is an important value in kidney function evaluation, and it is useful to identify chronic kidney disease (CKD) and its progression. Clinicians use various equations to calculate eGFR which is based on serum creatinine (Cr) or cystatin C (CysC) concentration with other variables such as age, sex, and height. However, there is a lack of consensus on which equation is proper for patients in transition from adolescent to adult. Therefore, we evaluated the reliability of various eGFR calculation methods compared to measured isotope GFR (iGFR) in adolescents and young adults with CKD.

Methods: Seventy-three patients aged from 15 to 23 years were included in the KoreaN cohort study for Outcome in patients With Pediatric Chronic Kidney Disease (KNOW-PedCKD). We compared measured iGFRs with various eGFR calculation equations; the bedside serum Cr based equation ($Schwartz_{Cr}$), the CysC based equation ($Schwartz_{CysC}$), combined Cr and CysC-based Chronic Kidney Disease in Children equation ($CKiD_{Cr\text{-}CysC}$), the Cr-only CKD-EPI ($CKD\text{-}EPI_{Cr}$), and combined Cr and CysC CKD-EPI equation ($CKD\text{-}EPI_{Cr\text{-}CysC}$).

Results: Fifty-two (71.2%) patients were male and 86.3% of patients had non-glomerular causes of CKD. A total of 136 measurements of iGFR was performed at the median age of 17.0 (interquartile range (IQR) 16.0–18.8) years. The mean iGFR was 42.2 ± 29.0 mL/min/1.73m^2. The $Schwartz_{Cr}$ equation had lowest bias (-0.6 mL/min/1.73m^2), high correlation (0.96), and highest accuracy (81.6% within 30% of iGFR) while $Schwartz_{CysC}$, $CKiD_{Cr\text{-}CysC}$, $CKD\text{-}EPI_{Cr}$ and $CKD\text{-}EPI_{Cr\text{-}CysC}$ had an overestimation bias (+1.4, +2.1, +15.5 and +8.9 mL/min/1.73m^2, respectively). In adolescents (n=93) from 15 to 18-year-old, the bias of $Schwartz_{Cr}$ equation was lowest (+0.3 mL/min/1.73m^2) and its accuracy was highest (81.7% within 30% of iGFR). In young adults (n=43) older than 18-year-old, the bias of the $CKiD_{Cr\text{-}CysC}$ equation was lowest (+1.3 mL/min/1.73m^2) and the accuracy of $Schwartz_{Cr}$ was highest (81.4% within 30% of iGFR).

Conclusions: The $Schwartz_{Cr}$ equation may be an optimal method to calculate eGFR in adolescents and young adults with CKD.

PO1976

The Effect of Anemia on Neurocognition in Children with CKD

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Background: Chronic kidney disease (CKD) has been shown to affect neurocognitive outcomes. Anemia is associated with CKD and has been associated with a decrease in neurocognition in adults with CKD. Few studies have looked at neurocognitive outcomes in children with both CKD and anemia. This study's purpose is to evaluate the impact of anemia on neurocognition in children with mild to moderate CKD.

Methods: Participants were > 7 y and in the Chronic Kidney Disease in Children Study (CKiD) with NIH Cognitive Toolbox data. Anemia was defined as hemoglobin < 5th percentile for age, sex and race or use of an Erythropoietin-Stimulating Agent. All outcomes were compared between anemic and non-anemic groups descriptively using box plots, t-tests, and the magnitude of differences using Cohen's U_3 statistic for effect size. Inverse probability weighting (IPW) was used to align the non-anemic and anemic groups on sex, estimated GFR level, urine protein/creatinine ratio, disease etiology, seizure history, hypertension and maternal education.

Results: 87 subjects total (25% with anemia) met criteria. Prior to weighting, groups were similar in age (17.9 vs 17.1 y, anemic vs non-anemic) with the anemic group trending towards a higher male percentage (73 vs 52%), and lower baseline eGFR (42 vs 64 ml/min|1.73m2). In the descriptive analysis, box plots displayed that anemic patients had a tendency towards lower scores than non-anemic patients. In the IPW-weighted analysis, subjects who were anemic were found to have worse Picture Vocabulary (U_3=+23), Crystallized Cognition (U_3=+22) and Total Cognition (U_3=+19), but better Pattern Comparison (U_3=-35), Working Memory (U_3=-22) and Fluid Cognition (U_3=-22). However, using the t-test, only Picture Vocabulary (p=0.02) and Crystallized Cognition Composite (p=0.03) were significantly different between the groups, with the anemic group performing more poorly than the non-anemic group.

Conclusions: Children with CKD and anemia had significantly lower scores on Picture Vocabulary and on the Crystallized Cognition Composite compared to non-anemic patients after adjusting for covariates, with moderate to large effect sizes. These results suggest that anemia may be a modifiable determinant of cognitive outcomes in children with CKD.

Funding: NIDDK Support

PO1977

Adverse Events Following Rituximab Infusion in Children with Nephrotic Syndrome: A Systematic Review

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Background: Rituximab (RTX) is often used off-label in children with various kidney diseases. However, there are limited data on the frequency and severity of adverse events and side effects (AE/SE) observed in children following RTX administration. The aim of this systematic review is to evaluate the AE/SE of RTX in children with nephrotic syndrome (NS).

Methods: Six databases were searched to include literature from 1991-2019 that provided AE/SE data on children (≤18 yrs) receiving RTX. Article screening, data extraction, and quality assessment were independently completed and verified by two reviewers. Primary outcome was the cumulative incidence of AE/SE. Secondary outcomes included the severity (evaluated by the Common Terminology Criteria for Adverse Events), timing, and affected body systems of each AE/SE.

Results: Out of 3364 citations, 40 articles were included and 13% were randomized controlled trials (Table). Most reported AE/SE were infusion-related reactions (22.0%), infections (13.9%), granulocytopenia (3.9%), and hypogammaglobulinemia (2.7%). Reporting of the timing or duration of AE/SE was heterogenous and frequently incomplete. Out of all patients experiencing AE/SE (n=455), 12.7% were severe (grade 3-5), 50.8%

were mild (grade 1-2), and the severity in the rest were indeterminable. Overall, 53/1143 (4.6%) children experienced severe AE/SE.

Conclusions: The majority of children receiving RTX for NS do not experience serious AE/SE and RTX is generally well-tolerated. However, standardized reporting of AE/SE including timing, duration, and severity grade is warranted in future studies.

Type of AE/SE	Description of AE/SE	Proportion of Patients Affected (n=1143)	CTCAE Severity Grading					
			1	2	3	4	5	Unclear
Infusion-related reaction	respiratory distress, bronchospasm, epistaxis, cough/itchy throat, hypotension, hypertension, tachycardia, bradycardia, arrhythmia, nausea, vomiting, chest discomfort, skin rash, itching, facial flushing, abdominal/ankle/pelvic pain, dyspnea, polypnea, pruritus, myalgia, chills, fever, allergic reaction	22.05%	146	43	1	0	0	62
General	fever, chronic cough, chest discomfort, severe obesity	1.05%	1	6	1	0	0	4
Cardiovascular	hypertension, transient electrocardiographic change	0.35%	3	0	1	0	0	0
Respiratory	respiratory distress/disturbance, RTX-associated lung injury, respiratory tract infection	1.92%	0	7	6	0	2	7
Dermatological	skin rash/dermatitis, urticaria, cellulitis, purulent folliculitis, hyperpigmentation, hypertrichosis, alopecia	2.19%	1	6	3	0	0	15
Renal	gross hematuria, acute kidney injury, hemorrhagic cystitis, renal tract infection	0.52%	0	0	2	0	0	4
Gastrointestinal	diarrhea, abdominal pain, irritable colon, gastrointestinal infection	1.57%	2	2	5	0	0	9
Hepatic	deranged liver enzymes	0.35%	0	0	1	0	0	3
Musculoskeletal and Connective	acute arthritis, osteopenia	1.14%	0	6	0	0	0	7
Metabolic	hyperuricemia, adrenal insufficiency	0.17%	0	0	1	1	0	0
Hematological	erythrocythemia, eosinophilia, leukopenia, lymphocytopenia, neutropenia, thrombocytopenia, thrombosis, reduced granulocyte count	5.16%	5	2	10	14	0	28
Infection, Immunologic, or Oncologic	hypogammaglobulinemia, axillary abscess, Kikuchi disease, lymphadenopathy, fibroadenoma, other non-specific infections	14.44%	7	61	3	0	0	94
HEENT (Head, Eye, Ear, Nose, and Throat)	gingivitis/gum infection, oral candidiasis, otitis	0.35%	1	0	2	0	0	1

PO1978

Efficacy and Safety of Long-Term Use of Rituximab in Pediatric Patients with Nephrotic Syndrome

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Background: Rituximab (RTX) is an effective therapeutic agent widely used in children with nephrotic syndrome (NS). However, long-term effects after the B cell depleting treatment remain unclear. We investigated the efficacy and safety of long-term use of RTX in pediatric NS patients.

Methods: We retrospectively reviewed the medical records of 58 patients with steroid-dependent or steroid-resistant NS who had received more than 3 cycles of RTX. Each cycle consisted of one to four infusions of RTX (375 mg/m^2 per dose) until the depletion of B lymphocytes.

Results: The first cycle of RTX was started at the median age of 12.1 (interquartile ranges (IQR) 8.8–14.1) years. Median 5 (IQR 4–8) times of RTX cycles were used during a period of median 4.0 (IQR 2.3-5.9) years. The B lymphocytes recovered to 1% at a median 5.7 (IQR 4.8–6.7) months after the completion of RTX administration. The relapse significantly decreased from median 2.0 (IQR 1.0–3.0) times per year to 0.2 (IQR 0.1–0.5) times per year after long-term RTX treatments (P <0.001). Height growth and hypertension improved significantly compared with prior to the long-term use of RTX. Acute infusion reactions were observed in 21 (36.2%) patients. During long-term RTX treatments, hypogammaglobulinemia developed in 7 (12.1%) patients, and neutropenia was noted in 4 (6.9%) patients. Severe infections which required hospitalization and/or intravenous antibiotic were observed in 6 (10.3%) patients, but no life-threatening infections were identified. No secondary neoplasms or opportunistic infections occurred during the study period.

Conclusions: Long-term therapeutic use of RTX could be effective and relatively safe in pediatric patients with NS. However, impaired immunity should be monitored and carefully followed up during the long-term use of RTX.

PO1979

Rates of Idiopathic Childhood Nephrotic Syndrome Relapse During the COVID-19 Pandemic

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Background: While most children with idiopathic nephrotic syndrome (NS) enter remission after a course of steroid therapy, as many as 60-90% eventually relapse with recurrence of nephrotic-range proteinuria. Infections are thought to be primarily responsible for triggering relapses. The COVID-19 pandemic promoted physical distancing, facial masking, and greater attention to infection prevention measures resulting in decreased transmission of common viral infections. We hypothesize that there will be a decreased rate of NS relapse during this period.

Methods: We conducted a retrospective chart review of children with NS followed at our center. Patients were identified by ICD 9/10 code for proteinuria and included if they had primary steroid-sensitive NS. Numbers of relapses and hospitalizations each year were collected for baseline data, March 1, 2015-March 1, 2020, and for the social distancing period (SDP), March 1, 2020-March 1, 2021.

Results: 137 children with NS were identified. The rate of relapse per year and the rate of hospitalizations per year were lower during the SDP compared with baseline pre-pandemic levels (76 vs 81 relapses per year and 14 vs 19 hospitalizations per year, respectively). Importantly, within a year of NS diagnosis, there was a baseline pre-pandemic average of 1.6 relapses per patient. This was much lower with an average of 0.6 relapses per patient during the SDP (p<0.01). In contrast, there was no difference in new diagnoses of NS comparing SDP vs baseline period (15 vs 14 new cases per year).

Conclusions: Our results support our hypothesis of lower rates of NS relapse and hospitalizations during SDP. Most notably, there were significantly fewer relapses within the year following NS diagnosis during SDP compared with baseline. This is likely attributable to decreased transmission of common infections and greater attention to infection prevention by caregivers. Less hospitalizations during the SDP would suggest decreased severity of relapse, perhaps due to earlier detection, increased caregiver awareness, or fewer infections. Interestingly, the number of new diagnoses was similar. Future analysis will focus on identification of relapse triggers and associations with steroid responsiveness and other demographic characteristics.

PO1980

Sparsentan for Treatment of Pediatric Patients with Selected Proteinuric Glomerular Diseases: Design of the Phase 2 EPPIK Study

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Background: Sparsentan is a novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA) being investigated for focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN). It is a dual acting, highly selective antagonist of both the endothelin A receptor (ET_AR) and the angiotensin II subtype 1 receptor (AT_1R). The Phase 2 EPPIK study will examine the long-term antiproteinuric and nephroprotective potential and safety of sparsentan in pediatric patients with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS).

Methods: The global, open-label, single-arm, multicenter study will evaluate the safety, efficacy, and pharmacokinetics (PK) of sparsentan in ~57 patients (aged ≥1 to <18 years), including ~30 with FSGS and/or MCD (population 1) and ~27 with IgAN, IgAV, or AS (population 2) over 108 weeks (**Figure**). See **Table** for inclusion/exclusion criteria. Sparsentan will be administered in a novel liquid formulation at a dose adjusted to body weight.

Results: Primary endpoints include safety (incidence of treatment-emergent adverse events) and change in urine protein/creatinine ratio (UP/C) from baseline over 108 weeks of sparsentan treatment. Secondary endpoints include PK outcomes, change from baseline over 108 weeks in albumin/creatinine ratio and eGFR, and the proportion of patients with FSGS/MCD who achieve partial remission (UP/C ≤1.5 g/g and >40% reduction in UP/C).

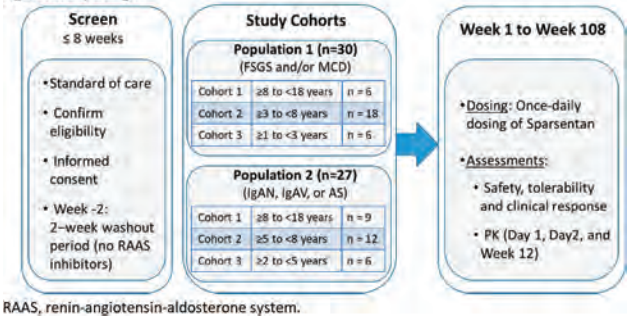
Conclusions: This Phase 2 study will evaluate the long-term safety, antiproteinuric, and nephroprotective effects of sparsentan in pediatric patients.

Funding: Commercial Support - Travere Therapeutics, Inc., San Diego, CA

Table. Key Inclusion and Exclusion Criteria

Inclusion All: eGFR ≥30 mL/min/1.73m^2; mean seated blood pressure 5th to 95th percentile for age, sex, and height
Population 1: Male/female age ≥1 and <18 years; UP/C ≥1.5 g/g at screening despite history or ongoing corticosteroid/immunosuppressive drugs; biopsy-proven FSGS/MCD or FSGS/MCD-associated genetic mutation in a podocyte protein
Population 2: Male/female age ≥2 and <18 years; UP/C ≥1.0 g/g at screening; biopsy-confirmed IgAN/IgAV nephritis or AS-associated genetic mutation
Exclusion All: Weighs <7.3 kg at screening; secondary FSGS/MCD/IgAN/IgAV; significant cardiovascular or hepatic conditions; new immunosuppressive therapy within 6 months of screening or not on stable dose of chronic therapy ≥1 month before screening

Figure. Study Design



RAAS, renin-angiotensin-aldosterone system.

PO1981

Efficacy of New Combination Therapy with Prednisolone, Mizoribine, and Lisinopril for Severe Childhood IgA Nephropathy

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Background: Our previous RCT shows that warfarin and dipyridamole added to prednisolone (PSL) and mizoribine (MZB) in the 2-year combination therapy have additional effect for proteinuria remission in severe (diffuse mesangial proliferation, WHO) childhood IgAN compared to that with only PSL and MZB (Pediatr Nephrol 2018;33:2103-12). However, we have to consider avoiding the use of warfarin and dipyridamole due to side effects. Meanwhile, angiotensin-converting enzyme inhibitors such as lisinopril have been widely used for childhood IgAN since the 2000s. Therefore, we intended to examine the effect of new combination therapy including PSL, MZB, and lisinopril.

Methods: This cohort study included 84 patients with severe IgAN enrolled among 546 pediatric IgAN between 1977 and 2017, and divided into 2 groups, 70 patients treated with the previous combination therapy and 14 patients with the new combination therapy. A 1:1 propensity score matching was performed to account for between-group differences and 12 matched pairs were obtained.

Results: Proteinuria remission was significantly more obtained in the new treatment group (100% vs 50.0%, p=0.001). The patients with the new treatment achieved significantly faster proteinuria remission (median 2.4 vs. 12.0 months, p=0.04). The median duration of PSL use was significantly shorter in the new treatment group (13 vs. 24 months, p<0.0001). The median observation period was 4.9 and 4.5 years, and the percentage of patients with normal urine at the latest observation was significantly higher in the new group (66.7% vs. 25.0%, p=0.04).

Conclusions: Our findings suggest the usefulness of the new combination therapy with PSL, MZB, and lisinopril for severe childhood IgAN in achieving early proteinuria remission and shortening PSL use. Further investigations with the larger-scale and long-term outcome will be needed.

PO1982

Renal Activity Index in Lupus (RAIL) Score Distinguishes Responder and Non-Responder in Pediatric Lupus Nephritis

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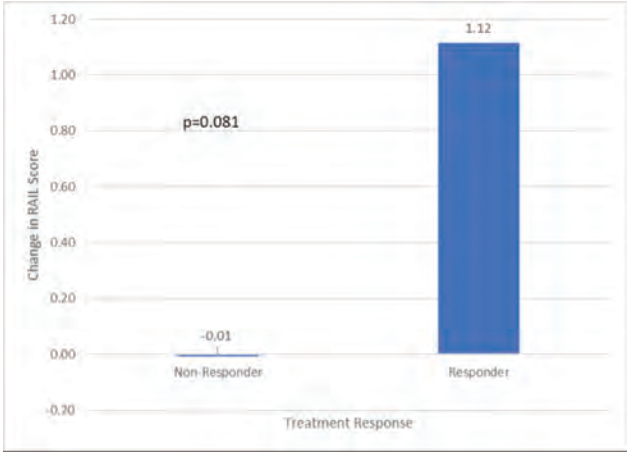
Background: Systemic Lupus Erythematosus (SLE) is a diagnostic and therapeutic challenge, particularly lupus nephritis (LN). We described a composite score, the Renal Activity Index for Lupus (RAIL), consisting of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), monocyte chemotactic protein 1 (MCP-1), adiponectin, hemopexin and ceruloplasmin, where higher scores reflect more active inflammation on biopsy. We hypothesize that when followed longitudinally during induction therapy, a change in RAIL score distinguishes clinical responders from non-responders.

Methods: Pediatric patients (<18 years) diagnosed with LN were included (IRB #2008-0635). Diagnosis was made according to ACR criteria for SLE with renal biopsy confirmation of LN. Urine was collected at diagnosis and end of induction. Responders were defined by urine protein to creatinine ratio <0.2 mg/mg, absence of hematuria, and normal glomerular filtration rate. Response also defined as improved activity index on follow up biopsy. 15 patients were included, 10 responders, 5 non-responders. Analysis by T-test, as well as sensitivity and specificity for no change in RAIL score.

Results: RAIL score in the responder group pre and post therapy was significantly different, p-value 0.015. T-Test between non-responder and responder difference scores showed trend towards significance, p-value 0.081 (Fig 1). Most responders had a difference of at least 0.5 during induction, whereas most non-responders had no difference or an increase in RAIL score, and a change scoreis >0 identified responders with 90% sensitivity.

Conclusions: A change in RAIL during induction therapy is promising for predicting responders vs non-responders, with average decrease of 1 compared to no change. To further evaluate, more samples are needed, which is on-going.

Funding: NIDDK Support, Private Foundation Support



PO1983

Collapsing FSGS in Siblings with Compound Heterozygous Variants in NUP93 Expand the Spectrum of Kidney Phenotype Associated with NUP93 Mutations

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Introduction: Focal segmental glomerulosclerosis (FSGS) is a major cause of end stage kidney disease, the collapsing form has the worst prognosis. Study of families with hereditary FSGS has provided insight into disease mechanisms. In this report, we describe a sibling pair with *NUP93* mutations and collapsing FSGS. This is the first report of collapsing FSGS associated with *NUP93* mutations.

Case Description: We identified a Caucasian sibling pair with early onset steroid resistant nephrotic syndrome. Kidney biopsy in both brothers performed at ages 5 and 2 years, respectively, showed collapsing FSGS. Lesions of segmental or global sclerosis with focal collapsing features involved 22/33 and 6/28 glomeruli, respectively. Clinical phenotypes are summarized in Table 1. We obtained DNA from the affected brothers and their unaffected parents and carried out whole genome sequencing on the two affected siblings. We applied our standard filtering algorithm[1] and identified segregating rare compound heterozygous variants 1) C.1772G>T p.G591V, 2) c.2084T>C p.L695S in *NUP93* in the two affected brothers. Both variants are rare with minor allele frequency <0.00015. Both variants are evolutionarily conserved and were predicted to be pathogenic by four *in-silico* tools. 3D modeling revealed that both variants created structural alterations throughout the protein including the amino and the carboxyl terminal residues. These structural alterations are predicted to alter the binding affinity for several NUP93 ligands, likely disrupting the function of the highly organized nuclear pore channel.

Discussion: To the best of our knowledge, this is the first report of collapsing FSGS in patients with *NUP93* mutations. Functional studies to determine the mechanisms by which these variants cause podocytopathy may provide insight into the pathogenesis of the more common idiopathic and virus-mediated forms of collapsing FSGS as well as aid in early disease detection and intervention.

Table 1 - Clinical Phenotypes

Subject	Age at disease onset (yr)	Proteinuria (g)	Age at ESKD (yr)	Kidney Transplant (Y/N)	Recurrence (Y/N)
1	5	25	7	Y	N
2	2	3.6	unknown	Y	N

PO1984

Leukocyte-Derived Human RNase 6 and RNase 3 Provide Resistance to Urinary Tract Infection

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Background: Urinary tract infections (UTIs) account for 7 million office visits and $1.6 billion dollars in health care spending annually in the United States. Uropathogenic *Escherichia coli* (UPEC) is the primary etiological pathogen causing over 80% of UTI. Currently, *there is a critical need for innovative and effective strategies to treat UTI and prevent UTI-associated sequelae.* Antimicrobial peptides (AMPs) are fundamental components of the innate immune system that serve instrumental roles in eliminating pathogenic microbes and thus represent a potential therapeutic tool to limit UTIs. We have identified AMPs within the Ribonuclease (RNase) A Superfamily that promote resistance against uropathogens. In this study, we determined the contribution of human RNase 6 and 3 to bacterial clearance following experimental UTI *in vivo*.

Methods: Humanized *RNASE6* and *RNASE3* transgenic mice (C57BL/6) were generated by integrating human *RNASE6* or *RNASE3* transgene fragments into the mouse genome. Humanized *RNASE6*–expressing or *RNASE3*-expressing transgenic female mice were transurethrally infected with UPEC strain UTI89. Non-transgenic littermates were used as negative controls. Bone marrow-derived macrophages (BMDMs) and BM neutrophils (PMNs) from *RNASE6* and *RNASE3* transgenic mice, respectively, were infected with UPEC *in vitro.* RNASE6 and RNASE3 expression were determined by western blot, flow cytometry and immunofluorescence. Bacterial burden was assessed via quantification of UPEC colony forming units.

Results: *RNASE6* and *RNASE3* transgenic mice showed reduced bacterial burden in the urine and bladder compared to non-transgenic mice following UPEC infection. $F480^+$ macrophages in the infected bladder were identified as the main source of RNASE6, while RNASE3 was predominantly expressed by $Ly6G^+$ neutrophils in the bladder submucosa. We also found that BMDMs from *RNASE6* transgenic mice had reduced intracellular bacteria compared to WT BMDMs after UPEC infection *in vitro*. Decreased extracellular bacterial burden was observed in cell cultures from *RNASE3* transgenic PMNs compared to non-transgenic PMNs.

Conclusions: Our findings indicate that RNASE6 and RNASE3 produced by innate phagocytes have a critical anti-microbial role against UPEC *in vivo* and *in vitro*. These RNases have the potential to effectively limit or prevent UTIs.

Funding: NIDDK Support

PO1985

Human Bladder Tissues Express Gb3 and Are Targeted by Shiga Toxin

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Background: Shiga-toxin (Stx) producing *E. coli* associated hemolytic uremic syndrome (STEC-HUS) is the main cause of acute kidney injury (AKI) in children. Glycosphingolipid globotriaosylceramide (Gb3) is the receptor for Stx and determines the tissue specificity of Stx. Previous studies have detected Gb3 in glomeruli, proximal tubules and collecting duct in human kidney, but whether Gb3 is also expressed in other urinary tissues such as bladders remains unknown.

Methods: We first established and validated two complementary detection methods for Gb3 on cultured cells, one with a monoclonal Gb3 antibody and the other detecting Stx bound to cells using an antibody against Stx. Wide-type (WT) and A4GALT (α-1, 4-galactose transferase, Gb3 synthase) knockout (KO) human bladder cancer 5637 cells were utilized as cell models. Using these two approaches, we examined Gb3 expression in the urinary system of human and different animal models. In addition, Stx was administered i.p. in WT and A4GALT KO C57 mice to evaluate the key role of Gb3 in Stx pathogenesis in kidney and bladder tissues. Finally, we examined the impact of Stx on bladder tissues with injection of Stx into the lumen of bladders.

Results: Gb3 is detected on the cell surface of WT 5637 cells, but not on A4GALT KO cells. Consistently, Stx binds to WT 5637 cells, but not A4GALT KO cells. We found that normal human bladder connective tissue and vascular endothelial cells express Gb3, which mediates binding of Stx. Gb3 expression were detected in Yorkshire pig, New Zealand white rabbit, CD1 and C57 mouse, but not in Dolly sheep. Exposure to Stx induced a large amount of inflammatory cells infiltration in the bladder submucosa in C57 mice, and bladder transitional cells necrosis were detected by pathological evaluation; while the transitional cells of A4GALT KO mice showed no corresponding changes.

Conclusions: Here we report the novel finding that Gb3 is expressed within bladder tissues in humans, suggesting that bladder tissues could be a key target of Stx in humans. Furthermore, we found that Gb3 expression varies among different animal models, which will guide the selection of proper animal models for investigating the impact of Stx on urinary tissues. Finally, our study revealed that Gb3 mediate bladder inflammatory cell infiltration and transitional cell necrosis in Stx treated C57 WT mice.

Funding: Other NIH Support - Borroughs Wellcome Fund

PO1986

Intercalated Cells Activate Innate Immune Defenses in Response to Uropathogenic Escherichia coli

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Background: Urinary tract infections (UTI), including pyelonephritis, are common in children. Intercalated cells (IC), positioned in the renal collecting duct, prevent and combat UTI by secreting antimicrobial peptides (AMPs) into the urine. The mechanisms regulating IC AMP production during UTI are unclear. Here, we challenged ICs *in vitro* with uropathogenic *E. coli* (UPEC) or bacterial cell membrane components to define the innate immune responses that control AMP production during UTI.

Methods: ICs (Clone C) were infected with a UPEC pyelonephritis strain (CFT073) or challenged with UPEC cell membrane components including lipopolysaccharide (LPS), muramyl dipeptide (MDP) and γ-D-Glu-mDAP (iE-DAP). Following stimulation, IC lysates were collected, and 87 immune genes were profiled using an antimicrobial response PCR array or targeted qRT-PCR. Western blot was performed to identify which innate immune responses are activated.

Results: In response to UPEC, ICs temporally activate immunomodulatory pathways and AMPs. Analysis of the PCR array data via STRING and Ingenuity Pathway Analysis identified 15 upregulated genes associated with Toll-like receptor (TLR), NOD-like receptor (NLR), and NF-kB signaling 4 hours post infection. Immunoblotting confirmed downstream targets in these pathways are activated in response to UPEC. qRT-PCR identified that AMPs like *Lcn2* are activated while others, including *Rnase8*, are suppressed. Upon stimulation with LPS, qRT-PCR showed upregulation of *Lcn2*, *Defb1*, and *Rnase8* – suggesting that TLR4 activation may regulate the expression of these AMPs. Additionally, qRT-PCR showed *Lcn2* is induced in response to the NOD2 agonist, MDP, while AMP expression did not change with the NOD1 agonist, iE-DAP.

Conclusions: During UPEC infection, TLR, NLR, and NF-kB responses are activated in ICs. Activation of TLR and NLR signaling may induce downstream targets like AMPs. Confirmation studies are needed to determine how these pathways regulate AMP expression and their differential regulatory targets. Identification of these nodes may serve as future targets to increase AMP production as an additional means to treat UTIs in children and adults.

Funding: NIDDK Support

PO1987

Renal-Derived Alpha-Defensins 1-3 Contribute to Enhanced Urinary Tract Protection in Humanized Mouse Transplant Model Challenged against Uropathogenic Escherichia coli

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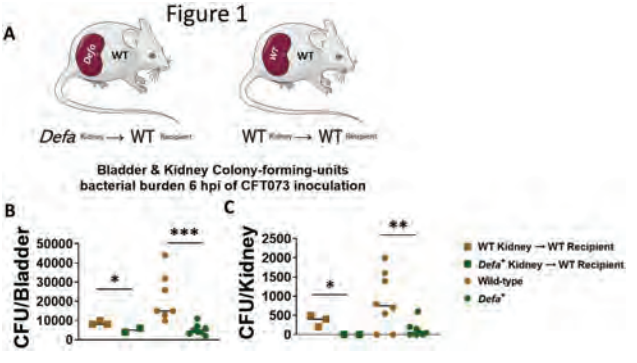
Background: Alpha-defensins 1-3 are potent antimicrobial peptides expressed from *DEFA1A3* gene locus by human neutrophils and kidneys. Decreased DNA copy numbers of *DEFA1A3* have been associated with UTI susceptibility. Here, we utilize a human *DEFA1* knock-in transgenic mouse (*Defa*$^+$) to study the role of *DEFA1A3* in UTIs. We hypothesized that *DEFA1* protects the murine urinary tract from uropathogenic *E. coli* (UPEC) challenge and renally derived *DEFA1A3* is the protective source.

Methods: Female wild-type (WT) and *Defa*$^+$ mice were infected by transurethral inoculation of UPEC; CFT073, pyelonephritis strain. Bacterial burdens in kidneys and bladders for each group of mice were analyzed at 6 hours post-infection (hpi). We performed transplant isografts of $Defa^{Kidney} \rightarrow WT^{Recipient}$ mice and used $WT^{Kidney} \rightarrow WT^{Recipient}$ as biological controls for UPEC challenges (Figure 1A).

Results: Murine bladder and kidney CFU bacterial burdens results are presented in Figure 1: Comparing the groups at 6 hpi, CFU burden averages were significantly lower in the $Defa^{Kidney} \rightarrow WT^{Recipient}$ infected bladder group, similarly to infected *Defa*$^+$ mice when compared to its WT counterpart (B). Strikingly, kidneys from $Defa^{Kidney} \rightarrow WT^{Recipient}$ were protected against bacterial growth, in contrast to $WT^{Kidney} \rightarrow WT^{Recipient}$ controls, which showed higher titers of CFU burdens per transplanted kidney following pyelonephritis challenge, and recapitulates the protective phenotype observed in the *Defa*$^+$ infected mice when compared to its WT control group (C).

Conclusions: Our findings support the role of renal-derived alpha-defensins 1-3 in not only protecting the transplanted kidney but the entire lower urinary tract from UPEC.

Funding: NIDDK Support



Murine isograft transplant model & CFU bacterial burden results of infected upper and lower urinary tract tissues

PO1988

Fate-Mapping Supports a Linear Model of Urothelial Formation and Regeneration

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Background: Urothelium is a highly specialized, slow turnover epithelium that lines the kidney, ureter, bladder and proximal urethra. Bladder urothelium contains several cell types organized into basal (B), intermediate (I) and superficial (S) cell layers. The progenitor responsible for urothelial repair has been the focus of many investigations, with

strong support for both B and I cell contenders. We have previously demonstrated that keratin 5^{+} (K5) urothelial cells (UCs) are context specific progenitors in the kidney. Here, we mapped the fate of K5-UCs across development and following cyclophosphamide (CYC)-induced urothelial injury in the bladder.

Methods: Using tamoxifen (TMX)-inducible *Krt5^{CreERT2};Rosa^{zsGreen}* mice, we permanently labeled K5-UCs with zsGreen (zsGreen^{K5}) across development and evaluated their capacity to form I and S cells during homeostasis or following CYC-induced urothelial injury. Immunofluorescence microscopy was used to determine whether zsGreen^{K5}-UCs were K5^{+}(B-cells), Uroplakin^{+} (Upk; I and S-cells), or K20^{+}(S-cells). Organoid forming assays were used to evaluate progenitor capacity *in vitro*.

Results: Baseline analysis of our Cre;LoxP strategy confirmed that zsGreen^{K5} is specifically expressed in basal K5-UCs 24h after TMX administration at all induction stages. The fate of zsGreen^{K5}-UCs varied, with neonatal (postnatal day [P]1, P7) stages giving rise to adult (P42) I and S cells, the juvenile (P14) stage giving rise to I but not S cells, and adult (P35, P42) stages not escaping the B cell layer. CYC-induced urothelial injury did not engage adult zsGreen^{K5}-UCs for repair, whereas neonatal and juvenile zsGreen^{K5}-UCs gave rise to I and S cells following CYC treatment. Organoid forming assays confirmed that zsGreen^{K5}-UCs could form organoids that express B and I cell markers, and neonatal UCs formed larger organoids than adult UCs.

Conclusions: We show that precise temporal populations of K5-UCs form I cells during homeostasis which in turn are engaged as adults for S cell formation in response to injury. We believe that these findings unite B and I cell progenitor models, by temporally linking a linear progression of B→I→S cell formation. A more complete understanding of the role of discrete urothelial cell populations will enable precise control of urothelial cell differentiation and will inform targeted tissue regeneration strategies.

Funding: NIDDK Support

PO1989

Urothelial Injury Triggers Adaptive Remodeling That Limits Congenital and Acquired Obstructive Nephropathy

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Background: Congenital urinary tract obstruction (UTO) is the leading cause of chronic kidney disease and end stage renal disease in children. Both congenital and acquired UTO induce renal urothelial cells to remodel and assume a bladder-like morphology, but the mechanisms and significance of these changes remain unclear. We hypothesize that urothelial remodeling occurs as a consequence of injury to Uroplakin (UPK) expressing cells and serves to attenuate obstructive nephropathy.

Methods: Urothelial injury markers were measured by ELISA in children undergoing pyeloplasty for congenital ureteropelvic junction obstruction (UPJO) versus non-obstructed controls. Male and female mice underwent acquired UPJO via unilateral ureteral obstruction (UUO). The fate of Upk+ cells during UUO was traced through the use of Cre/LoxP mapping. The impact of Upk plaque loss on the kidney's response to UUO was assessed through the use of *Upk1b$^{-/-}$* mice. The effects of Upk+ cell depletion during UUO were gauged by administering diphtheria toxin (DT) to *Upk2*iCre(+); *Rosa26$^{DTR/+}$* mice.

Results: Urine from children with congenital UPJO contains elevated urothelial injury markers – including KRT14, UPK2, and KRT20 – compared to unobstructed controls. Mice with UUO exhibit urothelial apoptosis and increased mRNA and protein expression of urothelial injury markers. Lineage analysis of Upk+ cells demonstrates that UUO triggers a sequence of Upk protein downregulation, proliferation, and elaboration of a bladder-like urothelial plaque. When this process is disrupted via *Upk1b* deletion or depletion of Upk^{+} cells, UUO results in augmented tubular injury and interstitial fibrosis.

Conclusions: Urothelial injury is a conserved response to UTO and initiates a series of events that culminate in protective, bladder-like remodeling. The resulting expansion of Upk+ cells and production of urothelial plaque represent an essential adaptation to limit renal parenchymal injury during UTO.

Funding: NIDDK Support

PO1990

An Ethical Decision-Making Framework for Genomic Testing in Pediatric Kidney Disease

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Background: Technological advances and increased access have led to genomics expanding beyond the genetics specialty. As a result, non-genetic specialists, including nephrologists, can now order genomic testing for their patients. Consistent decision-making around patient and test selection is required to ensure equitable access while maximizing the utility of genomic testing, from a patient and resource perspective. However, there are currently no frameworks to guide decision-making for genomic testing in pediatric nephrology. We aimed to develop an ethical decision-making framework to guide genomic testing decision-making in pediatric kidney disease.

Methods: A three-stage approach was used: 1) review of the literature on decision-making for genomic testing in nephrology and other disciplines; 2) observation of approaches to genomic testing in the general nephrology clinic and the renal genetics clinic at an Australian pediatric hospital; 3) review and revision of the framework with key stakeholders, including clinical geneticists, genetic counselors, pediatric nephrologists, clinical ethicists, and families from the renal genetics service. The initial framework was modified until consensus from key stakeholders was reached.

Results: A decision-making framework was created. This framework outlines the key decision-making categories and sub-categories for patient selection, with corresponding questions to aid usage. A number of case studies were developed to demonstrate the framework's application. Key factors influencing utilization of the framework were identified, particularly funding pathway, clinical environment, and patient population.

Conclusions: The framework will guide decisions around patient-selection for genomic testing in nephrology at the Australian pediatric hospital of origin as well as other institutions and disciplines. In doing so, it will facilitate consistent approaches to genomic testing, to maximise equity and utility.

PO1991

Genetic Testing and Biomarkers as Predictive Tools for Congenital Anomalies of Kidney and Urinary Tract (CAKUT)

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Background: Cincinnati Children's Hospital is 1 of ~5 centers offering fetal interventions (FI) (amnioinfusions/amnioshunts) & infant hemodialysis (HD) for oligo/anhydramnios (OA), increasing survival from 17 to 50%. As a result of this unique surviving Congenital Anomalies of Kidney & Urinary Tract (CAKUT) population, more investigation into genetics & biomarkers in severe CAKUT needs to be performed, particularly in our growing bilateral multicystic dysplastic kidney (bMCDK) population (fatal at most centers). We hypothesize identification of novel genetic mutations & biomarkers will aid in determination of the clinical course of infants & mechanisms of nephrogenesis.

Methods: Inclusion criteria for severe CAKUT are women undergoing FI for OA or infants starting HD by 1 month of life. We obtained amniotic fluid (AF) during FI and blood from the mother, father, & infant for trios whole exome sequencing (WES). We performed ELISA testing on AF of 4 renal tubular biomarkers produced by fetal kidneys and validated in AF (NGAL, Cystatin c, Uromodulin and ET-1). Controls are 2nd trimester AF from infants without CAKUT.

Results: We enrolled 18 families-6 with bMCDK & obtained 8 AF samples (2 bMCDK). We performed WES on 5 trios (4 bMCDK) & 3 singletons (1 bMCDK). We identified 4 strong candidate genes **(Table).** Biomarker testing included 8 AF samples & 10 controls. All 4 biomarkers are significantly lower in severe CAKUT than controls & are lower in bMCDK than bladder obstruction, likely as the bMCDK population has less renal endowment. Biomarkers are lower in those with intrauterine demise compared to liveborn.

Conclusions: In patients with severe CAKUT, we detected 4 strong candidate genes, 3 implicated in embryo development. This population is enriched for genetic variants, likely due to severity of presentation. We validated 4 biomarkers in AF with correlations to diagnosis & survival. WES & biomarker testing are promising techniques to predict the course of severe CAKUT prenatally. Our goal is to develop a polygenic risk score to predict disease severity in utero based on genetic & biomarker data in this unique population.

Funding: Other NIH Support - T-32 Training Grant

Genetic Variants in Bilateral MCDK Families

Gene	Chromosome	Variant	MCDK Family	Variant Frequency	Predicted Tolerance	Pathway	Gene Function	Syndromes affiliated with gene	Potential Biomarkers
FRAS1	4	G to A SNV	F1, F2	0.0037%	1/5	Integrin	Organogenesis	Fraser Syndrome	integrin α3β1
NSUN7	2	De novo frameshift	F2	N/a	N/a	RNA methylation transferase	Mitochondrial rRNA processing	Familial restrictive cardiomyopathy	None
MTMR3	22	C to T SNV	F3	0.000004076	2/5	Protein Tyrosine Phosphatase, mTOR	Cilia Signaling, Autophagy	Charcot-Marie-Tooth, Lupus Nephritis, IgA nephropathy	Low molecular weight protein-tyrosine phosphatase
CEP162	6	A to G SNV	F1, F2	0.0009%	1/5	Axonemal Microtubule Binding	Ciliogenesis, Organelle Biogenesis	Seckel Syndrome, Orofacial Digital Syndrome	None

PO1992

Genetic Kidney Disease: The Importance of Variants of Uncertain Significance

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Introduction: Diagnosing genetic kidney disease has become more accessible with the advent of low-cost and rapid genetic testing. The Invitae nephrolithiasis (NL) panel performs next-generation sequencing to evaluate 35 genes associated with NL and nephrocalcinosis (NC).

Case Description: A 7-month-old, ex-full term, white female was referred to pediatric nephrology clinic for recurrent urinary tract infections (UTI). Review of systems was positive for nonbloody diarrhea. She had no allergies or pertinent family history. Vital signs were normal with height at 14th percentile and weight at 6th percentile. Physical exam was unremarkable. Kidney/bladder ultrasound showed bilateral medullary NC. Voiding cystourethrogram was normal. Laboratory evaluation showed hyponatremia

(129 mmol/L), anion-gap metabolic acidosis, hypercalcemia (13.9 mg/dL, ionized calcium 1.52 mmol/L), hypophosphatemia (2.8 mg/dL), hypoparathyroidism (1.45 pg/mL), and hypercalciuria (urine calcium:creatinine 1.3 mg/mg). She was diagnosed with milk protein allergy with diarrhea and electrolyte derangements requiring supplementation. After the diarrhea resolved on milk-free formula, serum electrolytes normalized except for hypercalcemia. Hypercalciuria resolved with hydration and low sodium diet. All supplements were stopped except for potassium citrate. Invitae NL panel was sent and showed 2 heterozygous variants of uncertain significance (VUS) in gene SLC34A1. Mutations in SLC34A1 are associated with autosomal recessive (AR) infantile hypercalcemia 2 (IH2), autosomal dominant hypophosphatemic NL/osteoporosis, and AR Fanconi renotubular syndrome. Parental testing determined the VUS were in a trans-configuration. It was hypothesized that she may be a compound heterozygote for IH2, a disease associated with hypercalcemia, failure to thrive, dehydration, and NC. She was trialed on the treatment of IH2 (phosphorus supplementation) and within 1 week hypercalcemia resolved.

Discussion: Although this patient had VUS in SLC34A1 rather than known pathogenic variants, her clinical presentation was consistent with IH2. Had IH2 treatment not been trialed, this patient would have had continue hypercalcemia with associated morbidity. This case illustrates how genetic testing may change clinical practice by altering treatment strategies, and the importance of taking VUS into consideration.

PO1993

Genetic Causes for Congenital Nephrotic Syndrome: North American Mutations and the Contribution of Regulatory Factors

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Background: Congenital Nephrotic Syndrome (CNS) is a debilitating disease that affects children within the first few months of life and is characterized by severe proteinuria and loss of kidney function. A majority of CNS cases are caused by mutation of the *NPHS1* gene, particularly in other countries. Our first aim was to determine the specific genetic causes for CNS in North America (NA). Our second aim was to determine the contribution of FOXC1, FOXL1, and GATA3 to *NPHS1* transcription and nephrin production, which could serve as potential drug targets for CNS therapy.

Methods: A retrospective chart review was performed to determine the prevalence of CNS mutations in NA. A survey was administered to members of the Pediatric Nephrology Research Consortium (PNRC) and consisted of 65 questions pertaining to CNS. A questionnaire was developed by a team of pediatric nephrologists and was administered to members of the Pediatric Nephrology Research Consortium (PNRC) via Qualtrics. *In vitro* studies to determine the impact of FOXC1, FOXL1, and GATA3 on *NPHS1* were performed using mouse primary podocytes and siRNA knockdown was performed to determine the effect of these transcription factors on nephrin production.

Results: We found the average age of CNS diagnosis was 2.6 months, with 60.3% of patients being female. Sixty-eight percent of patients underwent genetic testing for their CNS and a majority of patients (65.1%) had *NPHS1* mutations, whereas 11.6% had *NPHS2* mutations. Interestingly, 7.0% had both *NPHS1* and *NPHS2* mutations and 11.6% had only *WT1* mutations. The remaining 4.6% had inconclusive results. We noted that the average age of onset for *NPHS1*-only mutations was 2.1 months, whereas patients with only *NPHS2* mutations had an average age of onset of 4.5 months. Interestingly, patients with either *WT-1* mutations or a combination of *NPHS1* and *NPHS2* mutations had younger ages of onset of 1.35 months and 1.25 months, respectively. In our *in vitro* studies, siRNA knockdown of FOXC1, FOXL1, and GATA3 resulted in alterations in the expression of nephrin.

Conclusions: The results of this study not only demonstrate the distribution of genetic causes for CNS in North America, but also show that transcription factors may play a role in *NPHS1* transcription.

PO1994

Mendelian Causes Are Identified at a Relatively Low Rate and Show a Unique Pattern in Brazilian Pediatric Patients with Steroid-Resistant Nephrotic Syndrome or Focal Segmental Glomerulosclerosis

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Background: Genetic and non-genetic factors have been associated with faster progression to chronic kidney failure (CKF) in children with steroid-resistant nephrotic syndrome (SRNS). The contribution profile of such factors in admixed populations, however, is still not well characterized.

Methods: 101 patients/98 families with idiopathic SRNS, age of onset <18yr, were sequenced for 62 NS genes or submitted to whole exome sequencing. Causative variants and *APOL1* risk alleles were confirmed by Sanger sequencing. Clinical data were retrospectively reviewed.

Results: Age of NS onset was 2.9yr (1.5-6.8), 61 (60.4%) were male, 61 (60.4%) self-declared white, 6 (5.9%) had parental consanguinity, and 14 (13.9%) familial disease. Focal segmental glomerulosclerosis (FSGS) was diagnosed in 54/95 (56.8%), minimal change disease (MCD) in 20/95 (21.1%) and collapsing glomerulopathy in 12/95 (12.6%). 43/101 (42.6%) progressed to CKF in 29 months (12.0-61.9) and 9/29 (31%) had recurrence after kidney transplant (KT). *APOL1* high risk genotypes (HRG) were identified in 8/98 (8.2%) and were associated with later NS onset [11.0 (10.0-14.5) *vs* 2.7 (1.4-4.9) yr, p<0.001]. Mendelian causes were found in other 14/98 (14.3%) families: *NPHS1*=4, *NPHS2*=3, *PLCE1*=2, *WT1*=2, *COQ2*=1, and phenocopies in *CUBN*=1 and *COL4A5*=1, all *APOL1* G0/G0. Poorer renal survival was observed in *APOL1* HRG *vs* non-Mendelian/non-*APOL1* HRG (p<0.001), and a trend in Mendelian *vs* non-Mendelian/non-*APOL1* HRG (p=0.06). The *APOL1* or Mendelian cases had no post-KT recurrence. Using Cox regression, age of onset <1yr (OR=6.5, CI:2.3-16.9, p=0.0007) or ≥ 9yr (OR=3.3, CI:1.3-7.9, p=0.015) were associated with reduced renal survival, independently of genetic findings, as well as self-declared non-white (OR=2.6, CI:1.3-5.64, p=0.01) and non-MCD histology (OR=14.2, CI:2.1-948, p=0.002).

Conclusions: Mendelian causes of SRNS/FSGS were identified in 14.3% - a lower rate than in PodoNET, SRNS Study Group and RaDar - and *APOL1* HRG in 8.2% of patients in this admixed population with a low frequency of parental consanguinity. Genetics factors, age of NS onset, ethnicity and biopsy pattern were independently associated with progression to CKF.

PO1995

Genetic Testing in Children with Nephrolithiasis and Nephrocalcinosis

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Background: Diagnosing genetic kidney disease has become more accessible with the advent of low-cost and rapid genetic testing. The study objective was to determine the sensitivity of genetic testing in diagnosing kidney disease in children with nephrolithiasis (NL) and nephrocalcinosis (NC).

Methods: A retrospective multicenter study was conducted on children ≤21 years with NL/NC that underwent the Invitae sponsored NL panel. Next-generation sequencing evaluated 35 genes. The sensitivity of genetic testing was calculated. Logistic regression examined the association of clinical variables with genetic diagnosis.

Results: Seventy-eight children from 5 centers were included (56 had isolated NL [iNL] and 22 had NC). Sensitivity of genetic testing was 31% (iNl 27%, NC 41%). Of those with genetic diagnoses (Figure 1), 25% had pathogenic mutations alone, 13% carried pathogenic mutations for recessive conditions, 13% carried a pathogenic mutation and variant of uncertain significance (VUS) in the same gene and 50% had VUS alone. Mutations were found in 25 genes, most commonly HOGA and SLC3A1 in iNL and SLC34A3 and CLDN19 in NC. Clinical features are shown in Figure 2. In multivariate analysis, subjects with hypercalciuria were less likely to have a genetic diagnosis (OR 0.35, 95% CI 0.13-0.95, p=0.04).

Conclusions: This study has demonstrated the utility of genetic testing, where explanatory genetic mutations were found in one-third of children with NL/NC. Genetic testing shows promise to improve clinical practice in this population.

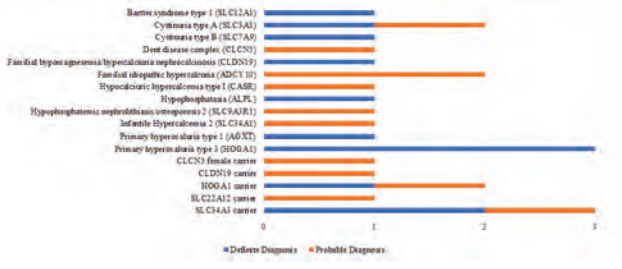

Figure 1: Genetic diagnoses.

Characteristics	All Subjects	Univariate Analysis OR (95% CI)	P value
Median age (IQR), years	11 (5-16)	1.04 (0.96 to 1.13)	0.37
Sex, n (%)			
Female	32 (41)	Reference	-
Male	46 (59)	0.46 (0.17 to 1.22)	0.12
Race, n (%)			
White Non-Hispanic	42 (54)	Reference	-
White Hispanic	14 (18)	0.89 (0.24 to 3.38)	0.87
Other	8 (10)	0.32 (0.04 to 2.86)	0.31
Asian	6 (8)	4.46 (0.72 to 27.51)	0.11
Black/African American	5 (6)	0.56 (0.06 to 5.49)	0.62
Unknown	3 (4)	1.12 (0.09 to 13.42)	0.93
Family history, n (%)	46 (59)	1.79 (0.67 to 4.76)	0.24
Hypercalciuria, n (%)	35 (45)	0.35 (0.13 to 0.95)	0.04
Prematurity, n (%)	15 (19)	2.05 (0.52 to 8.06)	0.31
Hypercalcemia, n (%)	13 (17)	0.21 (0.06 to 0.75)	0.02
Developmental delay, n (%)	13 (17)	2.81 (0.57 to 13.82)	0.20
Failure to thrive, n (%)	11 (14)	0.75 (0.20 to 2.83)	0.67
Metabolic acidosis, n (%)	6 (8)	0.20 (0.03 to 1.18)	0.08
Hypophosphatemia, n (%)	4 (5)	0.14 (0.01 to 1.45)	0.10
Elevated 1,25-dihydroxyvitamin D, n (%)	4 (5)	0.14 (0.01 to 1.41)	0.09
Hyperuricemia, n (%)	4 (5)	1.22 (0.11 to 13.07)	0.87
Chronic kidney disease, n (%)	3 (4)	0.89 (0.08 to 10.25)	0.92
Rickets, n (%)	3 (4)	0.86 (0.07 to 10.02)	0.91
Seizures, n (%)	3 (4)	0.85 (0.07 to 9.82)	0.89
Hypomagnesemia, n (%)	2 (3)	N/A	1.00
Dental abnormalities, n (%)	2 (3)	0.44 (0.03 to 7.33)	0.57
Eye abnormalities, n (%)	2 (3)	0.44 (0.03 to 7.38)	0.57
Deafness, n (%)	1 (1)	N/A	1.00

Figure 2: Subject characteristics.

PO1996

Experience from a Single Centre Following a Large Cohort of Children with Cystinuria (1996-2019)

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Background: Cystinuria is a rare monogenic disorder accounting for 5-10% of all paediatric urolithiasis cases. This study reviews epidemiologic, clinical and management data of a large, single centre cohort of cystinuric children.

Methods: Respective data collection from children with cystinuria between June 1996 to April 2019 in our centre.

Results: A total of 52 (54% female) patients were identified with a median (IQR: interquartile range) age at presentation of 6.2 (1.9-10.3) years. 24/52 (46%) had affected family members. Common presenting symptoms were abdominal pain 21/51(41%), urinary tract infection (39%), haematuria (18%); 14/51(28%) cases were diagnosed by family screening or incidentally. 9/52(17%) had cystinuria but did not form a stone. At presentation stone location was upper tract in 30/43(70%), bladder stones were found in 10/43(23%). Estimated GFR was <90ml/min/1.73m^2 in 14/52(27%) at diagnosis. Hyperhydration fluid target was met by 63% and 76% were prescribed alkali, median (IQR) dose was 0.5(0.3-0.7) mEq/kg/day and urine pH 7.0(7.0-8.0). 24/52(46%) patients had 26 treatment periods with cystine-binding thiol drugs (CBTD) for a median (IQR) duration of 34(18-65) months; 7/24(29%) patients on CBTD developed adverse effects leading to discontinuation in 3(13%). Median (IQR) urine cystine was lower (p=0.006) at 0.7 (0.5-0.9) mmol/L after CBTD was started compared to diagnosis at 1.3 (0.7-2.0) mmol/L. Stone removal procedure was performed in 37/43(86%) cases, those treated with CBTD had a higher median (IQR) number of surgical interventions of 4(2-8) vs no CBTD 1(0-2), p<0.001. The annual median (IQR) rate of stone removal procedures/patient was 0.2(0.1-0.4). At the end of follow up eGFR<90 was present in 12/35(34%).

Conclusions: Bladder stones were seen in a 23% of paediatric patients with cystinuria. Median stone removal procedure rate was 0.2/year in our cohort. CBTD significantly decreased free urine cystine levels, but was associated with complications in almost a third. The vast majority underwent a surgical intervention during follow-up, highlighting the burden of disease. Fortunately, eGFR remained stable in most of the patients.

PO1997

Systemic Oxalate Deposition in Patients with Primary Hyperoxaluria Type 3

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Background: In the contrary to previous reporting we now know, that patients with Primary Hyperoxaluria type 3 (PH3) remain symptomatic in adulthood with recurrent kidney stones. They also are on risk to develop chronic kidney disease (CKD). We therefore consider, that PH3 patients may also develop systemic oxalate deposition.

Methods: We are now examining PH3 patients regularly seen at the German Hyperoxaluria Center (GHC) for systemic depositions by eye exam (by fundus color photography and optical coherence tomography), hand x-rays, bone MRI (3 Tesla of the left knee and proximal tibia) and Speckle tracking echocardiography, which measures changes in global longitudinal strain (GLS), an index of left ventricular contractibility (normal GLS is ≤18%).

Results: At GHC we see 12 pediatric and 4 adult patients on a regular basis, at least twice a year. All 16 patients are in no less than CKD 2. So far the following examinations were performed: an eye exam was performed in 8 patients, it was normal in all. Speckle tracking echocardiography was done in 8 patients, it was abnormal in one (GLS – 17.3% and left ventricular hypertrophy) and borderline in another (GLS – 18.6%) in 2020. During 2021 GLS values returned to normal in both under increased treatment awareness (-23% and -21%, respectively). X-ray left hand was taken in 6 patients, one patient (multiple stone removal procedures, decline in GFR) had tiny sclerosing areas at caput MCP IV and the thumb. MRI of left knee and proximal tibia was performed in 6 patients, clearly visible textural changes as patchy areas of low signal intensity were found in one patient. Two patients had salivary stones in the parotid gland, found in a routine x-ray of the jaw before orthodontic treatment.

Conclusions: Although this is currently only data of a small cohort, systemic oxalate deposition may also occur in PH3. Of course, data in more patients are needed to elucidate the true risk of systemic oxalate deposition and we therefore recommend to screen all known PH3 patients.

PO1998

Temporal Relationship of Transplant, Dialysis, and Medications for Children with Primary Hyperoxaluria

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Background: Primary hyperoxaluria (PH), a rare inborn error of metabolism resulting in hepatic overproduction of oxalate, causes kidney stones and, for some, end-stage renal disease and systemic oxalosis. Our objective was to determine the timing of dialysis, renal transplant, and use of medications to treat PH manifestations in children relative to their diagnosis.

Methods: A retrospective cohort study was conducted in PEDSnet, a clinical research network of 7 US pediatric health systems. Data from PEDSnet were queried to identify patients <18 years old with a diagnostic code for or related to PH between 2009 – 2020. Outcomes queried were renal transplant, initiation of dialysis, first prescription for medications used to treat end-organ manifestations of PH, and specialty care visits. Outcomes were evaluated relative to cohort entrance date (CED), defined as date of first PH-related diagnostic code.

Results: 341 patients were identified. Median age at CED was 9.4 years (IQR 5.0, 13.0). Median follow-up was 2.9 years (IQR 1.1, 6.0). Median eGFR was 117.33 ml/min (IQR 95.75, 139.79). Most patients with renal transplant were transplanted prior to CED. Similarly, dialysis (n=14) was initiated in the majority before CED and at a younger age than those starting dialysis after CED. Prescription drug therapy before CED was high (29% patients with B6 use; Table). Nephrology was the specialty most commonly responsible for initial PH diagnosis (69% on CED).

Conclusions: In one of the largest cohorts of children in the US with PH, dialysis and renal transplant occurred before diagnosis, suggesting significant morbidity when diagnosis is delayed. Medications for the organs affected by PH were consistently prescribed before diagnosis, suggesting an opportunity for earlier PH identification to enable tailored therapy to potentially delay or prevent need for dialysis and transplant.

Funding: Commercial Support - Dicerna Pharmaceuticals

	Patients (n=341)	Number Pre-CED	Number On or After CED
Medications (*Denotes results where PEDsnet governance prevents reporting numbers <11 to maintain patient privacy)			
Pyridoxine (Vitamin B6)	58 (17%)	17	41
Citrate	146 (43%)	71	75
Thiazides	79 (23%)	38	41
Erythrocyte-stimulating agents	15 (4%)	<11*	<11*
Age in years at first dialysis, median (IQR)	2.31 [0.71, 5.92]	1.15 [0.54, 4.92]	17.45 [11.25, 20.36]

PO1999

Oxalate and Glycolate in Urine and Plasma Related to Kidney Function, Dialysis, or Transplantation in Patients with Primary Hyperoxaluria Type 1

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Background: Primary hyperoxaluria type 1 (PH1) is characterized by endogenous oxalate overproduction in the liver, extremely elevated urinary oxalate excretion (Uox), thus recurrent urolithiasis and/or progressive nephrocalcinosis and chronic kidney disease (CKD). It also leads to early renal failure, especially problematic in the young patient (infantile oxalosis). Uox and glycolate (Uglyc) and plasma oxalate (Pox) and glycolate (Pglyc) are used as biochemical markers for diagnosis, treatment and follow up, but also as primary endpoints in studies.

Methods: We retrospectively analyzed these parameters in urine and plasma of 87 genetically confirmed PH1 patients over the last 15 years. All parameters were analyzed by ion-chromatography/mass spectrometry and in the same lab. Correlation and comparative analyses were performed within groups of different renal function (normal,

CKD 1-5; n=48 patients), hemodialysis (HD; n=31), transplantation (Tx; n=32) and related to vitamin B6 medication.

Results: From normal kidney function to CKD3-4 Pox remained stable (median Pox 17 μmol/l), while Pglyc was more markedly elevated (median 90.12 μmol/l). Both were significantly higher in non-B6 versus B6 sensitive patients. Pox and Pglyc did not correlate with kidney function, except for Pox and CKD5. Highest Pox and Pglyc was found in HD (91 and 211 μmol/l, respectively), not related to B6. Uox and Uglyc remained stable at all CKD stages in B6 sensitive, but increased progressively in B6 unsensitive patients. Pox and Uox slowly declined post combined and sequential liver-kidney, but also in isolated kidney Tx, which was performed in adult B6-sensitive patients. In the contrary, PGlyc remained elevated post Tx.

Conclusions: Our findings are in many ways contradictory to previously published observations. Pox or Uox did not correlate to GFR. Pox was surprisingly low until HD and Uox increased until CKD3-4 in non-B6 sensitive patients. PGlyc remained elevated even years after transplantation, but no data are available to compare. Glycolate is widely accepted to be harmless, even at elevated values, but a fundamental proof is missing. So, consequences of this need further investigation.

Funding: Government Support - Non-U.S.

PO2000

Compassionate Use Treatment with RNAi Medication (Nedosiran) in Two Patients with Primary Hyperoxaluria Type 1 and Maintenance Hemodialysis

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Introduction: The primary hyperoxalurias (PH) are three ultra-rare, autosomal recessive genetic disorders characterized by oxalate overproduction in the liver. Hyperoxaluria induces recurrent kidney stones, nephrocalcinosis, progressive renal impairment, and systemic oxalosis, especially in PH1. Nedosiran is an investigational RNA interference (RNAi) therapeutic administered monthly by subcutaneous injection. It reduces hepatic LDHA protein thereby inhibiting the final step responsible of oxalate production in all types of PH.

Case Description: We report on two PH1 patients, a 40 year old woman (a) on hemodialysis (HD) 6 x 3 hours weekly, and a 6.5 year old boy (b) receiving 5 x 5 hours HD, both homozygous for *AGXT* c.508G>A and treated with pyridoxine. In patient (a), global longitudinal strain (GLS), an index of left ventricular contractibility, was impaired (-13%; normal ≤-18%). Patient (b), has massive oxalate osteopathy, myocardial hypertrophy and cardiac insufficiency (GLS of – 9.98). They received Nedosiran as compassionate use medication for now 6 months. Monthly plasma oxalate (Pox in μmol/l, normal <7.4) was measured, Speckle Echo and/or 3 Tesla bone MRI (left knee) were repeated. Speckle echo improved significantly in both (a: GLS – 23%; b: GLS -16.5%). Bone MRI ameliorated in patient (b) showing a nidus of normal trabecular structure.

Discussion: Clinics improved and Pox declined over the six months of treatment. Pox was influenced in (b) by severe oxalate osteopathy and therefore possibly dissolving oxalate and in (a) when dialysis regimen was reduced to 4 x 3 hours at month 6. We cautiously conclude, that Nedosiran treatment reduces plasma oxalate levels in a way, that liver transplantation may be avoidable in PH1 patients.

Follow up under Nedosiran administration

Patient	Pox Pre RNAi	Pox Month 1	Pox Month 2	Pox Month 3	Pox Month 4	Pox Month 5	Pox Month 6
(a)	64.2-71.6	40.9	60.2	52.8	37.7	23.2	32.4
(b)	73.1-101	96.5	40.6	56.9	48.1	69.7	51.3

PO2001

Functional Analysis of Novel CNNM2 Mutation in Autosomal Dominant Hypomagnesemia with Seizure

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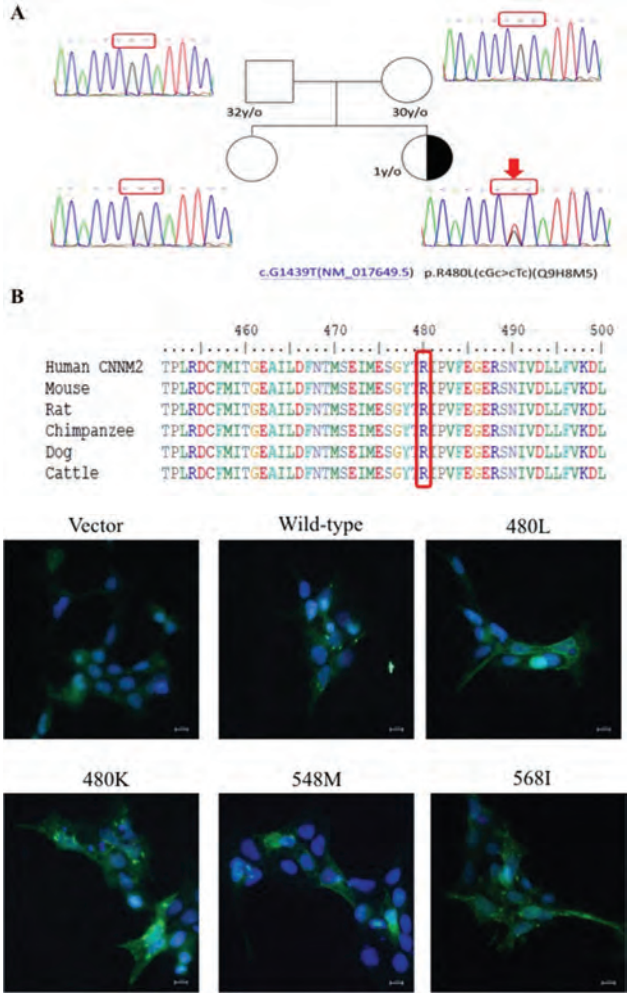
Background: *CNNM2* has been identified to be the responsible gene for patients with hypomagnesemia, seizure, intellectual disability (HSMR) syndrome. The functional impact of mutations in *CNNM2* remains unknown.

Methods: We have identified 1-year-old infant with HSMR featuring severe hypomagnesemia with renal magnesium (Mg^{++}) wasting requiring higher dose of Mg^{++} supplementation. Whole exome sequencing (WES) with direct Sanger sequence was performed to identify the responsible gene. The functional assay of this identified mutants was examined in vitro studies.

Results: With WES, we identified a *de novo* heterozygous mutation c.G1439T (R480L) in CBS domain of *CNNM2* gene without any other gene mutations related to hypomagnesemia. This missense *CNNM2 P480L* mutation was conserved in different species and very pathogenic based on the different software prediction models. This R480L mutation impaired the interaction between CNNM2 and ATP-Mg^{2+} by simulation model. In vitro studies, This CNNM2-R480L protein expression was higher than CNNM2-wild type. Immunocytochemistry images demonstrated the proper localization of CNNM2-R480L and CNNM2-wild type. Mg^{2+} efflux assay revealed significant increase of intracellular Mg^{2+} Green in CNNM2-R480L than CNNM2-WT, indicative of CNNM2-R480L mutation blocking Mg^{2+} efflux.

Conclusions: This novel R480L mutation in CBS domain of *CNNM2* gene diminishes the Mg^{2+} efflux probably through the impaired binding between Mg^{2+}-ATP and CNNM2, accounting for refractory hypomagnesemia.

Funding: Government Support - Non-U.S.



PO2002

Long-Term Outcome of Bartter Syndrome

Naye Choi,[1,6] Ji hyun Kim,[2] Seong heon Kim,[1] Eun Hui Bae,[3] Joo Hoon Lee,[4] Il-Soo Ha,[6] Yo Han Ahn,[1,6] Hyesun Hyun,[5] Hee Gyung Kang.[1,6] *[1]Seoul National University Children's Hospital, Seoul, Republic of Korea; [2]Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [3]Chonnam National University Hospital, Gwangju, Gwangju, Republic of Korea; [4]Asan Medical Center, Songpa-gu, Seoul, Republic of Korea; [5]Catholic University of Korea School of Medicine, Seoul, Seoul, Republic of Korea; [6]Seoul National University College of Medicine, Seoul, Republic of Korea*.

Background: Bartter syndrome (BS) is a rare salt-wasting tubulopathy caused by mutations in genes encoding sodium, potassium, or chloride transporters of the thick ascending limb of Henle and/or the distal convoluted tubule of the kidney. BS is characterized by polyuria, failure to thrive, hypokalemia, metabolic alkalosis, hyperreninemia and hyperaldosteronism. Previously, potassium and/or sodium supplements, potassium sparing diuretics and NSAIDS were known as possible treatment options for BS. While presenting symptoms and initial managements of BS are relatively well known, long-term outcomes and treatments are still unclear.

Methods: Through a survey for the members of Genetic Kidney Disease Working Group of the Korean Society of Nephrology, clinically and/or genetically diagnosed 54 Korean BS patients were recruited. We retrospectively reviewed their medical records between 1992-2020 for presenting symptom, laboratory findings, genotype, medication, and their final height and renal function.

Results: There were clinically and/or genetically diagnosed with BS at median age of 5 months old (range 0-271) and their median follow up was 8 years (range 0.5-27). Genetic diagnosis of BS was made in 40 patients; 4 patients with *SLC12A1* gene mutations, 2 patients with *KCNJ1* gene mutations, 33 patients with *CLCNKB* gene mutations, and 1 patient with *BSND* mutation were revealed, respectively. Potassium chloride supplements was administered in 94% of patients and potassium sparing diuretics were administered in 68% of patients. Average dosage of potassium supplementation was equivalent to 4.30 mEq/day/kg (body weight). At the last follow-up of 8 years after the initial diagnosis, 41% had short stature (height less than 3rd percentile) and CKD was observed in six patients (CKD stage 3 in four and stage 5 in two patients).

Conclusions: In conclusion, BS patients need huge amount of potassium supplementation along with potassium sparing agent throughout their lives. Despite of management, growth impairment was observed in significant portion of this population, while CKD was found in 11%.

PO2003

Walking in Patients' Shoes: Novel Approach to Increase Staff Empathy Through Adherence to Dietary Restrictions

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Background: Dietary recommendations for children with end-stage renal disease (ESRD) on dialysis include restrictions in potassium, phosphorus, and sodium. Children must take phosphate binders with meals and snacks. Renal diet compliance can be challenged by adherence difficulties. Patient perceptions of health care professionals' (HCPs) levels of empathy play an important role in improved patient satisfaction. Higher perceived empathy levels lead to improved patient compliance to treatment, diet, and overall positive health. The purpose of this study was to explore the impact of a novel intervention (adherence to a two-week renal diet) on levels of empathy among HCPs directly caring for children with ESRD on dialysis.

Methods: A quasi-experimental comparative interventional study design was utilized with a convenience sample of 37 HCPs who directly cared for children with ESRD on dialysis Through self-assignment, 14 HCPs completed a renal diet education class (control group); 23 completed the class and two-week renal diet and "phosphate binders" intake with logs (experimental group). Pre- and post-intervention levels of empathy were measured using the Jefferson Scale of Empathy. Renal diet logs were reviewed to calculate percentages of two-week compliance and "phosphate binder" use.

Results: Baseline empathy scores for each group were matched (p=0.825). Within the experimental group, post-intervention results showed statistically significant increases in empathy levels after adherence to a two-week renal diet (p=0.004). No significant differences in control group pre- and post-empathy levels were noted. Percentages of compliance to a two-week renal diet were 82% and to "phosphate binders," 83%.

Conclusions: Levels of empathy increased when HCPs followed a two-week renal diet, discovering similar patient adherence issues. HCPs reported less-than-perfect renal diet compliance and use of "phosphate binders." This study can be implemented in various pediatric settings, such as specialty areas treating patients on therapeutic dietary restrictions (e.g. diabetes, celiac disease, epilepsy).

Results from experimental group

Renal Diet Log Items	Renal Diet Class + 2- Week Renal Diet Trial (n=23)
Percentage of Compliance to Renal Diet	Mean(SD): 81.6 (11.39)% Median: 80.5% Range: 64-100%
Percentage of Compliance with Phosphate Binders	Mean(SD):82.75 (15.63)% Median: 86.5% Range: 37-100%
Percentage of Diet Log Record Keeping (out of 14 days)	Mean(SD): 93.25 (20.93)% Median: 100% Range: 7-100%

PO2004

Outcome of a 30-Month Screening, Education, and Treatment Program of Lower Urinary Tract (Dys)Function in Pediatric Kidney Recipients

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Background: Graft survival of pediatric kidney recipients increased dramatically over the past decades. Lower urinary tract disfunction (LUTD), as one of the factors that might contribute to graft function and survival, is seen in the majority of all recipients despite cause of kidney failure. This study presents the 30 months outcomes of a screening and early intervention program of all pediatric kidney recipients.

Methods: Since June 2018 all pediatric renal recipients underwent an active screening and education for LUTD pre-and post-transplant by our nurse specialist. Personalized education was given to all and urotherapy in case of LUTD. Those without LUTD, received yearly re-evaluation.

Results: A total of 56 recipients are screened thus far, aged 11.8±4.4yrs. Mean±SD time after transplant was 4.4±3.9yrs. After initial screening, LUTD was present in 71% of the patients (Table 1). Maximal bladder capacity exceeded in 59%, abnormal uroflowmetry was present in 58%, and residual voiding was present in 37% of the children. Longitudinal data showed that 16% remained dysfunctional despite urotherapy. In addition, 60% switched between a functional and dysfunctional pattern. Overall, after 30 months, 48% of the children with LUTD developed a persistent functional voiding pattern. Recipients with LUTD significantly needed more health care activities (2-6 times more compared to patients without LUTD). By consequence economic burden rises with €6000,- per patient each year.

Conclusions: LUTD is present in the majority of pediatric kidney recipients, regardless of the cause of kidney failure. Due to LUTD, patients need more health care. Resulting in a significant economic and psycho-social burden. This pro-active screening, treatment and education uro-transplant program was effective in 48% of the children with LUTD in the long term. A longer follow-up time is needed in order to analyze the impact on graft survival and cost-effectiveness.

Funding: Government Support - Non-U.S.

CAUSE OF KIDNEY FAILURE	NEPHROLOGICAL (N = 41)	UROLOGICAL (N = 15)	TOTAL (N = 56)	P-VALUE
Any type of voiding complaint	12%	33%	18%	0.08
Urinary incontinence—daytime	10%	20%	13%	0.31
Urinary incontinence—night-time	32%	20%	29%	0.27
Abnormal sensation of bladder filling	22%	40%	27%	0.18
Toilet behaviour (present > 50%)				
Holding manoeuvres	7%	6%	7%	0.93
Procrastination	46%	40%	45%	0.67
Sensation of incomplete emptying	2%	-	2%	0.54
Sent for voiding	34%	47%	38%	0.39
Rushed voiding	51%	60%	54%	0.56
Straining	7%	-	5%	0.28
LUTD	61%	100%	71%	0.005

Radboudumc

PO2005

Machine Learning Can Predict the Individual Risk of Acute Pyelonephritis in Children

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Background: Acute pyelonephritis (AP) is a common infection in children. Timely diagnosis of pediatric AP is necessary, since under-diagnosed AP increase infectious morbidity, whereas over-treatment of AP is responsible for an increase in antibiotic resistance and health costs. However, confirmed AP diagnosis requires validated urine cultures, which can take up to 3 days. Here we propose to use machine learning algorithms to predict the risk of AP in febrile children, using simple parameters available within the first hours of medical care.

Methods: We performed a retrospective study of medical and laboratory files of 102 pediatric patients with a suspected diagnosis of AP, treated between 2014 and 2020 at the pediatric National Reference Hospital of Luxembourg. Based on the results of urine cultures, patients were allocated to the AP or non-AP group. All patients were then randomly split into training and testing batches, used by a Random Forest machine learning algorithm to predict the individual risk of AP, using clinical (age, sex), blood (CRP, white blood cell and neutrophil counts) and urine (red and white blood cell counts) parameters.

Results: Patients' demographic and clinical characteristics were comparable between groups. In particular, sex ratios were not significantly different between AP and non-AP patients (0.86 versus 0.74). Random Forest algorithm mean performance metrics were: accuracy 90.48% [85-99%], sensitivity 91.67% [90-95%], specificity 88.89% [80-90%]. Given a prevalence of AP of 60%, positive predictive value was 92.52% [88-95%], negative predictive value 87.67% [82-89%]; mean AUC-ROC was 0.92. Predictions performed with a neural network or a support vector machine algorithm on the same population obtained comparable performance metrics.

Conclusions: Timely diagnosis of pediatric AP is necessary to minimize infectious morbidity, antibiotic resistance and health costs; however, it requires validated urine cultures, which can take several days. Here we showed that machine learning algorithms can accurately predict the individual risk of AP in pediatric patients within the first hours of medical care, helping pediatricians in daily clinical decision making.

PO2006

Associations Between Clean Intermittent Catheterization, Quality of Life, and Emotional-Behavioral Functioning in Children with CKD

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Background: Need for clean intermittent catheterization (CIC) can affect quality of life (QOL) and emotional functioning in pediatric populations, with some evidence that urethral catheterization is associated with poorer emotional adaptation than use of Mitrofanoff. Little is known about the impact of CIC on QOL and emotional functioning for children with chronic kidney disease (CKD).

Methods: Data from the CKiD study were used to evaluate QOL, emotions/behavior, and CIC in children age 6+ years with mild to moderate CKD (non-glomerular disease). We hypothesized that CIC would be associated with poorer QOL and more internalizing and behavioral symptoms (using ratings from BASC2, PedsQL), and that urethral CIC (versus Mitrofanoff) would predict worse outcomes. Linear mixed models adjusted for sociodemographic and disease-related covariates were used and included predictors for CIC use (vs non-users) as well as for urethral catheterization (vs Mitrofanoff).

Results: The sample included 1484 records (466 CIC non-users, median age 10 years, 66% male, median eGFR 52 ml/min|1.73m^2; 115 CIC users, median age 12 years, 67% male, median eGFR 45, 43% urethral, 48% Mitrofanoff). Median BASC2 scores

were in the average range for both CIC users and non-users. Median PedsQL scores were slightly lower than that of healthy populations for CIC non-users (parent-report 80 [IQR=66,89]; child-report 79 [IQR=70,88]) and even lower for CIC users (parent-report 73 [IQR=59,85]; child-report 76 [IQR=65,85]. CIC predicted higher scores on the BASC2 Internalizing Composite (β=3.33, CI=1.13, 5.54; p=.003), and Behavioral Symptoms Index (β=2.13, CI=0.08, 4.18; p=.04), and lower parent- and child-reported QOL (β=-5.11, CI=-8.46, -1.75; p=.003; β=-3.75, CI=-6.98, -0.52; p=.02). However, urethral CIC predicted lower scores compared to Mitrofanoff on the Internalizing Composite (β=-3.94, CI=-6.65, -1.22; p=.005).

Conclusions: For children with mild to moderate CKD, CIC is associated with poorer QOL and more parent-reported emotional-behavioral symptoms. Urethral CIC (versus Mitrofanoff) is associated with fewer internalizing symptoms. Additional research is needed to determine if other characteristics associated with need for CIC influence emotions and QOL.

Funding: NIDDK Support, Other NIH Support - National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI)

PO2007

Pneumococcal Vaccination in High-Risk Pediatric Nephrology Patients

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Background: Children with nephrotic syndrome (NS), chronic kidney disease (CKD) and immunosuppression (IS) are at high risk of invasive pneumococcal infection but are often under-vaccinated with PCV13 and PPSV23. We aimed to increase vaccination rates in high-risk pediatric nephrology (PN) patients from <10% to 75% by 2022.

Methods: Process measures of vaccine rates (percent of eligible patients monthly that received vaccines) were evaluated over 3 years. Initially, a designated nurse and fellow checked electronic medical records (EMR), Citywide Immunization Registry (CIR) and pediatrician records. PPSV23 was administered in PN clinic. A driver diagram was created to determine sources of improvement and 3 PDSA cycles were completed.

Results: 374 patients (20% up-to-date (UTD), 5% missing PCV13, 32% missing PPSV23, 34% missing both) were identified. Sources of failure to vaccinate with initial interventions were single stakeholder reliance, lack of follow-up and vaccine supply. Primary drivers were patient identification, vaccine administration and rate determination. All physicians and nurses were taught to identify patients, check vaccine history and use a vaccine algorithm. Study of our interventions revealed unanticipated obstacles with monetary cost, vaccine refusal and shared responsibility. To aid monetary issues a new stakeholder (manager) was created. Vaccines were re-offered at subsequent visits if initially refused. Reminders were sent to physicians on the importance of patient identification in clinic. Vaccination increased to >75% and has been sustained for 4 months (Figure 1). Percent UTD increased to 39%.

Conclusions: Incorporating and educating multiple stakeholders and adequate vaccine access improved vaccination rates at our center. Our methods appear successful without excess time expenditure. Further study is underway to ensure sustainability without excess monetary cost.

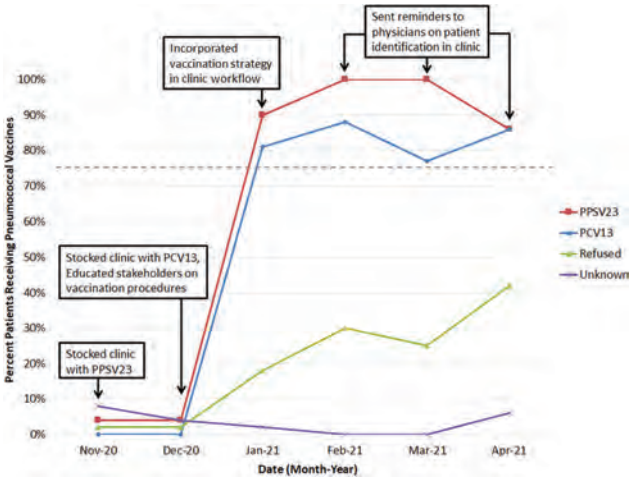

Figure 1: Run chart

PO2008

Psychosis in Adolescence and Young Adulthood with a Kidney Disease Diagnosis in Childhood

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Background: Advances in medical technology & management continue to improve the lifespan of children with kidney disease; yet, enhanced understanding of this population shows a relative lag. Prior studies examining pediatric kidney disease have repeatedly found neurocognitive deficits in areas of attention, memory, complex cognition, emotion identification and inhibitory control. Such deficits, when considered alongside nervous system injuries resulting from toxin retention and electrolyte aberrations, warrant further investigation. This study seeks to explore for any association among experiences of acute psychosis in adolescence and young adulthood (AYA) and defined history of childhood kidney disease.

Methods: To explore this, a retrospective cohort study using electronic medical records (EMR) was conducted. EMR queries were run to identify & categorize study samples into two groups: ICD-coding defined kidney disease vs healthy peer control. Patient data ranging from July 01, 2012, to February 13, 2021, was then queried for episodes of psychosis in both arms.

Results: Results identified 1192 patients as qualifying for study inclusion. Twenty-one (Prevalence= 1.76%; OR= 0.018) patients qualified for inclusion in the kidney disease group. 1171 (Prevalence= 98.24%; OR= 55.76) patients qualified for inclusion in the control group. Data analysis uncovered ten of 1192 (Prevalence= 0.84%; OR= 0.008) cases experienced acute psychosis throughout AYA. One of these ten cases occurred in CKD sample, representing a 4.76% prevalence (OR= 0.05). The remaining nine cases of AYA psychosis occurred in the control sample, representing a prevalence of 0.77% (OR= 0.008).

Conclusions: Preliminary data demonstrate, those with kidney disease had an increased likelihood of 6.46 (CI= 0.78-54.05) times that seen in control sample for development of acute psychosis in AYA. While unable to rule out the observed effect being due to random chance, acknowledgement of the attributions made by restricted data quantities are held. This pilot study, highlights a novel association deserving of further investigation in a large-scale, multicenter format. Establishing a significant association among childhood kidney disease and psychosis in AYA, would therefore prompt initiation of early education efforts aimed to persuade patient self-awareness, and ignite help-seeking mindsets prior to symptom onset.

PO2009

Pediatric Nephrologists' Perspectives on Palliative Care: A National Survey Study

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Background: Integration of palliative care (PC) within nephrology practice offers the chance to lessen the burdens experienced by children with chronic kidney disease (CKD) and their families. Yet, little is known about pediatric nephrologists' attitudes regarding engaging in and seeking PC services for children with CKD. We sought to ascertain pediatric nephrologists' perspectives in routine integration of PC for children with CKD.

Methods: A cross-sectional web-based survey was administered to pediatric nephrologists associated with the American Society of Pediatric Nephrology listserv. Three invitations were sent from May 3, 2021 to May 28, 2021. The survey was adapted from a previously validated instrument and pretested by stakeholders; studied areas included institutional and personal experience with PC, training and education, and physician confidence. Data were summarized descriptively.

Results: There were 64 participants (17.7% response rate). Most participants were female (62.5%), Caucasian (64.1%), and practice in urban (76.4%), academic centers (89.1%) with access to subspecialty PC teams (93.8%). Perceived institutional barriers to subspecialty PC consultations were low, and prior consultations were found to be helpful. However, nephrologists expressed concern that consultation may imply to parents that the team is "giving up" on their child. Though 63.6% indicated that consultation should happen at diagnosis for life threatening conditions where cure is feasible but may fail, 59.6% of nephrologists reported that PC is rarely or never consulted for ESKD patients at their center. Confidence in engaging in challenging communication was high, yet only 26.4% and 30.2% of participants, respectively, were comfortable managing pain or psychological distress of children with CKD.

Conclusions: Pediatric nephrologists are receptive to PC consultations for children with CKD, but utilization is low. Parental perception of the implications of consultation are of concern. Among primary PC skills, challenging communication is seen as a strength of pediatric nephrologists, but confidence is low in managing some physical and psychological symptoms. Routine integration of PC will require efforts to assess patient and family impressions of PC and shift that of providers, as well as targeted education to increase skills.

Funding: Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (5T32DK007662-30, PI Hingorani).

PO2010

Palliative Care Training in Pediatric Nephrology Fellowship: A Cross-Sectional Survey

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Background: The integration of primary palliative care (PC) in pediatric nephrology provides an opportunity to address the burdens faced by children with chronic kidney disease (CKD) and their families. Incorporation of PC education in training programs is recommended, but adult nephrology fellows report inadequate preparation to engage in primary PC. Similar experience of pediatric nephrology fellows is unknown. We sought to describe pediatric nephrology fellows' knowledge and confidence in providing primary PC and PC education received during training.

Methods: A cross-sectional web-based survey was administered to pediatric nephrology fellows associated with the American Society of Pediatric Nephrology listserv. Three invitations were sent from May 3, 2021 to May 28, 2021. The survey was adapted from a previously validated instrument and pretested by stakeholders; studied areas related to PC included institutional and personal experience, training and education, and physician confidence. Data were summarized descriptively.

Results: Response rate was 28.7% (29/101). Most respondents were female (79.3%), Caucasian (48.3%), and practiced in an urban setting (85.2%). Only 1 fellow participated in a PC rotation during fellowship, and 46.4% of respondents completed a rotation in medical school or residency. On a scale of 1-5, with 1 being 'no knowledge' and 5 being 'extensive knowledge' of PC principles, fellows reported a mean knowledge of 2.33 ± 1.04. A single fellow had performed over 10 family meetings to elicit goals of care compared to 64.3% of fellows who had performed over 10 kidney biopsies. A quarter of fellows had never led such a meeting. Confidence in ability to discuss goals of care or address psychological distress in a child with CKD or parent were low, with only 30.8% and 26.9%, respectively, feeling moderately or very confident in their ability. Many fellows (44%) felt low confidence in managing pain in a child with CKD. A desire for additional training was prevalent, with 96.2% of fellows indicating that this training should happen during fellowship.

Conclusions: Few pediatric nephrology fellows receive PC education and experiences during training, resulting in low rates of knowledge and confidence across care domains. Fellows indicate a need and desire for improved PC training.

Funding: Other NIH Support - Dr. House is supported by a National Institutes of Health training grant (5T32DK007662-30, PI Hingorani).

PO2011

Correlation Between Kidney Sodium and Potassium Handling and the Renin-Angiotensin-Aldosterone System in Children with Hypertension

Ella C. Perrin, Andrew M. South. *Wake Forest University School of Medicine, Winston-Salem, NC.*

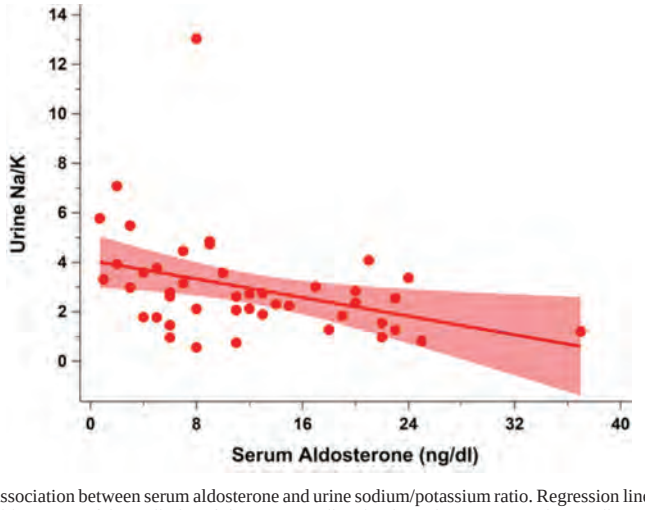
Background: Urine sodium and potassium concentrations are used as surrogate markers for dietary sodium and potassium consumption in adults with hypertension, but their association with components of the renin-angiotensin-aldosterone system (RAAS) is incompletely characterized. Some individuals with hypertension may have an abnormal RAAS response to dietary sodium and potassium intake, though this is incompletely described. Our objective was to investigate if plasma renin activity and serum aldosterone are associated with urine sodium and potassium in youth with hypertensive disorders.

Methods: This pilot study was a cross-sectional analysis of baseline data from 44 youth being evaluated for hypertensive disorders in a Hypertension Clinic. We recorded urine sodium and potassium normalized to urine creatinine, plasma renin activity, and serum aldosterone values and calculated the sodium/potassium (UNaK) and aldosterone/renin ratios. We used multivariable generalized linear models to estimate the associations of renin and aldosterone with urine sodium and potassium.

Results: Our cohort was diverse (37% non-Hispanic Black, 14% Hispanic), 66% were male, and median age was 15.3 years; 9% had a secondary etiology and 77% had obesity. Aldosterone was associated inversely with urine sodium/creatinine (β: -0.34, 95% CI -0.62 to -0.06) and UNaK (β: -0.09, 95% CI -0.16 to -0.03), adjusted for estimated glomerular filtration rate and serum potassium.

Conclusions: Higher serum aldosterone levels, but not plasma renin activity, were associated with lower urine sodium and UNaK at baseline in youth referred for hypertensive disorders. Further characterization of the RAAS could help define hypertension phenotypes and guide treatment.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute; National Center for Advancing Translational Sciences



Association between serum aldosterone and urine sodium/potassium ratio. Regression line with 95% confidence limits of the mean predicted values shown; $p<0.05$ by unadjusted and adjusted generalized linear regression.

PO2012

Aldosterone Producing Adenoma in an Adolescent Black Female

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Introduction: Aldosterone-producing adenoma (APA) is a rare clinical entity in the pediatric population resulting in severe hypertension and/or hypokalemia. Limited number of cases have been reported with somatic KCNJ5 mutation being described in only one case. We have shown that in APAs somatic CACNA1D mutations are more prevalent in the male black patients unlike KCNJ5 which is considered the most frequently mutated gene in black females.

Case Description: A 16-year-old black female was noted to be hypertensive while being evaluated for depression. She was referred to us a year later for recurrent headaches, chronic drug resistant hypertension and persistent hypokalemia. Family history was positive for a maternal uncle with hypertension. On examination, her wt was 98 kg [>99%], ht 178 cms [94%], heart rate 88 per minute and blood pressure 155/94 mmHg [>95%]. Pertinent labs: serum sodium 142, potassium 2.8, chloride 106, and CO2 content 26 mEq/L. Serum creatinine was 0.80, and BUN 10 mg/dL. Plasma aldosterone concentration (PAC) was 27.2 ng/dL and plasma renin activity (PRA) <0.6 ng/mL/h with PAC/PRA ratio of 45 [significant > 20]. Cortisol level was 8.7 [N 1.7-14.1] µg/dl. Timed urine aldosterone for estimated urine creatinine of 1980 mg was 20 µg/d [N <15.6]. Cardiac echocardiogram showed compaction cardiomyopathy. CT abdomen indicated a right adrenal nodule suggesting an adenoma. Robotic right adrenalectomy was performed and pathology was consistent with APA. Blood and right adrenal tissue was sent for germline and somatic mutations. Post-operatively PAC was <3.0 ng/dL. Her headaches resolved, her blood pressure significantly improved to 124/69 mmHg [<90%] with normalization of her serum potassium. One month after right adrenalectomy her blood pressure continues to be well controlled on two antihypertensive medications and her serum potassium levels remain normal.

Discussion: Unilateral APA should be considered in any child who presents with drug resistant hypertension and/or hypokalemia as early diagnosis and prompt adrenalectomy would prevent significant cardiovascular sequelae. The identification of somatic and germline mutations will provide further insight into the mechanisms of APA and assist in tailoring appropriate therapy especially in blacks who have high cardiovascular disease morbidity and mortality.

PO2013

Rare Case of Atypical Hemolytic Uremic Syndrome in a Child

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is rare with an incidence of 0.26-0.75 cases/million/year for individuals less than 20 years of age. Little is known about the time course of the disease and its clinical episodes. Individuals typically harbor genetic mutations and/or complement autoantibodies.

Case Description: A 7 year-old male presented with 2 weeks history of fatigue, pallor, and emesis. laboratory findings were consistent with HUS; serum creatinine 1.35 mg/dL, hemoglobin 7.5 g/dL, and platelets 86 thou/mcL. Schistocytes were identified on peripheral smear. Stool culture was negative for O157 STEC. Stool PCR was positive for Shigella/Enteroinvasive E. coli. STEC-HUS was diagnosed. Patient was hemodialysis dependent. Given severity of his course and persistent evidence of hemolysis and thrombocytopenia at 5 weeks, Eculizumab was initiated with improvement of hematological parameters. laboratory workup was done at the same time and came back positive for homozygous deletion of CFHR3-CFHR1 and complement factor H (CFH) autoantibodies (2140 AU). Eculizumab was continued for 8 doses with additional 2 doses of Rituximab followed by Mycophenolate Mofetil (MMF) before transition to Ravulizumab which was discontinued after 7 doses. He remained on MMF with no evidence of relapse. He has continued to be off dialysis 11 months after cessation of Ravulizumab at CKD stage III.

Discussion: To our Knowledge, this is the first published pediatric case with CFH-autoantibodies that achieved partial kidney recovery after prolonged dialysis dependent course. aHUS should be considered in children with severe and prolonged course of HUS even if laboratory results are suggestive of STEC-HUS. Aggressive therapy should be considered even if patients are dialysis dependent as this may reverse the course of the disease. There is limited published data on the course and effect of complement blockade therapy (Eculizumab or Ravulizumab) and immunosuppression (Rituximab and MMF) on the course of aHUS due to CFH-autoantibodies. There are variable reports on the efficacy of other therapies, like plasmapheresis, on the course of this specific aHUS entity. Our case highlights the importance of considering these therapies in this population even after prolonged dialysis as this may alter the course of the disease and help kidney recovery.

PO2014

Prenatal Nephrology Consultations and Neonatal Dialysis Survey

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Background: Little is known about pediatric nephrology (PN) prenatal consultations for congenital anomalies of the kidney & urinary tract (CAKUT) or possible initiation of kidney replacement therapy (KRT) in neonatal end stage kidney disease (N-ESKD).

The aims were to evaluate PN practice patterns for prenatal counseling of fetal CAKUT & to describe criteria used by PN to offer KRT in N-ESKD.

Methods: A 35 question Qualtrics® survey was distributed via the North American Pediatric Renal Trials and Collaborative Studies email list between 1/1/2021-3/31/2021.

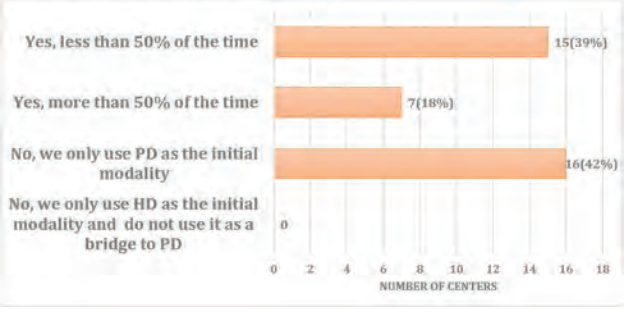
Results: 39 of 108(36%) participating pediatric sites in the US & Canada responded. Median number of faculty (MDs, APPs, APRNS) per center was 7. Median chronic hemodialysis (HD) and peritoneal dialysis (PD) patients per center were 8 & 8, respectively. 38(97%) centers provide prenatal consultation for fetal CAKUT and KRT for N-ESKD. Of those 38 centers, 71% report only a select number of non-trainee workforce members (median 2 per center) participate in prenatal consults. 47% of centers have either written/unwritten criteria for offering KRT in N-ESKD. The most common contraindications to KRT was parental refusal(61%;Table 1). The most common birth weight contraindication was <1500g(52%). 82% of centers reported <5 neonates with ESKD were started on KRT within the past year. 58% of centers use HD therapies as a bridge to PD in N-ESKD(Figure 1); 100% of centers report PD as the primary modality at discharge.

Conclusions: Many PN programs provide prenatal consultations for CAKUT diagnoses by a select group of non-trainee workforce members. Only 50% of centers use written/unwritten criteria for decisions about KRT initiation in N-ESKD. Further multi-center research regarding prenatal consultations and neonatal KRT outcomes is necessary to provide greater evidence based practice.

Table 1: Reported contraindications to dialysis initiation in neonates with ESKD amongst surveyed PN centers (n=38 centers)

Contraindications reported in > 50% of surveyed centers	Contraindications reported in 10-50% of surveyed centers	Contraindications reported in < 10% of surveyed centers
-Parent/Guardian choosing not to pursue dialysis (n=23; 61%) -Born below a minimum birth weight (n=21; 55%) -Surgeon indicates contraindication for dialysis access placement (n=21; 55%)	-Severe pulmonary disorder/respiratory disease (n=15; 39%) -Severe/life threatening genetic abnormality (n=13; 34%) -Severe neurologic impairment (n=7; 18%) -Refractory hypotension (n=7; 18%) -Severe/life threatening cardiac abnormality (n=7; 18%)	-Severe/life threatening liver abnormality (n=3; 8%) -Other severe/life threatening abnormality not already listed (n=3; 8%) -Other contraindication (n=3; 8%) -Below a minimum gestational age (n=2; 5%) -Disagreement between Nephrology and other services regarding the decision to initiate dialysis (n=1; 3%)

Figure 1: Reported use of hemodialysis/CKRT/PIRRT/modified Aquapheresis as a bridge to PD initiation in the neonate with ESKD (n=38 centers)



PO2015

Postnatal Maturation of Glomerular Filtration Rate in Term Born Neonates: An Individual Patient Data Meta-Analysis

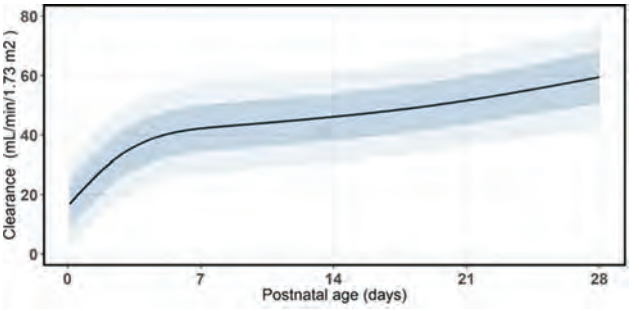
Nori Smeets,[1,2] Joanna IntHout,[1] Maurice J. van der Burgh,[1] George J. Schwartz,[3] Michiel F. Schreuder,[1] Saskia de Wildt.[1,2] *[1]Radboud University Medical Center, Nijmegen, Netherlands; [2]Erasmus MC, Rotterdam, Netherlands; [3]University of Rochester, Rochester, NY.*

Background: The evidence from individual studies to support the maturational pattern of measured glomerular filtration rate (GFR) in healthy term born neonates is inconclusive. This hampers the delineation between normal and abnormal kidney development as well as the diagnosis of acute kidney injury (AKI). Thus, we aimed to describe GFR maturation in the first month of life using an individual patient data meta-analysis (IPDMA) of measured GFR data.

Methods: The Pubmed and ClinicalTrials.gov databases were searched to identify studies reporting mGFR as measured by exogenous markers or creatinine clearance (CrCL) in healthy term born neonates. Articles were subsequently reviewed by two individual researchers. The relationship between postnatal age and individual clearance values was investigated using restricted cubic splines with generalized additive linear mixed models on individual data, taking into account clustering by study. Data from aggregated studies were used for sensitivity analyses.

Results: 1521 articles were screened and 50 relevant studies reported mGFR in healthy term born neonates. In total, 1055 measured GFR values from 958 neonates were included. Individual patient data (IPD) were available for 371 neonates and 587 neonates were represented by 46 aggregated datapoints as means/medians per cohort. Mean GFR increases rapidly in the first five days after birth from 16.8 (95% CI 11.2-22.5) ml/min/1.73m^2 at the first day to 39.8 at day 5 (95% CI 35.8-43.7), followed by a more gradual increase to 59.4 (95% CI 45.9-72.9) ml/min/1.73m^2 at end of the fourth week.

Conclusions: These normative values show a clear developmental pattern of GFR maturation in the first weeks of life and indicate a biphasic increase with the largest increase until day 5. Our IPDMA data can therefore serve as a useful baseline for neonatal GFR.



The development of GFR in the first month of life in term born neonates. Black line represents p50, darker blue area indicates p25-p75, lighter blue area indicates p10-p90.

PO2016

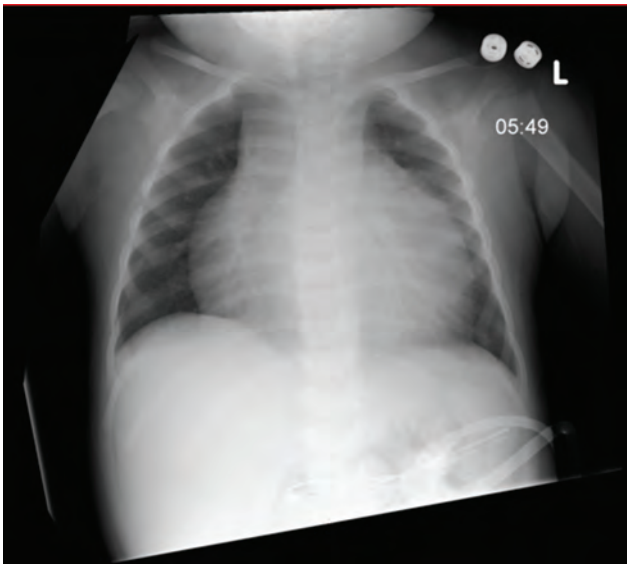
Impending Uremic Cardiac Tamponade in an Infant with ESKD

Cassandra A. Petri, Yalile Perez, Carl H. Cramer, Timothy M. Olson, Nathan Hull, Christian Hanna. *Mayo Clinic Minnesota, Rochester, MN.*

Introduction: Uremic pericarditis (UP) occurs in patients with advanced chronic kidney disease (CKD) prior to dialysis initiation. The incidence of UP is rare due to advances in CKD management by providing adequate and early dialysis. Additionally, it is extremely rare in children. We present a case of a toddler with advanced CKD presenting with UP and impending cardiac tamponade. Daily intensive hemodialysis resulted in a complete resolution of the pericardial effusion.

Case Description: A 2-year-old female presented with a 3-day history of dry cough and low-grade fever. Her medical history was significant for CKD stage 5 related to branchio-oto-renal dysplasia. Her physical examination was remarkable for increased respiratory rate and the presence of pericardial friction rub. A chest radiograph demonstrated enlargement of the cardiac silhouette **(Figure 1)**. An electrocardiogram (ECG) showed sinus rhythm without ST-segment changes and an echocardiogram demonstrated a large circumferential pericardial effusion. The following day, she developed low oxygen saturation and a repeat echocardiogram demonstrated features of early tamponade physiology. Pericardiocentesis was considered but not performed because the amount of apical fluid was deemed insufficient to safely perform the procedure. Daily intensive hemodialysis was initiated and resulted in a complete resolution of the pericardial effusion within a week.

Discussion: Our case of UP in a pediatric patient is exceptionally rare. The most common presentations of this condition are fever, chest pain, and pericardial friction rub. As seen in this case, a characteristic ECG in UP does not show the diffuse ST and T wave elevations often seen in other forms of pericarditis. UP is an absolute indication for dialysis which usually results in rapid resolution of the pericardial effusion.



PO2017

When Less Is More: Phosphate Homeostasis Insights from a Microvillus Inclusion Disease Patient

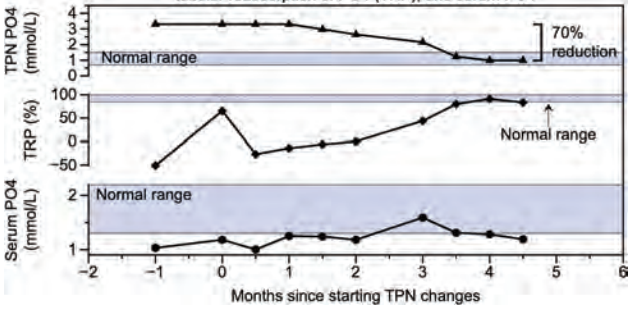
Cal Robinson,[1] Dianna Yanchis,[1,2] Elizabeth M. Garofalo,[1,2] Mathieu Lemaire.[1,2] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]SickKids Research Institute, Toronto, ON, Canada.*

Introduction: Microvillus inclusion disease (MVID) is a rare, severe congenital secretory diarrhea caused by recessive *MYO5B* or *STX3* mutations. Multiple cases of MVID with partial proximal tubule (PT) defects are reported (mostly hyperphosphaturia). While *MYO5B* is expressed in PT cells, MVID patients have normal PT brush border on kidney biopsy, and the PT defect resolves after intestinal transplant. Therefore, it is unlikely that the *MYO5B* genotype is causally related to the proximal tubulopathy.

Case Description: Like all patients diagnosed with *MYO5B*-MVID, our patient required cycled total parenteral nutrition (TPN). She was referred to nephrology at age 2 for persistent hypophosphatemia despite escalating TPN phosphate (PO4) content, and nephrocalcinosis. Urinary PO4 wasting was confirmed given the low (<65%) tubular reabsorption of phosphate (TRP). FGF-23 and PTH were elevated. A 24 hr balance study (on/off TPN) revealed that TRP was lowest and FeNa highest (~2%) while on TPN (these values were improved after 6h without TPN). It also confirmed that the negative PO4 balance was only due to renal losses. We hypothesized that high TPN electrolyte concentrations caused an obligate phosphaturic response. Gradual reductions of TPN sodium (Na^+) (by 13%), then TPN PO4 (by 70%) over 4 mo led to normalization of serum PO4 (Figure), TRP (83-91%) and FeNa (~0.3%).

Discussion: We propose that excessive TPN Na^+ and PO4 promoted a strong phosphaturic response: the combination of several physiologic factors likely explains this unusual phenomenon. Of interest, the intermittently negative TRP suggest that tubular phosphate secretion must have contributed to the massive phosphaturia. A counterintuitive reduction in TPN Na^+ and PO4 reduced renal PO4 wasting without impacting serum Na^+. We surmise that other MVID cases of PO4 wasting were also probably due to unusually high TPN electrolyte concentrations. Detailed balance studies are invaluable tools to assess complex fluid/electrolyte disorders.

Figure. Relationship between TPN PO4, tubular reabsorption of PO4 (TRP), and serum PO4



PO2018

Occurrence of Nephrogenic Systemic Fibrosis with Group II Gadolinium-Based Contrast Agent in a Pediatric Oncology Patient with AKI

Christian Hanna,[1] Amanda Scheuermann,[2] Amanda M. Hopp,[2] Kara Young,[2] John J. Dillon,[1] Scott K. Van Why.[2] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Nephrogenic Systemic Fibrosis (NSF) is a rare systemic disorder occurring in patients with chronic kidney disease (CKD) stage IV or V, end-stage renal disease (ESRD), or acute kidney injury (AKI). It is triggered by gadolinium-based contrast agents (GBCAs) and characterized by sclerodermic skin changes from fibrosis and internal organ damage. Almost all NSF cases are associated with group I GBCAs, and only extremely rare, unconfounded cases are reported with group II agent exposure including none in children. We present a case of a female child with acute myelogenous leukemia (AML) in remission and AKI on hemodialysis who presented with NSF six weeks following a magnetic resonance imaging (MRI) with group II GBCA.

Case Description: A 10-year-old female with intermediate risk AML in remission, complicated by prolonged neutropenia with colitis, invasive fungal sinus and pulmonary infection, and AKI with a renal biopsy-proven acute tubular necrosis on intermittent hemodialysis three times a week presented to the dermatology clinic for evaluation of progressive hardening of her skin. Dermatological examination revealed diffuse, indurated, and compressible plaques involving the lower back, buttocks, posterior thighs, and lateroposterior aspects of the arms. A skin biopsy showed findings consistent with NSF. Six weeks prior to her presentation, she underwent an MRI of the brain and orbits for exotropia evaluation and received intravenous gadobutrol injection, a group II GBCA. Treatment with photopheresis twice weekly over a 2-month period resulted in a gradual improvement of her condition.

Discussion: Our case of group II GBCAs induced NSF is exceptionally rare, with no unconfounded cases in pediatrics from group II GBCAs exposure reported to date. While NSF has been reported rarely in children who received group I GBCAs, the risk of NSF in children exposed to group II or even group III GBCAs is unknown. We strongly recommend that physicians continue kidney function screening prior to group II GBCAs administration in children and carefully evaluate the risk versus benefit of using or withholding group II GBCAs for clinically indicated MRIs in patients with CKD stage IV/V, ESRD, or AKI.

PO2019

Exploring Population Pharmacokinetic Models in Patients Treated with Vancomycin During Continuous Venovenous Hemodiafiltration (CVVHDF) on Different Anticoagulant Modalities

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Background: Achievement of target concentrations for antibiotics using therapeutic dose monitoring (TDM) is particularly challenging in septic patients requiring renal replacement therapy.

Methods: We conducted an exploratory population pharmacokinetic (PK) analysis in our tertiary level intensive care unit (ICU) on PK of vancomycin following intermittent infusion in critically ill patients receiving continuous venovenous haemodiafiltration (CVVHDF). Clinical, laboratory and dialysis data were extracted from the electronic healthcare record (EHR) using strict inclusion criteria. A population PK analysis was conducted with a one compartment model using the PMetrics population PK modelling package. A base structural model was developed and further analyses were performed with clinical and dialysis-related data, including regional citrate anti-coagulation (RCA) vs non-RCA, to improve model prediction through covariate inclusion. The final selected model simulated patient concentrations using probability of target attainment (PTA) plots to investigate the probability of different dosing regimens achieving target therapeutic concentrations.

Results: 107 vancomycin dosing intervals (155 levels) in 24 patients were examined. An acceptable base model was produced (Plots of observed vs. population predicted concentrations (Obs-Pred) R^2=0.78). No continuous covariates explored resulted in a clear improvement over the base model. Use of anti-coagulation modality and vasopressor use as categorical covariates resulted in similar PK parameter estimates, with a trend towards lower parameter estimate variability both with use of RCA and without vasopressor use. Simulations using PTA plots suggested that a 2 g vancomycin loading dose followed by 750 mg 12 hourly as a maintenance dose, commencing 12 hours after loading, is required to achieve adequate early target trough concentrations of at least 15 mg/L.

Conclusions: Using robust EHR data to construct a base model from a population known to have highly heterogenous antimicrobial PK, simulations based on PTA plots showed that we could achieve acceptable trough vancomycin concentrations early in treatment with a 2 g loading dose and a maintenance dose of 750 mg 12 hourly for ICU patients on CVVHDF.

PO2020

Evaluation of Gabapentinoid Dosing and Adverse Events in Patients with Advanced CKD

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Background: Gabapentinoids (GP, gabapentin and pregabalin) are frequently prescribed in individuals with chronic kidney disease (CKD); however, their exclusive renal elimination warrants dose adjustments to decrease the risk of toxicity. Data to describe prescribing patterns and incidence of adverse events in advanced CKD are limited. This study evaluated prescribing patterns for GPs and whether excessive dosing was associated with increased incidence of gabapentinoid-related adverse events (GRAEs).

Methods: A retrospective analysis of adult patients admitted to the Methodist LeBonheur Healthcare system from January 2014 – October 2020 with CKD stage 4, 5, or end-stage kidney disease (ESKD) receiving GPs prior to admission or during hospitalization for at least two days was conducted. Patients were grouped based on whether the average daily dose prescribed was higher than recommended [inappropriately dosed, (ID)] or as recommended [appropriately dosed (AD)] for CKD stage. The occurrence of GRAEs (altered mental status, respiratory depression, and falls) was compared between groups. Patient characteristics and CKD stage were evaluated to determine any association with GRAEs. Hospital length of stay (LOS) was also evaluated.

Results: The 200 patients included were predominantly female (51%), black (72%), CKD 5/ESKD (84%) with a mean age 61±14 years, and prescribed gabapentin (90%) with 111 (55%) in the AD group and 89 (45%) in the ID group. Baseline characteristics were similar between groups except type 2 diabetes and neuropathy were more common in the ID group. For the primary outcome, there was no statistically significant difference in GRAEs (18% *vs*. 19%, p=0.84). GRAEs were associated with older age (mean age 65±11 years for GRAE *vs.* 60±14 years for no GRAE; p<0.001) and seizure history (14% for GRAE *vs.* 3% for no GRAE, p=0.02), but not with CKD severity. LOS was significantly longer for patients who experienced a GRAE than for those who did not (8.5 vs. 5.3 days; p=0.04).

Conclusions: In patients with advanced CKD, appropriate dosing of gabapentinoids is important to minimize the risk of adverse events, particularly in patients of older age or with a history of seizures. There is a need for prescriber education given the high frequency of inappropriate gabapentinoid dosing in patients with advanced kidney disease.

PO2021

Chronic Dosing of Voclosporin at Clinically Relevant Exposure Levels Does Not Induce Renal Fibrosis Markers in Rats

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Background: Although prognosis of lupus nephritis (LN) has improved, the long-term outcome is still poor, with many patients progressing to end-stage renal disease. Calcineurin inhibitors (CNIs) like cyclosporine A (CsA) and tacrolimus have demonstrated benefit in LN; however, prolonged use is associated with renal fibrosis. CsA-induced fibrosis has largely been in the context of high doses required for immunosuppression in transplant patients. Voclosporin (VCS), a potent, novel CNI with a predictable PK/PD profile, is approved for treatment of LN. This study tested the hypothesis that the clinically effective dose of VCS used in LN patients, would not induce fibrosis markers in the chronic dosing rat model compared to CsA and vehicle controls.

Methods: Sprague Dawley rats (n=10/ group) on a low sodium (0.05%) diet were treated by oral gavage (QD) with VCS (4 mg/kg), cyclosporine A control (10 mg/kg) or vehicle control (5 mL/kg) for 3 or 6 weeks. Clinical chemistry was performed on serum and overnight urine. Gene expression (RT-qPCR) and histology were performed on kidneys. Data were analyzed as change from baseline.

Results: There were no significant differences in clinical measures of renal or liver function. There were no significant changes in urine protein/creatinine or fractional excretion. Serum total bilirubin and cholesterol were significantly increased in the CsA treated group compared to vehicle and VCS. At 3 weeks, there was a significant decrease in expression of *Tgfb1* and the epithelial-mesenchymal transition (EMT) marker *Cdh2* (N-cadherin) in VCS treated animals compared to vehicle and CsA, and significant decreases in expression of the EMT regulators, *Snai1* (SNAIL) and *Snai2* (SLUG), and the extracellular matrix components (ECM) *Col1a1*, *Col3a1* and *Vim* in the VCS treated group. At 6 weeks, trends between groups remained, and there were significant decreases in *Tgfb2* and *Col3a1* in the VCS treated group. At 6 weeks, there were no differences in renal histopathology.

Conclusions: This study shows that the clinically relevant dose of voclosporin does not induce renal fibrosis markers in rats, in contrast to the CsA control. Additionally, voclosporin may protect against renal EMT and ECM deposition, which are associated with CsA. Collection of data from a two-year continuation renal biopsy sub-study of AURORA-1 is ongoing.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

PO2022

The Effect on Renal Function of Patients on HIV Pre-Exposure Prophylaxis (PrEP)

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Background: Tenofovir, a nucleotide reverse transcriptase inhibitor, is used in management of hepatitis B and as part of a highly active antiretroviral medication regiments for HIV infected individuals. Tenofovir disoproxil fumarate (TDF) is one of two tenofovir nucleotide analog. The U.S. Food and Drug Administration (FDA) recommended on 16 July 2012 the use of tenofovir-emtricitabine combination medication as pre-exposure prophylaxis (PrEP) against HIV. TDF is cleared through glomerular filtration and tubular secretion. Its nephrotoxicity includes renal tubular acidosis type 2, acute tubular necrosis, and tubulointerstitial disease. Reported data regarding effect of renal function from tenofovir based PrEP are less than 24 months of follow-up. This study evaluates the effect on renal function in patients receiving TDF for PrEP over more than 24 months because it can affect the future of PrEP with more expensive analog of tenofovir (TAF) promoted as less nephrotoxic and other PrEP medications.

Methods: VA San Diego database on adults receiving PrEP is the source for this data. Serum creatinine and estimated glomerular filtration rate (eGFR) are obtained as part of PrEP protocol which started in 2014. The PrEP protocol follows the Centers for Disease Control and Prevention (CDC) recommendations of pre-initiation serum creatinine and eGFR then 3 months after the initiation and annually thereafter. Acute kidney injury is define as an increase in serum creatinine by > 0.3mg/DL within 48 hours or increase in serum creatinine to > 1.5 times baseline based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines which is the most recent preferred definition and used more consistently in clinical studies (1,2).

Results: Since 2014, 103 individuals are in the PrEP program. At one year, there are 87 individuals and none meets the criteria for AKI. After 2 years, there are 73 patients and 2 meet the criteria of AKI. Their kidney function returned back to baseline creatinine one month later. 55 individuals completed 3 years on PrEP and none meets the criteria for AKI. 41 individuals completed 4 years of PrEP and none meets criteria for AKI. The average change of eGFR at one year is 7.1%, 7.5% at 2 years, 8.6% at 3 years and 8.1% at 4 years.

Conclusions: Serum creatinine is stable on PrEP and none meet KDIGO AKI definition. The decrease in eGFR is not significant to warrant a change of TDF based PrEP.

PO2023

Tenofovir Kidney Clearance Predicted by Glomerular and Tubular Secretory Functions

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Background: Proximal tubular secretion is the primary kidney mechanism for eliminating most prescribed medications. Yet, kidney drug dosing is based on estimates of the glomerular filtration rate (GFR). In an empiric pharmacokinetic study, we compared GFR and secreted endogenous solute clearances for predicting the kidney elimination of tenofovir disoproxil fumarate (TDF), a drug with complex kidney handling.

Methods: We recruited 27 adult patients across a wide range of kidney function. Exclusion criteria were use of tenofovir or a secretory antagonist (cimetidine, digoxin, probenecid), dialysis, nephrotic syndrome, or cirrhosis. We administered a single 125mg oral dose of TDF and estimated its kidney clearance from the area under the plasma time concentration curve and urine drug recovery. We measured GFR by iohexol clearance (iGFR) and estimated secretory function from a 10-hour urine collection with mass-spectroscopy measurements of endogenous secretory solutes. We used linear regression, leave one out cross-validation, root mean squared error, and mean percentage error to describe agreement between kidney functions and TDF clearance.

Results: Mean age of the study population was 55 ±15 years, 63% were male, and median iGFR was 78 ml/min/1.73m^2 (IQR 52, 99 ml/min/1.73m^2); ten participants (37%) had an iGFR <60 ml/min/1.73m^2. The mean percentage error (MPE) between observed and iGFR-predicted TDF kidney clearance was 26.7% (Table). The clearances of four endogenous secretory solutes improved the prediction of TDF clearance beyond that of iGFR: cinnamoylglycine, indoxyl sulfate, isovalerylglycine, and tiglylglycine. Combining solute clearance and iGFR results in a lower overall mean percentage error in TDF kidney clearance prediction.

Conclusions: Measurements of secretory solute clearance represent a potential future strategy for improving kidney drug dosing.

Funding: NIDDK Support

Table. Prediction of kidney tenofovir disoproxil fumarate clearance.

Predictor	Root mean squared error (ml/min)	Mean percentage error (%)	Mean percentage error (%) – combined with iGFR[c]
Estimated GFR[a]	68.0	34.5	
Iohexol GFR	60.2	26.7	
Secretory solute clearance[b]			
Cinnamoylglycine	51.9	22.8*	22.4
Indoxylsulfate	43.8	24.0*	22.5
Isovalerylglycine	44.9	32.0*	22.3
Kynurenic acid	76.6	45.0	24.5
P-cresol sulfate	69.8	35.4	23.4
Pyridoxic acid	38.6	22.1	19.6
Tiglylglycine	47.9	30.6*	21.5
Xanthosine	77.4	48.9	24.1

Lower root mean squared errors and mean percentage errors indicate better prediction.

[a] Estimated GFR calculated using the 2009 CKD-EPI equation.

[b] 10-hour timed urine clearance of secretory solutes.

[c] Multiple linear regression including secretory solute AND iGFR as predictors.

**Significantly improves iGFR prediction of kidney tenofovir clearance (p <0.01).*

PO2024

Subcutaneous VIS649, an APRIL-Neutralizing Antibody: Preliminary Pharmacokinetic (PK) and Pharmacodynamic (PD) Results of VIS649-102, a Phase 1, Single Ascending Dose Study in Healthy Volunteers

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Background: Immunoglobulin A (IgA) nephropathy (IgAN) is in part driven by A proliferation-inducing ligand (APRIL). VIS649, a humanized immunoglobulin G (IgG2) monoclonal antibody that blocks APRIL, is currently in Phase 2 clinical development as a potential treatment for IgAN. The preliminary results of VIS649-102, a Phase 1 single ascending dose study of subcutaneously (SC) administered VIS649 in healthy volunteers is reported here.

Methods: VIS649 (200 mg/ mL liquid) was administered as a single dose via the SC route to four cohorts of 12 healthy adult volunteers each. Doses were 200 mg (1x1 mL SC), 400 mg (2x1 mL SC injections), 400 mg (1x2 mL SC injection), and 600 mg (1x2 mL and 1x 1 mL SC injection).

Results: SC-administered VIS649 was well tolerated, with no adverse events that led to study discontinuation, and no injection site reactions. Treatment Emergent AEs (TEAEs) were all mild and all resolved. There was no clinically relevant effect of treatment on laboratory tests, vital signs, or physical examinations. Preliminary PK results show bioavailability of approximately 75% compared to intravenous (IV)-administered VIS649 (Y. Suzuki et al, ERA-EDTA 2021). Single SC doses of either 400 mg or 600 mg suppress total IgA by up to approximately 50-55% from baseline values at 8 weeks post-dose. Single doses of 200 mg SC suppressed IgA by approximately 40% by 6 weeks post-dose. Overall, these preliminary results with SC VIS649 indicate a similar degree and

trajectory of IgA suppression as that achieved by the IV formulation in healthy volunteers, in which the 6 mg/kg single IV dose suppressed IgA by approximately 50% from baseline values at 8 weeks post-dose (Figure 1).

Conclusions: Preliminary results of this Ph1 study of SC-administered VIS649 demonstrated acceptable safety, tolerability, amd bioavailability, and suppressed total IgA by approximately 50-55% from baseline, comparable to IV doses.

Funding: Commercial Support - Visterra Inc, Otsuka Pharmaceuticals Inc

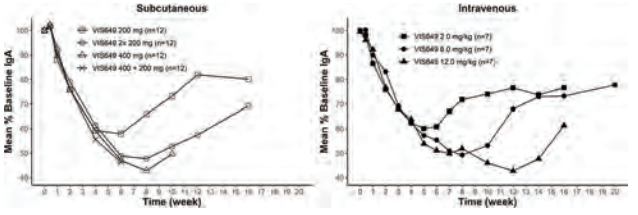

Figure 1. Total IgA Mean Percent Suppression From Baseline Following Single Dose VIS649 Administered Via SC or IV Route

PO2025

Association of Oxypurinol Exposure with Progression of CKD: Pre-Specified Substudy Results from the CKD-FIX Trial

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Background: The CKD-FIX trial evaluated the effect of allopurinol on eGFR slope over 104 weeks in patients with chronic kidney disease (CKD) and risk of progression. The aim of this pre-specified substudy was to assess whether exposure to oxypurinol, the active metabolite of allopurinol, predicts change in eGFR.

Methods: Adults with CKD stage 3 or 4 (n=369), no history of gout, and high risk of progression (urinary albumin-to-creatinine ratio ≥265 mg/g or eGFR decrease ≥3.0 mL/min/1.73 m^2 in the preceding year) were randomized to receive allopurinol (n=185) or placebo (n=184). Plasma oxypurinol concentrations were determined at weeks 16, 24, 40, 56, 72, 88 and 104 post-initiation of allopurinol. Non-compartmental pharmacokinetic analysis of oxypurinol concentrations was performed to determine oxypurinol exposure (area under the concentration time curve) using the SimBiology module of MATLAB. The association between eGFR slope and oxypurinol exposure was assessed using least-squares estimates linear regression.

Results: Overall 155 (84%) patients (mean eGFR 31.7 mL/min/1.73 m^2, mean serum urate 8.0 mg/dL) received allopurinol and had ≥1 plasma oxypurinol concentration available. At the end of the 12-week dose-escalation phase, the majority of patents (123; 79%) were prescribed allopurinol 300 mg and the remainder 100 mg (13; 8%) or 200 mg (19; 12%). The mean (standard deviation) eGFR slope and reduction in serum urate concentration were -3.32 (5.02) mL/min/1.73 m^2/year and 2.6 (0.14) mg/dL, respectively. Based on a total of 819 plasma oxypurinol concentrations (median n=6 per patient), there was no correlation between eGFR slope and total oxypurinol exposure (P=0.93), including after adjusting for allopurinol dose (P=0.99). These results were consistent across the three allopurinol dosing regimens. Greater oxypurinol exposure was associated with larger reduction in serum urate concentrations (P<0.0001).

Conclusions: In CKD-FIX participants, exposure to oxypurinol was not associated with change in eGFR. However, reduction in serum urate concentration was dependent on plasma oxypurinol exposure.

Funding: Private Foundation Support, Government Support - Non-U.S.

PO2026

Proof-of-Concept Study of Oxalate-Consuming Synthetic Biotic Medicine SYNB8802 in Enteric Hyperoxaluria after Roux-en-Y Surgery

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Background: High urinary oxalate levels (UOx) in patients with enteric hyperoxaluria (EH) can lead to recurrent kidney stones, nephrocalcinosis and chronic kidney disease. SYNB8802 is an engineered *E. coli* Nissle 1917 that contains an oxalate degradation pathway which converts oxalate to formate within the gastrointestinal (GI) tract, thereby reducing urinary oxalate. SYNB8802 is an oral, non-colonizing live biotherapeutic developed for the treatment of EH. SYNB8802 is explored in a Phase 1a/b study in healthy volunteers (HV) and Roux-en-Y (RYGB) patients with hyperoxaluria.

Methods: In Part A of the study [NCT04629170] hyperoxaluria was induced in adult HV by a high oxalate (400-600mg), low calcium (400mg) diet over 4 days. Subjects were then randomized (6 active:3 placebo) to receive 5 days of SYNB8802 or placebo TID. 24hr UOx levels were measured daily. Primary outcome was safety and tolerability. Part B is a double-blind, placebo-controlled crossover study of SYNB8802 in subjects with enteric hyperoxaluria and a history of RYGB. Up to 20 subjects will be randomized in a crossover design with a 2-week washout period to receive SYNB8802 (at 3e11 live cells/dose) or placebo, dosed up to TID with meals. Urine samples for determination of 24hr UOx levels will be collected over 3 days at baseline and on the last 3 days of each dosing period. Subjects will maintain their normal diet throughout the study. The primary endpoint is change from baseline in 24hr UOx amount excreted with SYNB8802 treatment versus placebo. Secondary endpoints include change from baseline in UOx:creatinine ratio with SYNB8802 treatment versus placebo.

Results: In Part A, a well-tolerated dose of 3e11 live cells was identified in HV. At this dose, the percent change from baseline UOx levels was -28.6% (90% CI: -42.4 to -11.6) compared to placebo in diet-induced hyperoxaluria. This dose is being studied in Roux-en-Y patients with hyperoxaluria in Part B. The results from the RYGB population will be reported.

Conclusions: These results provide proof of mechanism for UOx lowering by SYNB8802 through GI consumption of oxalate in diet-induced hyperoxaluria. Part B seeks proof-of-concept in patients with enteric hyperoxaluria.

Funding: Commercial Support - Synlogic Inc.

PO2027

Tacrolimus Induces Ligand-Independent TGF-β Receptor Signaling to Promote Renal Fibrosis

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Background: Although calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporin have dramatically improved the quality of patient care, long-term therapy causes **irreversible damage** to the kidneys in the form of renal fibrosis. These morphologic changes ultimately lead to a decline in renal function and can progress to end-stage renal failure. These detrimental outcomes present a critical need to identify the driving mechanisms by which CNIs cause renal damage. It is well established that TGFb is a major contributor to CNI-induced renal fibrosis. However, the underlying mechanisms remain unknown. The objectives of this study are to 1) investigate whether TGFb secretion is required to stimulate TGFb receptor signaling in a model of CNI-induced renal fibrosis and 2) investigate whether calcineurin plays a critical role in regulating TGFb receptor activity.

Methods: To examine the role of calcineurin inhibition in altered TGFb receptor signaling, wild type mice were treated with either vehicle (100% ethanol) or 10 mg/kg tacrolimus for 7 days. To confirm in vivo findings, wild-type mouse renal cortical fibroblasts were treated with either vehicle (100% ethanol) or 1nM tacrolimus for 24 hours in the presence and absence of anti-TGFb neutralizing antibodies. TGFb receptor expression and activation, TGFb receptor downstream signaling mediators, profibrotic markers and calcineurin activity were analyzed.

Results: Findings demonstrate that tacrolimus-induced loss of calcineurin activity is accompanied with enhanced TGFb receptor activation and signaling. Notably, increasing concentrations of anti-TGFb neutralizing antibodies failed to abolish aberrant TGFb signaling and increased expression of profibrotic markers.

Conclusions: Together, these results demonstrate that 1) CNIs promote ligand-independent TGFb signaling and 2) calcineurin plays a functional role in regulating TGFb receptor activity.

Funding: NIDDK Support, Other U.S. Government Support

PO2028

Immunoreactivity of CD3+CD4+ in Stable Young, Middle Aged, and Elderly Kidney Transplant Recipients Receiving Maintenance Tacrolimus and Mycophenolic Acid Immunosuppression

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Background: Tacrolimus and mycophenolic acid are the standard of care in most stable kidney transplant recipients (KTR) at U.S. transplant centers. However, there are limited data that determine within subject immunophenotypic responses over the adult age range. This study examined ex vivo immunoreactivity of CD3+CD4+ lymphocytes in stable young, middle age and elderly KTR receiving tacrolimus and mycophenolic acid.

Methods: Fifteen stable KTR greater than 1 yr post-transplant completed a 12-hour study with serial collections at pre-dose (trough-0 hr), 4, 8 and 12 hours. The immune response potential was evaluated by Interleukin-2 (IL-2) and Interferon gamma (IFN-γ) production by CD3+CD4+ T cells after ex-vivo treatment with PMA/Ionomycin with Brefeldin-A. Data was represented as within individual, timed collection and the mean for all time points of ex-vivo stimulation by cell sub-populations stratified by young, middle age and elderly. Comparisons were made using Kruskal-Wallis test.

Results: Table summarizes the major findings. There were no group differences between tacrolimus and mycophenolic acid troughs with all tacrolimus troughs within the therapeutic range. Increased IFN-γ from CD3+CD4+ T cells was quantitated by ex vivo immunoreactivity in middle age recipients at the 4 and 8 hours during the 12-hr study period. No significant differences were noted for interleukin-2 quantitated from CD3+CD4+.

Conclusions: These data indicate increased IFN-γ from CD3+CD4+ T cells for ex vivo immunoreactivity over a 12-hr dosing interval in middle age KTR receiving long-term maintenance immunosuppression. Variable immunodynamics and the implications of intra- and interpatient variability in immunoreactivity across the range of adult KTR require further investigation of clinical and allograft outcomes.

Funding: Other NIH Support - National Institute of Aging

	Young [21 to <45]	Middle Age [45 to<65]	Elderly [>65]	P Value
Age (years)	38.0(3.0)	56.4(3.4)	69.8(1.6)	0.002
Race [W=White; B=Black]	2W/1B	4W/3B	4W/1B	0.790
e-GFR (ml/min)	41.1 (12.5)	60.3 (14.5)	57.4 (14.3)	0.158
CD3+CD4+ IFN-γ+ at 0 hr [%gate]	1.15(0.14)	1.81(0.45)	1.40(0.63)	0.110
CD3+CD4+ IFN-γ+ at 4 hr [%gate]	0.74(0.36)	2.33(0.76)	1.24(0.35)	0.013
CD3+CD4+ IFN-γ+at 8 hr [%gate]	0.66(0.31)	2.37(1.16)	1.48(0.97)	0.037
CD3+CD4+ IFN-γ+ at 12 hr [%gate]	0.97(0.04)	1.92(1.56)	1.18 (0.60)	0.064
Mean CD3+CD4+ IFN-γ+[%gate]	0.88(0.12)	2.11(0.91)	1.33(0.61)	0.028

PO2029

Urinary Proteomics and Effects of Dapagliflozin Treatment in Persons with Type 2 Diabetes and Kidney Disease

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Background: About 40% of persons with type 1 (T1D) or type 2 diabetes (T2D) develop diabetic kidney disease (DKD) posing a major economic burden on health care systems. Sodium Glucose Co Transporter 2 inhibitors (SGLT2i) have emerged as a novel treatment option for T2D and DKD. Albeit the kidney-protective effects of SGTL2i are well documented, the mechanisms remain unclear. The current study aims to investigate SGTL2i function through urinary proteomics.

Methods: A double-blinded, randomized, placebo-controlled, crossover trial comprising 36 persons with T2D was treated with 10 mg of dapagliflozin for 12 weeks or matching portion of placebo on top of their standard diabetes treatment at the Steno Diabetes Center Copenhagen, Denmark. All participants had albuminuria (UACR ≥ 30 mg/g) and received RAAS medication. Clinical factors like BMI, blood pressure (BP), estimated glomerular filtration rate (eGFR), LDL and HDL cholesterol, were measured at baseline, and after trial. Changes in clinical factors were modelled using linear mixed effects model adjusting for relevant clinical covariates. Urinary proteomics data in pre and post treatment groups (n=32) were analyzed using paired Mann Whitney U test. Multiple testing correction was performed and $p < 0.05$ was considered significant. We further verified whether identified peptide levels differed significantly between T1D DKD vs. healthy controls (n=210) and performed pathway enrichment analysis with STRING database.

Results: Trial participants had a mean (SD) age of 63 (8) years, 88% males, diabetes duration 15.9 (4.7) years, BMI 33.7 (5.4) kg/m^2, HbA_{1c} 8.8 (1.2)%, median (IQR) UACR 154 (94–329), eGFR 85.5(19.1) ml/min/m^2, respectively. 19 proteins significantly changed after treatment. Type I and III collagen α (I), (II), and (III) chains, α-2-HS-glycoprotein, and polymeric immunoglobulin receptor peptides increased while albumin, α–1–antitrypsin, and α–1B–glycoprotein peptides decreased multifold. This was reflected in the DKD–control cohort.

Conclusions: We identified differential urinary peptide patterns in response to SGLT2i (Dapagliflozin) treatment on individuals with T2D and DKD. Extracellular matrix organization, inflammation, coagulation, renal fibrosis, and wound healing pathways were enriched. We suggest the involvement of expected and novel proteins.

PO2030

Antifibrotic Effects of Low-Dose SGLT-2 Inhibition in Comparison to Standard Angiotensin II Receptor Blockade in 5/6 Nephrectomised Rats on a High-Salt Diet

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Background: The lowest protective SGLT2 inhibitor dose is not well established.

Methods: We performed a dose-response pilot study. Based on the results of this study we compared the cardio-renal effects of the SGLT-2 inhibitor empagliflozin with placebo or telmisartan in rats with 5/6 nephrectomy (5/6 Nx) on a high salt diet (HSD), as follows: Sham operation (Sham) with normal diet and placebo; 5/6 Nx with 2% HSD and placebo; 5/6 Nx with HSD and empagliflozin (0.6 mg/kg/day, bid); 5/6 Nx with HSD and telmisartan (5 mg/kg/day, qd).

Results: Empagliflozin treatment increased urinary glucose excretion in parallel to empagliflozin plasma levels in a dose-dependent manner starting at doses of 1 mg/kg. 5/6Nx rats on HSD treated with this low empagliflozin dose showed significantly reduced cardiac (-34.85%; $p<0.05$) and renal (-33.68%; $p<0.05$) fibrosis in comparison to 5/6Nx rats on HSD treated with placebo. These effects were comparable to the effects of a standard dose (5mg/kg/day) of telmisartan (cardiac fibrosis: -36.37%; $p<0.01$; renal fibrosis; -43.96%; $p<0.01$). RNA-sequencing followed by confirmatory qRT-PCR revealed that both telmisartan and empagliflozin exert their cardiac effects on genes involved in vascular cell stability and cardiac iron homeostasis, whereas in the kidneys expression of genes involved in endothelial function and oxidative stress were differentially expressed. Urinary adenosine excretion, a surrogate marker of the tubuloglomerular feedback (TGF) mechanism, was not affected.

Conclusions: The antifibrotic properties of low dose empagliflozin were comparable to a standard dose of telmisartan. The underlying pathways seem to be TGF independent.

Funding: Commercial Support - Boehringer Ingelheim Pharma GmbH & Co. KG

PO2031

HIF Prolyl-4-Hydroxylase Inhibitor AKBX27922 Induces Cellular Metabolic Adaptation

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Background: Inhibition of prolyl-4-hydroxylase (PHD) enzymes leads to the stabilization of hypoxia inducible factor (HIF) and the expression of HIF target genes. Because of effects on erythropoiesis, several PHD inhibitors are undergoing clinical evaluation for the treatment of anemia with chronic kidney disease. However, the impact on other biological functions is not well investigated. We demonstrate that AKBX27922, a novel small molecule PHD inhibitor, can shift cellular metabolism from mitochondrial oxidative phosphorylation to glycolysis, mimicking adaptation to hypoxia.

Methods: Inhibition of PHD enzymatic activity was determined using the time-resolved fluorescence resonance energy transfer assay. HIF1a stabilization in Hep3B cells was measured by meso scale discovery technology and protein expression of HIF target genes by enzyme linked immunosorbent assay. Oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) were measured in HepG2 cells with the Seahorse technology. Pharmacodynamics of HIF stabilization were confirmed in vivo.

Results: In vitro, AKBX27922 potently and in a concentration-dependent manner, and without chelating iron, inhibited PHD1 and PHD2 enzyme activity, leading to HIF1a stabilization and expression of HIF target genes implicated in erythropoiesis, angiogenesis, glycolysis, and cell survival. Pretreatment of HepG2 cells with AKBX27922 dose-dependently reduced both basal and maximal OCR without affecting cellular viability, while ECAR was significantly increased. Reactive oxygen species production in human primary renal epithelial cells was decreased. In vivo, AKBX27922 stabilized HIF in the liver and kidneys, as measured by luciferase activity in the oxygen-dependent degradation domain (ODD)-luciferase reporter mouse. In rats, AKBX27922 induced time-dependent stabilization of HIF1a in the kidney medulla and papilla, and increased expression of glycolysis related (ALDOC, CAR9, PDK1, PFKFB4, LDH) and other HIF-target genes (EPO, ADM, HMOX-1) in the kidneys and liver.

Conclusions: PHD inhibitor AKBX27922 mimics hypoxia, leading to HIF-driven metabolic adaptation. This novel small molecule will be useful as an in vitro and in vivo research tool for additional mechanistic studies that probe the pleotropic biology of HIF.

Funding: Commercial Support - Akebia Therapeutics, Inc.

PO2032

Comparative Kidney-on-Chip Toxicity Assessment in Human, Rat, and Dog Kidney Tissue Chips

Sepand Bafti, John R. Williford, Laura V. Balbiani. *Nortis, Inc., Seattle, WA.*

Background: The proposed project comprises of the development of a kidney proximal tubule (KPT) microphysiological system (MPS) from human cells as well as two experimental animal species that are typically used in kidney toxicity screening: rat and dog. These KPT-MPS can serve as an important new tool in chemical toxicity screening, allowing cross-referencing animal-based MPS data within vivoanimal data and with human-based MPS data and clinical outcomes. It also has the potential to result in a significant reduction of the use of live animals in studies.

Methods: The Nortis chip is made from silicone in a polycarbonate casing and is designed to use the "mandrel" method for generating channels within a 3D extracellular matrix using retractable small glass fibers. The channels serve as starting points for generating tubular tissue structures, such as vessels or kidney tubules. The chip is compatible with high-quality imaging, tissue sampling, and up- and down-stream fluid collection. Multiple publications have documented the suitability of the Nortis system to generate functional human KPTs and how well they resemble the function of *in vivo* tubules. All 3D MPS experiments are accompanied by 2D controls for comparison, using a traditional culture dish system. To assess viability of tissue, Live-Dead staining assays were run on canine tubules with Calcein-AM (live) and the nucleic acid stain ethidium homodimer I (dead), the results of which indicated sufficiently viable tubules. Confocal imaging and 3D rendering of these tubules demonstrates presence of key ion and drug transport proteins in their respective basolateral and lumenal domains.

Results: Preliminary studies have shown that rat and canine derived KPT-MPS in the Nortis platform produce structurally viable tissue structures that elicit injury markers in response to nephrotoxic insults using in vivo relevant toxic compounds in a differential manner.

Conclusions: Our preliminary data suggests that Nortis kidney chip allows for an ideal predicitive platfrom for comparative toxicity studies, allowing for fast and highly predictive preclinical simulations.

Funding: Other NIH Support - NCATS

PO2033

Forced Saline Diuresis Successfully Treats Lithium Intoxication

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Background: Forced 0.9% normal saline (NS) diuresis (FSD) is not advised by poison control centers for lithium intoxication (LI) but 2 papers in '71 & '78 showed 350 - 500 ml/hr of FSD treated LI at 4mEq/L successfully. We studied all pts with LI over 10 years with both acute (A) overdoses and chronic(C) LI to compare FSD in both groups to pts requiring hemodialysis (HD).

Methods: We found 20 LI pts seen over 10 years. Our team uses NS at 200-500 ml/hr as FSD in pts w/o CHF. 9 pts had Acute overdoses of L & 5 had C LI due to reduced gfr, ACE drugs or NSAIDS. These 14 got FSD, 200-500 ml/hr until L was < 1 mEq/L. 6 pts needed HD due to severe toxicity (seizures, coma, hypotension). We compared & show the mean +SEM values for peak L level mEq/L, GFR calculated by the Cockcroft-Gault equation, the rate of L decrease in mEq/hr, the normalized rate of L decrease in mEq/24 hr & time in hrs to reach a L level of 1.0 mEq/L amongst the 3 groups.

Results: The mean peak L levels were: FSD A LI, 2.8+0.2 (range, 2.3-4), FSD C LI, 2.8+0.4 (range, 2-4.2), HD LI 3.5+ 0.4 (range, 1.8-4.9). There were no differences in L levels. The mean GFR was: FSD ALI, 127+11, FSD C LI, 66+17, HD LI 142+7, p< .05 FSD C LI vs FSD ALI or HD LI. The GFR was significantly lower in the C LI pts. The hourly rate of L decrease in mEq/hr was: FSD A LI, 0.13+.03, FSD C LI, 0.05+.01, HD LI, 0.22+.04. There was no difference in the rate of L decrease in FSD A LI v HD LI but both were much faster than FSD C LI, p<.05. The mean 24 hour decrease (mEq/L) in L was: FSD A LI, 3.1+2.2, FSD C LI, 1.1+ 0.2, & HD LI, 5.3+ 1.6. p<.05 FSD C LI vs FSD A LI or HD LI. The time to L level of 1 mEq/L was: FSD A LI, 14.4+1.3 h, FSD C LI, 36+4.3 h, HD LI, 11.5+2.3 h due to rebound after HD. There was no difference in the time to normal L between FSD A LI & HD & both were much faster than FSD C LI. Linear regression of the rate of L decrease compared to the hourly rate of NS in FSD A LI pts showed greater decreases in L level with greater rates of FSD, r =.82, p=,.006. No pt had a serum Na > 145 mEq/L.

Conclusions: FSD with NS at rates of 200-500 ml successfully treats A LI and rates of L reduction approximate those of HD for LI. C LI can be treated with FSD but the rates of L decrease are slower possibly due to lower GFRs in these pts. This is the first study in 40 years showing efficacy of FSD in LI.

Funding: Clinical Revenue Support

PO2034

Snow White and the Apple: When Drugs Become Poisons

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Introduction: Commonly used drugs can cause significant toxicity in unfavorable clinical scenarios. We present a case of a pregnant female on a high dose of baclofen which led to significant neurotoxicity as her GFR dropped during an episode of acute pancreatitis

Case Description: A 29-year-old pregnant Caucasian Female presented to an OSH with abdominal pain of a day's duration. She was obese and had DM-II, hypertension as well as H/O a brain tumor treated when she was 10 years old. She was 29 weeks pregnant. Abdominal pain was sharp, epigastric and radiating to her back with nausea and vomiting. She was found to have severe acute pancreatitis. Her kidney function was normal (creatinine 0.5 mg/dl) on admission but on hospital day 2 it rose to 1.5 mg/dl and was at 2.3 mg/dl the next day. On hospital day #2 she became obtunded without response to naloxone and flumazenil. She was transferred to our hospital. She was comatose with minimal movement on sternal rub. Her neck was supple without obvious cranial nerve lesions. MRI of the brain revealed prior (L) frontal craniotomy, post-surgical gliosis and encephalomalacia, stigmata of her brain surgery. EEG suggested encephalopathy but no active seizures. A review of medicines at OSH revealed baclofen 20 mg TID scheduled for neck muscle spasms. Neurotoxicity due to baclofen was suspected and urgent CVVH was instituted. By 12 hours, she started improving and by 48 hours, recovered completely. Her AKI as well as pancreatitis resolved. She eventually delivered a healthy baby girl. Mother and baby were discharged in stable condition. Baclofen level drawn prior to initiation of therapy was reported at 862 ng/ml.

Discussion: This is a unique case of baclofen neurotoxicity in a pregnant female. She was prescribed a relatively high dose of baclofen which she was taking sporadically. On admission, she was placed on this standing dose and at the same time lost GFR due to acute pancreatitis. This precipitated neurotoxicity. She was urgently dialyzed, and the patient and baby were spared neurotoxic sequelae. Prolonged dialysis may be required to remove baclofen and treat neurotoxic manifestations. This was all the more important in the case due to risk of fetal neurotoxicity It was a careful review of records of medicines dispensed at the OSH that helped clinch the diagnosis clinically, subsequently confirmed with elevated baclofen levels demonstrated on a send out test.

PO2035

Efficacy of Pi-Binder Lanthanum Carbonate in Reversing Systemic Effects of a High-Phosphate Diet in Mice

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Background: Modulating dietary inorganic phosphorus (Pi) is particularly important for patients suffering from chronic kidney disease (CKD) as excess Pi consumption and subsequent elevated serum Pi levels can lead to significant health problems, including increased mortality. Recent data now suggests that high Pi consumption might also have negative health consequences even in those with clinically normal renal function. The predominant clinical therapy to reduce serum Pi and related health complications of CKD patients is orally administered Pi-binders with meals, including the commonly used Lanthanum Carbonate (LaC). Our study assessed the strategy of binding Pi in the gut to reduce health consequences of a high Pi diet including changes in bone volume, Pi-responsive circulating factors, and gene expression in the kidney.

Methods: Healthy 10-Week-old, female C57BL/6J mice were fed diets with varying Pi for 5 weeks: Low Pi (LPD, 0.2% Pi), Normal Pi (NPD, 0.6% Pi), High Pi (HPD, 1.8% Pi), and HPD supplemented with LaC (3%). All diets contained 0.6% Calcium, similar protein, Kcals, and fat%. Circulating Pi-responsive factors (FGF23, OPN) were measured by ELISA, bone volume by micro-computed tomography, and gene expression in the kidney by quantitative real-time (qRT) PCR.

Results: HPD resulted in increased serum FGF23 and OPN, decreased bone volume (trabecular, cortical), and significant changes in kidney gene expression of inflammatory protein Lcn2, Pi responsive Klotho, vitamin D synthesis Cyp27b1, and Pi-transporter Slc34a2. LaC completely reversed the HPD-induced increase in serum FGF23, partially reversed gene expression changes in the kidney but did not alter HPD-induced bone loss.

Conclusions: The clinically used Pi-binder LaC only reversed certain HPD-induced consequences, suggesting a multifactorial mechanism, and therefore may require a therapeutic strategy beyond reducing gut Pi-absorption. Decreasing Pi consumption was substantially more effective at minimizing physiological repercussions like bone loss. Changes in kidney gene expression after a sustained HPD also reveal potential long-term consequences on kidney health/function in otherwise healthy individuals. Given divergent claims concerning LaC binder efficacy, our study shows LaC corrects some—but not all—effects of a high Pi diet.

Funding: Veterans Affairs Support, Private Foundation Support

PO2036

A Meta-Analysis Evaluating the Effect of Sacubitril-Valsartan on Renal Function in Heart Failure Patients

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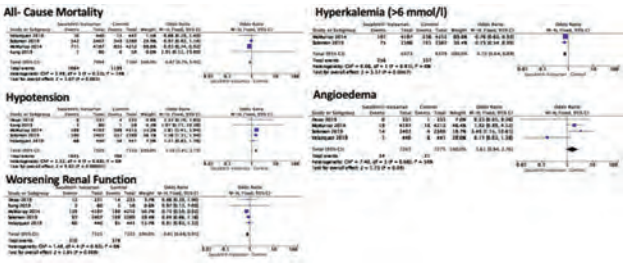
Background: Cardiorenal syndrome (CRS) has been associated with increased morbidity and mortality in heart failure (HF). Sacubitril-Valsartan is the first- in-class angiotensin receptor- neprilysin inhibitor which has been found to reduce all-cause mortality in HF with reduced left ventricular ejection fraction. The effect of sacubitril-valsartan on renal outcomes is unknown. This meta-analysis analyzes recent studies comparing renal outcomes between sacubitril-valsartan and RAS inhibitors in heart failure patients.

Methods: We performed a comprehensive literature search for all eligible studies comparing Sacubitril-Valsartan and RAS inhibitors in Pubmed, EMBASE, SCOPUS, and google scholar. Only recent clinical trials were included. All retrospective studies were excluded. Clinical outcomes comprised of all-causes mortality and renal complications.

Results: 5 Randomized clinical trials (RCT) were deemed eligible, which consisted of 7325 sacubitril- valsartan patients and 7333 RAS inhibitor patients. Meta-analysis confirmed that Sacubitril-valsartan was associated with reduced all-cause mortality (OR= 0.87, p = .002). A lower risk of worsening renal function, defined as increase in ≥ 0.3 mg/dl in serum creatinine compared with the value on admission (OR = .81, p = 0.008), was seen in the sacubitril-valsartan group. Hyperkalemia, defined as potassium greater than 6 mil/L was lower in the sacubitril-valsartan group (OR= 0.75, p = 0.0007) in comparison to RAS inhibitors. However, sacubitril-valsartan had a higher risk of symptomatic hypotension (OR = 156, p < 0.00001). There was no observed statistically significant differences in angioedema.

Conclusions: Sacubitril-Valsartan reduces the risk of all- cause mortality, diminished renal function, and hyperkalemia compared with RAS inhibitors. Further evaluation is required.



PO2037

Combination Therapy of Neprilysin Inhibitor with AT2R Agonist C21 Provides Superior Renoprotection Compared to its Combination with AT1R Antagonist Valsartan in High-Sodium Diet-Fed Obese Zucker Rats

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Background: The neprilysin (NEP) inhibitor sacubitril (SAC) combined with the angiotensin II type 1 receptor (AT1R) blocker valsartan (VAL) (i.e. Entresto) is clinically approved for the treatment of heart failure (HF) associated with reduced ejection fraction, owing mainly to its ability to preserve atrial natriuretic peptide (ANP), a substrate of NEP. However, many HF patients treated with Entresto have presented with increased albuminuria. We have reported that the agonist of angiotensin II type 2 receptor (AT2R) Compound 21 (C21) prevents proteinuria and is reno-protective in obese Zucker rats (OZR) fed high sodium diet (HSD). Thus, we hypothesized that SAC/C21 combination provides superior reno-protection compared to the current SAC/VAL therapy.

Methods: Male OZR 10-11 wks. old were treated daily via oral gavage with vehicle, SAC (10mg/kg/day) + C21 (1mg/kg/day), or SAC (10mg/kg/day) + VAL (10mg/kg/day) while fed HSD (4%) for 16 days.

Results: Untreated HSD-fed OZR showed reduced plasma ANP and increases in renal cortical Ang II (all $p<0.05$ vs OZR-fed 0.4% normal sodium diet (NSD)). These changes were associated with a modest increase in kidney weight and kidney dysfunction, evident by increased proteinuria, and reduced urinary excretion of urea nitrogen and creatinine (all $p<0.05$ vs OZR-fed NSD). Other indices of renal injury include increased cortical expression of nephrin ($p<0.05$ vs OZR-fed NSD), podocin, megalin, albuminuria, and increased urinary osteopontin (OPN). Treatment with SAC/C21 significantly prevented increases in renal Ang II, proteinuria, albuminuria, nephrin expression and kidney weight (all $p<0.05$ vs OZR-fed HSD), while SAC/VAL did not affect these parameters. Furthermore, SAC/C21 prevented the decline in the excretion of urinary creatinine and decreased urinary OPN (all $p<0.05$ vs SAC/VAL). Moreover, SAC/VAL therapy increased plasma renin concentrations ~3-fold compared to OZR-fed HSD and SAC/C21.

Conclusions: Together, this study suggests that combination therapy with SAC/C21 afforded superior reno-protection compared to SAC/VAL therapy in HSD-fed OZR.

Funding: NIDDK Support

PO2038

Is Basal Nitric Oxide Activity of the Renal Vasculature Altered? Analysis of a Randomized Controlled Trial Comparing Two Combination Therapies

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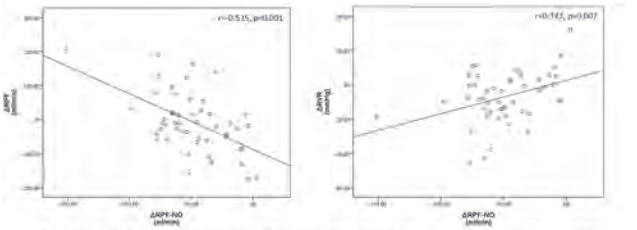
Background: Recently we demonstrated that a combination therapy with empagliflozin and linagliptin in patients with type 2 diabetes mellitus(T2DM) induce changes in renal hemodynamics. The purpose of this study was to analyze the influence of basal nitric oxide(NO) activity of the renal vasculature on the described changes of the renal hemodynamic profile.

Methods: In this study patients with T2DM were randomized to receive either empagliflozin and linagliptin(E+L group, n=50) or metformin and insulin glargine(M+I group, n=46), for 3 months. Renal hemodynamics were assessed with constant-infusion input-clearance technique with p-aminohippuric acid and inulin at baseline and after treatment. Due to withdrawal of inulin from the market during the study, glomerular filtration rate and filtration fraction(FF) were measured only in a sub-group of patients(E+L: n=34; M+I: n=31). Intraglomerular hemodynamics were calculated according the model established by Gomez. The basal NO activity in the renal circulation has been assessed by analyzing change in renal plasma flow(RPF) in response to intravenously administrated NG-monomethyl-l-arginine(NO inhibitor).

Results: After 3 months of treatment, we did not observe any change in basal NO activity compared to baseline in either of the groups. In the E+L group, we found a correlation between basal NO activity of the renal vasculature after 3 months of treatment and change in RPF($r=-0.535$, $p<0.001$), renal blood flow($r=-0.468$, $p=0.001$) and renal vascular resistance($r=0.377$, $p=0.007$) induced by treatment. Similar correlations with change in FF($r=0.639$, $p<0.001$), preglomerular($r=0.350$, $p=0.046$) and postglomerular resistance($r=0.588$, $p<0.001$) have been found. No such relationships were found in the M+I group after 3 months and with basal NO activity at baseline in both treatment groups.

Conclusions: Basal NO emerged as a determinant of the renal hemodynamic response in the combination therapy of empagliflozin and linagliptin, but not in the combination therapy of insulin and metformin.



E+L group: ΔRPF- change in renal plasma flow with treatment, ΔRVR- change in renal vascular resistance with treatment, ΔRPF-NO- change in renal plasma flow in response to infusion of NG-monomethyl-l-arginine (nitric oxide inhibitor) with treatment

PO2039

Urinary Cell mRNA Profile Diagnosis of Borderline T Cell-Mediated Rejection in Kidney Allografts

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Background: Borderline rejection (BR) is associated with inferior outcomes. In CTOT-04, we discovered and validated a urinary-cell signature of CD3ε mRNA, IP-10 mRNA and 18s rRNA diagnostic of TCMR (Suthanthiran et al. *N Engl J Med*,2013). We investigated whether this signature is diagnostic of BR.

Methods: Urinary cell mRNAs measured in 377 biopsy-matched urine samples from 300 kidney transplant recipients. Interstitial inflammation (i) and tubulitis (t) scored by Banff criteria. Diagnosis of BR=i1,t1, i2,t1, or i1,t2 and TCMR= i≥2,t≥2 (Loupy et al.*Am J Transplant*,2020). Exclusion criteria: inadequate biopsy;BKVN;+BKVN by urinary BKV-VP1 mRNA level(Dadhania et al.*Transplantation*,2010), i1 or t1 alone. RNA isolated from urinary cell pellet, absolute transcript levels measured by customized RT-qPCR and CTOT-04 signature computed.

Results: 293 biopsies included (Table 1). CTOT-04 signature distinguished i0,t0 biopsies from BR and TCMR($p<0.0001$,ANOVA)(Fig.1A).18S normalized CD3ε and IP-10 mRNAs elevated in BR and TCMR urine(Fig.1D-E). Accurate diagnosis of BR and TCMR shown(Table 2A-B).

Conclusions: Urinary-cell CTOT-04 signature discriminates i0,t0 from BR or TCMR biopsies. Our findings may help reduce biopsies performed to diagnose BR or TCMR and prognosticate graft outcome.

Banff *i* and *t* score based grouping	i0,t0	BR	i≥2,t≥2
Total, n	177	42	74
Concurrent pathology diagnosis, n (%)			
Normal/Nonspecific changes	48 (27)	3 (7)	0 (0)
AMR	12 (7)	8 (19)	0 (0)
MVI/TG	20 (11)	6 (14)	0 (0)
Mixed rejection	0 (0)	2 (5)	15 (20)
Borderline changes	0 (0)	6 (14)	0 (0)
TCMR (Acute)	0 (0)	0 (0)	48 (65)
TCMR (Chronic Active)	0 (0)	3 (7)	4 (6)
IFTA	10 (6)	1 (3)	0 (0)
Other (GN/TMA/pyelonephritis)	26 (15)	5 (12)	6 (8)
AIN	0 (0)	3 (7)	1 (1)
Acute tubular injury	45 (25)	5 (12)	0 (0)
Diabetes	16 (9)	0 (0)	0 (0)

Table 1. Distribution of i0,t0, BR (i1, t1, or i2, t1, or i1, t2), and i ≥2,t ≥2 groups among the 293 biopsies and concurrent histological features.

	CTOT-04 signature		18S/10^6		TGF-β1/(18S/10^6)		CD3/(18S/10^6)		IP-10/(18S/10^6)	
	i0,t0	BR	i0,t0	BR	i0,t0	BR	i0,t0	BR	i0,t0	BR
n	177	42	177	42	177	42	177	42	177	42
Median	-1.38	-1.025	2080	2080	7.46	7.315	0.75	1.335	0.14	0.32
25% Percentile	-2.23	-1.623	790	1180	3.59	4.195	0.236	0.54	0.035	0.0675
75% Percentile	-0.595	-0.028	5840	4970	14.31	15.72	2.195	5.765	0.425	0.805
Mann Whitney P value	0.0173		0.9317		0.6038		0.0115		0.0173	

Table 2A. Urinary cell 18S/10^6 normalized mRNA levels and CTOT-04 signature for i0,t0 and BR (i1, t1, or i2, t1, or i1, t2) groups.

	CTOT-04 signature		18S/10^6		TGF-β1/(18S/10^6)		CD3/(18S/10^6)		IP-10/(18S/10^6)	
	i0,t0	i ≥2,t ≥2	i0,t0	i ≥2,t ≥2	i0,t0	i ≥2,t ≥2	i0,t0	i ≥2,t ≥2	i0,t0	i ≥2,t ≥2
n	177	74	177	74	177	74	177	74	177	74
Median	-1.38	-0.205	2080	3585	7.46	8.525	0.75	2.425	0.14	0.56
25% Percentile	-2.23	-1.538	790	996.3	3.59	5.39	0.235	0.5625	0.035	0.1025
75% Percentile	-0.595	0.645	5840	8888	14.31	16.55	2.195	11.2	0.425	2.123
Mann Whitney P value	<0.0001		0.0646		0.1488		<0.0001		<0.0001	

Table 2B. Urinary cell 18S/10^6 normalized mRNA levels and CTOT-04 signature for i0,t0 and i≥2,t ≥2 groups.

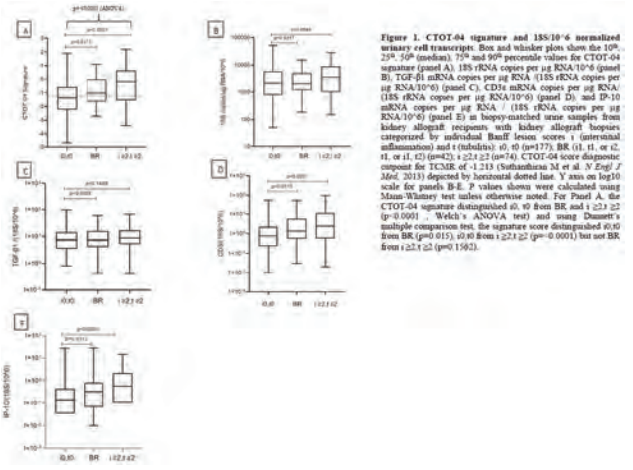

Figure 1. CTOT-04 signature and 18S/10^6 normalized urinary cell transcripts. Box and whisker plots show the 10th, 25th, 50th (median), 75th and 90th percentile values for CTOT-04 signature (panel A), 18S rRNA copies per µg RNA/10^6 (panel B), TGF-β1 mRNA copies per µg RNA (18S rRNA copies per µg RNA/10^6) (panel C), CD3ε mRNA copies per µg RNA/ (18S rRNA copies per µg RNA/10^6) (panel D), and IP-10 mRNA copies per µg RNA / (18S rRNA copies per µg RNA/10^6) (panel E) in biopsy-matched urine samples from kidney allograft recipients with kidney allograft biopsies categorized by individual Banff lesion scores i (interstitial inflammation) and t (tubulitis): i0, t0 (n=177); BR (i1, t1, or i2, t1, or i1, t2) (n=42); i ≥2,t ≥2 (n=74). CTOT-04 score diagnostic cutpoint for TCMR of -1.213 (Suthanthiran M et al. *N Engl J Med*, 2013) depicted by horizontal dotted line. Y axes on log10 scale for panels B-E. *P* values shown were calculated using Mann-Whitney test unless otherwise noted. For Panel A, the CTOT-04 signature distinguished i0, t0 from BR and i ≥2,t ≥2 (p<0.0001 , Welch's ANOVA test) and using Dunnett's multiple comparison test, the signature score distinguished i0,t0 from BR (p=0.015), i0,t0 from i ≥2,t ≥2 (p=<0.0001) but not BR from i ≥2,t ≥2 (p=0.1502).

PO2040

Preserved Kidney Allograft Function and Unique Urinary Biomarker Profiles in Living Donor Kidney Transplant (LDKT) Patients Tolerized with an Investigational Allo-Hematopoietic Stem Cell Transplantation Therapy

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Background: We previously reported that 37 patients were transplanted in an open-label, single-arm phase 2 protocol to induce immune tolerance in LDKT recipients.

Methods: The protocol was based upon tolerogenic CD8+/TCR- facilitating cells (FCR001), nonmyeloablative conditioning and enrollment agnostic to the degree of HLA mismatch. Tacrolimus/MMF based immunosuppression (IS) was weaned and discontinued at one year if durable chimerism and normal kidney function and transplant biopsy were confirmed.

Results: Durable chimerism enabled complete withdrawal of IS in 26/37 patients. Comparison of clinical outcomes in FCR001 and a SOC cohort showed comparable patient survival and graft survival at two, three and five years. Cardiovascular medication usage was more frequent in SOC than in tolerant FCR001 subjects for hypertension (83% vs 18%) and hyperlipidemia (43% vs 9%). Graft function (eGFR) was better and more stable for the FCR001 cohort compared to SOC, with the difference due to patients with durable chimerism and off IS. Urinary cell mRNA profiling of a subgroup of FCR001 patients identified a potential signature of tolerance, characterized by increased levels of CTLA4 mRNA, and a higher ratio of CTLA4 mRNA to mRNA for granzyme B and perforin mRNA. If validated, such a signature of tolerance might help identify kidney transplant patients in whom reduction of IS drugs might be safely undertaken. To date, we have accumulated approximately 235 patient-years of exposure to FCR001 in LDKT, and the safety profile is consistent with that expected if a patient were to receive both a kidney transplant and an allo-HSCT with nonmyeloablative conditioning.

Conclusions: We continue to monitor the patients in the Phase 2 trial for long-term safety and durability of immune tolerance and graft function. We are currently enrolling patients in FREEDOM-1, a randomized, controlled, open-label Phase 3 trial in the US in adult LDKT recipients.

Funding: Commercial Support - Talaris Therapeutics

eGFR	Month 1	Year 1	Year 2	Year 3	Year 4	Year 5
Chimeric off IS	58.8	60.6	65.4	65.0	64.3	66.1
ITT	55.0	60.5	63.7	63.7	62.9	62.6
SOC		58.9	58.1	55.4	51.5	

PO2041

Urinary T Cell Subsets and Tubular Epithelial Cells as Biomarkers for Kidney Transplant Rejection

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Background: Early detection of kidney transplant (KT) rejection remains a challenge in patient care. Previously we developed a biomarker combination to detect rejection by analyzing urine cells using Flow cytometry (FC). The aim of this study was to confirm our previous findings and develop further markers to detect KT rejection.

Methods: Urine samples of 275 KT patients were analyzed. Cell population were quantified in 150 and 125 cases by epigenetic analyses and FC, respectively. Professional diagnoses from renal biopsies served to uniquely group graft deterioration into borderline rejection (BR), T cell mediated rejection (TCMR), and antibody mediated rejection (ABMR), other specific pathohistological diagnosis (other) or no rejection (No RX). For FC analyses urine sediments were stained for T cells (anti-CD3, -CD4, -CD8, -CD45RO, -CD45, -CCR7, -HLA-DR, -CD28) and tubular epithelial cells (TECs) (anti-Cytokeratin, -Vimentin, -CD10, -CD13, -CD227, -CD326). Epigenetic qPCR approach was used to determine T cells und TECs based on specific DNA methylation patterns identified by bisulfite sequencing.

Results: Absolute numbers of urinary T cells and TECs discriminated patients with and without TCMR. Most strikingly in this regard were increased numbers of various T cell subsets observed by FC in patients with TCMR compared to patients without TCMR ($p<0.001$ for HLA-DR+ T cells and effector memory T cells) whereby CD8+ HLA-DR+ T cells were most distinctive ($p = 5.1e-07$, AUC = 0.866-0.967). Epigenetic analyses qualitatively confirmed T cell and TEC quantities as determined by FC. Furthermore, the ratio of absolute numbers of T cells and TECs determined by epigenetic analyses discriminated patients with TCMR from those with other specific biopsy proven diagnoses than rejection, but individual T cell populations showed a higher sensitivity and specificity in segregating both groups (TCMR vs other: CD8+ T cells p=5.1e-05, AUC 0.87 (CI 95% 0.77-0.98), CD3+ T cells/TEC p=0.004, AUC 0.78 (CI 95% 0.65-0.92); ABMR vs other: CD8+ T cells p=0.0041, CD3+ T cells/TEC p=0.04).

Conclusions: Urinary T cell subsets reflect intrarenal inflammation in TCMR. TECs mirror intrarenal damage accompanied by rejection. Jointly, they yield high potential to monitor KT patients and detect rejection.

Funding: Government Support - Non-U.S.

PO2042

Elevation of Serum IL-8 in Patients with Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy

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Background: Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for several different hematopoietic malignancies and disorders. However, HSCT-associated thrombotic microangiopathy (TA-TMA) represents a major obstacle to the success of this procedure in transplant recipients, and rapid progression to end-stage renal disease is a major complication of this disorder, affecting nearly 1 in 3 patients. Here, we sought to Identify a serum biomarker for the detection of TA-TMA and investigate its role in the pathogenesis of this severe disease.

Methods: We measured the concentrations of several different cytokines and vasoactive peptides in the sera of 14 adult human HSCT recipients at the time of transplantation and again at 5-6 weeks following HSCT. Levels of IL-1β, IL-6, IL-8, TNF-α, IFN-γ, VEGF-B, HIF1α, and GM-CSF were measured, using the highly sensitive ELISA single molecule array (Simoa) method.

Results: Statistical analysis of the change in each of the cytokines revealed that IL-8 was the sole marker that increased significantly over time in the TMA group. Next, we found that co-culture of irradiated peripheral blood mononuclear cells (PBMCs) with human umbilical vein endothelial cells (HUVECs) resulted in increased IL-8 expression by the PBMCs. Furthermore, *in vitro* treatment of HUVECs with IL-8 increased platelet adhesion and vWF expression. Treatment of platelets independently with IL-8 also increased their adhesion *in vitro* to HUVECs. Finally, treatment of HUVECs with IL-8 also induced senescence, and platelets were found to adhere more readily to senescent HUVECs *in vitro*. Moreover, exposure of these HUVECs to a senolytic agent abrogated the platelet adhesion.

Conclusions: These findings implicate IL-8 as a potentially important thrombogenic and pathogenic factor in TA-TMA. In addition, these data highlight senescence of endothelial cells for the first time as a possible mechanism for the microvascular thromboses observed in TA-TMA patients, suggesting that modulation of IL-8 could be an effective therapeutic pathway for this severe disease.

Funding: NIDDK Support, Other NIH Support - NIAID

PO2043

Three Distinct Phases in the Amount of Total and Donor-Derived Cell-Free DNA Are Observed over Time in Plasma from Kidney Transplant Recipients

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Background: Donor-derived cell-free DNA (dd-cfDNA) is a clinically validated biomarker for allograft rejection in kidney transplant (KT) recipients. Fluctuations in the total amount of cfDNA (including donor and recipient-derived cfDNA) can impact the reported dd-cfDNA fraction. Here we analyzed the changes in total and dd-cfDNA quantity, over time, in KT patients.

Methods: We selected 3,925 samples from 747 clinically stable patients with >3 longitudinal samples. The median time from KT to sample collection was 134 days (range: 1 day - 37 years). Total cfDNA and dd-cfDNA were measured using the Prospera™ test and expressed as relative units per ml plasma (RU/ml). Dynamic changes in dd-cfDNA and total cfDNA over time were compared to their respective medians for all samples at 3-year post-KT, defined as reference.

Results: One week following KT, median quantities of total cfDNA were elevated ~2-fold above the reference value (494 RU/ml), which normalized over the first month. At month 3, a 1.6-fold increase was observed, which normalized to the reference value over the first year post-KT. In contrast, the absolute quantity of dd-cfDNA was initially elevated ~100-fold above the reference (1.06 RU/ml) post-KT, which normalized over the first month to the reference level where it remained stable. The elevation in dd-cfDNA during the first week is likely due to trauma to the donor organ from surgery. Additionally, a significant elevation in both total and dd-cfDNA was observed in patients who received a kidney from a deceased donor as compared to a living donor.

Conclusions: Total and dd-cfDNA levels were highly dynamic in the first year post-KT but stabilized afterwards. Further investigation is needed to determine the causes of total-cfDNA increases at months 3 and 4. Potential factors include inflammatory responses and NETosis, viral infection or transient interstitial fibrosis and tubular atrophy (IF/TA) in the donor organ. The time dependent dynamics were statistically significant, but with a high coefficient of variance (CV>50%), which limits extrapolations to individual patients. Potential variability should be considered when interpreting dd-cfDNA tests performed within the first week post-KT.

PO2044

A Peripheral Blood Transcriptomic Signature Predicts the Progression of Chronic Kidney Damage Post Transplant

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Background: Chronic kidney damage post-transplant is a major risk of allograft loss. The aim of this study was to identify a transcriptomic signature from peripheral blood collected at 3 months post-transplant to predict the progression of chronic kidney damage after transplant.

Methods: We inspected kidney functional and histologic changes from the baseline (pre-implantation) to 1 year post-transplant in 112 kidney transplant recipients from the prospective Genomics of Chronic Allograft Rejection (GoCAR) study and identified the patients who developed chronic kidney damage within 1 year (progressors). We then carried out RNA sequencing on the whole blood collected from these patients at 3 months post-transplant to identify a transcriptomic signature predictive of the progression of chronic kidney damage in the training set and validated by the testing set.

Results: Among 112 patients, we identified 30 progressors who developed kidney damage within 1 year post-transplant with a Chronic Allograft Damage Index (CADI) score increase by ≥ 2, and 55 non-progressors with a normal histology at both the baseline (CADI<2) and 12 months (CADI<=2) post transplant. The remaining 27 patients had a histological lesion at the baseline with a high CADI >=2 but no progression at 12 months. From the progressors and non-progressors (total n=85), we randomly selected 55 patients as a training set and the remaining 30 patients as a testing set. From the training set, we identified a 9-gene set that predicts kidney damage at 12 months with AUC=0.88 and validated the prediction model in the testing set with AUC=0.79, superior to the Kidney Donor Risk Index (KDRI) in the deceased-donor population. The 9-gene set performed moderately in the patients who received a kidney with an intermediate or severe pathological lesion (n=27, AUC=0.68).

Conclusions: We presented a useful blood transcriptomic signature to accurately risk-stratify the progression of chronic kidney damage post-transplant, especially for those patients who received a healthy kidney.

Funding: Other NIH Support - NIAID

PO2045

Kidney Precooling Improves Renal Outcome After Transplantation due to Preserved Mitochondrial Function

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Background: Transplanted organs experience several episodes of ischemia and Ischemia-reperfusion. Ischemia-reperfusion injury (IRI) has remained one of the most serious hurdles for the survival of transplanted grafts. Temperature plays an important role in cellular metabolic rates since biochemical reactions are highly temperature dependent. Therefore, ischemia-triggered degradative reactions could be mitigated by lowering tissue temperature. Whether a local hypothermia on kidney before blockage of blood flow protects kidney grafts against IRI has not been investigated.

Methods: In the present study we performed kidney transplantation and applied local hypothermia on the donor kidney before blockage of renal blood flow, which procedure is called "kidney precooling". Kidney graft injury and function were evaluated at 7 days after transplantation.

Results: kidney precooling improved graft functions by >47% accompanied with about 50% less kidney graft injury. The protective mechanisms of kidney precooling are associated with preserved mitochondria function and significantly delayed ATP depletion. More impressively, the precooling enables us to double the storage time of the donor kidneys in preservation solution in rats. Retrospective analysis of patient data also showed close association between hypothermia and kidney graft function.

Conclusions: Taken together, reduction of the cellular metabolism and enzymatic activity to a minimum level before ischemia protects kidney graft against IRI during transplantation.

Funding: NIDDK Support

PO2046

p53 Is Activated in Cold Storage/Transplantation to Mediate Tubular Injury and Renal Graft Dysfunction

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Background: Kidney injury associated with cold storage/transplantation is a leading cause of delayed graft function and poor outcome of renal transplants. p53 has been implicated in both ischemic and nephrotoxic kidney injury, but its involvement in kidney cold storage/transplantation is not clear. This study aimed to investigate the role of p53 in cold storage/transplantation kidney injury and test the therapeutic effects of p53 inhibition.

Methods: Donor kidneys from C57BL/6 mice were preserved in ice-cold University of Wisconsin (UW) solution for 0.5, 2, 6 or 8.5h and transplanted into syngeneic recipients for 24h. Tubular injury, cell death and p53 activation were observed and their correlations were assessed. The acute response of kidneys from pifithrin-α and DMSO (the vehicle solution) treated mice was examined and compared, as well as response of kidneys from p53 conditional knock out (KO) mice and their wild type (WT) littermates. To explore the therapeutic potential of p53 inhibition, pifithrin-α was also administered to test its effect on graft injury and function on day 6, when the graft became the sole life-supporting kidney after native kidney removal at day 5. Rat kidney proximal tubule cells (RPTCs) were incubated in UW solution at 4°C for cold storage, followed by full medium replacement at 37°C for rewarming. Pifithrin-α was added to UW solution or dominant negative p53 was transfected into RPTCs, for the purpose of evaluating their effect on RPTCs death in cold storage/rewarming.

Results: p53 was activated in kidney tubule cells during cold storage transplantation, which correlated with tubular injury and cell death. Pifithrin-α significantly reduced acute tubular injury, cell death and inflammation during cold storage/transplantation. Similar effects were shown by ablation of p53 specifically from kidney proximal tubule cells. Notably, pifithrin-α also ameliorated kidney injury and improved the function of transplanted kidneys as the life-supporting graft. In RPTCs, cold storage followed by rewarming induced cell death and p53 activation. Both pifithrin-α and dominant-negative p53 could attenuate RPTC cell death during cold storage/rewarming.

Conclusions: p53 plays a critical role in kidney injury and dysfunction during cold storage/transplantation. p53 inhibitors may provide therapeutic benefits for donor kidney preservation and transplantation.

Funding: NIDDK Support, Veterans Affairs Support

PO2047

Multi-Omics Analysis Reveals Regulatory Mechanisms in Chronic Cyclosporine A-Induced Nephrotoxicity Studied in a Rat Model

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Background: Chronic calcineurin inhibitor (CNI) nephrotoxicity is a major drawback in current immunosuppressive regimens. In the chronic setting, arteriolar hyalinosis, decreased glomerular filtration rate, interstitial fibrosis and tubular dedifferentiation are the major adverse side effects. Regimens with cyclosporine A (CsA) and tacrolimus (Tac) have been compared before the background of potentially more harmful effects of CsA. Conversely, CsA is still widely used in transplant recipients and has been considered for replacement of Tac in posttransplant diabetes. To identify regulatory mechanisms in CsA nephrotoxicity we used quantitative transcriptomic, proteomic and phosphoproteomic methods. We tested the hypothesis that tubulointerstitial pathomechanisms play a significant role in chronic CNI nepropathy.

Methods: Whole transciptome RNA-seq as well as global proteomic and phosphoproteomic methodologies were performed on kidney extracts from normal Wistar rats receiving CsA (25mg/kg b.w./day) or vehicle for 3 weeks. Differentially expressed genes and proteins as well as their phosphorylation status were obtained.

Results: CsA treatment stimulated genome-wide alterations in rat kidney according to the RNA-seq data. We identified 342 transcripts upregulated which included Ribosome and Oxidative phosphorylation pathways, whereas 331 transcripts were downregulated, with enrichment in genes critical for amino acid metabolism. Data were controlled by the established upregulation of renin and downregulation of calbindin in global proteomics. KEGG pathway and GO analysis from proteomics largely corresponded to the RNA-seq results. Upregulated proteins were further related to ECM-receptor interaction and focal adhesion pathways (padj<0,05). Phosphoproteomics demonstrated functional phosphorylation of components from unfolded protein response pathways, indicating an activation of the integrated stress response upon CsA.

Conclusions: In sum, using integrated -omics analysis in CsA nephrotoxicity proves to be a powerful approach. Chronic CsA treatment is associated with enhanced energy metabolism and activation of the unfolded protein-response pathways. A tubulointerstitial focus has been demonstrated. Potential biomarker candidates have further been obtained and are currently verified in the rat model.

PO2048

Calcineurin Inhibitor Nephrotoxicity as Viewed by Comparative Analysis of the Effects of Cyclosporine A vs. Tacrolimus on Epithelial Pathology in Rodent Models

Suncica Popovic,[1] Hasan Demirci,[1] Junda Hu,[1] Duygu E. Yilmaz,[1] Carsten Dittmayer,[1] David H. Ellison,[2] Kerim Mutig,[1] Sebastian Bachmann.[1] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]Oregon Health & Science University Oregon Clinical & Translational Research Institute, Portland, OR.*

Background: Calcineurin inhibitors (CNI) are widely in use for immunosuppression in transplant recipients. Although essentially beneficial, their nephrotoxicity may cause or aggravate renal disease. We have challenged the hypothesis that the safety of the commonly applied CNI, cyclosporine A (CsA), and tacrolimus (Tac), differs regarding tubulointerstitial pathology. Mechanisms of proteostasis, autophagy and lysosomal dysfunction are addressed.

Methods: We have compared the effects of CsA and Tac in rat and mouse models. A focus was set on epithelial alterations. Adult Wistar rats received CsA (25 mg/kg/d), Tac (2 to 6 mg/kg/d), or vehicle via subcutaneously implanted minipumps. A megalin-deficient mouse model was tested for the role of endocytosis. After 4 wk kidneys were prepared for histopathology or biochemical analysis.

Results: In rats, CsA and Tac produced similar alterations in the tubulointerstitium (Fig. 1). Preferentially the initial proximal tubule (S1, and S2 segments) was affected, displaying dysmorphic lysosomes with peripheral LAMP1 signal, autophagic and mitophagic vacuoles. Dedifferentiation was focally strong, with loss of brush border, basement membrane thickening, and interstitial collagen accumulation. Alterations in unfolded protein response (UPR) and autophagy parameters included significant increases in p-eIF2a, pPERK, CHOP, BiP, and LC3B, and ATG5 products and enhanced epithelial TUNEL signal. Endocytosis was substantially impaired. Cultured NRK cells indicated sensitivity to chemical chaperones ameliorating proteostasis and revealed similar apoptosis rates upon CsA and Tac.

Conclusions: These results suggest that alterations in tubular epithelial proteostasis upon long term CsA- or Tac-induced nephrotoxicity are similar. Addressing restitution of epithelial proteostasis may have renoprotective potential for both drugs.

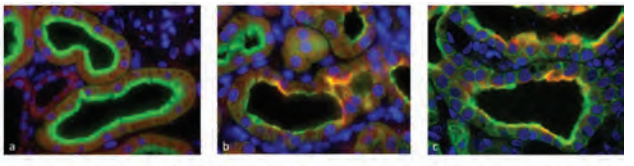

Figure 1. Proximal tubular damage with partial injury/loss of brush border after CsA (b; 25 mg/kg/day, 4 wk) and tacrolimus (c; 6 mg/kg/day, 4 wk) treatment in Wistar rats, compared to vehicle (a.). Green, aquaporin 1; red, kidney injury marker 1; blue, DAPI nuclear counterstaining.

PO2049

Cyclosporine A but Not Tacrolimus Promotes Pro-Apoptotic Endoplasmic Reticulum Stress in Cultured Kidney Cells

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Background: Current immunosuppressive regimen in organ transplantation include calcineurin inhibitors (CNI), cyclosporine A (CsA) or tacrolimus (Tac), as the first-line therapy. Both CNI may produce renal side effects, which are typically stronger in patients receiving CsA. Sustained clinical demand for CsA requires improved understanding of mechanisms underlying its nephrotoxicity. CsA builds complexes with cyclophilins, whereas Tac recruits FKBP12 for calcineurin inhibition. We hypothesized that cytotoxic effects of CsA may be related with impaired chaperone function of cyclophilins resulting in endoplasmic reticulum (ER)-stress and pro-apoptotic unfolded protein response (UPR).

Methods: Effects of CsA vs. Tac (10 μM for 6 h) on the UPR signaling were compared in cultured native HEK293 cells, as well as in genetically modified cells lacking critical ER-stress sensors, PERK or ATF6. An established ER-stress inducer, thapsigargin (Tg) served as a positive control.

Results: CsA and Tg, but not Tac, induced ER-stress and UPR in native HEK293 cells, which was reflected by increased abundance of key UPR products (CHOP, spliced XBP1, and phosphorylated IRE1a). Furthermore, CsA but not Tac increased the abundance of caspase 3-(cCas3) suggesting stimulated apoptosis. Similar to CsA, knockdown of cyclophilin A or cyclophilin B using siRNA augmented CHOP and cCas3 levels. Deletion of PERK or ATF6 blunted the CsA-induced UPR. Furthermore, the CsA-dependent ER-stress was significantly reduced by concomitant application of chemical chaperones, TUDCA or 4-PBA.

Conclusions: In summary, these results suggest that renal side effects of CsA are partially mediated by suppression of cyclophilins, ER-stress, and pro-apoptotic UPR. Pharmacological modulation of UPR bears potential to alleviate the CsA nephrotoxicity.

Funding: Government Support - Non-U.S.

PO2050

Prolonged IL-6 Secretion Activates Inflammation Amplifier Loop (IL-6+IL-17) in Fibroblast Derived from Chronic Antibody-Mediated Rejection in Renal Allograft Recipient

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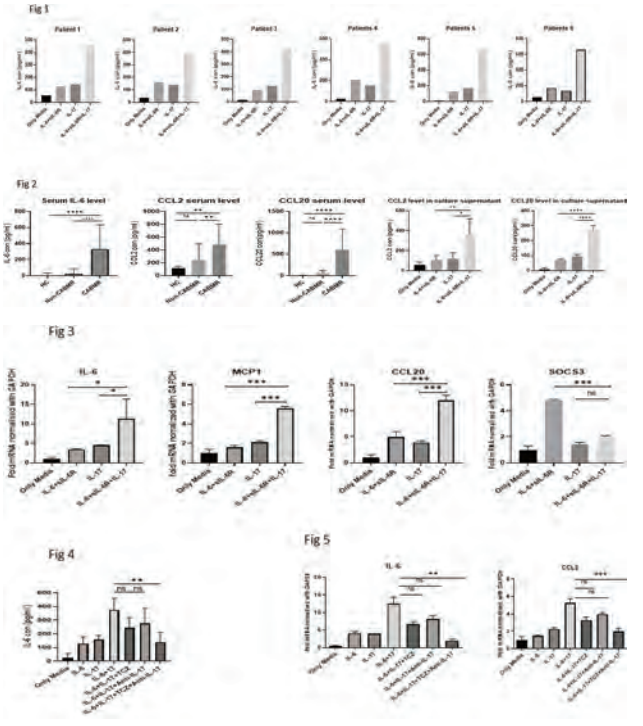
Background: Recently, non-immune cells like fibroblast have been postulated to mediate allograft rejection via activation of the IL-6 amplifier loop. We evaluated IL-6 amplifier loop activation by IL-6 and Il-17 in chronic antibody mediated rejection (CABMR).

Methods: Fibroblasts from grafted kidneys from CABMR patients (n=6) were cultured, stimulated with IL-6 (20ng/ μl), IL-17(50ng/ μl), IL-6 plus IL-17 for 24 hours. Levels of IL-6, MCP-1, and CCL20 were estimated in culture supernatants by ELISA as markers of IL-6 amplifier loop activation mRNA expression of IL-6, MCP1, CCL20, SOCS3 genes were measured in the stimulated fibroblasts. Additionally, IL-6, MCP1, and CCL20 levels were measured in Healthy control (n=10) CABMR (n=20) and non-CABMR (n=30) patients.

Results: IL-6 and IL-17 synergistically induced more IL-6, CCL-20 & MCP-1 production from fibroblasts. **Fig1** Gene expression analysis of IL-6, MCP1, and CCL20 was significantly higher with synergistic activation of IL-6 and IL-17 as compared to either IL-6 or IL-17 alone, while SOCS3 gene expression was downregulated. **Fig 3**. Additionally, concentrations of IL-6, CCL-20 & MCP-1 in sera were significantly higher in CABMR patients compared to non-rejection patients ($p<0.001$). **Fig 2**. There was a significant reduction in IL-6 concentration in culture supernatant with IL-6 and IL-17 inhibitor together **Fig 4** and mRNA expression of IL-6 and MCP-1 was significantly reduced. **Fig 5**.

Conclusions: CABMR is perpetuated by inflammation amplifier loop or synergistic induction of IL-6 and IL-17. Inhibition of IL-6 with Anti-IL-6 (Tocilizumab) and IL-17 with Anti-IL-17 together reduces the tissue injury marker IL-6, MCP1, CCL20 and allograft rejection.



PO2051

Circulating Donor-Specific Anti-HLA Antibodies Induce Immune Activation Independent of Kidney Transplant Histopathological Findings

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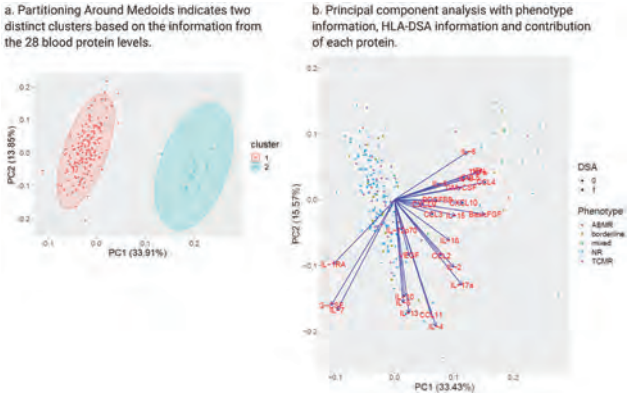
Background: Despite the critical role of cytokines in allograft rejection, the relation of peripheral blood cytokine profiles to clinical kidney transplant rejection has not been fully elucidated.

Methods: Levels of 28 cytokines were assessed using multiplexed Luminex testing in 293 peripheral blood samples, collected at time of a kidney allograft biopsy for graft dysfunction within the first year after transplantation in a cohort of 192 consecutive transplants at a single kidney transplant center.

Results: Unsupervised hierarchical clustering identified a subset of patients with increased pro-inflammatory cytokine levels (Figure a, cluster 2). This patient subset (N=20) was hallmarked by high prevalence (75%) of donor-specific anti-human leukocyte antigen antibodies (HLA-DSA) (Figure b) and histological rejection (70%), and had worse graft survival compared to the group with low cytokine levels (N= 172, HLA-DSA in 1.7% and rejection in 33.7%). Serum C-reactive protein and polyomavirus and/or CMV viremia did not differ between the two clusters. Thirty percent of patients with high pro-inflammatory cytokine levels and HLA-DSA did not have histological rejection. Single-cell RNAseq analysis on public data from kidney transplant biopsies demonstrated expression of these cytokines in endothelial cells, non-classical monocytes and natural killer cells. We confirmed the inflammatory cytokine profiles in *in vitro* models of HLA-DSA-mediated crosstalk between endothelial cells, NK cells and monocytes.

Conclusions: The expression of pro-inflammatory cytokines is increased in peripheral blood of kidney transplant patients with circulating HLA-DSA, even in the absence of histopathology of rejection. These results challenge the vision that kidney transplant histology is the gold standard for identification of ongoing allo-immune processes.



PO2052

Increased Autoantibodies Against Ro/SS-A, CENP-B, and La/SS-B in Patients with Kidney Allograft Antibody-Mediated Rejection

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Background: Antibody-mediated rejection (AMR) causes >50% of late kidney graft losses. In addition to anti-HLA donor-specific antibodies (DSA), antibodies against non-HLA antigens are also linked to AMR. Identifying key non-HLA antibodies will improve our understanding of AMR.

Methods: We analyzed non-HLA antibodies in sera from 80 kidney transplant patients with AMR, mixed rejection, acute cellular rejection (ACR), or acute tubular necrosis (ATN). IgM and IgG antibodies against 134 non-HLA antigens were measured in serum samples collected pre-transplant or at the time of diagnosis.

Results: Fifteen non-HLA antibodies were significantly increased ($p<0.05$) in AMR and mixed rejection compared to ACR or ATN pre-transplant, and seven at diagnosis. AMR and mixed cases showed significantly increased pre-transplant levels of IgG anti-Ro/SS-A and anti-CENP-B, compared to ACR. Together with IgM anti-CENP-B and anti-La/SS-B, these antibodies were significantly increased in AMR/mixed rejection at diagnosis. Increased IgG anti-Ro/SS-A, IgG anti-CENP-B and IgM anti-La/SS-B were associated with the presence of microvascular lesions and class-II DSA ($p<0.05$). Significant increases in IgG anti-Ro/SS-A and IgM anti-CENP-B antibodies in AMR/mixed rejection compared to ACR were reproduced in an external cohort of 60 kidney transplant patients.

Conclusions: This is the first study implicating autoantibodies anti-Ro/SS-A and anti-CENP-B in AMR. These antibodies may participate in the crosstalk between autoimmunity and alloimmunity in kidney AMR.

PO2053

A Sliding Window Approach to Investigate the Role of Donor-Recipient Interindividual Genetic Distance on Kidney Transplant Outcome

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Background: Although the role of HLA matching on kidney transplant outcome is well appreciated, the role of genetic matching between donors and recipients outside of the HLA region is less well understood. This is important as histological damage is a major issue in allografts and studies have suggested that non-HLA immune factors play a significant role in this process. However, the mechanism involved is presently unknown. Previous studies on relatively small datasets have looked at the role of genetic distance on kidney transplant outcome and found significant effects on graft survival. The regions of the genome which may contain these genes have not yet been searched for. Several methods can estimate genetic distance (mismatch) such as IBS, which measures allelic sharing or IBD which measures haplotype sharing.

Methods: Using 2,122 genotyped donor-recipient pairs from the United Kingdom and Ireland Renal Transplant Consortium (UKIRTC), we performed a survival analysis using a Cox Proportional Hazards model, investigating the role of various clinical and genetic factors. We focused investigation on the impact of IBS and total length of IBD between donor and recipient on kidney transplant outcome. We then used a sliding window approach to test the association between mismatch at any autosomal region of the genome and graft survival. This used a sliding window of 3 million base pairs on both IBS and IBD, resulting in 947 regions of the genome to be tested for association.

Results: Several clinical covariates were found to be significantly associated with graft survival; graft number (Bonferroni-Holm p-value: 1.5×10^{-7}), donor age (8×10^{-5}) and total HLA mismatch (0.03). These are well established risk factors, confirming the veracity of our methodology. Although a window at the start of chromosome 6 in the HLA region was the most significant, we did not detect a statistically significant association between IBS or total length of IBD and graft survival after correction for multiple testing.

Conclusions: We were unable to find an association between either IBS or total length of IBD and graft survival. In addition, there was no particular region of the genome that had a significant association with survival (though the effect of the HLA region was the most significant).

Funding: Government Support - Non-U.S.

PO2054

Prevention of Triglyceridemia by (Non-)Anticoagulant Heparin(oids) Does Not Preclude Transplant Vasculopathy and Glomerulosclerosis

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Background: Chronic Transplant Dysfunction (CTD) is associated with increased PCSK9 and dyslipidemia. We recently showed defective lipoprotein clearance by increased PCSK9–hepatic syndecan-1 interaction in renal condition. Targeting PCSK9 by heparin(oids) might be a therapeutic option to improve dyslipidemia and CTD. We investigated the effects of (non-)anticoagulant heparin(oids) on serum lipids, syndecan-1 and PCSK9 levels and CTD development.

Methods: Kidney allotransplantation was performed from female Dark Agouti to male Wistar Furth recipients. Transplanted rats received daily subcutaneous injections of saline, unfractionated heparin, RO-heparin or NAc-heparin (2mg heparin(oid)/kg BW) until sacrifice after 9 weeks of treatment.

Results: Saline-treated recipients developed hypertension, proteinuria, and loss of creatinine clearance, (all $p<0.05$ compared to baseline), along with glomerulosclerosis and arterial neointima formation. Saline-treated recipients showed significant increase in plasma TGs ($p<0.05$), borderline increase in non-HDLc to HDLc ratio ($p=0.051$), approximately 10-fold increase in serum syndecan-1 ($p<0.05$), without significant increase in serum PCSK9 level at 8 weeks compared to baseline. Heparin and non-anticoagulant RO-heparin administration in transplanted rats completely prevented increase in TGs compared to saline treated recipients at 8 weeks (both $p<0.05$). Heparin(oids) treatment did not influence serum TC, plasma syndecan-1 and PCSK9 levels, creatinine clearance, proteinuria, glomerulosclerosis and arterial neointima formation, 8 weeks after transplantation. Combining all groups, increased syndecan-1 shedding was associated with TC ($r=0.5$; $p=0.03$) and with glomerulosclerosis ($r=0.53$; $p=0.021$), whereas non-HDLc/HDLc ratio associated with neointima score in the transplanted kidneys ($r=0.65$; $p<0.001$).

Conclusions: Prevention of triglyceridemia by (non)anticoagulant heparin(oid) did neither influence PCSK9/syndecan-1, nor precluded CTD, which did however associated with shedding of lipoprotein clearance receptor syndecan-1 and unfavorable cholesterol profile.

PO2055

RBT-9 Antiviral Activity Against BK Virus

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Background: BK virus, a member of the polyomavirus family, is a significant risk factor for nephropathy and subsequent allograft loss in patients undergoing kidney transplantation. There are currently no approved treatments for BK virus-induced nephropathy. RBT-9, a novel formulation of stannous protoporphyrin (SnPP), exhibits broad antiviral activity against enveloped and nonenveloped viruses in vitro. It is also known to be protective against acute kidney injury (AKI) in animals when given prior to insult. Given the dual antiviral and kidney protective effects of RBT-9, the effect of RBT-9 against BK viral infection was investigated in vitro, as standard in vivo models that mimic BK virus complications are not currently available.

Methods: Two conditions were investigated: 1) standard qPCR-based antiviral assay – treatment with RBT-9 at the time of infection and 2) viral neutralization – pre-incubation of RBT-9 with BK virus for 1 hour prior to infection. RBT-9 was tested at concentrations up to 100 μM. Human foreskin fibroblast (HFF) cells were used as the host cell. Viral activity was assessed by real time qPCR and cellular viability was determined by CellTiter-Glo.

Results: RBT-9 exhibited moderate antiviral activity against BK virus under both treatment conditions. The 50% effective concentration (EC_{50}) averaged 5.5 μM in 2 independently run standard qPCR assays and 5.4 μM in the neutralization assay. The EC_{50} of RBT-9 in these assays is 11 times lower than the highest dose of RBT-9 tested in Phase 1 studies and considered to be well tolerated. The 50% cytotoxic concentration (CC_{50}) in the in vitro studies averaged 89.2 μM, indicating RBT-9 did not adversely affect host cell viability at concentrations 16.5 times higher than its effective concentration.

Conclusions: Given the antiviral activity of RBT-9 against BK virus in vitro and the safety profile of RBT-9 in Phase 1 human studies, a clinical study assessing the efficacy of RBT-9 is warranted in patients who are at risk of developing BK virus-induced nephropathy.

Funding: Other NIH Support - National Institute of Allergy and Infectious Diseases, Commercial Support - Renibus Therapeutics, Inc.

PO2056

The Survival Benefit of Re-Kidney Transplantation in Older and Younger Patients with Graft Failure

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Background: The survival benefit of re-kidney transplantation (re-KT) has been demonstrated two decades ago in younger patients. The proportion of patients with graft failure is increasing, particularly among those aged≥65. We compared the survival benefit of re-KT by patient age.

Methods: Using data from the Scientific Registry of Transplant Recipients, we identified 42,366 patients who experienced graft failure after their first KT and were listed for re-KT between 1990-2019. We treated re-KT as a time-dependent variable and used Cox regression to compare the risk of mortality between being listed for a re-KT and undergoing re-KT. We used the inverse probability weighting method to account for potential confounding. We also tested whether the risk of mortality differed by patient age at listing (18-64 versus ≥65 years) using a Wald test.

Results: Overall, 42,366 patients were listed for re-KT and 47.5% underwent re-KT by 10/31/2020. The number of patients being listed for re-KT tripled between 1990 and 2019. The mortality rate was 6.6 per 100 person-years among patients being listed and 3.0 per 100 person-years among those retransplanted. Overall, the risk of mortality was lower after re-KT than during listing (adjusted hazard ratio [aHR]=$_{0.42}0.43_{0.45}$). However, the association differed by age ($P_{interaction}$=0.03), but the survival benefit of retransplant was observed among both younger (aHR=$_{0.41}0.42_{0.44}$) and older patients (aHR=$_{0.43}0.49_{0.55}$).

Conclusions: Our finding suggests that re-KT is associated with a significant survival benefit in younger and older patients. In addition, long-term outcomes in older re-KT recipients were reported comparable to those in older first KT recipients. Transplant centers should consider expanding re-KT to appropriate older adults.

Funding: NIDDK Support, Other NIH Support - NIAID, NIA

Figure 1. Trends in being listed for retransplant and mortality rate per 100 person-years by calendar year of listing.

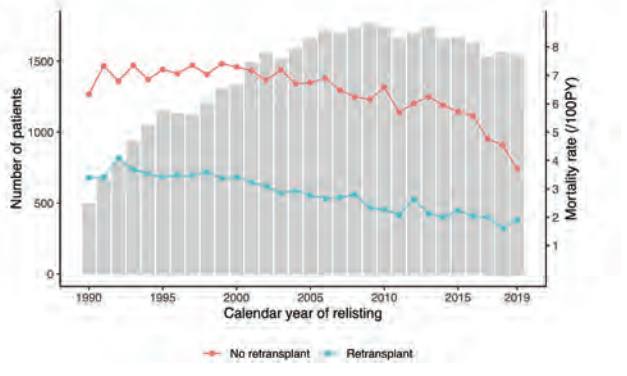

Table 1. Mortality rates per 100 person-years and adjusted hazard ratio for mortality comparing retransplant with being listed by age (18-64 versus ≥65 years)

	No retransplant (n=22,222)	Retransplant (n=20,144)	aHR (95% CI)[1]	P for interaction
Overall	6.6	3.0	$_{0.42}0.43_{0.45}$	-
Age, years				0.03
18-64 (n=40,016)	6.3	2.8	$_{0.41}0.42_{0.44}$	-
≥65 (n=2,350)	8.3	6.3	$_{0.43}0.49_{0.55}$	-

[1]Adjusted for age, sex, race/ethnicity, education level, insurance, body mass index, hypertension, diabetes, malignancy, lifetime of first allograft, listed before failure using the inverse probability weighting method.

PO2057

Development and Determinants of Quality of Life After Kidney Transplantation in Elderly Recipients

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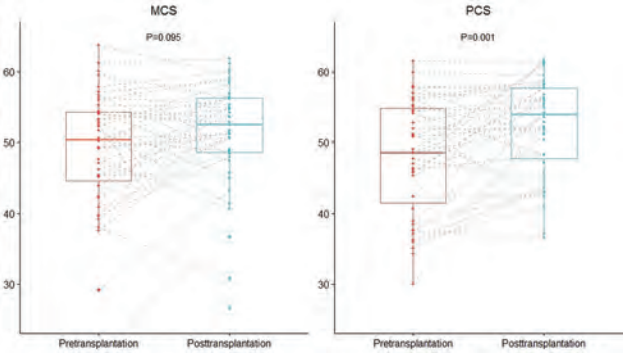
Background: Kidney transplantation is regarded as the best treatment for end-stage kidney disease, with survival benefits also in elderly patients. However, little is known regarding (determinants of) health-related quality of life (HRQoL), and changes in HRQoL in elderly kidney transplant recipients (KTR).

Methods: We used data from KTR ≥65 years old at the time of kidney transplantation, enrolled in the ongoing prospective TransplantLines Biobank and Cohort Study. Data on HRQoL were assessed using SF-36 mental and physical component scores (MCS and PCS). Side effects of immunosuppressive drugs were assessed using MTSOSD-59R questionnaires. In a subgroup with available data on HRQoL before transplantation, we investigated HRQoL trajectories.

Results: We included 111 KTR (age 70±4 years, 39% pre-emptive and 45% living procedures). At one year after transplantation, eGFR was 48±16 ml/min/1.73m, MCS was 51±8, and PCS was 52±7. MCS was lower in females ($P_{t\text{-}test}$=0.018), and in KTR that suffered from rejection in the first year ($P_{t\text{-}test}$=0.005). PCS was higher in KTR that were pre-emptively transplanted ($P_{t\text{-}test}$=0.010) and lower in those with post-transplantation diabetes mellitus (PTDM, $P_{t\text{-}test}$=0.008). Number of side-effects of immunosuppressive drugs was strongly associated with both MCS and PCS (both $P_{linear\ regression}$<0.001). Age, eGFR, hemoglobin, pre-transplant comorbidities, hospitalizations and infections in the first year were not associated with HRQoL. In 43 KTR with available data both before and after transplantation, PCS increased significantly after transplantation (48 to 52; $P_{paired\ t\text{-}test}$ = 0.001, **Figure 1**), while MCS did not significantly improve (49 to 51; $P_{paired\ t\text{-}test}$ = 0.095).

Conclusions: Medication-related side-effects, transplant rejection, transplantation after start of dialysis and PTDM were associated with worse HRQoL among elderly KTR, whereas eGFR and age were not. Moreover, HRQoL improves after kidney transplantation in KTR ≥65 years old.



PO2058

Elderly Kidney Transplantation Donors After Circulatory Death: Is It Worth It?

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Background: Kidney transplantation (KT) remains the treatment of choice for end-stage renal disease, since it offers better outcomes and quality of life and is less costly in the long run compared with stay on dialysis. In order to expand the donor pool, donation after circulatory death (DCD) has become an increasingly popular strategy, and eligibility criteria for this procedure have widened in the last few years.

Methods: Single-center retrospective study in which we described the clinical characteristics and outcomes of all the patients who underwent Maastricht category-III (controlled) DCD (cDCD) KT from January 2006 to October 2019. IBM SPSS (v25.0) was used for all the statistical analysis. Two-sided p values of <0.05 were considered statistically significant.

Results: We performed 54 cDCD KT, median follow-up was 36 (0.5-155) months. Donors' mean age was 50.2 years (range 19-81), 20.4% were ≥70 years, 64.8% male, 22.2% diabetics, 25,9% suffered hypertension. 24 (44.5%) recipients presented delayed graft function and 6 (11.1%) suffered primary nonfunction, with no differences depending on donor age (≥ or <70 years). Primary nonfunction was the main cause of graft loss, which occurred in 8 patients (14.8%), and it was significantly higher in donors ≥70 years old (p=0.021). In the multivariant analysis only donor age ≥70 years was related to graft loss. Other factors examined such as cold ischemia time >14 hours, warm ischemia time >17 minutes and the presence of cardiovascular disease, didn't show statistically significant differences. At one-year follow-up, renal function was significantly better in donors <70 years compared to donors ≥70 years, with mean serum creatinine 1.4 vs 2.1 mg/dl respectively (p=0.003), and estimated filtration rate 36.4 ± 19 vs 57.9 ± 18.9 ml/min per 1.73 m2 (p=0.008). The mortality rate was higher among recipients from older donors (3 [23.7%] vs 2 [4.6%], p=0.021).

Conclusions: cDCD KT donors ≥70 years have inferior outcomes than KT from donors <70 years concerning graft loss, overall survival and renal function 12 months after transplantation. Therefore, it is essential to evaluate cautiously whether or not to proceed with this transplants.

PO2059

Immunosuppression, Osteoporosis, and Fractures in Younger and Older Adults After Kidney Transplantation

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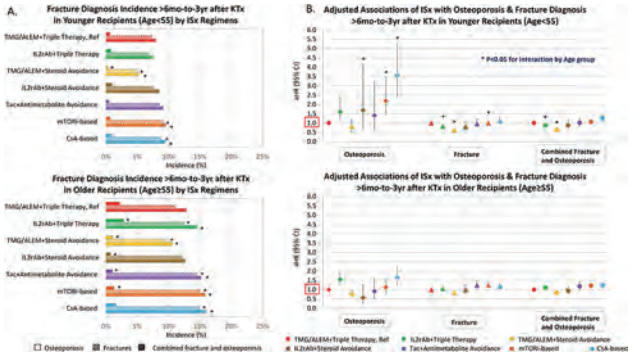
Background: Osteoporosis and fractures are important complications among kidney transplant recipients (KTx) that may be exacerbated by immunosuppression (ISx) and aging. We examined relationships of osteoporosis and fractures with ISx among older and younger adults in a national sample of Medicare beneficiaries.

Methods: We examined USRDS data (2005-2017) to explore associations of ISx regimens (within 6 mo) with osteoporosis and fracture diagnoses >6 mo-to-3 yr post-KTx among Medicare-insured younger (age <55) and older (aged ≥ 55) adults. We used multivariate Cox regression with inverse propensity weighting to compare cancer risk vs. reference regimen of Thymoglobulin (TMG) or Alemtuzumab (ALEM) + Tacrolimus + antimetabolite + prednisone.

Results: Among 67,362 KTx Medicare-insured recipients, the 3-year composite risk of osteoporosis and fractures varied by age and ISx regimen. Among older adults, incidence ranged from 11% with TMG/ALEM no Pred, to 16% in those managed with CsA and mTORi-based regimens (**Fig. A**) In adjusted models, TMG/ALEM + no Pred was y associated with lower risk (aHR, $_{0.76}0.84_{0.792}$) than TMG/ALEM + triple therapy (**Fig. B**). Conversely, mTORi-based regimens (aHR,$_{1.08}1.23_{1.40}$) and CsA-based regimens (aHR, $_{1.07}1.21_{1.38}$) were associated with greater risk. Patterns were generally similar but relative impacts were amplified in younger patients, including greater benefits of steroid-avoidance (aHR, $_{0.55}0.55_{1.38}$).

Conclusions: Among Medicare insured KTx recipients, steroid avoidance after TMG/ALEM inductions is associated with reduced risk of fractures and osteoporosis. Fracture risk is a consideration in tailoring ISx in older KTx recipients.

Funding: NIDDK Support



Osteoporosis and fracture incidence (A) and adjusted risks (B) in relation to ISx, in younger and older adult KTx recipients

PO2060

Organ Procurement and Transplantation Network Effort to Increase Kidney Transplantation Through Kidney Accelerated Placement

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Background: In 2017 just over a quarter of kidneys deemed hard to place were transplanted while the rest were discarded. The Kidney Accelerated Placement (KAP) project aimed to increase the acceptance of these deceased donor kidneys, declined by a large proportion of programs, through the creation of a novel allocation system. Offering hard-to-place kidneys to transplant centers with a history of transplanting similar organs, utilization would increase by reducing time to find an acceptor and cold ischemia time (CIT) within the deceased organ allocation process. We hypothesized CIT mediated the effect of KAP on transplant center organ-level offer acceptance.

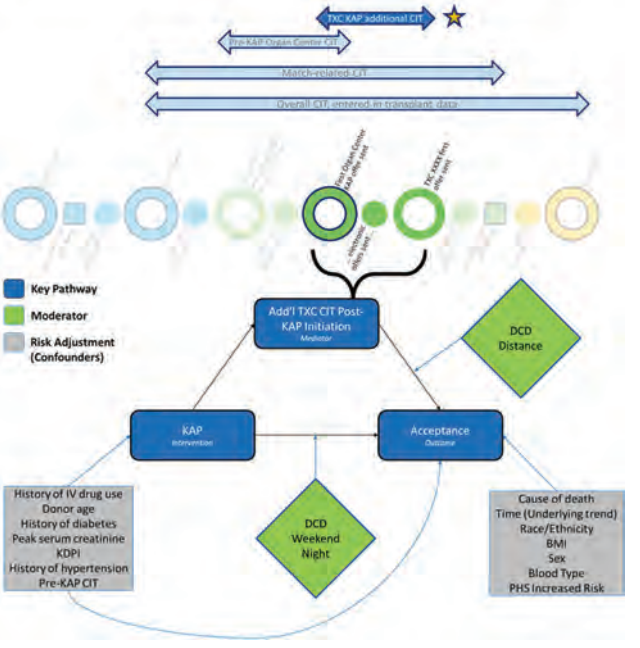
Methods: We used a pre/post design mediation analysis with OPTN database offers from kidney matches meeting criteria for KAP 7/18/18-7/15/19 (pre-KAP) and 7/18/19-7/15/20 (KAP). We employed logistic regression models of KAP and CIT on organ acceptance and a linear regression model of KAP on CIT, adjusting for additional risk factors (Fig 1).

Results: Transplant center organ-level offer acceptance rates were 0.37%(pre-KAP) and 0.23%(KAP). The total effect indicates that KAP increased odds of acceptance by 0.07. Decreases in CIT increased odds of acceptance by 0.02 (indirect effect) and the remaining portion of the total effect is attributable to other possible mechanisms (direct effect).

Conclusions: While KAP affected offer acceptance, the magnitude of the effect was small. Because the baseline level of offer acceptance was also small, our analysis indicates that KAP works conceptually to increase the use of these kidneys. At the same time, there is evidence that alternative approaches to KAP are needed to potentially decrease organ discard. Future iterations plan to consider complex risk adjustment including behaviors and the differential impact for donor types.

Figure 1. Directed acyclic graph (DAG) illustrating the relationships measured.

BMI = body mass index, CIT = cold ischemia time, DCD = donation after circulatory death, IV = intravenous, KAP = Kidney Accelerated Placement, KDPI = kidney donor profile index, PHS = Public Health Service, TXC = transplant center.



PO2061

A Geospatial Method to Improve Sociodemographic Characterization of Transplant Referral Regions

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Background: Progress towards health equity in kidney transplant requires robust characterization of transplant center referral populations. Transplant referral regions (TRRs) define geographic catchment areas for transplant centers in the United States and have previously been linked to sociodemographic data using ZIP codes. We compared a spatial intersection method to a ZIP code crosswalk method of linking sociodemographic data to TRRs.

Methods: A spatial intersection method was used to assign census block groups to TRRs based on area of intersection. We compared the spatial congruence of the spatial intersection and ZIP code crosswalk methods by calculating the number of census block groups assigned to more than one TRR and calculating the total area assigned to the incorrect TRR.

Results: We defined 105 TRRs for 238 transplant centers (figure 1a). The ZIP code crosswalk method resulted in 4,627 census block groups being included in more than one TRR, while the spatial intersection method eliminated this problem. The spatial method resulted in a mean and median reduction in misassigned area of 65% and 83% across all TRRs, respectively, compared to the ZIP code crosswalk method (figure 1b).

Conclusions: Characterizing TRRs with census block groups increases spatial resolution, and provides more balanced population counts. Our spatial approach avoids errors due to duplicative assignments and allows more accurate characterization of referral population sociodemographics. This approach can enrich transplant center knowledge of local referral populations, assist researchers in understanding the influence of social determinants of health on access to transplant, and inform interventions to improve heath equity.

Funding: Other NIH Support - Research reported in this publication was supported by the National Institute on Minority Health and Health Disparities under Award Number U54MD012530., Private Foundation Support

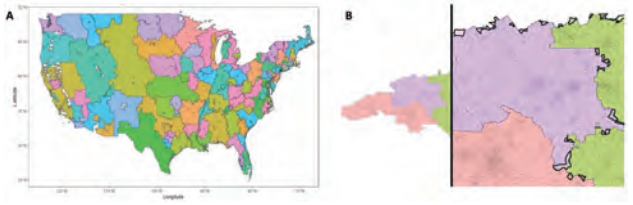

Figure 1A. National Kidney transplant referral regions (TRRs). Figure 1B. Left: Census block groups colored by TRR in North Carolina. Right: Spatial congruence between census block group boundaries and derived TRR boundaries; bold lines show misassigned area.

PO2062

Association of Medicaid Expansion with Medicaid Uptake and Uninsurance Among US Kidney Transplant Recipients

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Background: The differential uptake of Medicaid expansion among U.S. states following the Affordable Care Act created a natural experiment to investigate the association between Medicaid expansion and health insurance usage patterns among kidney transplant (KT) recipients. Adolescents and young adults (AYA) are at particular risk for insurance access disruption.

Methods: Using data from the Scientific Registry of Transplant Recipients, we constructed a multivariable difference-in-differences model to evaluate the association between living in a state with Medicaid expansion (vs. a state without) and two outcomes: primary insurance of Medicaid at the time of KT, and being uninsured 5 years following KT. We included U.S. recipients of kidney-alone transplantation between 1/1/2005 and 3/12/2020. We analyzed AYA (ages 15-26 years) and other nonelderly adults (ages 27-64 years) separately.

Results: The AYA group included 17,158 KT recipients, while the group of adults 27-64 years included 198,914 KT recipients. The effect of living in a Medicaid expansion state (vs. a nonexpansion state) on use of Medicaid as the primary insurance type at the time of KT was +1.9% (95% CI -0.4% to +4.3%) for the AYA group and +1.7% (95% CI +1.3% to +2.1%) for the non-elderly adult group. The effect of living in a Medicaid expansion state (vs. a nonexpansion state) on being uninsured 5 years after KT was -3.6% (95% CI -6.5% to -0.7%) for the AYA group and -0.9% (95% CI -1.3% to -0.4%) for the non-elderly adult group.

Conclusions: Living in a Medicaid expansion state was associated with greater use of Medicaid at the time of KT for adults ages 27-64, but not in the AYA group. In both age groups, living in a Medicaid expansion state was associated with a modest reduction in being uninsured 5 years following KT. Increased access to Medicaid may provide a protective effect against becoming uninsured after KT.

Funding: NIDDK Support

Results of difference-in-differences analysis examining the association of exposure to Medicaid expansion with insurance outcomes among U.S. KT recipients.*

Outcome	Age group (years)	Adjusted change after expansion in EXPANSION states, percentage points (95% CI)	Adjusted change after expansion in NON-EXPANSION states, percentage points (95% CI)	Adjusted difference-in-differences estimate, percentage points (95% CI)
Medicaid as primary insurance at the time of KT	15-26	+4.1 (+2.6, +5.6)	+2.6 (+0.9, +4.2)	+1.9 (-0.4, +4.3)
	27-64	+2.2 (+1.9, +2.5)	+0.8 (+0.5, +1.0)	+1.7 (+1.3, +2.1)
Uninsured 5 years following KT	15-26	-1.1 (-2.6, +0.3)	+2.8 (+0.2, +5.3)	-3.6 (-6.5, -0.7)
	27-64	-0.4 (-0.6, -0.1)	+0.2 (-0.1, +0.6)	-0.9 (-1.3, -0.4)

*Adjusted for gender, race/ethnicity, cause of kidney failure, year of KT, and state fixed effects.

PO2063

Construct Validity of the Patient-Reported Outcomes Measurement Information System (PROMIS®) Profile Summary Scores in Patients with Kidney Failure

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Background: The PROMIS® profiles include a single pain intensity item and 7 multi-item scales (e.g., physical function, fatigue, depression, social participation, etc.). These domains can be summarized into physical (PHS) and mental health summary (MHS) scores. We examine correlations of the PHS and MHS with generic and kidney-disease targeted measures in patients treated with kidney replacement therapies and compare the summary scores between patients on dialysis vs kidney transplant.

Methods: Cross-sectional convenience sample of 606 adults. Higher PHS and MHS scores correspond to better health. We estimated correlations of the PHS and MHS with the SF-12 physical (PCS) and mental component score (MCS), the Patient Health Questionnaire (PHQ-9), EQ-5D-5L, KDQOL-36 symptom scores, and serum albumin. The PHS was hypothesized to be strongly associated with other measures of physical health, and the MHS with other measures of mental health.

Results: Correlations with the PROMIS PHS and MHS (Table) with legacy health-related quality of life measures were large. The patterns of correlations of the PHS and MHS were consistent with a-priori hypotheses. Patients on dialysis were older (mean[SD] age 64(14) vs 50(15) years), and less likely to be White (32% vs 68%); p<0.01 for all. Kidney transplant recipients reported better health than patients on dialysis: PHS (mean[SD] 47[10] vs 37[9], p<0.001) and MHS (50[9] vs 45[9], p<0.001) and this remained significant in multivariable adjusted (age, sex, ethnicity, marital status, comorbidity, serum albumin and hemoglobin) regression models (coefficient[95% CI] of difference between dialysis and transplant for PH:5.9 [3.8-7.9]; for MH: 3.2 [1.0-5.3]; both p<0.01).

Conclusions: These results support the construct validity of PROMIS PHS and MHS scores among patients treated with kidney replacement therapies. PHS and MHS was substantially better among kidney recipients compared to patients on dialysis.

Table

PROMIS Profile	PCS	MCS	PHQ-9	EQ5D5L	KDQOL-36 Symptoms	Serum albumin
PHS	0.81	0.39	-0.48*	0.66	0.58	0.44
MHS	0.65	0.66	-0.74*	0.67	0.69	0.24

Footnote: * : higher PHS and MHS indicates better health; higher PHQ-9 score indicates more severe depressive symptoms; the correlation is negative

PO2064

Association of Physical Performance with Death or Delisting in Patients Waitlisted for Kidney Transplantation

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Background: Patients awaiting kidney transplantation (KT) often report impairments in functional status, which are associated with higher risk of death or delisting. However, self-reported functional status is subjective and can differ from objective assessments of physical performance. We sought to determine whether objective metrics of physical performance were associated with death or delisting prior to KT and whether these metrics improve prediction of death or delisting compared with more routinely available clinical data.

Methods: We enrolled 443 patients from the UCSF KT clinic from 12/17–3/20 at an initial or re-evaluation for eligibility for a first KT. We administered the Short Physical Performance Battery (SPPB; including gait speed, balance, and sit-to-stand) and measured grip strength by dynamometer. We performed univariable and multivariable Cox models to examine the association between physical performance and death or delisting. We created models using combinations of metrics in addition to a "base" model for death or delisting (age, sex, diabetes, CAD, CVD, PVD, years on dialysis) and calculated Harrell's concordance index for each model.

Results: Median age was 55 years, and 63% were male. Median SPPB score was 10 (8, 11), with 25.1% having gait speed <0.8 m/s. In multivariable analysis, lower SPPB and slower gait were associated with higher risk of death or delisting, and higher grip strength with lower risk (Table 1). Compared with the base model (C-index 0.70, strongest predictor: age), addition of SPPB (0.74; p=0.03) and SPPB + grip strength (0.75, p=0.03) improved discrimination.

Conclusions: SPPB, grip strength, and slower gait were associated with death or delisting. SPPB and grip strength improved prediction of death or delisting. Transplant centers should consider routinely evaluating physical performance for waitlisted patients to help with clinical decision making.

Funding: NIDDK Support

Association of physical performance with death or delisting among 443 patients evaluated for primary KT

	Unadjusted HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value***
SPPB (per category)*	2.26 (1.70, 3.02)	<0.01**	1.99 (1.41, 2.81)	<0.01
Gait speed <0.8 m/s	2.55 (1.46, 4.47)	<0.01	1.89 (1.01, 3.52)	0.05
Grip Strength (per kg)	0.95 (0.92, 0.98)	<0.01	0.94 (0.90, 0.97)	<0.01

*SPPB: 10-12 [ref], 7-9, 4-6, <4

**Linear test for trend among categories of SPPB p <0.01

***Adjusted for covariates in "base" model

PO2065

Development of a Conceptual Model to Understand Disease Burden in Kidney Transplantation

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Background: While kidney transplantation offers patients with end stage kidney disease significant health benefits compared to dialysis, the immunosuppressive therapies designed to improve graft survival result in complex treatment regimens and side effects for patients. The development of new therapies to reduce this patient burden and improve long-term patient outcomes is needed. To guide selection of patient-reported outcome (PRO) measures for clinical trials, it is important to understand how patients feel or function related to a health condition or its treatment. This study sought to develop a preliminary conceptual model in kidney transplantation to provide a visual representation of the concepts of importance to patients (signs, symptoms, and impacts).

Methods: A targeted review of published literature was conducted in Embase, Medline, and PsycInfo databases to identify qualitative articles describing the patient experience following kidney transplantation and associated use of immunosuppressive treatment. Studies were selected based on number of concepts and direct patient quotations available for thematic analysis.

Results: From 61 eligible publications identified for full-text review, 20 were selected for data extraction. All studies involved qualitative interviews, focus groups, or analysis with kidney transplant recipients, and were conducted across various geographic locations (US, Europe and Australia). The most frequently reported concepts across studies included: 'feeling anxious/worried' (100%, n=20); 'feeling distressed, overwhelmed' (75%, n=15); 'fatigue' (60%, n=12); and 'weight gain/loss' (60%, n=12). The conceptual model identified nine domains to group the concepts as reported in the literature. These domains were delineated into the proximal effects of kidney transplantation (side effects and illnesses; physical/cosmetic changes; functional limitations; taxing medication regimen; and frequent medical appointments); and the more distal impacts (impacts on emotions, work, lifestyle, and relationships).

Conclusions: The conceptual model was based on a rich source of patient quotes and provides an important first step to understand the patient experience of kidney transplantation and inform the selection of PRO measures for use in clinical trials based on their conceptual coverage.

Funding: Commercial Support - Novartis

PO2066

Customizing PROMIS-Depression Computer Adaptive Testing Stopping Rules for Patients with Kidney Failure

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Background: The Patient Reported Outcomes Measurement Information System Depression (PROMIS-D) computer adaptive testing (CAT) allows precise and tailored assessment of depressive symptoms. Due to the default stopping rules, many respondents without depression may need to answer 10-12 items. The maximum number of items required by the stopping rule can be reduced which could improve efficiency when the tool is used for screening. We assess the screening performance of customized CAT stopping rules in patients with kidney failure.

Methods: A cross-sectional convenience sample of adults with kidney failure treated with dialysis or kidney transplant completed PROMIS-D CAT as well as the Patient-Health Questionnaire-9 (PHQ-9). Moderate/severe depressive symptoms were defined as a PHQ-9 cut-off score ≥10. Sociodemographic and clinical characteristics were obtained from self-report and medical records. All patients completed CAT using the original stopping rule (CAT_0) that requires a reliability of >90% or maximum 12 items. We compare this to three simulated CAT customizations with maximum 8, 6 and 4 items (CAT_8, CAT_6 and CAT_4) respectively. Reliable T score range (reliability is >90%), sensitivity and specificity of each version were assessed.

Results: Of the 336 patients, the mean SD age was 55(16), 63% were male, 49% were Caucasian and 32% were on dialysis. Based on PHQ-9, 16% reported moderate/severe depressive symptoms. Using a PHQ-9≥10 as a reference for moderate/severe depressive symptoms, sensitivity and specificity of a T score of 55 with CAT_0 was 79% and 81% respectively. CAT_8 presented no change in the reliable range (T-score 41 to 84), while CAT_6 and CAT_4 presented a small reduction in the reliable range (41-76 and 45-73 respectively) compared to CAT_0. Sensitivity and specificity of the modified CAT versions remained essentially the same.

Conclusions: Customizing PROMIS-D CAT stopping rules have the potential to improve efficiency of screening for moderate/severe depressive symptoms. This reduces question burden without change in the discrimination of the T score. A PROMIS-D CAT with modified stopping rule (maximum 6 or even 4 items) could be used for screening for depressive symptoms among patients with kidney failure.

PO2067

Pre-Transplant Sarcopenia Does Not Predict Graft Function or Mortality in Kidney Transplantation

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Background: Sarcopenia is common in end stage kidney disease (ESKD), and is associated with increased risk of cardiovascular events and mortality. The association between pre-transplant sarcopenia and post-transplant outcomes is unknown.

Methods: We conducted a single-center retrospective study to evaluate the association between pre-transplant psoas muscle cross-sectional area at level of L4 and post-transplant outcomes; change in graft function, length of hospitalization, rehospitalization at 30- and 90-days post-transplant, graft loss, and mortality.

Results: Of the 573 patients with pre-transplant CT images, 465 received kidney transplant (KT) alone, 71 received simultaneous liver-kidney transplantation (SLK), and 37 received simultaneous pancreas-kidney (SPK) transplantation. Pre-transplant psoas muscle cross sectional area was associated with longer hospitalization in KT alone and SPK transplants, but not with post-transplant graft function, rehospitalization rates or mortality (Table 1).

Conclusions: Unlike ESKD patients on dialysis, pre-transplant psoas muscle cross-sectional area is not associated with adverse post-transplant outcomes. Thus, sarcopenia should not be an exclusion criterion for transplant eligibility.

Cox proportional hazard models (adjusted for age, sex, race and diabetes) for normalized psoas cross sectional area and post-transplant outcomes.

	Exp(Estimate) (95%CI – HR)		
Model	KT alone	SLK	SPK
Change in eGFR	-0.005 (-0.01, 0.0009)	-0.01 (-0.03, 0.002)	-0.02 (-0.05, 0.0008)
Graft Loss	0.999 (0.998, 1.001)	0.99 (0.994, 1.004)	1.004 (0.996, 1.013)
Length of Hospitalization	-0.003 (-0.005, -0.0007)	-0.007 (-0.02, 0.004)	0.03 (0.01, 0.05)
30-day rehospitalization	1 (0.999, 1.001)	1 (0.998, 1.002)	0.999 (0.996, 1.003)
90-day rehospitalization	1.002 (0.9996, 1.0001)	1 (0.998, 1.002)	0.999 (0.996, 1.002)
Mortality	0.99 (0.996, 1.001)	0.99 (0.995, 1.002)	N/A

PO2068

Utility of Genetic Testing in Kidney Transplant Evaluation

Lauren Beretich,[1] Neeraj Singh,[2,3] Arianna Palermini,[4] Aleeza Qamar,[2,3] Daniel Luksic,[1] Sarah McCormick,[1] Hossein Tabriziani,[1] Paul R. Billings.[1] *[1]Natera, Inc., San Carlos, CA; [2]John C. McDonald Regional Transplant Center, Shreveport, LA; [3]Willis-Knighton Physicians Network, Shreveport, LA; [4]Arkansas College of Osteopathic Medicine, Fort Smith, AR.*

Background: Genetic testing is an emerging tool in pre-kidney transplant (KT) evaluations for individuals with end-stage renal disease (ESRD). A known genetic etiology can inform the risk of disease recurrence, guide transplant management, and enable evaluation of living related donors. Despite these benefits, there is a paucity of literature describing the use of diagnostic genetic testing as part of the pre-KT evaluation. Here we describe the initial experience incorporating a broad renal genetic testing panel for KT candidates in one Louisiana center.

Methods: A retrospective review was conducted on 31 patients that underwent a KT evaluation in April 2021 with Renasight™, a NGS-based >380-gene kidney disease test. The patients were primarily female (20/31), African American (16/31), and <50 years of age (17/31). The primary clinical causes of CKD were hypertension (HTN) and/or diabetes (20/31).

Results: Positive findings were identified in 32.3% (10/31) of patients in the *APOL1*, *CFI*, *COL4A4*, and *PKD2* genes. Additionally, 29.0% (9/31) of the patients were identified as heterozygous carriers of autosomal recessive conditions. Of the positive cases, 60% (6/10) were either homozygous or compound heterozygous for the G1 and G2 risk alleles in the APOL1 gene. One individual, heterozygous for a likely pathogenic variant (c.57+1G>C) in the *CFI* gene, associated with atypical hemolytic uremic syndrome, along with biopsy-proven thrombotic microangiopathy was tested for complement proteins in plasma. Due to the potential increased risk of recurrence, simultaneous liver-kidney transplant and Eculizumab was considered.

Conclusions: In this initial experience, kidney genetic testing was an informative tool resulting in a change in patient management. The genetic testing yield in this cohort is likely enriched as many of these patients had a positive family history of kidney disease, significant proteinuria, or ESRD attributed to HTN. Genetic testing in pre-KT patients has potential clinical impact on post-KT management and selection of living-related donors. Further research is needed to describe the utility of genetic testing for kidney transplant candidates.

PO2069

Transplant Clinician Opinions on Use of Race in the Estimation of Glomerular Filtration Rate: A National US Survey Study

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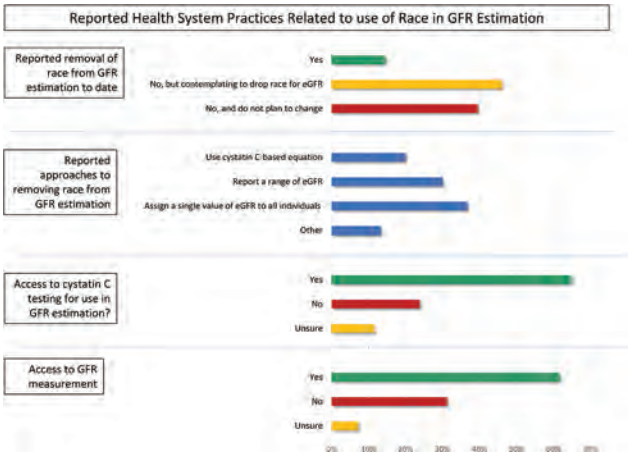
Background: Inclusion of race in eGFR calculation has raised controversies based on concern that assigning a higher GFR to Black patients delays opportunity for pre-emptive kidney transplant listing.

Methods: We conducted a survey of adult kidney transplant center staff in U.S (12/17/2020–2/28/2021) to assess opinions on use of race-based estimated GFR (eGFR) equations for waitlisting and living donor candidate evaluation, availability of serum cystatin-C testing and measured GFR, and related practices.

Results: Respondents represented 57% (124/218) of adult kidney transplant centers and 70.3% of recent practice volume. Nearly 95% of respondents felt that current race-based eGFR calculators need revision, primarily due to concerns around healthcare disparities and inaccuracies around reporting of race, particularly among multi-racial individuals. A majority of respondents (70.5%) believed that elimination of race would allow preemptive kidney transplant wait listing for Black patients, but a similar number (69%) also raised concern that removing race from GFR estimation could incur harms. One-third of responding programs lacked or were unsure of availability of cystatin C or mGFR at their institution. Nearly 15% of responding centers have removed race from GFR estimation and were either reporting eGFR for non-Black or ranges; 46% were planning to do so and 39.5% did not plan to change for now (**Figure**). There was no difference in GFR acceptance threshold for Black versus non-Black living donors.

Conclusions: This national survey highlights a broad consensus that extant approaches to eGFR calculations are unsatisfactory, but a range of opinion on what should replace the status quo. National consensus, guidelines, and infrastructure for laboratory testing are necessary to facilitate best practices to prevent further disparities in transplant care.



PO2070

Defining the Living Donor Transplant Evaluation Process for Optimization of a One-Day Evaluation Program

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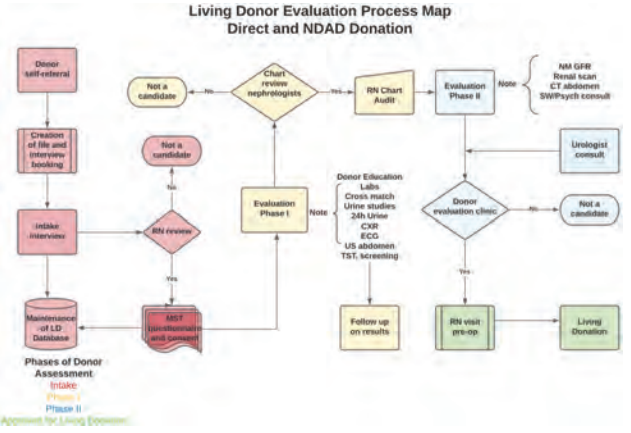
Background: Living donor transplantation provides patients with end stage kidney disease increased longevity and quality of life compared with dialysis. The donor evaluation process can be inefficient and costly for patients and the healthcare system. There is a paucity of research on evaluation optimization in living kidney transplantation. We investigated our living donor evaluation process to develop a one-day program, improving program efficiency.

Methods: Living donor staff and patient partner from The Ottawa Hospital Living Kidney Donor program participated in individual, semi-structured interviews to develop a Lucidchart process map of the donor evaluation process and ascertain the time associated with each step. A one-day evaluation program model was developed based on our process map and interview participant feedback. Amount of time for each step of the process was collected for future cost assessment.

Results: Mean time to complete the evaluation process and reach donor approval is 9 months. The donor evaluation process can be divided into 3 phases: Initial Interview, Phase I, and Phase II. Phase I requires the most nursing and administrative time. The greatest barriers to process efficiency are 24-hour urine collections to estimate kidney function and coordinator time spent on correspondence with laboratories. A one-day evaluation will reduce the evaluation process and approval to approximately 4 weeks. Greatest barriers for patients included need for increased education and time off work. Next steps will include cost estimates of the current program with the goal of implementing a one-day evaluation program at The Ottawa Hospital.

Conclusions: A one-day evaluation program will increase the efficiency of the living donor process for donors, coordinators, and recipients. Phase I investigations are a barrier to program efficiency and can be streamlined with a one-day evaluation. The development of donor educational resources will improve the donation experience for patients.



PO2071

Comparison of CT Volumetry vs. Nuclear Renography to Predict Remaining Kidney Function After Living Kidney Donation

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Background: Computed tomography(CT) and nuclear renography are performed to decide kidney procurement. The aim of this study was to compare single kidney(sk) function and single kidney(sk) volume in predicting post-donation kidney function. Further, we aimed to investigate which modality is better to decide which kidney is more appropriate in terms of kidney function recovery, especially when the results were contradictory.

Methods: CT volumetry and nuclear renography from 835 kidney donors were retrospectively included. We investigated correlation between sk-volume and sk-mGFR and the agreement of two modalities. Mismatch was defined as sk-volume higher and sk-mGFR smaller than the other kidney, or vice versa. We compared the predictive value for post-donation kidney function between two modalities in total group and in mismatched group. Based upon decision preference, we compared kidney function recovery between two modalities at 6 months after donation.

Results: Mean baseline estimated GFR was 100.01ml/min/1.73m^2. The mean right and left sk-volume were 171.18 and 179.71cm^3 and mean right and left sk-mGFR were 53.72 and 53.44ml/min, respectively. 701(83.96%) donated left kidney. Sk-mGFR and sk-volume showed significant correlation(r=0.484, P<0.001) and the results showed significant agreement in Bland-Altman plot and Intraclass correlation coefficient was 0.647(P<0.001). In total group, CT volumetry was superior to nuclear renography in predicting kidney function after donation(1 month: β_{CT}=0.402, P<0.001, $\beta_{renography}$=0.242, P<0.001; 6 months: β_{CT}=0.448, P<0.001, $\beta_{renography}$ =0.214, P<0.001) by multivariable linear regression analysis. In mismatched group(326 donors), CT volumetry still outweighed nuclear renography(1 month: β_{CT}=0.453, P<0.001, $\beta_{renography}$=0.259, P<0.001; 6 months: β_{CT}=0.480, P<0.001, $\beta_{renography}$=0.285, P<0.001). When mismatch occured, 260(79.75%) procurements were decided by nuclear renography. Functional recovery was higher in CT volumetry preferred group, although it did not reach statistical significance(33.99% vs 30.09%, P=0.098).

Conclusions: CT volumetry was appropriate to assess single kidney function and it outperformed nuclear renography in predicting kidney function after donation. Therefore, when contradictory results between left and right kidney occur, CT volumetry can be preferred in procurement strategy.

PO2072

The Impact of New-Onset Diabetes After Transplantation on Survival and Major Cardiovascular Events in Korean Kidney Transplantation Recipients

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Background: New-onset diabetes after transplantation (NODAT) is a frequent complication in kidney transplant (KT) recipients with unfavorable outcomes, although a nationwide study on epidemiology and clinical outcome of NODAT in Korean KT recipients remain rare.

Methods: We identified KT recipients by using a Health Insurance Review and Assessment Service of South Korea from the year of 2008 to 2017. We excluded patients with preexisting diabetes, multi-organ transplantation, and being progressed to graft failure less than 1 year after KT. NODAT was defined as consecutive 30 days prescription history of antidiabetic medication after KT. We analyzed the impact of NODAT on death censored graft failure (DCGF), death without graft failure (DWGF), and major adverse cardiovascular events (MACE) by time-dependent Cox analysis.

Results: Among a total of 16,719 KT recipients, 10,311 were included after exclusion. 19.8 percent of KT recipients were diagnosed to NODAT. The proportion of patients developing NODAT tended to increase, and 64% of NODAT was diagnosed within the first 6-months after KT. NODAT patients were older, more men, having longer pre-KT dialysis vintages, and being exposed more basiliximab induction and more rejection episodes requiring high-dose steroids treatment after KT. During follow-up, 520 DCGF, 180 DWGF, and 213 MACE events were occurred. NODAT patients showed higher risks of DCGF (adjusted hazard ratio [aHR], 1.87; 95% confidence interval [CI], 1.52-2.3; p < 0.001), DWGF (aHR 1.77;95% CI, 1.28-2.43;p<0.001), and MACE (aHR 1.46;95% CI, 1.08-1.96;p=0.013) than patients without NODAT. Twenty-one percent of NODAT patients could be stopped their anti-diabetic medications after the diagnosis, although this did not affect the clinical outcomes.

Conclusions: About 20% of diabetes-naïve KT recipients were diagnosed with NODAT with a recently increasing pattern. NODAT in KT recipients affected worse graft and patients outcomes as well as MACE.

Funding: Government Support - Non-U.S.

PO2073

Association Between Early Post-Transplant Hypertension or Related Antihypertensive Use and Prognosis of Kidney Transplant Recipients: A Nationwide Observational Study

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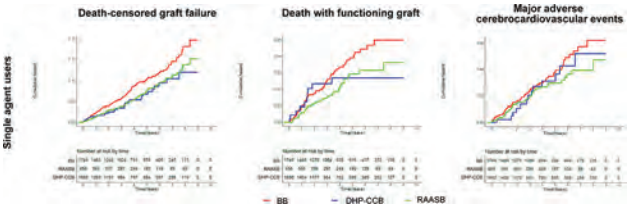
Background: Additional research is warranted for the clinical significance of post-transplant hypertension and related antihypertensive medication usage in kidney transplant (KT) recipients.

Methods: This observational study included nationwide KT recipients who maintained functioning graft for at least 1 year after KT in South Korea during 2008 to 2017. The usage of antihypertensive medications between 6 months to 1 year was the main exposure, and those who had inconsistent/transient usage of antihypertensive drugs were excluded. The prognostic outcome included death-censored graft failure (DCGF), death-with functioning graft (DWGF), and major adverse cerebrocardiovascular events (MACCEs).

Results: We included 8014 patients without post-transplant hypertension and 6114 recipients who received treatments for hypertension in the post-transplant period. Those with post-transplant hypertension had significantly worse risk of DCGF than those without [adjusted hazard ratio (HR) 1.27 (1.09-1.48)]. Post-transplant hypertension patients who required multiple drugs showed significantly higher risk of DWGF [HR 1.57 (1.17-2.10)] and MACCE [HR 1.35 (1.01-1.81)] than the controls. Among the single-agent users, those who received beta-blockers showed a significantly higher risk of DCGF, although the risks of DWGF or MACCE were similar between the types of antihypertensive agents. Among the multiple agent users, the prognosis was similar regardless of the prescribed types of antihypertensive agents.

Conclusions: Post-transplant hypertension was associated with poor post-transplant prognosis, particularly when multiple types of medications were required for treatment. During initial prescription of antihypertensive medication, clinicians may consider that beta-blockers were associated with a higher risk of DCGF in the single-agent users.



PO2074

Mortality, Graft Survival, and Cardiovascular Outcomes in Adult Kidney Transplant Recipients with Post-Transplant Anemia: An Updated Meta-Analysis

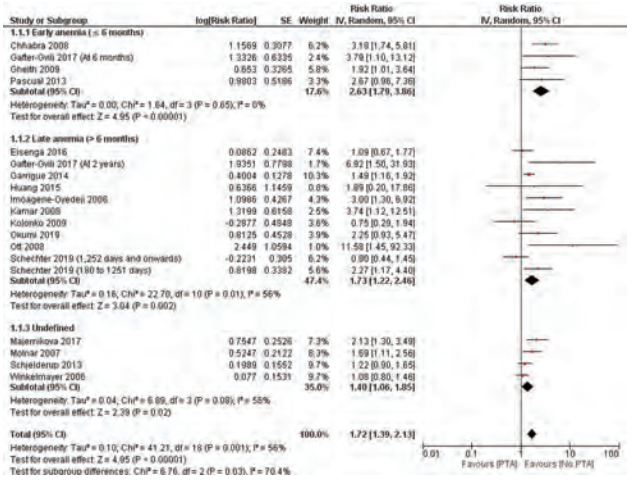
Poemlarp Mekraksakit,[1] Natnicha Leelaviwat,[1] Boonphiphop Boonpheng,[2] Wisit Cheungpasitporn,[3] Camilo Pena,[1] Gaspar Del Rio-Pertuz,[1] Ramesh Saxena.[4]
[1]Texas Tech University Health Sciences Center, Lubbock, TX; [2]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [3]Mayo Clinic Minnesota, Rochester, MN; [4]The University of Texas Southwestern Medical Center, Dallas, TX.

Background: Post-transplant anemia (PTA) is a common finding after kidney transplantation. A previous meta-analysis reported an association between PTA and graft loss. However, data on cardiovascular outcomes have not yet been reported. We conducted an updated meta-analysis to examine the association between PTA and prognosis in adult kidney transplant recipients.

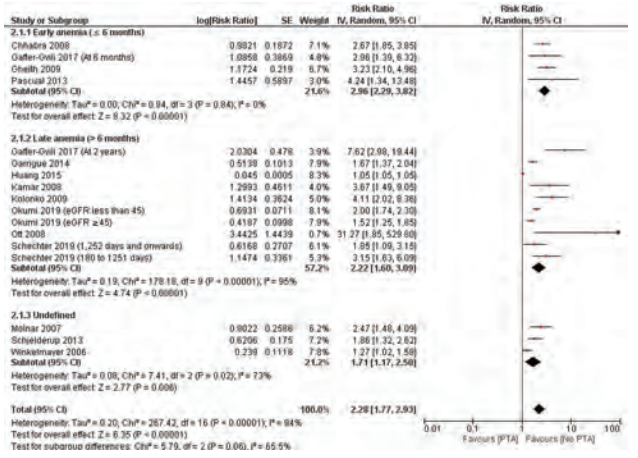
Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to January 2021. Data from each study were combined using the random-effects model.

Results: Seventeen studies from August 2006 to April 2019 were included (16,463 KT recipients). The PTA was associated with overall mortality (pooled RR=1.72 [1.39, 2.13], I^2=56%), graft failure (pooled RR=2.28 [1.77, 2.93], I^2=94%), cardiovascular death (pooled RR=2.06 [1.35, 3.16], I^2=0%), and cardiovascular events (pooled RR=1.33 [1.10, 1.61], I^2=0%). Early PTA (≤ 6 months), compared with late PTA (> 6 months), has higher risk of overall mortality and graft loss with a pooled risk ratio of 2.63 (95% CI 1.79-3.86, I^2=0%) and 2.96 (95% CI 2.29-3.82, I^2=0%), respectively.

Conclusions: Our meta-analysis demonstrates that PTA was significantly associated with overall mortality, graft failure, cardiovascular death, and cardiovascular events.



The association between PTA and overall mortality



The association between PTA and graft loss

PO2075

Mortality Risk Factors of COVID-19 Infection in Kidney Transplantation Recipients: A Systematic Review and Meta-Analysis of Cohorts and Clinical Registries

Suwasin Udomkarnjananun,[1,2] Stephen J. Kerr.[1] [1]*Chulalongkorn University, Bangkok, Thailand;* [2]*Erasmus MC, Rotterdam, Netherlands.*

Background: Kidney transplantation recipients (KTR) with coronavirus disease 2019 (COVID-19) are at higher risk of death than general population. However, mortality risk factors in KTR are still not clearly identified. Our objective was to systematically analyze published evidence for risk factors associated with mortality in COVID-19 KTR.

Methods: Electronic databases were searched for eligible studies on 8 January 2021. All prospective and retrospective studies of COVID-19 in KTR were considered eligible without language restriction. Since data in case reports and series could potentially be subsets of larger studies, only studies with ≥50 patients were included. Random-effects model meta-analysis was used to calculate weighted mean difference (WMD) and pooled odds ratio (OR) of factors associated with mortality.

Results: From a total 566 articles retrieved, 10 were included in the meta-analysis comprising 1,778 KTR. Of these, 1,349 (76%) were survivors and 419 (24%) were non-survivors. Compared with survivors, non-survivors were significantly older (WMD 10.5 years, 95%-CI 9.0-12.0) and had shorter symptom onset before admission (WMD -1.3 days, 95%-CI -2.2, -0.3). KTR of deceased donor were at higher risk of death (OR 2.08, 95%-CI 1.03-4.20). Comorbidities including diabetes, cardiovascular disease, and cancer significantly increased mortality risk. KTR with dyspnea (OR 3.40, 95%-CI 2.51-4.60) and pneumonia (OR 3.01, 95%-CI 1.63-5.55) at presentation were at higher mortality risk, while diarrhea decreased the risk (OR 0.53, 95%-CI 0.39-0.72). Acute kidney injury was associated with mortality (OR 1.74, 95%-CI 1.01-2.98). Inflammatory markers were significantly higher in the non-survivors, including lactate dehydrogenase, C-reactive protein, D-dimer, pro-calcitonin, and interleukine-6.

Conclusions: A number of COVID-19 mortality risk factors were identified from KTR patient characteristics, presenting symptoms, and laboratory investigations. KTR with these risk factors should receive more intensive monitoring and early therapeutic interventions to optimize health outcomes.

PO2076

Impact of Native Kidney Disease on Post-Transplant Cancer Development

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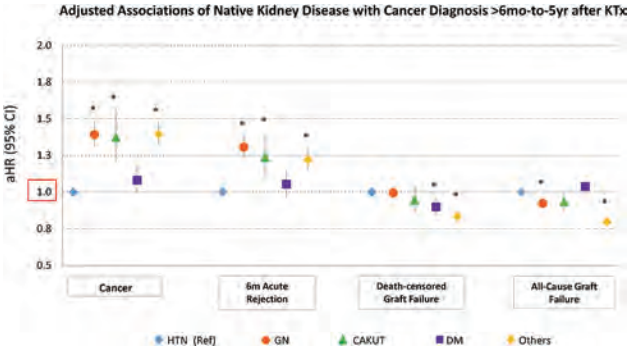
Background: Long-term risk of cancer development among patients with glomerulonephritis (GN) and congenital anomalies of the kidney and urinary tract (CAKUT) have been shown previously. However, the association between native kidney disease and *de novo* cancers after kidney transplantation (KTx) needed to be clarified.

Methods: We examined national Scientific Registry of Transplant Recipients (SRTR) data for patients underwent KTx (2000-2021) to investigate the association of native kidney disease with *de novo* cancer diagnoses after KTx. Patient with history of previous transplant and patients with history of cancer before KTx were excluded. We identified KTx recipients with hypertension (HTN) (n=68432), diabetes mellitus (DM) (n=79809), glomerulonephritis (GN) (n=54381), CAKUT (n=6508) and others (n=56048) as cause of native kidney disease.

Results: Compared with the reference HTN group, GN (aHR, $_{1.31}1.39_{1.48}$) and CAKUT (aHR, $_{1.20}1.37_{1.57}$) groups are significantly associated with higher risk of new onset cancers at 5 years post-KTx (Figure 1). GN (aHR, $_{1.23}1.31_{1.39}$) and CAKUT (aHR, $_{1.09}1.24_{1.40}$) groups are also associated with a higher risk of acute rejection within the 6 months post-KTx. Regarding graft failure, GN (aHR, $_{0.89}0.92_{0.95}$) and others (aHR, $_{0.77}0.80_{0.82}$) groups have significantly lower risk of 5 years all cause graft failure compared to reference group. However, the risk of death censored graft failure was significantly lower in DM (aHR, $_{0.84}0.90_{0.96}$) and others (aHR, $_{0.80}0.83_{0.87}$) groups.

Conclusions: Native kidney diseases, GN and CAKUT, have been associated with acute rejection and *de novo* cancers after KTx. Immunosuppressive treatment and cancer screening may need to be modified according to native kidney disease.



PO2077

Effect of Cold Ischemia Time on Death-Censored Graft Survival of Post-One-Year Survivor Deceased Donor Kidney Transplant Recipients in the United States

Bhamidipati V. Murthy, Ahmed A. Awan, Abbas Rana, John A. Goss. *Baylor College of Medicine, Houston, TX.*

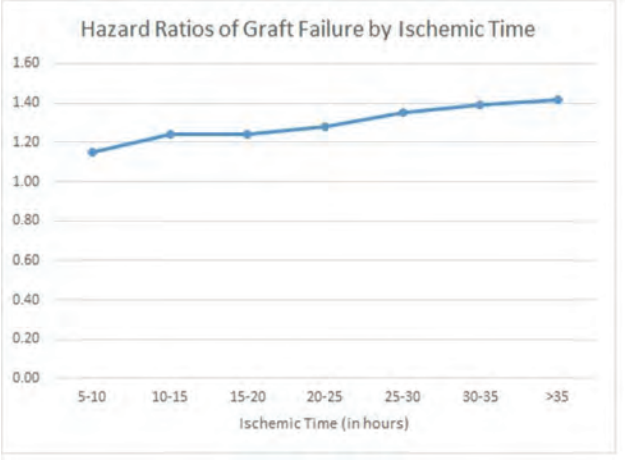
Background: Prolonged cold ischemia has been associated with increased incidence of delayed graft function and poor short term graft survival among deceased donor allografts. However, the data on long term graft survival is less clear. Our aim was to evaluate long-term graft survival for deceased donor kidney recipients who survived one year after transplantation such that the immediate adverse outcomes do not cloud the long term outcomes

Methods: We retrospectively analyzed data from the United Network for Organ Sharing (UNOS) from 1995 to 2017. Living donor transplants, multi-organ transplants, recipients <18 years age at transplantation, and those who died within 1 year of transplantation were excluded. Using multivariable Cox regression analysis, a total of 145,680 recipients were analyzed with death censoring to estimate graft survival with varying cold ischemia times

Results: Compared with cold ischemic time of <5 hours, the graft failure probability steadily increased with increasing cold ischemia time such that the hazards of graft loss were 42% higher with ischemic time greater than 35 hours (Figure 1). Worse graft survival was also observed in males (HR 1.08), increasing donor age beyond 30 years, Blacks (HR 1.77), BMI >30 (HR 1.13), those who had dialysis prior to transplant (HR 1.41), diabetes (HR 1.12), and PRA >90% (HR 1.16). Recipients older than 40 years had a lower graft loss compared to those between 18 and 40 years age.

Conclusions: Prolonged cold ischemia time adversely affects long-term graft survival among deceased donor kidney transplant recipients in the US. The hazards of graft loss appear to be proportional to the duration of cold ischemia time.

Funding: Clinical Revenue Support



Hazards of Graft Loss with Increasing Cold Ischemia Time In Deceased Donor Kidney Allografts

PO2078

Polygenic Burden for Intracranial Aneurysm and Hypertension in Deceased Kidney Donors Who Died of Intracranial Haemorrhage

Kane E. Collins,[1] Gianpiero Cavalleri,[1] Edmund H. Gilbert,[1] Elhussein A. Elhassan,[2] Peter J. Conlon.[2,1] Human Genetic Variation Research Group *[1]Royal College of Surgeons in Ireland, Dublin, Ireland; [2]Beaumont Hospital, Dublin, Ireland.*

Background: A polygenic risk score (PRS) estimates the cumulative effect of common genetic variation on an individual's disease status. It is calculated by summing up all the effect alleles present in the individual, weighted by the effect size, as measured in a GWAS. Intracranial haemorrhage is a common cause of death among kidney donors, but limited research has been done to investigate polygenic burden for intracranial aneurysm (IA) and hypertension in deceased transplant donors.

Methods: Our data consisted of 2,122 genotyped donor-recipient pairs from the United Kingdom and Ireland Renal Transplant Consortium (UKIRTC) and 5,519 controls from the 1958 British Birth Cohort and UK Blood Service. We created polygenic risk scores for IA and hypertension using published GWAS summary statistics from 7,495 cases and 71,934 controls for IA and 76,566 cases and 206,305 controls for hypertension. We investigated the difference in PRS between the UKIRTC donors who died of intracranial haemorrhage (1,303 individuals) and the controls while adjusting for covariates of sex and the first 4 principal components.

Results: We found that the IA PRS explained 4.1% of the variance between case and control status (p-value: 9.6×10^{-39}). The odds ratio on the phenotype for those in the lowest demi-decile of the IA PRS was 0.52 (95% CI: 0.34-0.82) compared to 2.8 (1.9-4.0) for those in the highest demi-decile. Similarly, the PRS for hypertension explained 1% of the variance (p-value: 7.5×10^{-10}) and the corresponding odds ratios were 0.68 (CI: 0.46-1.0) and 1.5 (1.1-2.3) for those in the lowest and highest demi-deciles respectively.

Conclusions: PRSs for IA and hypertension based on these data appear to explain 4% and 1% respectively of the variance in case-control status between kidney donors who have died of intracerebral haemorrhage and controls. These observations could have utility in testing relatives of donors who died of intracranial haemorrhage to determine if they share the same risk for intracerebral haemorrhage and if so to may be useful in advising regarding screening or other precautions to minimise their risk of intracerebral haemorrhage. These observations need to be confirmed in other cohorts. Further studies using similar approaches could investigate other causes of death among kidney donors.

Funding: Government Support - Non-U.S.

PO2079

Characteristics of Potential and Actual Living Kidney Donors: A Single-Center Experience

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Background: Living kidney donors contribute only 28% of all transplanted kidneys. Our study aimed to examine characteristics of potential compared to actual living kidney donors, in order to better understand barriers to successful donation.

Methods: We performed a retrospective analysis of 1,815 intake forms completed by kidney donor candidates from 2016-2018 at a single transplant center. We analyzed data from all potential donors who completed the intake until they became ineligible or withdrew, or, until donation was reached. Baseline characteristics were compared between potential and actual donor groups.

Results: The donation process was deconstructed into 5 steps. The percentage of potential donor drop out at each step and the most common reason for drop out are shown in Table 1. Of the 125 actual donors, 115 (94.3%) were white and 81 (64.8%) were female. A family member was more likely than an unrelated individual to complete the process. At the intake step 35.5% of potential donors identified as family of the potential recipient; at donation 72.7% were family, $p < 0.001$. Many potential and actual donors were referred by the transplant candidate (56.0% and 43.5%, respectively). Social media networking was a larger contributor to the potential donor pool than a source for actual donors (16.5% in potential donors v 2.4% in actual donors, $p < 0.0001$). There were no significant differences between potential and actual donor group with respect to substance use, marital status, level of education, and employment status.

Conclusions: Kidney donor interest is high in the early steps, but few donor candidates become actual donors. A family relationship increases the likelihood a potential donor will become an actual donor. There is a significant drop out of potential donors for incompatible immunologic testing. Our ability to track all potential donors from initial touchpoint to transplant center will help us develop interventions to counteract identified barriers to successful donation, including better outreach to minority populations and education about kidney exchange programs.

Funding: NIDDK Support

Table 1: LKD Candidate Drop Out by Donation Step

	Intake Questionnaire	Donor Immunologic Compatibility Testing	Clinical Evaluation	Selection Committee Review	Successful Donation
Number of potential donors (% of total)	1266 (69.8)	305 (16.8)	53 (2.9)	66 (3.6)	125 (6.9)
Most common reason for drop out (% at each step)	No response to follow-up phone call (23.9)	Incompatible crossmatch (36.1)	Failure to complete required medical testing (41.5)	Medical disqualification (54.6)	N/A

PO2080

Remnant Kidney Hypertrophy Is Negatively Associated with Albuminuria After Donor Nephrectomy

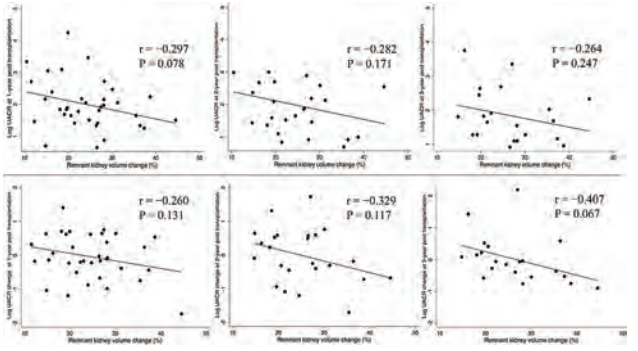
Masatomo Ogata, Takamasa Miyauchi, Kiyomi Osako, Maho Terashita, Naohiko Imai, Yugo Shibagaki, Masahiko Yazawa. *St. Marianna University School of Medicine, Kawasaki, Japan.*

Background: Glomerular ultrafiltration pressure in the remnant kidney remains after donor nephrectomy by the compensatory increase in the glomerular ultrafiltration coefficient, consisting of renal blood flow and cortex volume, namely compensatory hypertrophy. This compensation may be related to the protection for the newly or progressively incident albuminuria, a well-known predictor for kidney damage. To elucidate this theory, we analyzed the relationship between the percentage of change in the remnant kidney volume over 1-year post donation and albuminuria after donation.

Methods: This was a retrospective observational study, with 36 living donors who underwent nephrectomy at our hospital between 2011–2018. The mean age of the participants was 59±8 years and 72% of them were female. We reviewed the computed tomography before and 1 year after donation to calculate the change (%) in remnant kidney volume and investigated the associations with absolute values and relative changes in urinary albumin to creatinine ratio (UACR) 1, 2, and 3 years after donation. Pearson's correlation coefficients was used for the significance of association. This study is approved by Institutional Review Committee of St. Marianna University School of Medicine (No. 1574).

Results: Mean remnant kidney volume change percentage 1-year after donation was 24.2±8.0%. Although statistically non-significant, negative associations were suggested between the change in remnant kidney volume and both the absolute values of and % change in UACR (Figure).

Conclusions: Although relationships between change in remnant kidney volume and albuminuria were statistically insignificant due to the small sample size and analysis for not at-risk population, consistently negative associations would suggest the clinical significance. To assess the long-term safety of living donors, the focus might be on whether the remnant kidney can be hypertrophic by compensation.



PO2081

Short-Term Fast Does Not Alter Physiological Parameters in Living Kidney Donors

Keren Tzukert,[1,2] Roy Abel,[1,2] Iddo Z. Ben-Dov,[1,2] Michal Dranitzki Elhalel.[1,2] *[1]Hadassah Medical Center, Jerusalem, Israel; [2]Department of nephrology and hypertension, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel.*

Background: Living kidney donation is widely practiced and short and long-term outcomes are acceptable. Within the living Kidney donor population there are unique ethnic groups, such as Jewish or Muslim individuals, who practice customs that may affect kidney function. In Judaism, YOM KIPPUR (Day of Atonement) is a 25-26 hr fast practiced yearly. This fast, revered and practiced by secular and religious Jews, has enormous cultural significance. There are no studies that describe the effect of this fast on LKD's. We aim to compare kidney function and physiological parameters between healthy controls and LKD's

Methods: LKD's were approached via e-mail. Exclusion criteria were conditions considered prohibitive of fasting. Controls were potential LKD's that have been approved by the standard medical evaluation but have not yet donated. Blood and urine samples were obtained at three time points: Baseline –3 months before fast, Fasting: 1 hr after 24 hr fast, Follow up - 14 days after fast.

Results: 85 LKD's & 27 controls were included. Donors were older (42.8 vs. 38.8 years) and had a higher baseline creatinine (103 vs. 72 umol/L). All other parameters were the same. The change between fasting and non-fasting creatinine was smaller in LKD's than in controls (0.12 vs. 0.21% change P=0.04). Values of sodium, albumin & osmolarity were not different between groups. Time from donation did not influence these results

Conclusions: LKD's practicing a 24 hr fast show a different pattern from controls regarding the change in creatinine levels. This pattern cannot be considered hazardous for LKD's. The emotional wellbeing of LKD's is of utmost importance and this first report of the safety of a 24 hour fast is reassuring. These findings may be of interest to other religious groups, e.g. the Muslim community who practice RAMADAN. Further follow-up is needed to explore the long term effects of a 25-26 fast in the LKD population

PO2082

African American Kidney Donor Denial

Ivan E. Porter. *Mayo Clinic's Campus in Florida, Jacksonville, FL.*

Background: Previous studies have demonstrated that the rate of living kidney donation is lower in African American (AA) compared to the Caucasian population but whether this low donation rate is related to higher denial rates in AA donors is unclear. Comorbidities play a major role in live donors exclusions, especially hypertension and DM, which could affect the pool of potential donors. The aim of our study is to report the rates and causes of living kidney donor denial in our facility and to further stratify the exclusion rate based on race.

Methods: A retrospective cohort study of 439 denied candidates (age ≥18) who underwent evaluation for living kidney donation at our facility in the period from 2006 to 2014 was performed. Donors underwent a 24 hour ambulatory blood pressure monitor, iothalamate GFR, 24 hour urinary protein excretion and CT angiography as part of their donor evaluations. Reasons for denying donors were identified and grouped into 4 groups: 1) Low GFR, 2) Anatomical variation 3) Hypertension and 4) Other causes.

Results: The cohort consisted of 84 AA, 304 Caucasian and 32 Hispanic donors. Hispanic donors were excluded from further analysis. AA donors were younger (P=0.01) compared to Caucasians. Day time and night time systolic and diastolic arterial blood pressure were comparable between AA and Caucasian (P>0.3 for all) Table 1 summarizes the different reasons for donor denial by donor race. There was no difference between AA and Caucasians or Hispanics in the reason for denial for donation

Conclusions: In this limited study the reasons for denial of kidney donation was not different between AA and Caucasians. Given that the disparity remains, other causes for the low donation in the AA population should be explored and mitigated.

Potential Donor Characteristics

	AA donors n=84	Caucasian Donors n=304	p
Caucasian Donors n=304	126 ± 15	127 ± 12	0.46
Day time average diastolic BP	76 ± 9	77 ± 9	0.43
Night time average systolic BP	114 ± 14	112 ± 16	0.39
Night time average diastolic BP	65 ± 8	65 ± 10	0.82
Reason for Denial			
Low GFR	6 (8)	31 (10)	0.70
Anatomical Variation	18 (21)	79 (26)	0.64
Hypertension	19 (23)	65 (21)	0.70
Other	48 (57)	164 (54)	0.61

PO2083

"I Just Don't Trust It": Exploring the Role of Mistrust in Shaping Living Donor Kidney Transplant Pathways for African, Caribbean, and Black communities in Toronto, Canada

Lydia-Joi L. Marshall. *University Health Network, Toronto, ON, Canada.*

Background: In Canada, African, Caribbean, and Black [ACB] patients with kidney failure are 40-70% less likely to receive a LDKT compared to Whites. To date, research has focused on individual factors, neglecting the impact of systemic racism in shaping ACB community attitudes toward LDKT. Further absent is Canadian research using qualitative methodologies.

Methods: We used an exploratory qualitative approach to understand perspectives and attitudes about LDKT in Canadian ACB communities. Using purposive and snowball sampling, we recruited 81 self-identified ACB community participants to take part in eight focus group discussions between January and November 2020. Participants were asked questions about their racial and ethnic identities, medical experiences and attitudes, and knowledge and perspectives on LDKT. We then applied a Critical Race analytical framework to analyze transcripts, focusing on the tenets of racial consciousness, social location, power dynamics, and counternarratives.

Results: Of the 81 participants 63% was female, 46% were <50 years of age, 53% were immigrants to Canada. 36% self-identified as North American Black/African; 48% as Caribbean; 6% as North African; and 4% as Central/West African. Three key themes emerged from the data. First, we found that like in the U.S., participants expressed medical mistrust. Second, this medical mistrust was rooted in a combination of processes of racialization (medical racism), historical legacies of medical mistreatment, and lived negative experiences within the health care system. Lastly, medical mistrust informed health and illness related decision-making risk assessment, perspectives on LDKT, (lack of) engagement with traditional health care settings, and medical needs.

Conclusions: ACB community attitudes and decision-making processes about LDKT are complex, historically-rooted, and informed by broader medical mistrust. This suggests that broader systemic racial barriers to adequate health care outside of the LDKT pathway, may have far-reaching effects. Further research is needed to better understand how the broader medical experiences of ACB communities may be an underappreciated factor that shapes racial disparities in transplantation, and the kinds of interventions needed to facilitate better access to LDKT.

Funding: Government Support - Non-U.S.

PO2084

Employment Status and Work Functioning in Kidney Transplant Recipients

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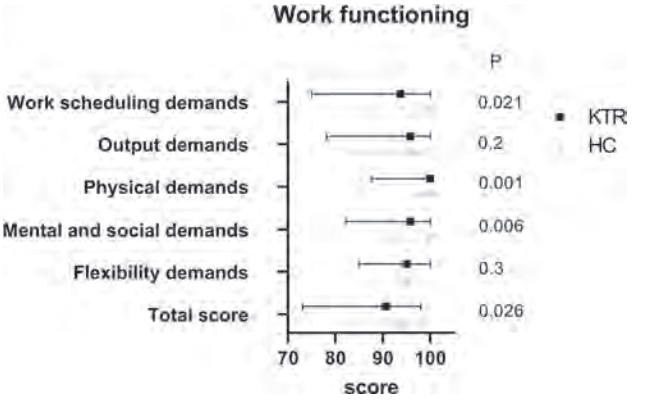
Background: Reliable employment figures of stable kidney transplant recipients (KTR) in Europe are lacking. Additionally, little is known about work functioning among employed KTR, and which clinical factors and (drug-related) side-effects are associated with work functioning.

Methods: We included 668 KTR of working age (59% male, age 51±11 years), at a median of 3 [IQR: 2 to 10] years after transplantation), enrolled in the ongoing TransplantLines Biobank and Cohort Study (NCT03272841, Groningen, The Netherlands). Work and work-related functioning were assessed using the work role functioning questionnaire (WRFQ). Self-reported work ability was assessed using an item of the Work Ability Index (WAI). Results were compared to 246 (43% male, age 53±9 years) potential kidney donors used as healthy controls (HC).

Results: Employment rates were significantly lower among KTR compared to HC (56% vs. 79%, respectively, p<0.001). Employed KTR reported lower work functioning compared to employed HC (median [IQR] WRFQ total score: 94 [75 to 100] vs. 100 [83 to 100], P=0.026, Figure 1). Similarly, self-reported work ability was lower in KTR compared to HC (mean 7.8±1.9 vs. 8.6±1.5, p<0.001). Among KTR, fatigue was most strongly associated with work functioning, independently of potential confounders. Other parameters including anemia, blood albumin, use of beta-blockers, and neurological and mental drug-related side-effects were also independently associated with work functioning.

Conclusions: In our large representative population, only 56% of KTR in their working age were employed. In addition, employed KTR frequently experience impaired work functioning and have limited self-reported work ability. These results underline the individual and societal need to improve employment rates and work-related functioning among KTR. Fatigue, anemia, nutritional status, beta-blocker use, and drug-related side-effects may be potential targets, and should be further investigated.



PO2085

A2 to B Deceased Donor Renal Transplantation Outcome Analysis: A Single-Center Experience

Sandiya Bindroo, Mona D. Doshi. *University of Michigan, Ann Arbor, MI.*

Background: A2 to B renal transplantation has been underused and significant knowledge gaps are noted in areas of rejections, infection rate, and anti-A titer thresholds post-transplant. The purpose of our study is to assess antibody mediated rejection (AMR) rates in A2 to B DDKT and determine association with anti-A IgG titers. We also assessed graft function, rejection and infection rates.

Methods: Retrospective chart review of 55 A2 to B DDKT performed at the University of Michigan from January 2015 to September 2020 was done. All patients received Thymoglobulin for induction and were maintained on triple immunosuppression. All patients underwent monitoring of anti-A2 titers and surveillance biopsy at 3-, 6- and 12- months after transplant. Other outcomes included graft function, rejection and infection rates at last follow-up.

Results: Our cohort consisted of 55 recipients with mean age of 54(±13) years, 67% males and 29% African Americans. The median follow-up time was 2.5 [0.5-5] years. Ten developed acute rejection at 3 [1-6] months after transplant. One patient developed hyper-acute rejection due to ABO incompatibility, five developed T cell mediated rejection, and four had AMR due to donor specific antibodies (DSA) against HLA. Anti-A titers remained undetectable or less (< 1:4) in 98% patients in post-transplant period with no increase in titers at 3-6 month follow up. Anti-A titer increased to 1:128 in one patient with hyper acute rejection. Overall, 20% mortality was noted, unrelated to graft dysfunction at median follow-up of 1.8 [0.08-4] years. Post-transplant infections (bacterial, viral and fungal) accounted for 41% cases. BK viremia noted in 20% with BK nephropathy in six. The mean (SD) glomerular filtration rate, creatinine and urine protein creatinine ratio at three months, one year and at last follow up post-transplant was 49 (14.69), 1.4(0.47), 0.32 (0.55); 54 (14.49), 1.3 (0.43), 0.17 (0.20) and 52.8 (14.69), 1.4(0.59), 0.22 (0.27) respectively.

Conclusions: Our study showed no overall increase in AMR due to ABOi in A2 to B DDKT and is the first study to assess AMR along with anti-A titers in A2 to B DDKT. More such studies are needed to assess anti-A trajectory with AMR. We also noted high infection and BK viremia rates, attributed to use of Thymoglobulin induction therapy. While A2B transplants have good graft outcomes, infectious complications are more frequent.

PO2086

A Successful Approach for A2 to B Cadaveric Renal Transplantation

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Background: Approximately 20% of blood group A individuals have reduced levels of A-antigen, termed A2, with less immunogenicity toward anti-A1 immunoglobulins. This allows the safe transplant of A2 kidneys into B or AB recipients. In 2014, the Kidney Allocation System was modified to encourage transplant centers to provide A2 kidneys for type B patients to reduce inequities in access. Studies have reported that rates of A2 to B transplants remain underutilized due to high rates of early acute rejection or thrombotic microangiopathy (TMA). We report on outcome metrics of A2 to B transplantation at the University of Texas Medical Branch (UTMB).

Methods: A retrospective, single center analysis of 29 patients who received A2 to B kidney transplants at UTMB between July 2015 and December 2020. We included stable (2 consecutive) anti-A IgG titers ≤ 1:8 for A2 identified individuals. Anti-A titers were monitored quarterly in B waitlisted patients. All A2/A2B to B eligible recipients underwent pre-transplant volume exchange plasmapheresis, followed by 2 additional sessions on post-op days 1 and 3. Thymoglobulin was used for induction and steroids for maintenance immunosuppression.

Results: A major concern in A2 to B transplant is the development of TMA or graft rejection. The incidence of rejection within the first year of all types of renal transplants ranges from 7.9% to 21.4%. We instituted an aggressive plasmapheresis protocol to reduce levels of potential pre-formed IgM anti-A antibodies that may induce graft failure. We report a rate of 3.4% for rejection or TMA within the first year of graft life which is less than previously published reports. This is due to pre- and post-transplant plasmapheresis in combination with intravenous immunoglobulin therapy. We elected not to follow anti-A titer levels post-transplant which did not result in higher rates of graft loss.

Conclusions: Our A2 to B transplant patients had a low rate of rejection and TMA demonstrating the efficacy of our triple maintenance immunosuppression protocol. Anti-A titers need not be followed post-operatively.

RESULTS

OUTCOME	
Cellular or Antibody mediated rejection at 1 year (%)	3.45
Thrombotic Microangiopathy at 1 year (%)	3.45
Kidney Allograft Survival at 1 year (%)	96.55
Patient Survival at 1 year (%)	100.00

Table 1

PO2087

Pneumocystis Jiroveci pneumonia in Renal Transplant Recipients: Experience at a Tertiary Care Center

Arunkumar Subbiah, Sanjay K. Agarwal. *All India Institute of Medical Sciences, New Delhi, India.*

Background: Pneumocystis jiroveci pneumonia (PJP) is an important cause of morbidity and mortality in post renal transplant recipients. Data on PJP in renal transplant recipients from India is lacking and we have attempted to address these lacunae.

Methods: This single center retrospective study included all cases of PJP in renal transplant recipients diagnosed at our institute. Demographic, clinical, laboratory and therapeutic outcomes of all these patients were analyzed.

Results: Of the 1870 renal transplant recipient records analyzed, 37 (1.9%) recipients were diagnosed with PJP. The median age of the patients was 38 years (17-74) with 31 males (83.8%). Three (8.1%) patients had deceased donors while 34 (91.9%) had living donors. Induction on the basis of immunological risk profile was ATG in 3 patients (8.1%), daclizumab in 2(5.4%), basiliximab in 11(29.8%) and 21 patients (56.7%) received no induction. All patients received steroid based triple drug immunosuppression along with Tacrolimus in 27(72.9%), Cyclosporine in 10(27.1%), MMF in 34(91.9%) and Azathioprine in 3(8.1%.). Septran prophylaxis was given for 6 months. The median time from transplantation to infection was 11 months(1-132). Eight recipients (22%) had PJP in the first six months post-transplant. Among them, five had co-infection with CMV, three had received prior anti-rejection treatment (ART) and three were non-compliant to PJP prophylaxis. The remaining 29 patients developed PJP after cessation of septran prophylaxis. Out of 29, 9 had received ART prior to PJP infection, 11 had CMV co-infection & 5 had prior history of CMV infection. Diagnosis was microbiologically confirmed in 17 patients by PJP PCR in BAL and in others, diagnosis was made by clinic-radiological features and response to treatment. The most common clinical presentation was dyspnea in 29(78.3%) and 9(31%) required mechanical ventilation. Patients were treated with septran + steroid (9,24%); Clindamycin + steroid (4,10.8%); septran + Clindamycin + steroid (24,64.8%). Three patients (8.3%) expired during PJP infection.

Conclusions: Prophylaxis and tailored immunosuppression explains the low incidence of PJP in our center. Majority of patients had prophylaxis noncompliance, prior anti-rejection therapy or CMV infection before PJP infection. Early diagnosis and timely therapy resulted in better patient outcome.

PO2088

COVID-19 Infection in Kidney Transplant Patients: An Italian One-Year Single-Center Experience

Mariarosaria Campise,[1] Carlo Alfieri,[1,2] Donata C. Cresseri,[1] Maria Teresa Gandolfo,[1] Valentina Binda,[1] Anna Regalia,[1] Piergiorgio Messa.[1,2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy.*

Background: COVID-19 is a life-threatening infection among elderly, comorbid patients, or transplanted patients. Lombardy (Region of Italy), accounts for 786.324 cases as of April 21st, 2021.

Methods: We retrospectively describe our single Centre experience in 82 adult kidney-transplant patients with COVID-19 infection during two pandemic outbreaks: 27 (first outbreak) and 65 (second).

Results: Thirty-seven patients were hospitalized (HP) and 65 were home managed (HM). Infection presented with fever (80 %), cough (51 %) and dyspnea (33 %). HP were older (60±11vs 50±14 years, p=0,001), had more severe respiratory symptoms (dyspnea 62.1%, p<0.0001 – cough 67% p=0.008), and a longer length of disease (30±28 vs 21±10, p=0.04). Incidence of acute kidney injury (AKI) was 29.7% (p<0.0001). Steroid dosage was increased in 66% of patients, p=0.0003 while Calcineurin Inhibitors were reduced up to one third in 45% of cases, p<0.0001. Eleven patients died (13%). HM patients recovered completely without sequelae. In the overall cohort, AKI development (p=0.006 OR 50.4 CI 95% 3.0-836) and age (p=0.04 OR 1.1 CI 95% 1.0-1.2) were the most important factors influencing the probability of death during the infection.

Conclusions: Although we report a relatively low incidence of infection (5.1 %) incidence of death is almost four times higher than in general population.

Variable	
Number of patients (n)	82
Gender (n) (M/F)	54/28
Median age (years)	55 (46-46)
Type of transplant, n (deceased donor/living donor)	65/17
Median transplant vintage (months)	118(39-229)
Steroids; CyA-Tac; MMF-MPA; mTor inhibitors (n)	74; 18-63; 55; 6
iRAS therapy (n/%)	21/26
Relevant comorbid conditions	N/%
Hypertension	67/82
Diabetes	9/32.1
Heart diseases/peripheral vascular disease	18/22
Active Neoplasia	2/2
Previous Neoplasia	12/14.3
Median laboratory values	
s-Creatinine (mg/dL)	1.46(1.2-1.8)
Hb (g/dl)	12.9(11.7-13.7)
s-Albumin (g/dL)	4.2(3.9-4.5)
Prot-U (g/24 h)	0.16(0.10-0.43)

Table 1: patients characteristics before COVID-19 infection.

PO2089

The Impact of COVID-19 on Deceased Donor Renal Transplant Program in a Federal State of South India

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Background: The Covid 19 pandemic has had an impact on all facets of health care system, including organ donation, procurement and transplantation in many countries. India is the country most affected with covid 19 and also the country with a huge waiting list for all solid organ transplants. ESKD is unique that different forms of RRT are available to sustain life. The risk - benefit ratio for delaying elective transplantation during the pandemic is not clear.

Methods: A decsriptive cross sectional study. All the deceased donor solid organ transplantations that took place in the state of Telangana from Jan 2020 to May 2021 were included. Live transplants were excluded. Comparison of the number of transplants of different organs, before and during the pandemic was done. Unpaired t test was used to compare the outcomes between the waitlisted and transplanted group.

Results: The total number of solid organ transplants from deceased donors in the pandemic year of 2020 dropped down to 54% compared to the previous year. Comparison between different organs revealed the maximum decline in number for kidney transplantation (51%), compared to liver (42%), heart (18%) as opposed to 110% increase in lung transplantation. Infectivity rate of covid 19 in the waitlisted group (top 50 in each blood group) registered for deceased renal transplantation is 0.16%. The infectivity rate in the transplanted group (deceased donor renal transplant) during the pandemic in the post transplant period of 6 months is 0.19%. The mortality rate of covid 19 between the two groups is also similar (0.04 in the waitlisted group and 0.06% in the transplanted group). The unpaired t test showed no statistical difference between the two groups.

Conclusions: There is a significant decline in the number of transplantations during the pandemic. Kidney is the most affected organ with 51% decline. Lung transplantation had a 110% rise in numbers during the pandemic. There is no statistical difference of the infectivity rate and mortality rate of covid 19 between waitlisted group and transplanted group of deceased donor renal transplant during the pandemic.

	waitlisted group (n = 200)	transplanted group (n=166)	p value (unpaired t test)
covid 19 infectivity rate	32/200 = 16 %	27/166 =16.2 %	< 0.05
covid 19 mortality rate	11/200 = 5 %	8/166 = 4.6 %	<0.05

PO2090

The Impact of COVID-19 on Kidney Transplant Listing and Referral on the Mexican-American Border

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Background: Laredo, Texas is a city on the Mexican-American border in South Texas that ranked as the most affected area in the United States relative to population in terms of COVID-19 in January 2021. The hospitalization rate, the area's total resources devoted to treating coronavirus patients, reached 45.8% and it averaged 229.9 cases daily per 100,000 citizens. We reviewed data early in the COVID-19 pandemic in May 2020 and later in May 2021 to evaluate whether the pandemic affected rates of referral and/or waitlisting.

Methods: Data was gathered from three dialysis clinics in Laredo, TX. The number of patients waitlisted or scheduled for living donor transplantation was determined early in the COVID-19 pandemic in May 2020 and later in May 2021. The number of patients referred for transplantation but not yet waitlisted was also obtained as well as the number of patients not referred both early in the COVID-19 pandemic in May 2020 and in May 2021.

Results: In May 2020, a total of 285 patients were available for analysis. 52 patients (18.2%) were waitlisted or scheduled for living donor transplantation. An additional 91 patients (31.9%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 140 (49.1%) were not referred. In May 2021, a total of 244 patients were available for analysis. 36 patients (14.8%) were waitlisted or scheduled for living donor transplantation. An additional 71 patients (29%) were referred but not yet waitlisted nor scheduled for living donor transplantation. A total of 135 (55%) were not referred.

Conclusions: There was a smaller percentage of ESRD patients waitlisted or scheduled for living donor transplantation in May 2021 than early in the COVID-19 pandemic in May 2020. There was also a smaller percentage referred but not waitlisted and a larger percentage not referred. The 3.4% decrease in patients waitlisted or scheduled for living donor transplantation may be a result of the high COVID-19 burden in Laredo, TX and the wariness to travel approximately 150 miles to the nearest transplant center. It is not known whether this decrease will have lasting implications on access to transplantation.

PO2091

Coronavirus Disease 2019 and Kidney Transplantation in Saudi Arabia

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Background: Kidney transplant services all over the world were severely impacted by the coronavirus disease 2019 pandemic. The optimum management of kidney transplant recipients with coronavirus disease 2019 remains uncertain.

Methods: We conducted a multicenter cohort study of kidney transplant recipients with coronavirus disease 2019 infection in Saudi Arabia. Multivariable Cox regression analysis was used to study predictors of graft and patient outcomes at 28 days after coronavirus disease 2019 diagnosis.

Results: We included 130 kidney transplant recipients, with a mean age of 48.7(±14.4) years. Fifty-nine patients were managed at home with daily follow-up utilizing a dedicated clinic, while 71 (54.6%) required hospital admission. Acute kidney injury occurred in 35 (26.9%) patients. Secondary infections occurred in 38 (29.2%) patients. SARS-CoV-2 antibodies testing was carried out in 84 patients, of whom 70 tested positive for IgG and/or IgM. Fourteen patients died (10.8%). A multivariable Cox regression analysis showed that age, creatinine at presentation, acute kidney injury, and use of azithromycin were significantly associated with worse patient survival. Graft loss was associated with requiring renal replacement therapy and development of secondary infections.

Conclusions: Despite kidney transplant recipients with coronavirus disease 2019 infection having higher rate of hospital admission and mortality compared to the general population, a significant number of them can be managed using a telemedicine clinic. Most kidney transplant patients seem to mount an antibody response following coronavirus disease 2019 infection, and it remains to be seen if they will have a similar response to the incoming vaccines.

PO2092

Vitamin D Status and SARS-CoV-2 Infection in a Cohort of Renal Transplanted Patients

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Background: Immunomodulatory and anti-inflammatory properties have been hypothesized for native vitamin D (nVD). Very little is reported about nVD and risk of Sars-CoV-2 infection (COV) in renal transplant (RTx). In a cohort of renal transplanted patients (RTxp) we retrospectively evaluated: a) nVD status in patients with (COV+) and without (COV-) COV infection; b) the impact of nVD status on severity of COV.

Methods: The study includes 61 COV+ in whom nVD status was available in the year before the infection, and 122 COV- matched 1:2 for age (53[45-64]years), gender (M=60.7%), RTx vintage (7[2-15]years), presence of diabetes (18%), arterial hypertension (85%) and cardiac symptomatic disease (3%). Renal function, 24-h proteinuria, mineral metabolism (MM) parameters were evaluated at 1, 6 and 12 months before COV whereas nVD status was considered as the mean 25-OH-VD levels at the same timepoints. Severity of COV was based on the need for hospitalization (HOSP+: 27/61, 44.3%) and death (D+: 6/61, 9.8%).

Results: a) nVD levels were significantly lower in COV+ than in COV- (19 [12-26] ng/mL and 23[16-30] ng/mL, respectively, p=0.01). No differences in the other biochemical parameters were found. The COV discriminative power of nVD status was evaluated by ROC curve (AUC 0.61, 95% CI 0.54-0.68, p=0.01), with a value of 25-OHVD 23.9 ng/mL showing the best discriminative power (sensibility 72%, specificity 47%). b) nVD levels showed a trend towards lower values in HOSP+COV+ than HOSP-COV+ (17[8-25] ng/mL vs 20[14-26] ng/mL) and in D+COV+ than D-COV+ (13 [6-23] ng/mL vs 20[13-26] ng/mL), although these differences did not reach the statistical significance (p=0.1 and p=0.2, respectively).

Conclusions: With the limitations of the retrospective nature of the study and the small sample size, our data report that: a) COV+ showed lower nVD levels in the year preceding the infection compared to controls with similar main demographic features and comorbid conditions; b) No differences were found in renal function, proteinuria, and other MM parameters between the two groups; c) No association was found between nVD levels in the year preceding the infection and COV severity.

PO2093

Treatment with Monoclonal Antibodies Minimize Severity of COVID-19 Illness Among Kidney Transplant Recipients

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Background: The mortality rate of kidney transplant recipients with COVID-19 is significantly higher than the general population, indicating a need for effective treatment to minimize potential severe symptoms in this population. We sought to evaluate the efficacy of monoclonal antibody therapy in decreasing the severity of COVID-19 symptoms among our kidney transplant recipients.

Methods: We reviewed 17 kidney transplant recipients who were infected with SARS-CoV2 and received treatment with monoclonal antibody therapy. All patients were on standard immunosuppression with Tacrolimus and Prednisone, and 88% were on Mycophenolate prior to COVID diagnosis, which was subsequently reduced or held for at least 2 weeks.

Results: Of the 17 patients reviewed, median age was 61 years (range 42 to 77 years), 47% were male, 59% were Hispanic, and 29% were African American. Additionally 94% had history of hypertension, 47% diabetes mellitus, 18% coronary artery disease, and median BMI was 28.8 (range 23.4 to 41.9). Eighteen percent were transplanted <1 year, 29% between 1-5 years, 24% 6-10 years, and the remaining >10 years. All patients had mild symptoms without evidence of hypoxia, and 94% received monoclonal antibody therapy within 7 days of diagnosis. Bamlanivimab 700mg was the most commonly administered agent at 59%, while 18% received Bamlanivimab 700mg and Etesevimab 1400mg. Casirivimab 1200 mg and imdevimab 1200 mg was used in 24%. Only 2 out of the 17 patients (11.8%) required hospitalization, and both were non-COVID-19 related reasons. Five out of 17 patients (29.4%) were evaluated in the Emergency Department but not admitted. All 17 patients (100%) recovered from their COVID-19 illness. There were no episodes of graft failure.

Conclusions: Our experience suggests that monoclonal antibody therapies may be beneficial in preventing severe COVID-19 in renal transplant recipients and possibly reduce the need for COVID-19 related hospitalization in this high risk population. However, larger studies are needed to confirm these findings.

PO2094

Antibody Response to SARS-CoV-2 mRNA Vaccines in Pediatric Kidney Transplant Recipients

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Background: In the general population, mRNA SARS-CoV-2 vaccines are highly efficacious and patients form an antibody to S1 subunit of the SARS-CoV-2 spike protein. Early reports suggest a decreased antibody response in immunosuppressed adult solid organ transplant (SOT) patients. However, the serologic response in adolescent SOT patients has not yet been characterized.

Methods: Kidney transplant recipients (KTR) at our center who received both doses of an mRNA SARS-CoV-2 vaccine had SARS-CoV-2 spike protein antibody presence evaluated 4-8 weeks after their second dose of the vaccine as part of routine clinical care. We utilized the Abbott chemiluminescent microparticle immunoassay or Siemens Atellica IM SARS-CoV-2 IgG. Patients were characterized as vaccine responders or non-responders.

Results: Of 47 vaccine-eligible KTR in our program, 34 received both doses of a SARS-CoV-2 mRNA vaccine. Twenty-three patients had spike antibody titers obtained. The median age was 21.5 years and all except one were transplanted over 3 years ago. Twenty-two received Pfizer-Biontech vaccine and one received Moderna. Twelve patients (52%) had a positive spike antibody. Of those who responded, eight patients' immunosuppression regimens included mycophenolate (mean dose 719 mg/m2/day), three were treated with azathioprine and one was not taking an antimetabolite due to EBV viremia. All non-responders were treated with mycophenolate (average dose 755 mg/m2/day). Three patients had prior COVID-19 infection, and all had a positive antibody response.

Conclusions: Our results suggest vaccine response in adolescent KTR is suboptimal and lower than the general population. However, 52% response rate is similar to that previously described in adult SOT patients. While our study is limited by small sample size and lack of standardized timing for measuring antibodies, it provides further evidence of lower immunogenicity to SARS-CoV-2 vaccination in SOT. Those who did not respond tended to have a higher average dose of mycophenolate and this supports further study of alternative antimetabolite dosing strategies around the time of vaccination or the potential utility of a third vaccine dose in SOT patients. At our center, efforts to continue characterizing antibody response of pediatric KTR are ongoing and we anticipate additional data in the coming months as vaccine eligibility expands to younger patients.

PO2095

A Tale of Survival: COVID-19, Disseminated Cryptococcus, and Cytomegalovirus Disease in an ABO-Incompatible Kidney Transplant Recipient

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Introduction: We present a rare case of Collapsing Focal Segmental Glomerulosclerosis (FSGS) in Covid-*19* (COVAN), disseminated Cryptococcus and CMV infection in a kidney transplant recipient with dialysis dependent acute kidney injury and successful renal and critical illness recovery.

Case Description: 63yo black male with an ABO incompatible kidney transplant 8yrs ago, baseline creatinine (Cr) of 1.4 mg/dl with acute Covid-*19* infection with presenting Cr of 5.5 mg/dl and nephrotic range proteinuria (5.9gm/gm). Started hemodialysis on day 21 of the acute illness. Normal imaging, stable anti-ABO titers and transplant kidney biopsy with collapsing FSGS and ATN. Blood cultures ordered for persistent fevers were positive for Cryptococcus neoformis. Biopsy of painful indurated skin of the left flank revealed variably sized yeast forms within the dermis consistent with cutaneous Cryptococcus. Treated with amphotericin B/flucytosine followed by fluconazole with clearance of fungemia, resolution of fever and improvement of skin lesions. Immunosuppression was continued with reduced dose of tacrolimus and prednisone 10mg/day. Antimetabolite was discontinued. Persistent weakness and diarrhea lead to testing for CMV with PCR at 51,000copies/ml, treated with IV ganciclovir with complete resolution of symptoms. Discharged home on maintenance dialysis with valganciclovir and fluconazole prophylaxis. He returned on day 70 of illness with a Cr of 1.2 mg/dl, a 24hour urine collection with a creatinine clearance of 28 ml/min and 2gms of proteinuria. Dialysis was discontinued due to renal recovery. At last clinic follow up, day 100 from diagnoses, Cr remains stable at 1.7 mg/dl off dialysis.

Discussion: Immune dysregulation in the setting of acute Covid-*19* infection coupled with long term immunosuppression may have contributed to multiple opportunistic infections. Optimal approach for immunosuppression in KTRs with acute Covid-*19* infection is still evolving. Our patient was successfully treated without stopping all immunosuppression. Our case underscores importance of having low threshold to test for various opportunistic infections even in the setting of active Covid-*19* infection. While data on COVAN in KTRs is limited, our case shows potential for renal recovery even in a high immunologic risk kidney transplant recipient.

PO2096

Cytomegalovirus Infection in Renal Transplant Recipients: Incidence, Clinical Profile and Outcome

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Background: Cytomegalovirus (CMV) is one of the commonly encountered opportunistic infection following renal transplantation, usually seen in the first 6 months of transplant. CMV diseases, untreated has a mortality rate of about 90% however has good response with prompt detection and antiviral therapy. With the changing immunosuppressive regimen, variation in pattern and occurrence of CMV infection can be seen. We studied the incidence, clinical profile and outcomes of CMV infection in renal transplant recipients at our center.

Methods: 291 renal transplant recipients between 2014 and 2020 were reviewed, 27 patients who had CMV infection, diagnosed by CMV DNA detection with polymerase chain reaction were included in the study and their demographic details, clinical profile and outcome were noted and analyzed.

Results: Among the 291 renal allograft recipients, 27 patients had 34 episodes of CMV infection with an incidence of 9.27% with a mean follow up of 52.6 months. 37.1% received deceased donor renal transplant and 62.9% received live renal transplant. Mean age at transplant was 33.8yrs, 81.4% were males, 18.6% were females. rATG as induction was given in 11.1%, Basiliximab in 37.1% and 51.8% received no induction therapy, all of them received triple immunosuppression with steroid, tacrolimus and MMF as maintenance immunosuppression. PTDM was present in 33.4%. Valganciclovir prophylaxis post- transplant was given in 77.8% where as 22.2% did not receive prophylaxis. 20.5% infection episodes occurred in < 3months, 26.5% between 3-6 months, 11.8% between 6-12 months and 41.2% in >12months post-transplant. Symptomatic disease with fever, malaise and leucopenia was the most common presentation in 73.5% of patients and 26.4% had asymptomatic infection with leucopenia and transaminitis. All patients received iv Ganciclovir for 14-21days followed by oral valganciclovir for 90 days as treatment of infection episode. Patient survival and graft survival rate was 85.2% and 77.7% at our center.

Conclusions: Changing immunosuppressive regimen with early withdrawal of steroid and use of valganciclovir prophylaxis has been associated with lower incidence and milder form of CMV disease in our population. There seems to be a change in the traditional risk factors for CMV infection which needs to be further studied.

PO2097

Resistant Cytomegalovirus After Kidney Transplant: Reduced Immunosuppression, High-Dose Valganciclovir, and Letermovir Prophylaxis Guided by T Cell Immunity Assessment

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Introduction: CMV infections resistant to available antivirals are associated with increased morbidity and mortality after kidney transplant.

Case Description: A 58 yo male with ADPKD underwent pre-emptive LURTx. IS included Thymoglobulin, followed by tacrolimus, mycophenolate (MMF), and prednisone. Ten days after completing 6 mos. of valganciclovir(VGCV) prophylaxis (ppx) for CMV D+/R- serostatus he developed malaise and fever; CMV PCR was 197,033 IU/ml. VGCV 900 mg BID was started and MMF reduced. CMV PCR declined to 1399 IU/ml after 6 weeks, but then plateaued. CMV resistance testing (VGCV treatment day 62) found wild-type and mutated virus (UL54 T503I mutation and UL97 H520Q mutation) with predicted resistance to ganciclovir and cidofovir, but susceptibility to foscarnet. MMF was stopped and VGCV was increased to 1350 mg BID (150% dose for GFR). Foscarnet was avoided due to risk of nephrotoxicity, lack of disease, and time from transplant. There was no significant leukopenia on VGCV. Over the next 2 months, CMV PCR decreased to several hundred IU/ml to Below the Limit of Quantification. Letermovir ppx was started (VGCV t. day 85) and VGCV stopped 8 days later. CMV PCR remained negative to BLQ on letermovir. Low dose MMF was restarted. T cell immunity panel (Viracor) showed good CD8 (5.04%), but low CD4 (0.15%) response, suggesting CMV infection would recur without prophylaxis. The patient remains on letermovir ppx. Letermovir is a CYP3A inhibitor, and tacrolimus required 25% dose reduction. DSA is negative at 1 yr post-transplant; creatinine remains around 1.1 mg/dl. Letermovir is a new CMV selective antiviral with novel mechanism of action inhibiting the viral terminase complex in late stages of replication. It is approved for prophylaxis in HCT, active against resistant strains, and not associated with myelo or nephrotoxicity.

Discussion: Resistant CMV infection is a clinical challenge. While susceptibility to foscarnet was predicted in this case, it was avoided (nephrotoxicity). Instead, immunosuppression was cautiously reduced and higher-dose VGCV was tolerated well. Once CMV viral load was negligible, a newer agent with novel mechanism of action, letermovir, was used for prophylaxis. Letermovir has been continued based on a low level of anti-CMV CD4 response, predicting high-risk for CMV recurrence.

PO2098

Rare Oral Lesions from Cytomegalovirus in Kidney Transplant

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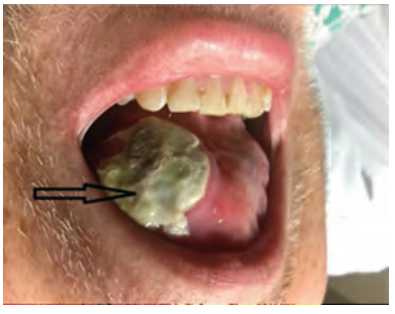
Introduction: Cytomegalovirus (CMV) infection occurs frequently with kidney transplant recipients and it can affect any segment of gastrointestinal tract, but intra-oral localization is exceedingly rare. We present an interesting rare oral lesion from CMV infection in kidney transplant recipient

Case Description: A 49-year-old male with a history of kidney transplant admitted with odynophagia, pancytopenia, neutropenic fever and new tongue lesion for two weeks. Examination showed a 3X3 cm elevated, adherent plaque. He has a history of resistant CMV viremia with failed therapy to low-dose valganciclovir, ganciclovir, and letomovir. He attained an undetectable CMV viral load with Foscarnet but it was complicated with acute renal injury, and he was transitioned to a high dose valganciclovir. His CMV PCR was < 50 on admission and biopsy of the tongue-lesion revealed a positive immunohistochemical stain for CMV. We held his Valcyte on admission and his pancytopenia improved with filgrastim. Repeat CMV PCR increased to 17,000 IU/mL. He refused Foscarnet and was restarted on oral valganciclovir (1350 mg twice daily) and topical cidofovir. Even with undetectable CMV at presentation, he was noted to have disseminated infection. Myfortic and Gengraf were held and discharged on prednisone alone. At 2-week follow-up, the lesion and its associated symptoms had resolved

Discussion: The presentation of oral CMV infection is highly variable with mucosal erythema, painful deep ulcers, erosions, but elevated tongue lesion have rarely been reported in literature to our knowledge. Treatment options includes ganciclovir, valganciclovir, foscarnet, letomovir and cidofovir. Early diagnosis is important because CMV increases other opportunistic infection and allograft rejection. Saliva and periodontal packets serve as reservoirs for CMV infection and frequent monitoring of periodontal health is needed post-transplant



3X3 cm elevated, adherent tongue lesions

PO2099

Use of Epstein-Barr Virus (EBV) Cytotoxic T Lymphocyte Therapy in a Kidney Transplant Recipient with EBV-Associated Smooth Muscle Tumors

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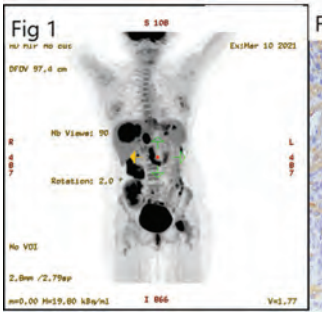
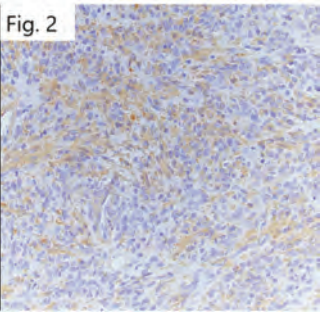
Introduction: Epstein-Barr virus (EBV) is commonly associated with malignancies in transplant recipients, the most frequent being Post-transplant lymphoproliferative disorder. A rare, yet distinct, oncological entity are the EBV-associated smooth muscle tumors (EBV-SMTs). We present the case of multiple, malignant EBV-SMTs in a 34-year-old kidney transplant recipient, and the use of Tabelecleucel (EBV cytotoxic T lymphocyte therapy) as a targeted therapy for these tumors.

Case Description: A 34-year-old female kidney transplant recipient presented with fatigue, anorexia, and nighttime chills. Subsequent lab analysis revealed lymphopenia, elevated creatinine, hypercalcemia and high EBV viral load. PET scan revealed intensely avid FDG liver, splenic and lytic lesions of the left femoral head (Fig.1). Diagnosis of EBV-SMTs was confirmed by immunohistochemistry positive for smooth muscle actin, supporting smooth muscle differentiation (Fig.2), and confirmatory in situ hybridization for EBV-encoded RNA. Patient's immunosuppression was switched from tacrolimus to sirolimus, and treatment was initiated with Tabelecleucel. At the time of the writing of this report, the patient has completed the first cycle of treatment with Tabelecleucel and is preparing for a second cycle of treatment. The patient's symptoms have improved significantly and creatinine, calcium and white cell counts have returned to baseline, EBV viral load fell from 4120 to 133 and PET scan showed stabilization of disease. We will continue to report on the patient's progress.

Discussion: EBV-SMTs are rare tumors which can present in a variety of ways and are easily missed. They are typically aggressive, with a poor response to radiation and chemotherapy. Tabelecleucel is an EBV cytoxic T lymphocyte therapy, primarily used in immunosuppressed and stem cell transplant recipients. Use in kidney transplant recipients is promising but requires further investigation to better understand optimal HLA matching of cell lines with recipients and allografts.





PO2100

Economic and Insurance Outcomes for Living Kidney Donors and Matched Comparators in Korea

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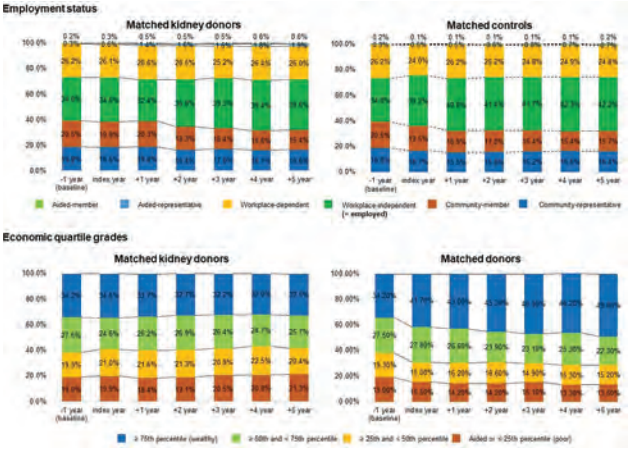
Background: Although studies have reported kidney donation's adverse health outcomes, its socioeconomic impact on living donors requires further study.

Methods: We performed a retrospective observational cohort study including a matched control group. We included 1,285 living kidney transplant donors from seven tertiary hospitals and a matched control group consisting of the same number of health screening examinees with similar baseline clinical and socioeconomic status from 2003 to 2016. Changes in employment status and household income were identified from the linked claims database, which includes employment and economic status information. The outcomes were compared between the donor and matched control groups on an annual basis using multivariable logistic regression analyses adjusted for various clinicodemographic characteristics.

Results: The median ages of the donors and matched controls were 45 and 46 years, respectively; 44.6% of the sample was male. The living donors were at higher risk of being unemployed or struggling to maintain employment during the first two years after donation [e.g., first-year loss of employment, odds ratio (OR) 2.27 (1.55–3.33)]; however, this situation did not persist, compared with the matched control group. The donors also showed significantly lower odds for improvement in economic grades [OR 0.57 (0.47–0.71)] or higher odds for deterioration in financial status [OR 1.54 (1.23–1.93)] than the control group in the first year and succeeding time periods.

Conclusions: Live kidney donors may suffer from poor employment or low economic status even after their altruistic donation. Whether an advanced reimbursement program can reduce these disincentives should be further evaluated.



PO2101

When Is a Second Kidney Transplant Lifesaving? Effect of Waiting Time on Mortality in a Retrospective Cohort Study Using Target Trial Emulation

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Background: The median kidney transplant half-life is 10 to 15 years, and because of the scarcity of donor organs and immunological sensitization of candidates for retransplantation, there is a need for quantitative information if, and when a second transplantation is no longer associated with a reduced risk of mortality compared to waitlisted patients treated by dialysis. Therefore we investigated the association of time on waitlist with patient survival in patients who received a second transplantation versus remaining on waitlist with continued dialysis treatment.

Methods: In this retrospective study we used data of 2346 patients from the Austrian dialysis and transplant registry merged with data from Eurotransplant who were waitlisted for second kidney transplantation during the years 1980 to 2019. The analysis was based on target trial emulation via a sequential Cox approach, in which each observed transplant allocation started a virtual trial mimicking a randomized trial via inverse probability weighting. The analysis was adjusted for recipient age and sex, year and duration of first transplantation, duration of dialysis, and time between first graft loss and initial joining date of the waiting list for the second transplantation.

Results: Second kidney transplantation showed an increased restricted mean survival time (RMST) at 10 years of follow-up compared to remaining on the waiting list (5.8 life-months gained, 95% CI 0.9 to 11.1). However, this survival benefit was diminished in patients with longer waiting time after first graft loss: RMST differences at 10 years of follow-up were 8.0 (95% CI 1.9 to 14.0) and 0.1 life-months gained (95% CI -14.3 to 15.2) for patients with a waiting time after first graft loss of less than one year, and eight years, respectively.

Conclusions: Based on these data we conclude that a second kidney transplant leads to prolonged patient survival compared to remaining waitlisted and treatment by dialysis, but that the survival benefit diminishes with longer waiting time. Nevertheless, the higher quality of life after transplantation could be an argument to favour retransplantation if a suitable donor organ is available.

Funding: Government Support - Non-U.S.

PO2102

Correlation Between CT Volumetric and Nuclear Renal Scans in Donors with Renal Asymmetry

Nisarg Gandhi, Hassan N. Ibrahim, Duc T. Nguyen, Edward A. Graviss, Hana Nguyen. *Houston Methodist Hospital, Houston, TX.*

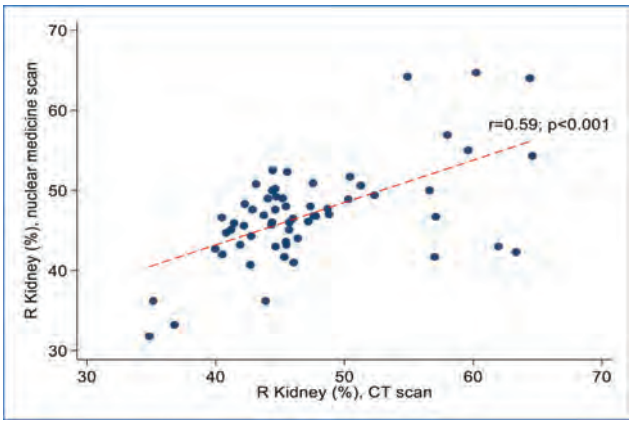
Background: The Organ Procurement and Transplant Network (OPTN) lists renal asymmetry as a relative contraindication to donation. Clinicians resort to nuclear medicine scans to address discrepancies in kidney size observed by commuted tomography (CT) volumetric. Our study looked at the correlation between CT volumetrics and nuclear medicine scan in addressing renal asymmetry.

Methods: At a large US transplant center, 62 potential donors with discrepancies in kidney size underwent both CT volumetric and nuclear medicine renal scans. The concordance correlation between the CT scan and nuclear medicine scan results was determined separately for the right and left kidney.

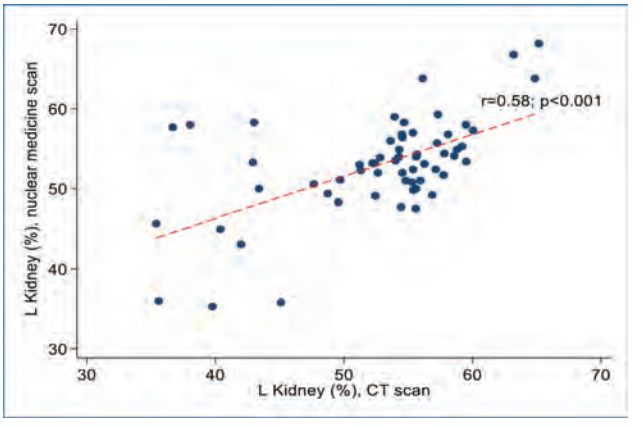
Results: The donors were 52.2 years of age (median IQR: 38.5, 61.7), 29.0% male, and 59.7% white. By CT, the right kidney was 45.5% and left kidney was 54.5% of the overall volume. On nuclear medicine scans, right kidney was 46.8% and left kidney was 53.3% (Table 1). The Pearson correlation coefficient was 0.59 for the right kidney and was 0.58 for the left kidney (Figure 1, 2).

Conclusions: Nuclear medicine seems to offer no advantage over CT volumetrics and it adds to the overall time (30-60 minutes) and cost (~$1,587) of the donor evaluation process.

	Right	Left
CT Volumetrics (%), median IQR	45.5 (43.0, 49.5)	54.5 (50.5, 57.0)
Nuclear Medicine Scan (%), median IQR	46.8 (43.6, 49.4)	53.3 (50.6, 56.4)



Correlation between CT scan and nuclear medicine scan for right kidney



Correlation between CT scan and nuclear medicine scan for left kidney

PO2103

The Effect of Race Coefficients on Preemptive Listing for Kidney Transplantation

Vinay Nair, Jamie S. Hirsch, Nicholas Jandovitz, Kenar D. Jhaveri, Ernesto P. Molmenti, Mersema Abate. *Northwell Health, New Hyde Park, NY.*

Background: Race coefficients of glomerular filtration rate estimation (eGFR) formulas may be partially responsible for racial inequality in preemptive listing for kidney transplantation. The objective was to determine whether differences in racial distribution of preemptively listed candidates are reduced by calculating eGFR irrespective of race.

Methods: The Scientific Registry of Transplant Recipients database was used to evaluate differences in racial distribution of preemptive listing before and after application of the MDRD and CKD-EPI race coefficients to all preemptively listed non-Black kidney transplant candidates (eGFR modulation). Non-Black patients who had a recalculated eGFR > 20 were removed from the preemptive group. Odds ratios of preemptive listing were calculated by race with Black as the reference before and after eGFR modulation. Variables known to influence preemptive listing were included in the multivariable model.

Results: Among 385,087 kidney-alone transplant candidates from January 1, 2010 to December 2, 2020, 118,329 (30.7%) were identified as preemptively listed (median [IQR] age 56 [45-64]; 57.7% male; 71.7% White, 19% Black, 7.8% Asian, 0.6% multi-racial, 0.6% Native American, 0.3% Pacific Islander). After eGFR modulation, non-Black patients with an eGFR ≥ 20ml/min were removed. Compared to Black candidates, the adjusted odds of preemptive listing for White candidates decreased from 2.01 (CI 1.78-2.26; p<0.001) before eGFR modulation to 1.18 (CI 1.0-1.39; p=0.046) with the MDRD and 1.37 (CI 1.18-1.58; p=0.001) with the CKD-EPI equations after adjusting for race coefficients.

Conclusions: The racial distribution of preemptively listed candidates closely mirrored the distribution on the wait list when all races were subject to the Black race coefficients. Removing race coefficients in GFR estimation formulas may result in more equitable racial distribution of preemptively listed candidates.

PO2104

Increasing Frequency of Kidneys Allocated Out of Sequence by Organ Procurement Organizations

Kristen L. King,[1] Syed A. Husain,[1] Sumit Mohan.[1,2] *[1]Columbia University Irving Medical Center, New York, NY; [2]Columbia University Mailman School of Public Health, New York, NY.*

Background: Allocation of deceased donor kidneys follows a ranked match-run list of potential recipients. Organ procurement organizations (OPOs) deviate from the mandated match-run in exceptional circumstances with unknown frequency.

Methods: Using SRTR data on all deceased donor kidney transplants (Ktx) in the US from 2015-2019, we identified cases where an OPO-initiated allocation exception occurred (Operational-OPO, Donor Medical Urgency, Expedited Placement). We examined the frequency of Ktx from these exceptions over time and characteristics of donors with kidneys placed out-of-sequence.

Results: From 2015-2019, 981 kidneys from 673 donors were transplanted via OPO-initiated allocation exception. These transplants (median KDPI 67, age 47 yrs) nearly doubled from 2015-2019: 153 kidneys in 2015 (1.5% of all Ktx) to 291 in 2019 (2.1%). 52 of 58 OPOs used this process at least once (median <1 per year), but 2 outlier OPOs accounted for 54% of the exceptions over 5 years [426 (43%) and 110 (11%), Figure 1]. Only 56% of transplant centers received any allocation-exception Ktx, with 2 centers receiving 26% [129 (13%) and 132 (13%)]. Donor kidneys placed via allocation exception had less favorable characteristics, but only 25% had KDPI≥85% (Table 1). Allocation exception Ktx went to recipients with 2 fewer priority points (median score: 4.3 vs. 6.3 in-sequence), equivalent to 2 less years of waiting time.

Conclusions: Two OPOs and a few Ktx centers are driving an Increase in OPO-initiated exceptions in kidney allocation. Although kidneys placed out-of-sequence were lower quality, the majority did not meet the traditional threshold for marginal kidneys. Without monitoring, increasing pressure to improve organ utilization risks increasing out-of-sequence allocation potentially exacerbating disparities in access to transplantation.

Figure 1. Temporal trends in kidneys transplanted with an OPO allocation exception

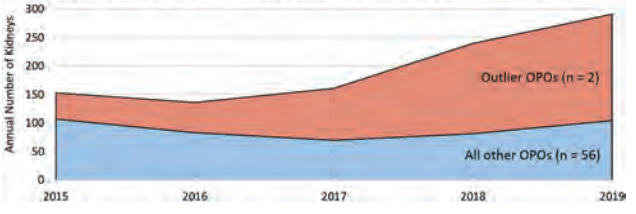


Table 1. Characteristics of donors with kidneys allocated through regular allocation policy or with an OPO-initiated allocation exception

Donor Characteristics, median (IQR) or n (col %)	Regular Allocation n = 35,359 (98%)	Allocation Exception n = 673 (2%)
Age (years)*	37 (25 - 50)	47 (31 - 56)
Female Sex	13,575 (38%)	271 (40%)
Kidney Donor Profile Index (KDPI)*	45 (23 - 69)	67 (44 - 85)
KDPI ≥ 85*	3,398 (10%)	169 (25%)
Diabetes*	2,335 (7%)	63 (9%)
Public Health Service: Increased Risk	8,724 (25%)	154 (23%)
Cause of Death: stroke*	8,262 (23%)	194 (29%)
Peak Serum Creatinine*	1.3 (1.0 - 1.8)	1.5 (1.1 - 2.5)
Biopsy Performed*	17,051 (48%)	485 (72%)
Donation after Circulatory Death*	7,339 (21%)	212 (32%)

* Indicates statistical significance with p<0.05

PO2105

Survival Time Gained by Kidney Transplantation Compared to Remaining Waitlisted on Dialysis: A National Registry Study Using Target Trial Emulation

Maria C. Haller,[1,2] Christine Wallisch,[1] Susanne Strohmaier,[1,4] Michael Kammer,[1,3] Georg Heinze,[1] Rainer Oberbauer.[3] *[1]Medical University of Vienna, Center for Medical Statistics, Informatics and Intelligent Systems, Section for Clinical Biometrics, Vienna, Austria; [2]Ordensklinikum Linz, Elisabethinen Hospital, Department of Medicine III, Nephrology, Hypertension, Transplantation, Rheumatology, Geriatrics, Linz, Austria; [3]Medical University of Vienna, Department of Medicine III, Division of Nephrology and Dialysis, Vienna, Austria; [4]Medical University of Vienna, Department of Epidemiology, Center for Public Health, Vienna, Austria.*

Background: It is widely taken for granted that kidney transplantation improves survival compared to remaining on dialysis. However, the previous evidence based on cohort studies is at high risk of bias and randomized controlled trials are not feasible. We aimed to investigate survival differences of kidney transplantation compared to remaining waitlisted on dialysis across different transplant candidate ages as well as depending on waiting time applying causal inference methodology.

Methods: We included all dialysis patients recorded in the Austrian Dialysis and Transplant Registry who were waitlisted for their first kidney transplant between 2000 and 2018 and utilized repeated updates on waitlisting status and relevant covariates. To estimate causal effects of kidney transplantation across ages, we specified a target trial protocol mimicking a series of controlled clinical trials initiated at the ordered times of transplantation relative to waitlisting. At each trial in the series patients were classified as either treated (transplanted) or control (remained on waitlist). We estimated restricted mean time gained by transplantation using sequential Cox regression adjusted for confounding and adherence to the treatment strategy by inverse probability weights for treatment and censoring, and stratified our analysis by pre-transplant waiting time (up to 1 year, 1 to 2 years, more than 2 years).

Results: 4445 patients were included, 33% were women, mean age was 50 years. 3621 patients (81%) were transplanted, 1392 patients died. Transplanted patients had longer 5- and 10-year restricted mean survival times compared to patients remaining waitlisted across all ages. E.g. a patient aged 70 at transplantation gained 0.85 years within 5 years posttransplant. Stratified analyses showed a gain of 0.61 years conditional on having been waitlisted up to 1 year and 0.82 and 1.35 years conditional on having been waitlisted for 1 to 2 years or more than 2 years respectively.

Conclusions: Our study provides evidence based on state-of-the-art causal inference methodology for moderately increased survival after kidney transplantation in the elderly and irrespective of time on waiting list.

PO2106

Meta-Analysis of Association Between TCF7L2 rs7903146 and Risk of New-Onset Diabetes After Kidney Transplantation

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Background: Single nucleotide polymorphisms may influence the risk of development of new-onset diabetes after transplantation (NODAT), a post-transplant clinical complication that is often implicated in allograft rejection and mortality. We performed a meta-analysis of association between TCF7L2 rs7903146 and risk of post-transplant diabetes mellitus.

Methods: A systematic search was conducted using PubMed and ScienceDirect electronic databases for studies published between January 2001 to January 2021. Case-control or cohort studies reporting association between NODAT (diagnosis based on American Diabetes Association [ADA] criteria) and TCF7L2 rs7903146 were included. MetaGenyo was used for meta-analysis (random effects model). Pooled odds ratios with 95% confidence intervals were reported to evaluate the strengths of association.

Results: Two reviewers independently screened for articles. A total of six case-control studies were included for full-text review and quantitative analysis after screening for eligibility. Genotypic distributions were in Hardy-Weinberg equilibrium for included studies. All papers reported statistically significant association of TCF7L2 rs7903146 for risk of NODAT, except for one study. There was moderate heterogeneity among studies ($I^2 = 60.6\%$). Pooled analysis revealed 51% odds of developing NODAT with TCF7L2 rs7903146 T allele (Allele Contrast Model: OR = 1.51, 95% CI 1.13 – 2.02, adjusted $p = 0.03$).

Conclusions: The present meta-analysis demonstrated association between TCF7L2 variant rs7903146 and risk of developing NODAT. This finding may have clinical implications for individuals undergoing kidney transplantation.

PO2107

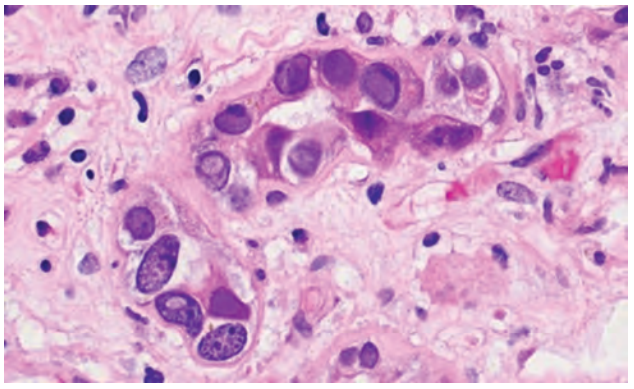
A Case of Native BK Virus Nephropathy in a Lung Transplant Patient

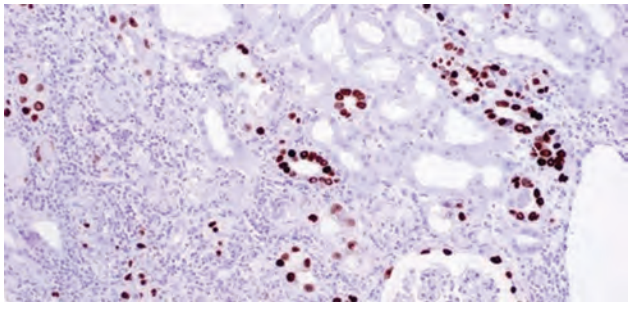
Waseem Albasha, Golnaz Vahdani, Ankita Ashoka, Erika R. Bracamonte, Amy Yau. *The University of Arizona College of Medicine Tucson, Tucson, AZ.*

Introduction: BK virus nephropathy (BKVN) is an opportunistic infection that can lead to progressive kidney dysfunction. Classically described in the allograft of kidney transplant patients, it is increasingly recognized in native kidneys of other non-renal solid organ transplants (NRSOTs). Here we describe a patient with a history of lung transplant with native BKVN.

Case Description: Our 68-year-old woman with a history of bilateral lung transplant for idiopathic pulmonary fibrosis was referred thirteen months post-transplant for worsening renal function. Her creatinine slowly increased from a baseline of 0.6 mg/dL to 1.9 mg/dL. Work up revealed a serum BK virus PCR level of 28,381,300 copies/ml. Kidney biopsy revealed numerous tubular epithelial cells with enlarged nuclei and intranuclear inclusions (Figure A) which stained positive for SV 40 (Figure B). Her tacrolimus and sirolimus were already reduced by the lung transplant team. Mycophenolic acid was discontinued. She was already on monthly intravenous immunoglobulin, and so she was admitted for intravenous cidofovir. Her creatinine preceding cidofovir treatment was 2.2 mg/dL with a serum BK virus PCR of 59,225,688 copies/ml. Unfortunately, after a total of 2.5 mg/kg of intravenous cidofovir, her creatinine worsened to 4.68 mg/dL with no significant change in BK viremia. Cidofovir was discontinued.

Discussion: Native BKVN is more common than previously recognized in NRSOTs. There is unclear guidance if lung transplant patients should be screened for BK viremia routinely, and there is a lack of safe and efficacious treatment options. This case adds to the growing literature of lung transplant recipients who develop native BKVN and the challenges of BKVN treatment beyond reduction of immunosuppression.





PO2108

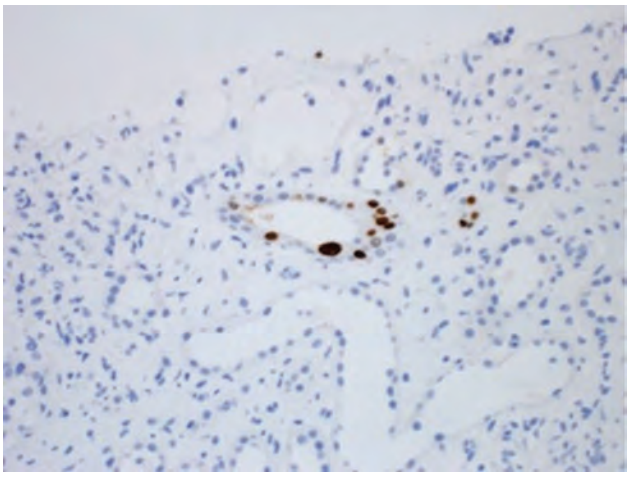
Late Presentation of JC Virus-Associated Nephropathy in a Renal Transplant Recipient

Mohamedanwar M. Ghandour, Samah S. Suleiman, Noreen F. Rossi, Mareena Zachariah. *Wayne State University, Detroit, MI.*

Introduction: JC virus (JCV) is a Polyomaviridae family member. JC virus-associated nephropathy (JCVAN) is more common in renal transplant recipients in comparison to other organ recipients. We report a case of JCVAN presenting after fourteen years post-renal transplantation.

Case Description: A 65-year-old female with primary kidney disease attributed to chronic hypertension, who received a preemptive renal transplant in 2006. Postoperatively, her hospital course was uneventful, with a baseline creatinine of 1.1 mg/dL at discharge. Induction immunotherapy consisted of anti-thymocyte globulin, maintenance immunosuppression (IS) regimen consisted of triple immunotherapy with mycophenolate mofetil, tacrolimus, and low dose prednisone. Approximately 14 years after renal transplant, the patient's renal function deteriorated with creatinine increasing from 1.55 mg/dL to 2.43 mg/dL. The patient underwent a renal biopsy, which revealed positive staining for SV40 in multiple tubular nuclei suggestive of a persistent polyomavirus in the renal tubules (Fig 1). Plasma levels of BK virus were negative. Plasma JC virus titers were 61,400 copies/mL. Mycophenolate was stopped, and tacrolimus was reduced to trough level 3-5ng/dl. JC Viremia responded to lowering IS and became negative. The allograft function declined and the patient returned to dialysis in less than a year.

Discussion: JCVAN is unusual in renal transplant recipients. Risk factors include previous acute rejection episodes and male gender. Notably, this female patient had no proven previous episodes of acute rejection. JCVAN usually occurs within the first year post-renal transplant. However, the reported case was an older female diagnosed with JCVAN fourteen years following the living donor kidney transplant. The diagnosis of JCVAN is confirmed histologically by obtaining a kidney biopsy and the mainstay of management is reducing the degree of immunosuppression.



PO2109

A Case of Unexplained Encephalopathy in a Kidney Transplant Recipient

Anjana Easwar, Laila S. Lakhani, Arpita Basu, Stephen O. Pastan. *Emory University, Atlanta, GA.*

Introduction: Progressive multifocal leukoencephalopathy is a fatal demyelinating disease caused by the JC virus. Kidney transplant patients who are immunosuppressed are at higher risk of this infection.

Case Description: A 42 year old woman with CKD5 from FSGS who underwent a living donor kidney transplant 5 months ago, on immunosuppression with tacrolimus, mycophenolate and prednisone, presented with acute confusion, expressive aphasia and gait disturbance. Differentials included structural, infectious, metabolic and nutritional causes. A lumbar puncture and MRI brain were unremarkable. She was treated for suspected thiamine deficiency with intravenous thiamine. She developed myoclonus and hyperreflexia. Benzodiazepines and cyproheptadine were started with concern for serotonin syndrome. Tacrolimus dose was reduced with concern for calcineurin neurotoxicity. On hospital day 10, she developed status epilepticus; but MRI brain was unremarkable and EEG showed generalized encephalopathy. A second lumbar puncture revealed high opening pressures, WBCs and protein concerning for meningoencephalitis with negative gram stain and culture. CNS virus panel including HSV was negative. Empiric treatment with broad spectrum antimicrobials was begun. Tacrolimus was switched to sirolimus without neurologic improvement. A third CSF sample showed pleocytosis and elevated protein. Extended viral panel testing was sent to an outside lab. On day 16, she developed hemodynamic instability with worsening neurological exam, rapidly progressing to fixed dilated pupils and absent cough and gag reflexes. Within hours she developed cardiac arrest and was successfully resuscitated. CT head post arrest demonstrated diffuse cerebral edema and tonsillar herniation indicating devastating neurological injury. She was declared brain dead on hospital day 17. The CSF metagenomic testing panel later returned positive for JC virus.

Discussion: This is a complex and unfortunate case of PML due to JC virus in a newly transplanted patient, highlighting the ability of opportunistic CNS infections to masquerade as a nutritional deficiency/drug toxicity and the challenges of pursuing advanced diagnostic work up beyond standard testing. Immunosuppression in kidney transplant recipients remains a double edged sword where tilting the fine balance in favor of over-immunosuppression can lead to catastrophic infectious complications.

PO2110

Boron Exposure and Decreased Risk of Mortality in Kidney Transplant Recipients

Daan Kremer,[1,2] Adrian Post,[1,2] Ulrike Seidel,[3] Yvonne van der Veen,[2] Dion Groothof,[1,2] Antonio W. Gomes Neto,[1,2] Tim J. Knobbe,[1,2] Gerald Rimbach,[3] Stephan J. Bakker.[1,2] TransplantLines Investigators *[1]Rijksuniversiteit Groningen, Groningen, Netherlands; [2]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [3]Christian-Albrechts-Universitat zu Kiel, Kiel, Germany.*

Background: In a search for potential modifiable factors to improve long-term outcome among kidney transplant recipients (KTR), we studied dietary patterns in the Blue Zones, and hypothesized that boron exposure is associated with improved long-term outcome in KTR.

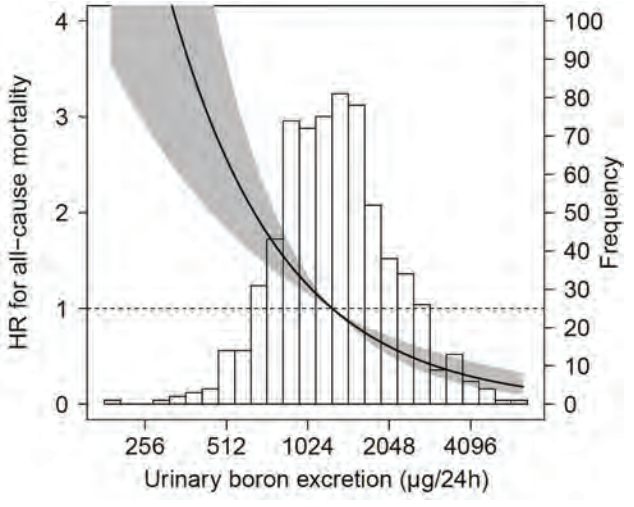
Methods: We determined 24h urinary boron excretion using inductively coupled plasma mass-spectrometry as a measure of boron intake in 693 stable KTR (57% male, mean age 53y), enrolled in the TransplantLines F&N Biobank and Cohort Study. Dietary intake was assessed using validated food-frequency questionnaires.

Results: Linear regression analyses showed that dietary intake of fruit, wine and nuts were key determinants of boron excretion. In contrast, boron excretion was negatively associated with homocysteine and inflammation parameters. In total, 73 (32%), 47 (20%) and 30 (13%) patients died among the lowest, middle and highest tertiles of boron,

respectively ($P_{log\text{-}rank}$ <0.001). Cox regression analyses showed that high boron excretion was strongly associated with lower risk of mortality, independent of age, sex, eGFR and history of cardiovascular disease (HR per doubling: 0.51, 95%CI:0.40 to 0.66, P<0.001, **Figure**), and other potential clinical and dietary confounders.

Conclusions: Boron may be an overlooked target to improve long-term outcome among KTR and potentially other patients, partly through suggested beneficial effects on inflammation, the methionine-homocysteine cycle, and ageing processes. Interventional trials are warranted to confirm the potential of dietary boron supplementation in KTR and other patient populations.

Funding: Clinical Revenue Support



Associations of urinary boron excretion with risk of all-cause mortality, based on a Cox proportional hazards regression model adjusted for age, sex, eGFR, and history of cardiovascular disease, presented in relation to the histogram of urinary boron excretion.

PO2111

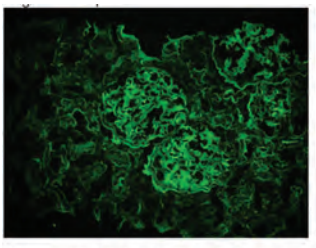
HIV-Associated Lupus-Like Nephropathy in a Transplanted Kidney: An Etiology for CKD

Kiran Shivaraj, Hay Me Me. *Westchester Medical Center, Valhalla, NY.*

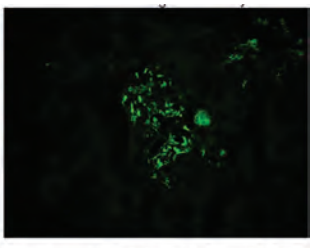
Introduction: The mortality of chronic Kidney disease in HIV is about 3 times higher in patients with HIV when compared to non HIV. With improved coverage of antiretroviral therapies with incidence of HIVAN a form of collapsing FSGS are decreasing but HIVICK a immune mediated form of nephropathy is increasing. One particular type called the HIV associated Lupus Like nephropathy has been described classically in a native kidney, we describe this lesion in a transplanted kidney and might be the cause of chronic kidney disease.

Case Description: 51 y o female patient with history of HIV on antiretroviral therapy who had a Living donor Kidney transplant from her HIV negative brother in about 4 years back and having a chronic kidney disease ckd stage 2 presented with intermittent watery diarrhea for 2 month and was found to have an acute kidney injury. The preliminary workup for Acute kidney injury including BK virus and DSA was negative. Renal transplant biopsy showed immune complex mediated glomerulonephritis with features of lupus like glomerulonephritis (full house stain with positive C1q), chronic transplant glomerulopathy with mild interstitial fibrosis and tubular atrophy, With a negative ANA and a negative ds DNA.

Discussion: The HIV lupus like nephropathy was picked up incidentally on biopsy while looking for acute rejection as the cause for the AKI which resolved with hydration. It was contributing to the underlying chronic elevated creatinine. The case is interesting as it has been described for the first time in a transplanted kidney and also that it's seen a kidney received from a non HIV donor as the pathogenesis requires the entry of viral particle into the renal cells in order to manifest the disease. The good immune system as indicated by the CD4 count and the viral titers supports the development of HIVICK. With the growing number of transplant in HIV positive patients HIV associated lupus like nephropathy a type of HIVICK should be considered as the cause of chronic elevated creatinine and might need adjustment of the immunosuppression accordingly.



IgG: granular stain in GBM and mesangial Areas.



C1q: granular staining in mesangial areas and GBM.

PO2112

Disseminated Adenovirus Infection in a Kidney Transplant Recipient

Boonyanuth N. Maturostrakul, Vinay Nair, Vanesa Bijol, Mersema Abate, Madhu C. Bhaskaran, Marcia Epstein, Gayatri D. Nair, Lewis Teperman, Hye Jeong Jang, Lawrence Lau. *Northwell Health, New Hyde Park, NY.*

Introduction: Adenovirus as an opportunistic pathogen can cause infections in immunocompromised hosts. Cases of disseminated adenovirus infection in renal transplant patients have been described to be detrimental.

Case Description: 28 year-old male with end stage renal disease from focal segmental glomerulosclerosis with 2 prior failed renal transplant on hemodialysis received a 3rd renal transplant from a deceased donor. Though initially planned for thymoglobulin induction, was switched to Basiliximab due to anaphylaxis during thymoglobulin infusion. Patient received plasmapharesis, IV immuglobulin and rituximab in view of his sensitized status and presence of donor specific antibodies with persistent elevated creatinine early post-transplant. Subsequent allograft biopsy showed Banff 1B rejection. He was treated with steroids and Alemtuzumab. Patient was discharged, but was readmitted with high fever. Blood and urine cultures were negative. Respiratory viral panel was positive for Adenovirus. Due to persistent high fever, immunosuppression was minimized. Hydronephrosis was drained with the nephrostomy. Repeat allograft biopsy was performed for rising creatinine. Light microscopy revealed severe necrotizing tubulitis with numerous basophilic nuclear viral inclusions and extensive polymorphonuclear inflammation consistent with adenoviral nephritis. Immunohistochemistry confirmed positive nuclear staining for adenoviral antigens. Patient was found to have moderate pericardial effusion and bilateral ground glass opacities. He was treated with Cidofovir, IV immunoglobulin and reduced immunosuppression. Due to persistent allograft dysfunction, he was maintained on dialysis. At the time of this report patient continues to be on dialysis.

Discussion: Adenoviral infection in healthy individual is often self-limited, rarely requiring more than symptomatic treatment. However, in immunosuppressed individuals it can lead to severe multisystem disease. In this patient, adenoviral infection following robust immunosuppression for early severe allograft rejection led to severe injury to allograft and near fatal illness. A high level of suspicion and prompt treatment can help improve the patient outcome.

PO2113

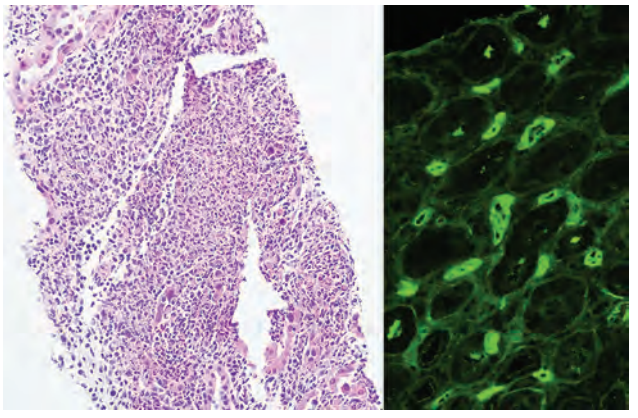
A Rare Case of Adenovirus Interstitial Nephritis and AMR Within Two Weeks of Kidney Transplant

Maliha Ahmed, Mohammed R. Karim, Hae Yoon Grace Choung. *University of Rochester, Rochester, NY.*

Introduction: Adenovirus nephropathy is a rare but devastating complication of kidney transplant. We report a case of adenovirus nephropathy associated with AMR within two weeks of renal transplant.

Case Description: 56 year old African American male with ESRD secondary to FSGS with history of LDKTXP in 2010 complicated by recurrent FSGS, BK viremia and chronic TCMR resulting in allograft failure and return to hemodialysis. He underwent DDKTXP in April, 2021 with rATG induction. He was noted to have slow graft function, serum creatinine trended down to 2.58 on post-op day 7 however again started to rise associated with fever and fatigue. PCR for BKV, EBV, CMV, COVID 19, influenza A and B remained negative. Adenovirus DNA was detected in sputum, urine and blood on post-op day 13. The patient underwent allograft biopsy on post-op day 16 which revealed severe necrotizing interstitial nephritis consistant with adenovirus nephropathy and early AMR (diffuse C4d positivity in peritubular capillaries with mild to moderate peritubular capillaritis, c4d3, ptc1-2). MMF was held, he received 5 plasmapharesis sessions and total of 1.1 g/Kg IVIGs. Cidofovir 1mg/Kg was staretd on alternate days. His course was complicated by anuric renal failure requiring return to hemodialysis. No evidence of donor associated ADV could be established.

Discussion: The case highlights the importance of distinguishing adenovirus interstitial nephritis from acute allograft rejection on biopsy . The case also highlights the dilemma of treating adenovirus interstitial nephritis and AMR concomitantly. Our patient has history of prior kidney transplant which is a risk factor for ADV infection. Viral infection of allograft predisposes it to rejection by stimulating various immune pathways



H&E stain shows Necrotizing interstitial nephritis with prominent tubular necrosis and destruction associated with poorly formed necrotizing granulomas and neutrophils.

IF shows diffuse C4d staining in peritubular capillaries

PO2114

Medial Arterial Calcification and Transplant Outcomes

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Background: Medial arterial calcification, a disorder distinct from atherosclerosis, is common in ESRD and associated with poor outcomes. Since this lesion does not regress after renal transplantation, it may be associated with poor outcomes in these patients as well. This was tested in a retrospective cohort of females undergoing renal transplantation using breast arterial calcification (BAC) as a specific marker of medial arterial calcification.

Methods: We identified all females with renal transplantation (Tx) through 2017 with digital mammograms performed at this institution. Mammograms were examined for arterial calcification, which was quantified by summing the lengths of calcified arterial segments. BAC was considered present at Tx if present any time prior to Tx or within 1.5 years after Tx. BAC was considered absent if absent within one year before Tx and any time after Tx. Medical records were reviewed for graft loss, cardiovascular disease (CVD: myocardial infarction, amputation, stroke, or any revascularization), and risk factors.

Results: 132 patients were identified with qualifying mammograms, which were performed a median of 0.50 years from Tx date. Clinical follow-up ranged from 3-13 years after Tx (mean: 6.4), time to graft loss 1.3-9.4 years (mean: 3.9), and time to CVD event 0.3-7.9 years (mean: 4.1). Patients with BAC (n=58) were older (55 vs. 50, p=0.004), had more diabetes (55 vs. 35%, p=0.02), parathyroidectomies (16 vs. 1.4%, p=0.005), and somewhat more pre-Tx CVD (12 vs. 4.1%, p=0.10). Graft loss (14 vs. 2.7%, p=0.022) and new CVD (21 vs. 5.4%, p=0.014) occurred more frequently in patients with BAC. BAC remained an independent predictor of graft loss in a logistic model including age, prior Tx, pre-Tx CVD, diabetes, and smoking (OR: 8.8; 95% CI: 1.2-62, p=0.029). The effect on CVD was no longer significant when pre-Tx CVD and diabetes were added to a logistic model. CVD was more common in those with BAC above vs. below the median quantity.

Conclusions: Medial arterial calcification was an independent predictor of renal allograft failure. It also predicted post-Tx CVD events but this was largely accounted for by the association with pre-Tx CVD and diabetes. Since all women undergo screening mammography prior to Tx, BAC could be a convenient marker of outcomes and targeting of risk factor modification and should be investigated in a larger cohort.

Funding: Clinical Revenue Support

PO2115

Pre-Transplant Hypoalbuminemia Is Associated with Lower Risk for Rejection Among Kidney Transplant Recipients

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Background: Serum albumin is a marker of health status. Hypoalbuminemia is a common complication among patients with end-stage renal disease. Many patients would have hypoalbuminemia before getting a kidney transplant. The association of hypoalbuminemia and early post kidney transplant outcomes is not well studied.

Methods: All adult kidney transplant recipients at our center between 01/01/2001 and 12/31/2017 who had serum albumin levels ≤30 days prior to transplantation were included. Categorized recipients into four pretransplant albumin levels: normal albumin (≥4.0 gm/dL, reference group), mild (≥3.5-<4.0), moderate (≥3.0-<3.5), and severe (<3.0). We looked at pre-transplant hypoalbuminemia and outcomes incuding length of stay after transplant, readmission within 30 days, delayed graft failure, need for re-operation related to transplant. We also looked for the rate of rejection, graft failure, and death within the first six months of transplant.

Results: 2807 patients were included in the study. Of those, 1224 were identified as normal, 992 with mild, 466 with moderate, and 125 with severe. Albumin groups differed by age (p<0.001), BMI (p<0.001), pre-transplant dialysis (p=0.0011), cause of ESRD (p<0.001), and induction agent (p<0.001). The mild group was associated with -1.24 days less LOS (95% CI -1.73 to -0.75; p<0.001); and moderate by -0.82 day (95% CI -1.46 to -0.19, p=0.01) but not a significant difference in severe group, after adjustment of multiple confounding factors, compared to reference. There were no differences in the rate of DGF, re-hospitalization within 30 days across the groups. The moderate group was associated with a lower need for re-operation (HR: 0.39; 95% CI: 0.17 to 0.89; p=0.025). The moderate (HR: 0.54, 95% CI: 0.30-0.85; p=0.008) and severe (HR: 0.20, 95% CI: 0.06-0.65; p=0.007) groups were associated with a significantly lower rejection rate within six months compared to reference levels.

Conclusions: Our results suggest that the hypoalbuminemia is associated with a lower risk of acute rejections and some other complications, were also comparable compared to recipients with normal albumin levels. These findings may guide transplant providers in the selection of patients and anticipate and mitigate some of the post-transplant complications.

PO2116

Peripheral Arterial Disease and Risk of Infection-Related Complications After Kidney Transplantation

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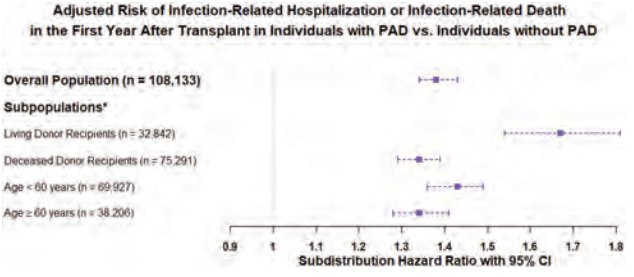
Background: Infection-related hospitalizations after kidney transplantation are a common complication associated with significant morbidity and increased healthcare costs. Peripheral arterial disease (PAD) is a common comorbidity associated with poor wound healing and frailty, and may be an unrecognized risk factor for serious infections.

Methods: We included adults who received a kidney transplant in the US between 2006 and 2016. We used Fine-Gray models to assess the relationship between PAD and the composite outcome of infection-related hospitalization or infection-related death within the first year after transplant, while accounting for the competing risks of non-infection-related death or graft failure. We evaluated for presence of interactions between PAD and specific factors including age<60, diabetes, and donor type (living vs. deceased) for the outcome.

Results: Out of 108,133 kidney transplant recipients (KTRs), 22,442 experienced the composite outcome in the first year after transplantation. In adjusted models, PAD was associated with a 38% higher hazard of the primary outcome (95% CI 1.34-1.43) [Figure]. Statistically significant interactions were present between PAD and donor type and age category. In subgroup analyses, PAD was associated with a higher risk for the composite outcome in living donor KTRs and with slightly higher risk in younger vs. older KTRs.

Conclusions: PAD was associated with an increased risk of infection-related hospitalization or death in the first year after transplantation, especially in subgroups who traditionally may not be evaluated for PAD prior to transplant, such as living donor KTRs and younger populations. Better screening for PAD even in young populations may improve our ability to reduce the risk of complications post-transplant.



Models Adjusted for Sex, Race, BMI, Dialysis Vintage, Diabetes, Stroke, Primary Cause of Kidney Failure, Smoking History, and Transplant Year, and age or donor type depending on the subpopulation of interest; *P-interaction < 0.05.

PO2117

Pegloticase for Uncontrolled Gout in Kidney Transplant Recipients: Provisional Data Report of a Multicenter, Open-Label, Efficacy and Safety Study

Abdul A. Abdellatif,[1] Lin Zhao,[2] Paul M. Peloso,[2] Katya Cherny,[2] Brad Marder,[2] John D. Scandling,[3] Kenneth G. Saag.[4] *[1]Baylor College of Medicine, Houston, TX; [2]Horizon Therapeutics plc, Deerfield, IL; [3]Stanford University School of Medicine, Stanford, CA; [4]University of Alabama at Birmingham, Birmingham, AL.*

Background: Kidney transplant (KT) recipients have a high prevalence and severity of gout. Pegloticase (pegylated recombinant uricase) rapidly metabolizes urate and efficacy is not impacted by CKD stage. Immunomodulator co-therapy with pegloticase has improved treatment response rates over phase 3 monotherapy trials by attenuating anti-drug antibodies (ADAs). This ongoing Phase 4 trial (PROTECT NCT04087720) examines safety and efficacy of pegloticase in KT patients with uncontrolled gout (UCG).

Methods: KT recipients with UCG (serum urate [SU]≥7 mg/dL, intolerance/inefficacy to urate lowering therapy, and ≥1 of the following: tophi, chronic gouty arthritis, ≥2 flares in past yr) and functioning KT graft (eGFR≥15 ml/min/1.73m^2) on stable immunosuppressive (IMS) therapy are included (KT>1 y earlier). Pegloticase (8mg q2w for 24wks) safety and efficacy are examined. Primary endpoint was SU responders during Month 6 (SU <6 mg/dL for ≥80% of time). Health Assessment Questionnaire (HAQ) pain (most severe: 100) and Disability Index (HAQ-DI) scores (max: 3) were evaluated.

Results: 20 patients enrolled (mean±SD; age: 53.9±10.9 y, time since KT: 14.7±6.9 y, SU: 9.4±1.5 mg/dL, gout duration: 8.4±11.6 y; all on ≥2 IMS). At the time of analysis, 10 patients completed treatment, 3 discontinued study, 2 met SU monitoring rules (pre-dose SU>6 mg/dL at 2 consecutive visits) and discontinued pegloticase, and 5 were ongoing. All patients experienced initial substantial reductions in SU, which was maintained in the majority; 2 patients met monitoring rules. At week 24, no notable eGFR changes were observed. In patients that completed treatment, HAQ-pain and HAQ-DI scores improved by 26.7±30.3 (baseline: 35.9±30.2) and 0.2±0.5 (baseline: 1.0±1.0), respectively, at Week 24 (n=10). 7 SAEs (2 cellulitis, duodenal ulcer, sepsis, a-fib, diverticulitis, and localized infection) deemed unrelated to pegloticase, were reported in 5 patients. No anaphylaxis or IR events have occurred.

Conclusions: Preliminary results from the PROTECT trial, with Fall 2021 completion, demonstrate substantial and sustained SU decrease in the majority of KT recipients with uncontrolled gout. These findings are consistent with other reports on the effect of immunomodulation use with pegloticase.

Funding: Commercial Support - Horizon Therapeutics plc

PO2118

Discontinuation of Renin-Angiotensin System Blockade Among Kidney Transplant Recipients

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Background: Cardiovascular disease is common among recipients of kidney transplantation and is associated with high morbidity and mortality. While recent studies have shown evidence of cardiovascular benefit with the continuation of renin-angiotensin system (RAS) blockade for transplant-naïve patients with CKD there are little data on whether cessation of RAS blockade among kidney transplant recipients has kidney, cardiovascular, or survival benefits (or risks).

Methods: We performed a retrospective cohort study of kidney transplant recipients from the FAVORIT study. We included participants enrolled in the US who received an ARB or ACEi by self-report at one or more FAVORIT visits and performed a propensity score (PS) weighted Cox survival analysis to examine the risks or benefits of RAS discontinuation (vs. continuation). Outcomes were risk of death, return to dialysis, and major adverse cardiovascular events (MACE; stroke, myocardial infarction, coronary revascularization, or heart failure). Doubly robust estimation was also used on the PS weighted sample to provide conservative estimates.

Results: 2,009 US participants had at least one visit where they reported taking a RAS inhibitor. 30% (n=598) of participants discontinued RAS blockade. Compared to those who continued RAS blockade, participants who discontinued RAS blockade were significantly less likely to experience mortality, return to dialysis, and MACEs (Table).

Conclusions: Kidney transplantation recipients who stopped RAS blockade had lower rates of mortality, return to dialysis, and MACEs compared to those who continued RAS blockade. These data may be useful when deciding on the risks and benefits of continuing RAS blockade for patients receiving kidney transplantation.

Hazard of adverse outcomes for kidney transplantation recipients discontinuing vs. continuing ACEi/ARB

	Mortality HR (95% CI)	Dialysis HR (95% CI)	MACE HR (95% CI)
Unweighted adjusted model	0.72 (0.54-0.96)	0.71 (0.51-0.99)	0.63 (0.47-0.85)
Propensity-score weighted unadjusted model	0.75 (0.57-1.00*)	0.77 (0.56-1.07)	0.64 (0.48-0.85)
Propensity-score weighted adjusted model (doubly robust)	0.72 (0.55-0.96)	0.71 (0.51-0.99)	0.62 (0.46-0.83)

*p<0.05

Adjusted for age at discontinuation, sex, race, ethnicity, use of calcineurin inhibitor or mTOR inhibitor use, diabetes, systolic blood pressure, and eGFR

PO2119

Blood Transfusion and Venous Thromboembolism in Kidney Transplant Patients

David Massicotte-Azarniouch. *University of Ottawa, Ottawa, ON, Canada.*

Background: Receipt of a red blood cell transfusion (RBCT) is common in kidney transplant patients and could have pro-thrombotic effects predisposing to venous thromboembolism (VTE). The aim of this study is to examine the risks for the development of VTE associated with the receipt of RBCT in kidney transplant patients.

Methods: We conducted a retrospective cohort study of all adult kidney transplant recipients at The Ottawa Hospital from 2002 to 2018, using administrative databases and medical chart review. The exposure of interest was receipt of a RBCT after transplant. Cox proportional hazards models were used to calculate hazard ratios (HR) for venous thromboembolism [VTE] (deep venous thrombosis [DVT] or pulmonary embolism [PE]) using RBCT as a time-varying, cumulative exposure.

Results: Out of 1,258 kidney transplants recipients, 468 (37%) received a total of 2,373 RBCT after transplant (incidence of 33 RBCT per 100 patient-years). During follow up, 79 study participants (6.3%) developed VTE, 72 had a DVT (5.7%) and 22 had a PE (1.8%). For the receipt of 1, 2, 3-5 and >5 RBCT, compared to individuals never transfused, the number of events and adjusted HR (95% CI) for VTE was 6 events (6.2%) HR 1.57 (0.69 to 3.58), 9 events (7.6%) HR 2.54 (1.30 to 4.96), 15 events (11.9%) HR 2.73 (1.38 to 5.41) and 23 events (18.1%) HR 5.77 (2.99 to 11.14) respectively; for DVT it was 6 events (6.2%) HR 1.94 (0.84 to 4.48), 9 events (7.6%) HR 2.92 (1.44 to 5.94), 14 events (11.1%) HR 3.29 (1.63 to 6.65) and 21 events (16.5%) HR 6.97 (3.53 to 13.76), respectively. For PE, among transfused individuals there were 14 events (3.0%) and the HR was 2.40 (1.02 to 5.61).

Conclusions: The risk for developing VTE, DVT and PE was significantly associated with the receipt of a RBCT in kidney transplant patients. Receipt of a RBCT should prompt considerations for judicious monitoring and assessment for possible thrombosis.

Cox model HRs for VTE events based on RBCT exposure

Outcome	# RBC units received	# events (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	Any RBCT vs No RBCT: adjusted HR (95% CI)*
VTE (DVT or PE)	None 1 2 3-5 >5	26 (3.3) 6 (6.2) 9 (7.6) 15 (11.9) 23 (18.1)	Reference 1.85 (0.82 to 4.18) 2.67 (1.38 to 5.16) 3.59 (1.86 to 6.95) 7.45 (3.95 to 14.06)	Reference 1.57 (0.69 to 3.58) 2.54 (1.30 to 4.96) 2.73 (1.38 to 5.41) 5.77 (2.99 to 11.14)	2.75 (1.73 to 4.38)
DVT	None 1 2 3-5 >5	22 (2.8) 6 (6.2) 9 (7.6) 14 (11.1) 21 (16.5)	Reference 2.25 (0.98 to 5.15) 2.96 (1.47 to 5.95) 4.27 (2.17 to 8.43) 8.90 (4.62 to 17.13)	Reference 1.94 (0.84 to 4.48) 2.92 (1.44 to 5.94) 3.29 (1.63 to 6.65) 6.97 (3.53 to 13.76)	3.29 (2.01 to 5.40)
PE	None 1 2 3-5 >5	8 (1.0) 3 (3.1) 2 (1.7) 2 (1.6) 7 (5.5)	Reference 2.51 (0.70 to 8.99) 2.08 (0.58 to 7.51) N/A 8.25 (2.77 to 24.58)	Reference 2.42 (0.67 to 8.72) 2.10 (0.58 to 7.57) N/A 7.70 (2.55 to 23.21)	2.40 (1.02 to 5.61)

* Adjusted for age, sex, transplant type, PRA, presence of diabetes, presence of cardiovascular disease, and type of maintenance therapy. PE analysis was adjusted only for age given low number of events (22)

PO2120

AV Fistula Leading to High-Output Cardiac Failure in a Kidney Transplant Population: Our Experience

Yahya R. Ahmad, Hasan Fattah. *University of Kentucky, Lexington, KY.*

Background: Among kidney allograft recipients, cardiovascular death continues to remain the major cause of mortality. Arteriovenous (AV) fistula is the optimal access for most end stage kidney disease (ESKD) patients. AV fistula can lead to hemodynamically significant left-to-right sided shunting resulting in permanent structural and functional cardiac changes. We herein reviewed our center cases of high cardiac-output cardiac failure secondary to AV fistula who were followed up after surgical intervention.

Methods: Retrospective chart review was performed on kidney transplant patients who had a diagnosis of high output cardiac failure confirmed on right heart catheterization and required AV fistula ligation for symptomatic high output cardiac failure at University of Kentucky.

Results: A total of 595 kidney transplants were performed at University of Kentucky during the study period (January 2015 until May 2021). 19 patients underwent fistula ligation, 7 of them (36.8%) required AV fistula ligation due to high output cardiac failure. Average peak blood flow across the AV fistula that required ligation was 2.8 L/min. Cardiac catheterization showed drop in cardiac output (CO) with AV fistula closure as seen in Figure 1. Improvement in renal functions was notable in most cases as seen in Figure 2. Symptoms of heart failure improved in all 7 patients with no re-admissions for heart failure exacerbation after AV fistula closure, up until writing this data.

Conclusions: High output heart failure from AV fistula is an under recognized entity. Early diagnosis and management is crucial as it can prevent irreversible changes in cardiac and renal physiology and improve quality of life.

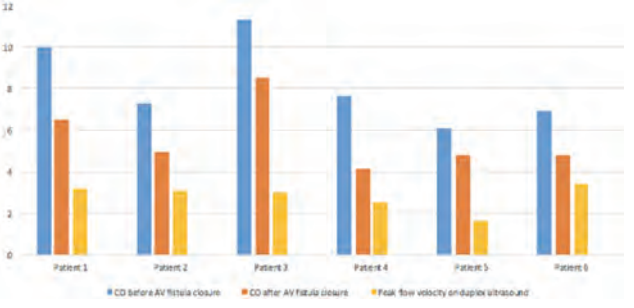


Figure 1

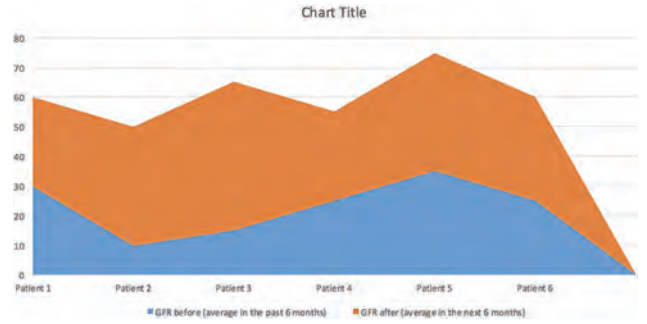


Figure 2

PO2121

Hypophosphatemia in the Context of Hematopoietic Stem Cell Transplantation: An Underappreciated Complication

Thangamani Muthukumar,[1] Carlos Flombaum.[2] *[1]Weill Cornell Medicine, New York, NY; [2]Memorial Sloan Kettering Cancer Center, New York, NY.*

Background: Hypophosphatemia (and hypokalemia) occur frequently in the context of hematopoietic allogeneic stem cell transplantation (allo-SCT) and during autologous SCT (auto-SCT) and have been attributed to uptake of these electrolytes by the reconstituting bone marrow. Similar metabolic complications can also occur after chemotherapy and during stem cell mobilization prior to auto SCT. These metabolic abnormalities have not been well described in the nephrology literature and in current textbooks of onconephrology. Aim of the research was to describe the clinical course of patients with these electrolyte abnormalities in the context of SCT, chemotherapy and after bone marrow stimulation prior to SCT harvesting.

Methods: Chart review of patients undergoing SCT, after chemotherapy and SCT for harvesting.

Results: We identified 42 patients with 67 episodes of hypophosphatemia and hypokalemia. The clinical features and course are provided in the table.

Conclusions: Besides uptake of phosphorous and potassium by the reconstituting bone marrow under the stimulation of granulocyte colony a stimulation factor, other factors contributing to these metabolic abnormalities include poor oral intake, the use of phosphate binders, diuretics and losses during renal replacement therapy.

Characteristics	Chemotherapy-related	Auto-SCT-related	Allo-SCT-related	During Stem Cell Mobilization
Number of patients, N	15	17	9	9
Number of episodes, N	31	18	9	9
Kidney injury (acute or chronic), N	15 (48%)	12 (67%)	4 (44%)	8 (89%)
Renal replacement therapy, N	11 (36%)	6 (33%)	0 (0%)	6 (67%)
Use of G-CSF, N	29 (94%)	18 (100%)	9 (100%)	9 (100%)
Number of days with hypophosphatemia, median (IQR)	7 (4-12.5)	4 (2-9.5)	10 (7-13)	2 (2-3)
Nadir serum phosphate, median (IQR)	1.4 (1.15-1.80)	1.35 (1.05-1.88)	1.3 (1.1-1.5)	1.5 (1.2-2.2)
Use of phosphate replacement, N	22 (71%)	14 (78%)	9 (100%)	5 (56%)
Use of phosphate binders, N	8 (26%)	8 (44%)	1 (11%)	5 (56%)
Hypokalemia, N	21 (68%)	16 (89%)	8 (89%)	5 (56%)
Nadir serum potassium, median (IQR)	3 (2.9-3.1)	3.2 (3.1-3.3)	3.2 (3.1-3.2)	2.9 (2.6-3.1)
Use of diuretics, N	6 (19%)	7 (39%)	6 (67%)	1 (11%)
Use of potassium replacement, N	21 (68%)	15 (83%)	7 (78%)	3 (33%)

PO2122

Kidney Graft Ultrasound (US) After Elective JJ Stent Removal (EJJR)

Haridian Sosa Barrios,[1] Victor Burguera,[1] Elizabeth R. Viera,[1] Daniel Villa,[1] Cristina Galeano,[1] Sara Jimenez Alvaro,[1] Irene Martin Capon,[1] Milagros Fernandez-Lucas,[1] Maite Rivera Gorrin.[1,2] *[1]Hospital Universitario Ramon y Cajal, Madrid. IRYCIS, Spain; [2]Universidad de Alcala de Henares Facultad de Medicina y Ciencias de la Salud, Alcala de Henares, Spain.*

Background: Improving kidney transplant (KTx) outcomes remains a primary challenge and KTx ureter JJ stenting has been used to prevent urological complications. There is no consensus about EJJR timing, and literature regarding routine US imaging after EJJR to detect complications is lacking.

Methods: We retrospectively analysed all routine KTx US done in our Unit from 2016-2020 by an experienced interventional nephrologist. US post EJJR findings were compared with previous US. KTx characteristics, treatment and outcomes were recorded. We aimed to define incidence of urological complications diagnosed, US utility and best time interval to perform it.

Results: 345 KTx were done: 62.9% were male receptors, 81.7% had a first KTx and 91.5% of the organs were from a deceased donor. No routine US post EJJR was done in 20.9% due to COVID pandemic. Mean timing to elective JJ stent removal was 36.4 ± 25 days (SD). Mean time from EJJR to US was 16.3 ± 28.8 days (SD). Urinary tract ectasia was not considered pathological. Of those with an US, 45.1% (123) had a complication detected: 41.4% had a newly diagnosed collection and 21% had urinary tract dilatation (UTD): 10% grade I UTD. 6% grade II UTD. 5% grade III UTD. Of the 123 patients with a complication, 3 required a surgical approach, 2 had a drainage inserted, 2 nephrostomies, 11 required admission without surgical intervention and 51 had US follow up. Cumulative frequency analysis of complications post EJJR showed the highest diagnostic yield of US imaging was around day 10 post removal (figure 1).

Conclusions: Routine US after EJJR allowed timely diagnosis and early treatment of urological complications, a key factor for successful transplantation. KTx US is an effective, cheap and reproducible test that provides crucial information to guide clinical decisions, being most effective when performed 10 days post stent removal. Interventional nephrologists could do this examination promptly.

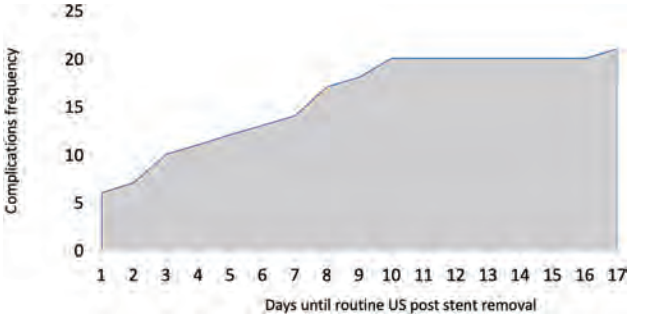


Figure 1. Cumulative frequency of complications

PO2123

A Cardiac Magnetic Resonance (CMR) Study with Native T1 Mapping in Patients Listed for a Kidney Transplant

Jordana Yahr,[1] Sadeer Al-Kindi,[2] Scott E. Janus,[2] Aparna Padiyar,[2] Mahboob Rahman,[2,3] Sanjay Rajagopalan,[2,3] Anne M. Huml,[1,3] Mirela A. Dobre.[2,3] *[1]Cleveland Clinic, Cleveland, OH; [2]University Hospitals, Cleveland, OH; [3]Case Western Reserve University, Cleveland, OH.*

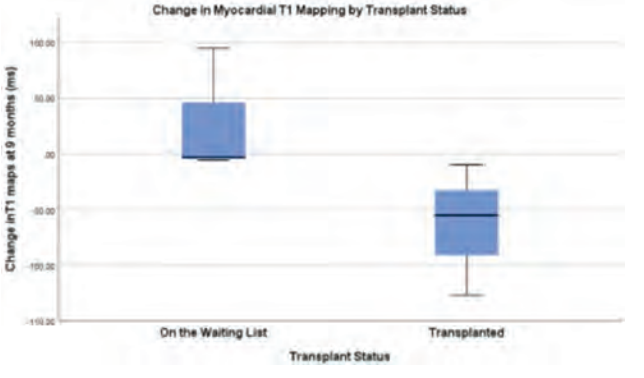
Background: Uremia causes activation of cardiac fibroblasts, a decrease in capillary density and promotes fibrosis by impairing oxygen diffusion to cardiomyocytes and promoting apoptosis. Assessment of myocardial fibrosis can be done non-invasively by non-contrast CMR T1 mapping. Though reversal of myocardial fibrosis post kidney transplant has been postulated, no study has systematically assessed it in transplant recipients compared to patients who remain on the waiting list. We aimed to assess the change in T1 maps post transplant in comparison to that in waitlisted patients.

Methods: Patients from 2 clinical sites, scheduled to receive a living kidney transplant underwent a non-contrast CMR prior to and 9 months post-transplant. An age-, sex-, race- and dialysis vintage-matched control group was selected from the patients waitlisted for a deceased donor, and had non-contrast CMR performed at baseline and after 9 months. Cardiac fibrosis measured by T1 maps were compared between the 2 groups.

Results: A total of 34 participants underwent CMR at study baseline. Mean age±SD was 55±14 years, and 13(38%) were women, 7(21%) Black and 16(47%) were on dialysis. There was no difference in baseline T1 level in pre-dialysis (1063±50 ms) vs dialysis (1062±51 ms) participants, and in transplant (1063±60 ms) vs waitlisted (1063±48 ms) participants. In multivariable adjusted models, age, diabetes, and heart failure were significantly associated with T1 levels. In a subgroup of 7 participants with available follow-up CMR, compared to control group, those transplanted had a reduction in T1 levels (-64±59 ms vs 20±49 ms, p=0.09) Figure. Participants with high baseline T1 had the least decline in follow-up T1 levels.

Conclusions: Myocardial fibrosis as measured by native CMR T1 maps is reduced post kidney transplantation and continues to worsen for patients who remain actively listed for a transplant.

Funding: Private Foundation Support



PO2124

SGLT-2 Inhibitor Treatment in Renal Transplant Recipients: A Single-Center Experience

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Background: Dapagliflozin, a sodium glucose transport protein 2 inhibitor (SGLT2-i), was recently approved for use in chronic kidney disease patients regardless of the presence of diabetes, after studies demonstrated improved renal and cardiovascular outcomes even in the absence of diabetes. The use of SGLT2-i in transplant recipients have been limited due to concerns for acute kidney injury (AKI) resulting from volume depletion or urinary tract infections (UTI) or other genital infections due to their glucosuric effect.

Methods: Retrospective review of all adult renal transplant recipients transplanted at our center between January 2013 and June 2020.

Results: 22 adult renal transplant patients at our center received treatment with an SGLT2-i during the study period. The patient's ethnicity was representative of our patient's population with 45% being Hispanic and 40% black. 68% of the patients were men and the median age was 64 years old. The vast majority of patients, 77%, had diabetes mellitus as the etiology of ESRD. 73% received a deceased donor kidney transplant and were started on SGLT2-i at a median time of 38 months post-transplant. 13 patients were treated with empagliflozin with a starting dose of 10mg daily, 7 with canagliflozin at 100mg daily, 1 dapagliflozin at 5mg daily, and 1 ertugliflozin at 2.5mg daily. The median creatinine at the start of treatment was 1.1mg/dl, urine protein creatinine ratio was 206 mg/g, and A1C 8.6 %. SGLT2-inhibitors were well tolerated without significant adverse events. 4 patients developed hypoglycemia. Two patients developed a UTI and only 1 patient developed AKI requiring discontinuation of the drug. The median creatinine one-year post treatment initiation was stable at 1.1mg/dl, UPCR was 448.4 mg/g, and A1C was 7.7. Finally, there was no significant interaction with the immunosuppression medications. The tacrolimus level remained stable and the patients did not require dose modifications post therapy initiation.

Conclusions: Treatment with SGLT2-i was well tolerated in our transplant population. Larger prospective studies are required to evaluate clinical outcomes in this patient population.

PO2125

Immunosuppression and Incident Cancer Risk in Older Kidney Transplant Recipients

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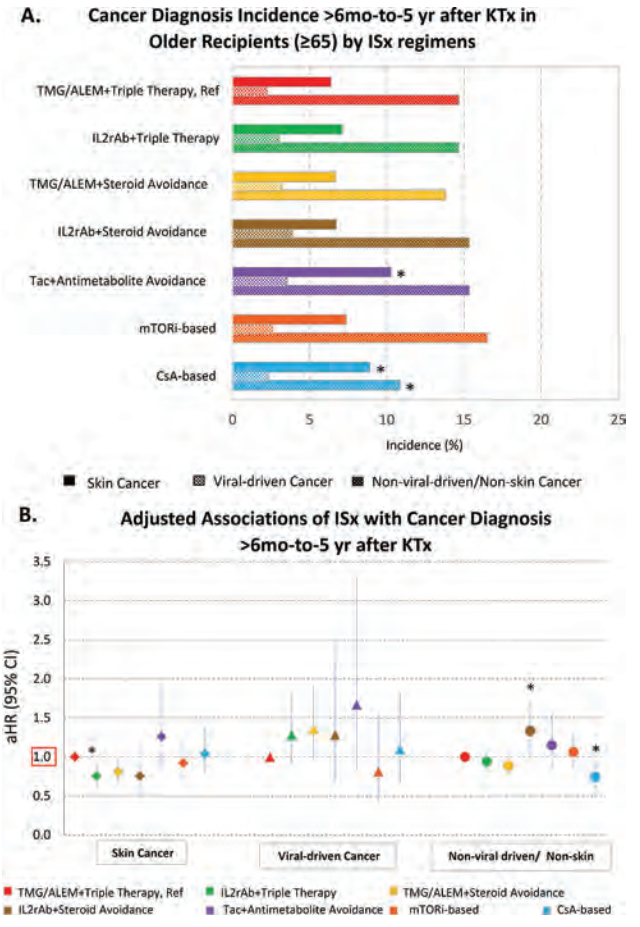
Background: Cancer is a serious complication after kidney transplant (KTx), especially among older adults. The relationship of immunosuppression (ISx) to cancer in older KTx recipients is not well described.

Methods: We examined USRDS data (2005-2017) to explore associations of ISx regimens (within 6 mo) with new-onset cancer diagnoses >6 mo-to-5 yr post-KTx among Medicare-insured older (aged ≥ 65) adults. We used multivariate Cox regression with inverse propensity weighting to compare cancer risk vs. reference regimen of Thymoglobulin (TMG) or Alemtuzumab (ALEM) + Tacrolimus + antimetabolite + prednisone. Cancer diagnoses were also examined as time-dependent mortality predictors.

Results: Among 12567 older recipients, skin cancer incidence was higher with Tac+antimetabolite avoidance (10.3%) and CsA-based ISx (8.9%) compared to TMG/ALEM+triple ISx (6.4%; P=0.03 and P=0.002), while non-viral driven/non-skin cancer was less common with CsA-based ISx (10.9% vs 14.7%; P=0.03) (**Fig. A**). In adjusted models, IL2rAb+triple ISx was associated with lower skin cancer risk (aHR, $_{0.60}0.76_{0.96}$). IL2rAb+steroid avoidance was associated with increased non-viral driven/non-skin cancer (aHR, $_{1.03}1.34_{1.75}$), while CsA-based ISx predicted lower risk (aHR $_{0.59}0.75_{0.95}$) (**Fig. B**). However, adjusted for time-varying impact of viral-driven (aHR $_{1.99}2.27_{2.58}$) and non-viral driven/non-skin cancers (aHR $_{2.11}2.27_{2.43}$), CsA use (aHR $_{1.12}1.24_{1.37}$) predicted increased mortality in older recipients.

Conclusions: Although CsA-based ISx appears beneficial for non-skin cancer risk in older KTx recipients, this regimen is associated with increased mortality. Cancer risk is a consideration in tailoring ISx in older KTx recipients.

Funding: NIDDK Support



PO2126

Belatacept Conversion in Proteinuric Kidney Transplant Recipients: Data from a Retrospective Cohort and a Prospective Trial

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Background: Proteinuria is a strong predictor of graft loss in kidney transplant (KT) patients. Treatment options for proteinuria are limited to ACEis/ARBs. Belatacept targets B7-1 which is also expressed on podocytes and has been linked to proteinuria by inducing podocyte migration. We examined the utility of belatacept conversion in proteinuric KT recipients.

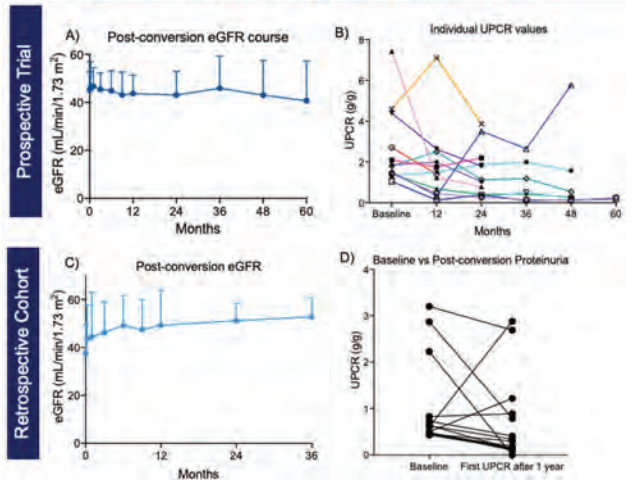
Methods: In the phase I multicenter trial, we recruited EBV IgG+ adult KT recipients > 6 months post-KT with an eGFR > 30ml/min/1.73m^2, proteinuria > 1g/day on CNI-based immunosuppression. Patients were converted from CNI to belatacept. The primary outcome was 25% reduction in proteinuria at 12 months. In the retrospective cohort, we included patients who were converted to belatacept in 2015-2019.

Results: In the retrospective cohort, 12 of 77 belatacept conversion patients had pre-conversion proteinuria > 0.4 g/g and follow up values. Baseline proteinuria decreased from 1±0.9 g/g to 0.69±0.9 g/g at >12 months (p=0.070). Mean eGFR increased from 37±12 to 49±15 ml/min/1.73m^2 at 12 months. In the prospective cohort, 15 KT recipients were recruited. At 12 months post-conversion, mean (+SD) eGFR remained stable at 43.7±12.9 ml/min/1.73m^2 and proteinuria improved from 2.5±1.9 to 1.7±1.8 g/g (p=0.068). Primary outcome was reached in 53% of the patients. None of the patients had graft rejection in the first year. One patient had worsening of proteinuria and discontinued belatacept. At 24 months, eGFR remained stable and proteinuria was 1.4±1.2 g/g. Figure 1 summarizes eGFR and proteinuria course from both cohorts.

Conclusions: Belatacept conversion in proteinuric KT recipients was associated with stable allograft function and reduction in proteinuria at 1 year and beyond.

Funding: Commercial Support - Bristol Myers Squibb

Figure 1. Pre and post-conversion mean eGFR and individual urine protein/creatinine ratio (UPCR) values from prospective (A & B) and retrospective cohort (C & D).



PO2127

Outcomes of Thymoglobulin vs. Basiliximab Induction Therapies in 2DR Mismatch Living-Donor Renal Transplant Recipients

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Background: 2DR HLA mismatch indicates a high immunological risk of renal transplant. Induction therapy with Thymoglobulin and Basiliximab result in a marked reduction of acute allograft rejection rate and improve graft survival. However, the outcomes in 2DR HLA mismatched renal transplant recipients (RTRs) in the tacrolimus era remain understudied

Methods: Using data from UNOS, all 2 DR mismatched RTRs who were maintained on tacrolimus and mycophenolate mofetil immunotherapy between September 2017 and September 2019 were included. Follow-up data was until September 2020. Patients who received transplants from living donors were included in the study. Collected data included recipient (age, sex, ethnicity, diabetes, body mass index), transplant (delayed graft function, cold ischemia time, number of previous transplants, panel reactive antibodies, HLA-mismatches, induction therapies, maintenance immunotherapy, and donor factors (donor type, donor age). RTRs were divided based on induction therapy into r-ATG and IL-2RA. Instrumental variable regression models were used to assess the effect of induction therapy on acute rejection episodes at 12 months post-transplant, serum creatinine levels at 12 months post-transplant, and graft survival. Type of induction therapy was instrumented for the transplant center to reduce the center effect on the choice of the induction therapy. The regression models were adjusted for the collected recipient, donor, and transplant factors

Results: 788 patients received Basilximab while 1727 patients received Thymoglobulin induction. There were no significant differences between Basiliximab versus Thymoglobulin induction in acute rejection episodes at one-year post-transplant (coefficient=-0.229, P value=0.106, 95% Confidence interval:-0.508to 0.049), serum creatinine levels at one-year post-transplant (coefficient=-0.024, P value=0.128, 95% Confidence interval:-0.055to 0.006) or overall graft survival (coefficient=0.008, P value=0.801, 95% CI:-0.001 - 0.001)

Conclusions: The study showed no significant difference in acute rejection episodes or graft survival when using Thymoglobulin or Basiliximab in 2DR HLA mismatched living donor renal transplant recipients in the current tacrolimus-based maintenance immunosuppression era. Therefore, Basiliximab is a safe induction therapy in this group of patients

PO2128

Outcomes of Early and Late Calcium Oxalate Deposition Following Kidney Transplantation

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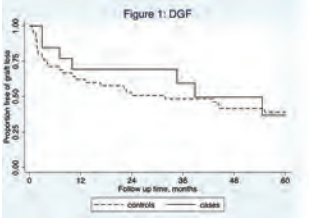
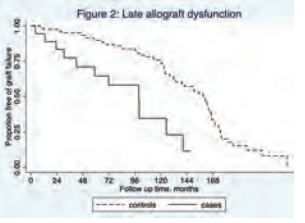
Background: Calcium oxalate deposition (CaOx) can result in progressive native kidney disease. The pathophysiology of hyperoxaluria in kidney transplant (KT) differs, especially early after surgery where the allograft encounters high levels. It is not clear whether CaOx in a kidney allograft portends worse outcomes. Determining its clinical relevance will influence the need for aggressive dietary or medication-based interventions.

Methods: All KT recipients at our center with CaOx on kidney allograft biopsy were categorized into two cohorts: delayed graft function (DGF; n=13) and late graft dysfunction (n=25). Up to 5 controls were selected per DGF case through event density sampling matched for organ type (kidney vs. simultaneous pancreas-kidney), prior transplants, and history of prolonged DGF prompting a biopsy (n=46). Controls for 'late' cases were matched for organ type, prior transplants, and living vs. deceased donor (n=125). Variables found to be statistically significantly associated with case status in bivariate analysis (p<0.10) were included in multivariate Cox regression analyses of allograft outcomes.

Results: DGF cases were more likely to have had gastric bypass surgery (7.7% vs. 0%, p=0.06) and less likely to have a history of rejection (7.7% vs. 37.0%, p=0.06) than controls. CaOx during DGF was not associated with increased risk of graft failure after adjustment (HR 1.1, p=0.87; Figure 1). 'Late' CaOx cases diagnosed median of 56.7 months (IQR: 9.8-108.9 months) after transplant were older at time of transplant (53.9 vs. 48.4 years, p=0.04) and less likely to be male (36% vs 61%, p=0.03) than controls. 'Late' CaOx was associated with a higher risk of allograft failure after adjustment (HR 3.2, p<0.001); Figure 2).

Conclusions: CaOx in kidney allograft during DGF may be a consequence of high circulating oxalate levels and was not associated with worse KToutcomes. 'Late' CaOx, likely related to increased intestinal oxalate absorption, a phenotype similar to secondary hyperoxaluria in native kidneys, was associated with increased risk of allograft failure.





PO2129

HLA Antibody Elevation Following Red Blood Cell Transfusions in CKD: Results from the START-CKD Trial

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Background: Red blood cell (RBC) transfusion avoidance wherever possible is recommended in kidney transplant candidates in order to prevent the risk of allosensitization. We have previously reported allosensitization following RBC transfusions in dialysis patients with anemia and advanced CKD, but no study has addressed allosensitization in patients with CKD not on dialysis. The START-CKD trial evaluated an ESA treatment on the incidence of RBC transfusions in anemic CKD subjects. This study prospectively collected transfusion data along with antibody (Ab) samples. We hypothesized that RBC transfusions would be associated with: a) development of de novo Abs, b) increase in relative strength of existing HLA Abs, and c) increase in calculated panel reactive Ab (cPRA).

Methods: We used two different cohort designs: matched cohort containing subjects with RBC transfusion in between 2 HLA Ab samples, versus subjects with 2 HLA Ab samples without intervening RBC transfusion event. Each transfused subject was matched with up to 2 non-transfused subjects with 4 variables. The second identified cohort consisted of cross-over subjects with longitudinal pre- and post-transfusion Ab samples allowing the subject to serve as their own control. In total, 476 samples from 211 subjects were tested for Ab reactivity to HLA by LabScreen single antigen (OneLambda).

Results: We identified 72 transfused and 124 matched non-transfused patients, and 54 crossover transfused patients. A greater proportion of patients experienced changes in MFI ≥ 25% for class I and ≥ 30% for class II antigens in the transfused compared with non-transfused patients in both matched (any change, 25% vs 7%; significant change, 24% vs 3%) and cross-over cohorts (any change, 19% vs 9%; significant change, 17% vs 2%). In the matched and cross-over cohorts, positive cPRA change occurred in 19% and 11% of transfused subjects, respectively, vs 5% and 6% of non-transfused subjects respectively.

Conclusions: RBC transfusion in patients with anemia and advanced CKD not on dialysis was associated with new HLA antibody development, increased risk of relative strength of antibodies and higher cPRA. These findings establish an important causal relationship between RBC transfusions and clinically relevant HLA Ab development for the first time in this population.

Funding: Commercial Support - AMGEN

PO2130

Chronic Active Antibody-Mediated Rejection: Response Rates to Treatment and Predictors of Graft Survival

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Background: There is limited information on response rates to Rx and predictors of graft survival following chronic active antibody mediated rejection (cABMR).

Methods: We reviewed changes in kidney function, DSA, and histology in 3-month surveillance biopsies after initial therapy with pulse steroids/IVIG ± rituximab in kidney transplant recipients with cABMR between 01/2017 and 08/2020. Rx response was defined as 3M eGFR within 10% of baseline, proteinuria (UPC) decline by > 15%, DSA decline by > 50%, and MVI (ptc + g) score = 0.

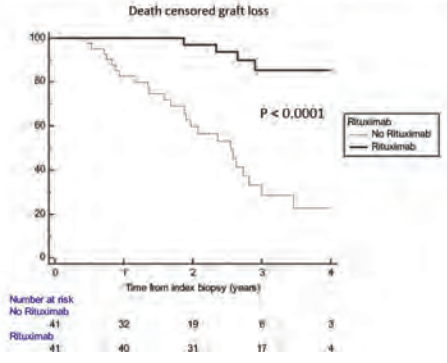
Results: The study included 82 patients. 50% received rituximab. Mean time from Tx to cABMR was 10 yrs. Mean ptc, g, C4d, and cg Banff scores at index biopsy were 1.1, 2.1, 0.2, and 2, respectively. 47 patients (57%) had measurable circulating DSA. Mean eGFR and UPC were 38 mL/min and 1.6 g/g. Thirty (37%) patients lost their allograft during the mean follow-up of 2.4 yrs. At 3M, Rx with pulse steroids/IVIG was associated with eGFR, UPC, DSA, and MVI response in 27%, 49%, 7%, and 19% of patients. The addition of rituximab improved response to 66%, 61%, 20%, and 69%, respectively. On univariate analysis, rituximab use (HR=0.13, p=0.0001, 95%CI 0.05 to 0.34) and a response in eGFR (HR=0.03, p=0.001, 95% CI 0.004 to 0.26), UPC (HR=0.38, p=0.01, 95%CI 0.18 to 0.82), and DSA (HR=0.11, p=0.004, 95%CI 0.02 to 0.49) were associated with improved death-censored graft survival. Multivariate analysis only retained eGFR response (HR=0.12, p=0.01, 95%CI 0.02 to 0.64).

Conclusions: Our study suggests that a return to baseline eGFR at 3M after initial biopsy is the best predictor of graft survival in patients with cABMR. Short-term histological and immunological response to treatment were not independently associated with graft survival.

Response Rate at Surveillance Biopsy

Response	Steroids/IVIG	Steroids/IVIG/Rituximab	p-value
eGFR	11/41 (27%)	27/41 (66%)	0.004
UPC	20/41 (49%)	25/41 (61%)	0.3
DSA	4/21 (19%)	18/26 (69%)	0.007

Figure. Rituximab was Associated with Improved Graft Survival



PO2131

Outcomes of Acute and Chronic Antibody-Mediated Allograft Rejection in Kidney Transplant Recipients

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Background: The optimal treatment regimen for antibody-mediated rejection (AMR) in kidney transplant recipients (KTRs) has yet to be established. The purpose of the study was to evaluate the outcomes of KTRs with acute and chronic AMR managed with different treatment regimens.

Methods: We conducted a retrospective cohort study of all KTRs with biopsy-proven acute or chronic AMR between January 2017 and September 2020 at a single center. The primary outcome was allograft loss at last follow up. Secondary outcomes included differences in allograft survival between treatment regimens, and changes in estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UPCR) at last follow up.

Results: 53 KTRs with AMR were included in the study. Mean age was 51 years, 50% were female and the most common cause of end-stage kidney disease was glomerular disease. 57% received living donor transplants, median number of human leukocyte antigen ABDR mismatches was 4, and 38% had pre-transplant donor-specific antibodies. For induction immunosuppression, 61% received anti-thymocyte globulin, 35% received basiliximab and 4% received alemtuzumab. 35% had acute AMR and 65% had chronic-active AMR. At the time of biopsy, median (IQR) eGFR was 32 (22-42) ml/min/1.73 m^2 and UPCR was 1.1 (0.4-2.5) g/g. For treatment, 72% received pulse steroids, 64% received intravenous immunoglobulin, 51% received plasma exchange (PLEX) and 43% received bortezomib. At a median follow up of 23 months, patient survival was 94% and death-censored allograft survival was 74%. Median (IQR) eGFR was 27 (11-43) ml/min/1.73m^2 and UPCR was 0.48 (0.17-0.97) g/g. There was no difference in the risk of allograft loss in patients who received PLEX compared to those who did not (RR=0.97, 95% CI: 0.4-2.4) and in those who received bortezomib compared to those who did not (RR=0.8, 95% CI: 0.3-2.0). The risk of allograft loss was higher in KTRs with UPCR>3g/g at AMR diagnosis compared to those with <3g/g (RR 4.3, 95% CI: 1.6-11.6).

Conclusions: Higher proteinuria at AMR diagnosis is associated with a higher risk of allograft loss. Use of PLEX or bortezomib was not associated with lower risk of allograft failure in KTRs with AMR. Novel treatment regimens are needed to improve the outcomes of KTRs with acute and chronic AMR.

PO2132

Cerebrovascular Response in Kidney Transplant Recipients During an Acute Bout of Exercise

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Background: Kidney transplant (KT) recipients have a high risk of cerebrovascular disease. Cerebrovascular response (CVR) or change in cerebral blood flow (CBF) from rest to steady-state exercise is a measure of cerebrovascular reserve and is blunted with aging, and in stroke. In this study we explore CVR and middle cerebral artery (MCA) kinetics response in KT recipients.

Methods: We measured CVR and MCA kinetics response during moderate intensity exercise in KT recipients and compared findings with age- and sex- matched controls without kidney disease. Transcranial doppler ultrasound (TCD) was used to measure MCA velocity (MCAv). Our primary outcome was CVR and secondary outcome was MCAv kinetics response profile.

Results: Data from 50 KT recipients and 50 controls with adequate TCD signal were analyzed. There was no difference in the resting MCAv between KT recipients and controls, but CVR was lower in KT recipients (p< 0.001) (Table 1). Three KT recipients did not have a detectable rise in MCAv with exercise. The remaining 47 showed altered MCAv kinetics response profile compared to controls with a shorter time delay (time after exercise onset when MCAv rises exponentially) (p< 0.001), and lower peak amplitude (peak MCAv in response to the acute bout of exercise) (p= 0.01) (Table 1; Figure 1).

Conclusions: KT recipients had a blunted CVR and altered MCAv kinetics response during moderate intensity exercise compared to controls. These altered cerebral hemodynamics may explain the increased cerebrovascular risks in KT recipients.

Funding: Other NIH Support - National Institutes of Health grant K23 AG055666, Commercial Support - Novartis and Veloxis

Table 1

Outcome measures	Healthy Controls	KT Recipients	P value
Resting MCAv (cm/s)	53.1 ± 9.2	55.7 ± 14.6	0.31
CVR (cm/s)	12.4 ± 5.7	9.1 ± 4.9	< 0.001
Time delay (s)	50.6 ± 30.7	22.6 ± 41.2	< 0.001
Peak amplitude (cm/s)	12.2 ± 3.7	9.3 ± 4.3	0.01

Values are means ± SD.

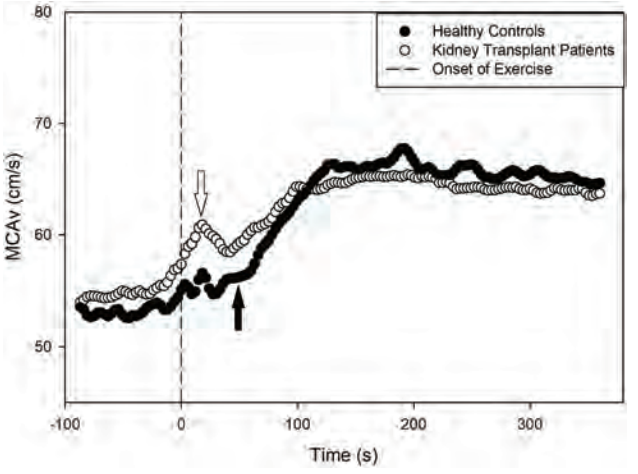

Figure 1

PO2133

Monoclonal Gammopathy in Kidney Transplanted Patients: Novel Insights into Long-Term Outcomes

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Background: Monoclonal gammopathy(MG) is a frequent condition affecting 0,05 to 6% of general population. Little is known about the prevalence of MG and its consequences on long-term outcomes in the setting of kidney transplantation(KT).

Methods: We conducted a monocentric retrospective cohort study based on 2272 patients who underwent a KT from January 2007 to June 2019 at Necker Hospital Paris, France. A systematic extraction of serum protein electrophoresis(SPE) results performed during this period was used to distinguish patients with MG at the time of KT(MGKT) and patients who developed de novo MG(DVMG) after KT. Serum free light chain(sFLC) were retrospectively measured on stored frozen sera from MGKT patients, taken at the day of KT.

Results: We identified 66 patients with MGKT and 79 with DVMG. Patient's characteristics are summarized in Table 1. Eleven (6%) patients developed a hematological disorder, i.e. post transplantation lymphoid disorder (n=6) and multiple myeloma (n=5), without difference between groups. Infectious complications were similarly frequent, regarding viral (n=68, 47%), bacterial (n= 96, 66%) and fungal infections (n=12, 14%). Strikingly, median overall survival was significantly lower in MGKT patients compared to DVMG patients (78 months vs not reached, respectively, p=0.005). The five MGKT patients with an abnormal sFLC ratio (<0,3 or >3,3) at the time of KT tended to have lower OS compared to those with normal sFLC ratio (p= 0.07), suggesting that abnormal FLC ratio might represent a risk factor for early death in KT recipients. Death censored graft survival was not different between groups.

Conclusions: By analyzing the most important cohort of KT patients with MG reported to date, we found that MGKT affects overall survival and that sFLC measurement at the time of KT may refine risk stratification. Measurement of sFLC and SPE should be incorporated to the pre-transplant evaluation workup.

Funding: Government Support - Non-U.S.

General characteristics

	All N=145	KTMG N=66	DVMG N=79	P value
Men	90 (62)	45 (68)	45 (57)	0.17
Age at KT	60 [50-67]	62 [56-67]	57 [43-69]	0.06
Heavy chain isotype, n=144 IgG / IgA / IgM	112 (78) / 18 (13) / 14(10)	46 (71) / 12 (19) / 7 (11)	66 (84) / 6 (8) / 7 (9)	0.12
Light chain isotype, n=143 Lambda / Kappa	74 (52) /69 (48)	37 (57) / 28 (43)	37 (47) / 41 (53)	0.31

Qualitative variables are described as n (percentages), quantitative variables as median [interquartile range]

PO2134

Renal Outcome and Infectious Complications Associated with Induction Regimens for Kidney Transplantation Among Children: A NAPRTCS and PHIS Collaborative Study

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Background: Few studies compare induction agents in pediatric kidney transplants (KTx), and induction is often guided by local practice more so than specific outcome data. We evaluated how different agents affected outcomes in children enrolled in both the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry and the Pediatric Health Information System (PHIS).

Methods: Retrospective study of merged data from NAPRTCS and PHIS between 1999-2019. Participants grouped by induction agent: no induction, IL2 RB only, rATG/ALG, alemtuzumab. Estimated GFR (eGFR) was calculated with adjustments for age, diagnosis, repeat KTx status, delayed graft function, and rejection. Subgroup analysis evaluated rejection rates and infectious complications between 2009-2019. Outcomes were compared using chi-square or Kruskal-Wallis tests.

Results: 2410 KTx recipients with data in both datasets were identified. 340 subjects (14.1%) received no induction, 960 (39.8%) IL2 RB only, 934 (39.1%) ATG/ALG, and 176 (7.3%) alemtuzumab. Table 1highlights eGFR decline, using ratios obtained by dividing any year's eGFR by the preceding year. Annual decline in eGFR was slower in the ATG/ALG group vs IL2RB or alemtuzumab and higher among children transplanted between ages 0-4 years. Table 2 summarizes rejection and infectious frequencies. Alemtuzumab had lower rates of rejection and BK viremia compared to IL2RB and ATG/ALG.

Conclusions: Longitudinal decline in eGFR was similar across all induction agents, though decline with ATG/ALG was lowest. Although rejection and BK viremia was lowest with alemtuzumab, there was no difference with EBV or CMV infection or post-KTx malignancy.

Funding: Private Foundation Support

	Ratio (95% CI)	p-value
Overall (per year)	0.941 [0.934,0.948]	**<0.001**
Induction Rx		
IL 2	0.936 [0.925,0.947]	
ATG/ALG	0.956 [0.945,0.966]	
Alemtuzumab	0.932 [0.918,0.947]	**0.009**
Age at KTx (yrs.)		
0-4	0.908 [0.896,0.921]	
5-9	0.948 [0.932,0.963]	
10-14	0.955 [0.942,0.968]	
15-17	0.957 [0.941,0.973]	
18+	0.983 [0.950,1.018]	**<0.001**

Table 1: Annual change in eGFR

Variable	Total	IL2	ATG/ALG	Alemtuzumab	p-value
N, Transplants	830	260 (31.3%)	419 (50.5%)	151 (18.2%)	
Rejection					
No	635 (76.5)	189 (72.7)	316 (75.4)	130 (86.1)	**0.006**
Yes	195 (23.5)	71 (27.3)	103 (24.6)	21 (13.9)	
Days to first rejection, Median (IQR)	377 (177,771)	420 (193,928)	384 (178,754)	211 (116,504)	0.097
BK Viremia					
No	758 (91.3)	234 (90.0)	377 (90.0)	147 (97.4)	**0.015**
Yes	72 (8.7)	26 (10.0)	42 (10.0)	4 (2.6)	
Days to first BK Viremia, Median (IQR)	530 (181,1086)	733 (342,1924)	373 (178,1030)	538 (352,755)	0.479
Days to first CMV Viremia Median (IQR)	376 (340,781)	432 (340,869)	370 (343,732)	382 (37,781)	0.903
Days to first EBV Viremia Median (IQR)	750 (363,1643)	1354 (545,2253)	747 (356,1500)	522 (210,1006)	0.123
Malignancy					
No	823 (99.2)	259 (99.6)	416 (99.3)	148 (98.0)	0.213
Yes	7 (0.8)	1 (0.4)	3 (0.7)	3 (2.0)	

Table 2: Outcomes by induction therapy between 2009-2019

PO2135

Bacteremia in Kidney Transplant Recipients with Septic Arthritis Is Perilous

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Background: Features and clinical sequelae of septic arthritis in the general population have been described; however, the epidemiology and outcomes of septic arthritis in kidney transplant recipients (KTRs) is limited, and the potential impact on graft function has not been reported.

Methods: A single-center, retrospective, observational cohort study including patients with a history of kidney transplant and subsequent septic arthritis between 1/1997-12/2017 was performed.

Results: During the 20-year study period 6,184 patients received kidney and kidney-pancreas transplants, of these 65 (1%) patients had documented diagnosis of septic arthritis. 51 patients had kidney alone transplants and 14 had simultaneous kidney and pancreas transplants. The mean age at the time of transplant was 50 ± 10.4 years. The mean time from the transplant to the septic arthritis diagnosis was 6.6 ± 6 years. The most commonly affected joint was the knee (38%), followed by the shoulder (11%) and hip (9%). Joints with hardware accounted for 14 (21.5%) cases. Staphylococcus species were the most commonly isolated bacteria (52%) followed by gram-negative rods (14%). Only two patients had fungus isolated from joint aspiration (one histoplasma and one aspergillus). Antimicrobials were used in all of the patients. The majority of patients were treated with either joint aspiration (39%) or I&D (39%). The need for curative amputation was uncommon (4%). When evaluating subsequent graft function, the mean eGFR declined 12 ± 8 ml/min/1.73 m2 at one year after diagnosis. The presence of bacteremia at time of diagnosis was associated with significant worse joint (HR 5.37, p 0.01, 95%Cl 1.57 to 18.41) and graft outcomes (HR 5.37, p 0.0004, 95%Cl 1.51 to 9.35). By last follow up, 21 patients lost their allografts and 28 patients died with functional kidney graft.

Conclusions: Septic arthritis is an uncommon complication in KTRs. When seen, it typically occurs >1 year after transplant with similar pathogens and management as in the general population. However, it appears to be associated with negative graft effects. A high index of suspicion, timely diagnosis, and appropriate management are needed to ensure optimal outcomes for septic arthritis in KTRs

PO2136

Clinical Significance of Vitamin D on Preexisting and Post-Transplant Diabetes Mellitus in Kidney Transplantation: Korean Cohort Study for Outcome in Patients with Kidney Transplantation (KNOW-KT)

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Background: Kidney transplant recipients (KTRs) with preexisting DM or post-transplant diabetes mellitus (PTDM) have poor clinical outcomes. An association between vitamin D and diabetes mellitus (DM) has been reported, but there are few reports for impact of vitamin D on preexisting DM and PTDM.

Methods: A total of 995 KTRs were enrolled in KoreaN cohort study for Outcome in patients With Kidney Transplantation (KNOW-KT) between July 2012 and August 2016. KTRs were categorized into 3 groups: nondiabetic, preexisting DM and PTDM. Vitamin D status at KT was defined to deficiency (<10 ng/ml), insufficiency (10-30 ng/ml), and normal (≥30 ng/ml). This study aims to investigate clinical significance of vitamin D based on diabetic status in KTRs.

Results: Nondiabetic group was 643 (64.6%), preexisting DM group, 267 (26.8%), and PTDM group, 85 (8.5%). In all groups, vitamin D levels gradually increased after KT, then showed equilibrium at 2 years, and decreased after 4 years, but there was no significant difference of vitamin D levels. The proportion of vitamin D deficiency at KT was the highest in preexisting DM group compared with other groups, but there was no significant difference of that since 1 year after KT. There were no significant differences of immunologic findings among them. The rate of cardiovascular event was significantly higher in preexisting DM group compared with other groups (P<0.001). Death-censored graft survival rate was significantly lower in preexisting DM group compared with other groups (P=0.049), but there was no significant difference according to vitamin D status. Death-censored graft survival rate in KTRs with preexisting DM and vitamin D deficiency was the lowest, and it showed the significant synergistic effect on the allograft outcome (P=0.022). In the multivariate analysis, older age was an independent risk factors for allograft failure (HR 1.045, 95% C.I. 1.005-1.087, P=0.026). Patient survival rate was significantly lower in preexisting DM group compared with other groups (P=0.008).

Conclusions: The prognosis of KTRs with preexisting DM and vitamin D deficiency was the worst comparing nondiabetic and PTDM groups. Therefore, careful monitoring after KT of candidates with pre-transplant DM and vitamin D deficiency is required.

PO2137

Preeclampsia and Kidney Transplant: Offspring and Mother Outcomes in a Single-Center Cohort in the West of Mexico

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Background: Pregnancy in a kidney transplant recipient (KTR) is possible and safe after a 1-2 year post transplantation, stable serum creatinine (<1.5 mg/dl), controlled or no hypertension, proteinuria in 24 hours <500 mg and stable immunosuppressive levels. Preeclampsia is a common complication in KTR pregnant women associated to worse maternal and offspring outcomes, there is scarce available information this topic in a KTR in Latin America

Methods: Retrospective cohort study from October 2018 to April 2021 included 18 patients: >18 years who got pregnant after KT. Serum creatinine (SCr), proteinuria before, during pregnancy and after delivery, the presence of hypertension before pregnancy, episodes of kidney graft rejections, immunosuppressant therapy, and preeclampsia were recorded from medical chart, and compared it to the offspring's gestational age, weight, APGAR score, NICU requirement and NICU stay.

Results: The frequency of preeclampsia was 33%, none of them were diagnosed with hypertension before pregnancy. Three women died after delivering (no obstetric associated), 1 lost graft function (in PD). SCr was higher during pregnancy and after delivery, offspring's gestational age was lower, offspring's weight was considerably lower, as well as APGAR score in women with preeclampsia, all NICU requirement were in children whose mother had preeclampsia and they had a NICU media stay of 19 days. In a logistic regression analysis, preeclampsia is a risk factor to a lower APGAR SCORE (p<0.001), requirement of NICU (p=0.001) and NICU stay. Other results are shown in the table.

Conclusions: Age, time between KT and pregnancy, gestational age, hypertension, serum creatinine, cesarean delivery was not different among preeclampsia, compared to the control group. Children from preeclamptic women tend to have lower weight and had lower apgar score and higher NICU requirement.

Funding: Government Support - Non-U.S.

	No Preeclampsia N=12	Preeclampsia N=6	p Value
Age (years)	26.4 ± 5.2	27.8 ± 6.0	0.61
Time between KT- PREGNACY (years)	7.0 ± 3.9	5.3 ± 3.6	0.41
Gestational age (weeks)	31.1 ± 10.2	30.0 ± 3.5	0.81
Hypertension before pregnancy %	17%	0%	0.29
Serum creatinine during preg (mg/dL)	0.94 ± 0.35	1.37 ± 0.78	0.25
Serum creatinine post preg (mg/dL)	1.05 ± 0.36	1.32 ± 0.74	0.31
Cesarean delivery (%)	17%	17%	1.0
Offspring weight (grams)	2945 ± 703	1744 ± 595	0.006
Apgar score	8.0 ± 1.0	5.0 ± 1.5	***<0.0001***
NICU requirement (%)	0%	67%	***0.001***
Days in NICU		19.0 ± 3.0	

PO2138

Network Science and Hemodialysis Patients' Kidney Transplant Attitudes

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Background: Hemodialysis patients' attitudes towards kidney transplantation may depend on their local (egocentric) and overall characteristics of their clinic social network. We determine whether these local and overall social network characteristics improve machine learning (ML) logistic regression and neural network models of the patient's transplant attitudes.

Methods: We surveyed hemodialysis patients' social networks and transplant attitifudes in two hemodialysis clinics. We evaluated which ML model (logistic regression vs. neural network) best classified a patient's transplant attitude using survey and egocentric network data. Then, we tested whether multidimensional overall network information represented as a vector (node2vec) improved the model. Models were evaluated for accuracy, precision, recall, and F1-score using Python (version 6.1.4) and Gephi (0.9.2).

Results: The mean age of the 116 surveyed participants was 60 ± 13 years old. Half (55%) identified as male, and 75% identified as Black. Figure 1 shows the 83 participants (circles) who were in a clinic social network. The 33 network isolates are not shown. Network members with postive attitudes (57%) are the red circles. Green circles are those with negative attitudes. Adding egocentric network data improved the accuracy of the ML logistic regression model of transplant attitudes from 58% to 68% and the F1 score from 65% to 74%. The ML logistic regression model outperformed the neural network model in F1 score (73% vs. 66%) when including isolated participants. Addition of the overall network data (node2vec) further improved the F1-score of the ML logistic regression model to 77%.

Conclusions: The participant's social network characteristics improved ML classification of the participant's attitude towards kidney transplantation. The ML logistic regression model outperformed the neural network model, testing the limits of ML models on smaller data. Future research will examine how patient social networks disseminate information and affect attitudes and behaviors towards kidney transplantation.

Funding: NIDDK Support

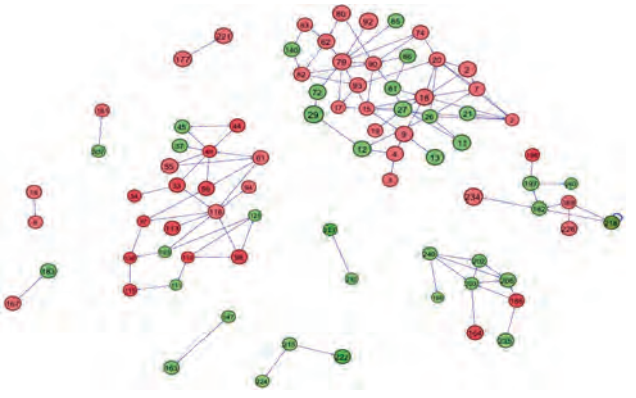

Figure 1.

PO2139

Assessing Social Difficulties in Patients Treated with Kidney Replacement Therapy (Dialysis or Kidney Transplant)

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Background: The Social Difficulties Inventory (SDI) is used in the clinical management of patients with cancer in the UK. We examine the construct validity of the SDI in patients with kidney replacement therapy (KRT: dialysis or kidney transplant [KT]).

Methods: This is a secondary analysis of data collected in multicenter, cross-sectional studies. Adults receiving KRT completed the SDI and other patient reported outcome measures. Clinical and sociodemographic characteristics were also collected. For SDI, the degree of difficulty is rated: no difficulty, a little, quite a bit or very much. 16 items form the SD16 and three subscales: "Everyday Living", "Money Matters" and "Self and Others." We used Cronbach's alpha to assess reliability. We assessed the correlation of SD16 and its subscales with variables that measure similar constructs. Further, we compared scores between groups that are expected to have different degree of difficulties.

Results: 788 participants (mean[SD] age 57[15] years) completed the SDI. 61% of them were male and 58% were on dialysis. Internal consistency was good for all scales: α=0.87, 0.82, 0.75, 0.88, for "Everyday Living", "Money Matters", "Self and Others" subscales and the SD16, respectively. The "Everyday Living" subscale was moderately

correlated depression (Rho=0.61, p<0.001) and physical functioning (Rho=0.72, p<0.001). The Self and Other" subscale was moderately correlated with depression (Rho=0.56, p<0.001). SD16 scores were higher for patients on dialysis vs KT (median[interquartile range – IQR] 7[3,13] vs 3[1,8]p<0.001). "Everyday Living" scores were higher in patients with Charlson Comorbidity Index of ≥4 ([3[0,6.5] vs 1[0,3.5]p<0.001). "Money Matters" scores were higher in individuals facing high vs low material deprivation (1[0,4] vs 0[0,3] p<0.008). "Self and Other" scores were higher in participants that are uncomfortable or reluctant in relationships vs those that find it easy (3[1,7] vs 1[0,3]p<0.002).

Conclusions: These results suggests that the SD-16 and its subscales have good reliability and structural validity. Further research is required to explore the potential clinical benefits of using the SD16 in patients with kidney failure.

PO2140

Symptom Management Preferences of Kidney Transplant Recipients and Caregivers

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Background: Kidney transplant (KT) recipients frequently experience physical, emotional, and social challenges. These are often undermanaged and can lead to impaired quality of life. Better understanding of the perspectives of KT recipients and their caregivers about their symptom experiences and management needs will improve post-transplant care for KT recipients.

Methods: As part of a larger study aimed at developing a patient-centered electronic assessment toolkit, adult (≥18 years) KT recipients and caregivers of KT recipients were recruited for this study via flyers. Patients not fluent in English or cognitively impaired were excluded. Qualitative description was used to explore and understand participants' post-transplant experiences and preferences. A semi-structured interview guide with open-ended questions was used to facilitate in-depth, individual interviews. Interviews were recorded and transcribed verbatim. Transcripts were analyzed via content analysis using deductive and inductive coding strategies. Codes and categories were developed and refined by the research team.

Results: Seven KT recipients and one caregiver (age: 52-76 years, 8-20 years post-transplant, 5/8 male) participated. Participants identified significant challenges in physical (e.g. fatigue, sleep disturbances, weight or mobility issues); emotional (e.g. depression, anxiety); and social (e.g. financial challenges, self-care, social roles) domains. Participants considered fatigue as the most troublesome symptom. Furthermore, patients described the clustering of their post-transplant symptoms across domains. For example, fatigue overlapped with depression and the inability to perform self-care activities and maintain relationships. Participants also expressed that their post-transplant care centered on physical symptoms with little exploration and support of psychological and social issues. Finally, participants emphasized that a care plan integrating all aspects of health is needed to adequately support their needs.

Conclusions: This analysis identified a range of patient-valued physical, emotional, and social concerns, with fatigue being the most troublesome symptom. These findings will inform the development of future interventions to improve patient-centered post-transplant care.

PO2141

Airflow Limitation, Fatigue, and Health-Related Quality of Life in Kidney Transplant Recipients

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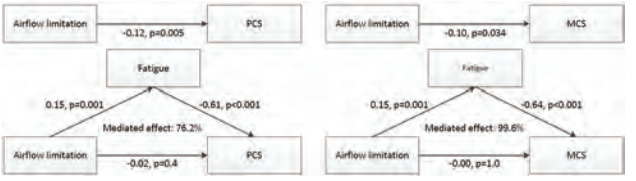
Background: Many kidney transplant recipients (KTR) suffer from fatigue and poor health-related quality of life (HRQoL). Airflow limitation may be an underappreciated comorbidity among KTR, which could contribute to fatigue and poor HRQoL in this population. In this study, we compared the prevalence of airflow limitation between KTR and healthy controls (HC), and investigated associations of airflow limitation with fatigue and HRQoL in KTR.

Methods: Data from the ongoing TransplantLines Biobank and Cohort Study (NCT03272841) were used. Airflow limitation was defined as forced exhaled volume in one second (FEV1) <5th percentile of the general population. Fatigue and HRQoL were assessed using CIS20R and SF-36 questionnaires.

Results: A total of 539 KTR (58% male, mean age 56±13 years) and 244 HC (45% male, mean age 57±10 years) were included. Prevalence of airflow limitation was higher in KTR than in HC (133 (25%) vs. 25 (10%), p<0.001). Airflow limitation was independently associated with higher risk of severe fatigue (OR 2.53, 95%CI 1.41 to 4.55, p=0.002) and poor HRQoL (physical component score (PCS): st. β -0.12, 95%CI -0.20 to -0.04, p=0.005 and mental component score (MCS): st. β -0.10, 95%CI -0.19 to -0.01, p=0.034) in KTR. Fatigue mediated the association of airflow limitation with PCS and MCS for 76.2% and 99.6%, respectively (Figure 1).

Conclusions: Airflow limitation is common among KTR. Its occurrence more than doubles the risk of severe fatigue, and is associated with poor HRQoL. Mediation analyses suggest that airflow limitation causes fatigue, which in turn decreases HRQoL. Since airflow limitation can be improved by treatment and training, it may be a promising therapeutic target to reduce fatigue, and consequently to improve HRQoL among KTR.



PO2142

Outcomes of Liver Transplant Recipients Who Developed AKI Before Liver Transplant

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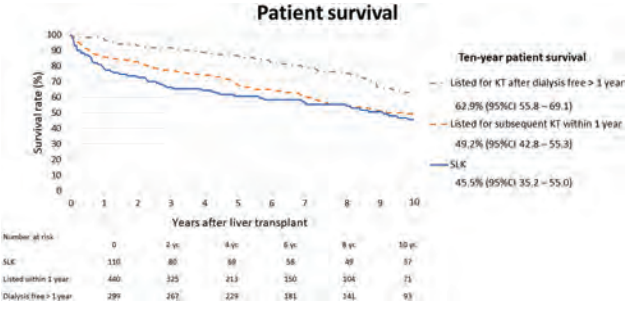
Background: Multiple factors including level of kidney function, patient comorbidities and functional status may influence the decision whether to simultaneous liver-kidney (SLK) transplant or waiting for kidney function recovery in end stage liver disease. Consequence of waiting for subsequent kidney transplant (KT) those without kidney recovery is unknown.

Methods: The Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data of patients who were initially listed for liver transplant (LT) alone who also developed acute kidney injury (AKI) requiring dialysis within 60 days before LT and subsequently listed for KT during year 2000 – 2018 were included. Kidney function recovery defined as discontinuing dialysis >1 year. Our cohort therefore included 1) SLK, 2) listed for subsequent KT within one-year after LT and 3) listed for subsequent KT after recovery.

Results: A total of 7,853 liver recipients received dialysis within 60 days before LT. There were 110 patients receiving SLK and 445 patients listing for subsequent KT within one-year. Seven thousand two hundred and ninety-eight patients had kidney function recovery and 301 (3.8%) patients were listed for subsequent KT after dialysis free >1 year. One-year patient survival rates were 78.1% (95%CI 69.2 – 84.8) and 86.0% (82.4 – 88.9) among receiving SLK and listing for subsequent KT within one-year group, respectively. Ten-year patient survival rates were 45.5% (35.2 – 55.0) and 49.2% (42.8 – 55.3), respectively. Patients who survive and had dialysis-free more than one year had the best ten-year survival which were 62.9% (55.8 – 69.1).

Conclusions: Only 7.1% of liver recipients who developed AKI requiring dialysis within 60 days before LT did not have kidney recovery and remain on dialysis. These patients who received SLK had lower one-year patient survival but comparable ten-year patient survival compared to patients who listed for subsequent KT within one-year after LT.



PO2143

Clinical Outcome After Combined Liver and Kidney Transplantation in Children in Europe: A CERTAIN Registry Analysis

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Background: Combined liver and kidney transplantation (CLKT) in children is still a challenging procedure and therefore performed only in specialized centers. Outcome of these patients is mostly published as single center reports. To gain more insights in outcome and specific challenges of this rare disease group we aimed for an European registry analysis.

Methods: We conducted a multi-center, retrospective, cohort study using data of the Cooperative European Pediatric Renal Transplant Initiative (CERTAIN) registry (www.certain-registry.eu). The CERTAIN registry provides transplantation-related data of kidney allograft recipients ≤ 21 years at transplantation of 75 pediatric renal transplant centers in Europe. For this specific study we established an additional dataset for liver allograft recipients which includes essential liver transplantation-related data. The survival curves were assessed with the Kaplan-Meier method and compared with the log-rank- test. The statistical analyses were performed with SPSS, Version 27.

Results: Included in the study were 159 patients from 13 transplantation centers. The diagnosis leading to transplantation was primary hyperoxaluria type 1 (PH1) in 64 patients, in 70 patients autosomal recessive polycystic kidney disease (ARPKD), and in 25 patients various other diagnoses. The median follow-up time was 3.9 years (range, 5 days-17 years). Patient survival was good with 9 deaths reported. This led to an overall patient survival of 94% with no difference between PH1 and ARPKD. The kidney and liver graft survival rates were 92.5% and 91.1%, respectively. Long-term eGFR calculations showed stable renal function until 9 years of follow-up. Thereafter, kidney function slowly deteriorates. Liver function tests were stable over the whole study period.

Conclusions: CERTAIN registry data showed that CLKT lead to an excellent patient and organ survival with no difference between PH1 and ARPKD patients. In addition, patient survival after CLKT is comparable to isolated liver or kidney transplantation. The retrospective study design may have led to a reporting bias.

PO2144

Renal Outcomes After Liver Transplantation in the MELD-Na Score Era in Patients with Pre-Transplant Renal Impairment

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Background: Post-liver transplant (LT) renal insufficiency is an established predictor of morbidity and mortality for liver transplant recipients. Current reports on renal outcomes after LT have exclusively focused on patients from the MELD era. There is little information on the progression of kidney disease since the implementation of the MELDNa scoring system. We sought to characterize the prevalence of kidney disease after LT and its risk factors during the MELDNa era.

Methods: This is a retrospective cohort study of 107 adult, single-organ, primary liver transplants performed at the University of Maryland Medical Center between January 2016 and January 2017, after implementation of the MELDNa scoring system. We determined the pre-transplant chronic kidney disease (CKD) status (defined as eGFR <60ml/min or dependence on renal replacement therapy) by using the CKD-EPI Creatinine equation, available lab values, and the renal replacement therapy (RRT) status within the 90 days prior to transplant. The primary outcome was persistent CKD or mortality at 12 months. Recipients of MELDNa exception scores as well as Status 1 liver transplants were excluded.

Results: The mean patient age was 54.2 ± 11 years, 74 male, 85 Caucasian, 30 had diabetes, 55 were hypertensive, and 27 had HCV. 32 patients had pre-LT renal insufficiency and 25 patients were on RRT at the time of LT. The overall 1-year mortality rate post-LT was 11.2%. 36 patients had CKD at 12 months. Among the patients with pre-LT renal insufficiency, 13 demonstrated improved renal function, 13 remained with CKD, 2 ended up on long-term RRT, and 4 died by 12 months. Renal insufficiency equivalent to CKD stage 4 prior to LT (OR 8.75, CI 0.97-78.7, p=0.053) and RRT at time of LT (OR 3.68, CI 1.42-9.55, P=0.007) were associated with increased risk of recipient death or CKD at 12 months. Other variables including age, sex, HCV, DM, HTN, CKD Stage 3, MELDNa score, BMI, and organ rejection were not predictive of the outcome.

Conclusions: Our study in the MELDNa era patients suggests that 40% of the patients with impaired renal function pre-LT recover renal function by 12 months post-LT. RRT at the time of LT, and moderate to severe renal impairment prior to LT are risk factors for recipient mortality or persistent CKD at 1 year post-LT.

PO2145

Gender Disparities in Access to Simultaneous Liver-Kidney Transplantation in the Pre- vs. Post-Allocation Policy Eras

Giselle Peschard,[1] Mei Wang,[1] Yazen Al-Hosni,[1] Krista L. Lentine,[2] Su-Hsin Chang,[1] Tarek Alhamad.[1] [1]*Washington University in St Louis, St Louis, MO;* [2]*Saint Louis University School of Medicine, Saint Louis, MO.*

Background: Gender differences in receiving simultaneous liver-kidney transplant (SLKT) is not well-understood. We recently found that women are disadvantaged in access to SLKT, especially women not initially listed for SLKT. No studies have examined these disparities in SLKT access after the implementation of the SLKT allocation policy in 2017, intended to facilitate equity and utility organ allocation.

Methods: Using retrospective data from the Organ Procurement and Transplantation Network (OPTN) database, we identified two cohorts of patients on the liver transplant (LT) waiting list with renal dysfunction (RD) from February 28, 2002 to August 9, 2017 (pre-SLK allocation policy) and from August 10, 2017 to March 31, 2020 (post-SLK allocation policy). Multilevel time-to-competing-events regression adjusting for center effect was used to examine the likelihood of receiving SLKT in both cohorts.

Results: A total of 23,389 candidates with RD listed for LT only were included and 5,823 candidates with RD listed for SLKT in the pre-SLKT allocation policy era. 9,668 candidates with RD listed for SLKT in the post-SLKT allocation policy era. Pre-SLKT allocation policy era, females with RD listed only for LT had a 55% lower likelihood of receiving SLKT (multivariable-adjusted hazard ratio, aHR 0.45, 95% confidence interval, CI, 0.28-0.72); and those listed for simultaneous organs had 12% lower likelihood of receiving SLKT (aHR 0.88, 95% CI 0.80-0.96), compared to males (Figure 1). Post-SLKT allocation policy era, females still had 22% lower likelihood of receiving SLKT (aHR 0.78, 95% CI 0.70-0.88), compared to males (Figure 1).

Conclusions: Prior to the implementation of the SLKT allocation policy, women had a lower likelihood of receiving SLKT compared to male candidates regardless whether they were listed for SLKT. After the policy implementation, these disparities are reduced but persist. This calls for further work on developing new policies that address gender disparities in access to organ transplantation.

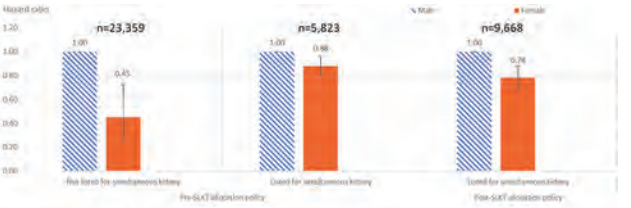

Figure 1. Multivariable-adjusted hazard ratios for receiving SLKT pre- and post-SLKT allocation policy by gender.

PO2146

Gender-Based Disparities in Access and Survival Outcomes of Simultaneous Liver-Kidney Transplant Among Liver Transplant Candidates with Renal Dysfunction in the United States

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Background: The frequency of simultaneous liver-kidney transplantation (SLKT) has risen since the implementation of the Model for End-stage Liver Disease (MELD)-liver allocation system. Gender disparities in access to SLKT and outcomes post-transplantation are not well described. We examined these gender-based disparities in the MELD era.

Methods: We included a retrospective cohort of patients wait-listed for liver transplant (LT) between 2002-2017 with renal dysfunction (RD). Multilevel time-to-competing-events regression adjusting for center effect was used to examine the likelihood of receiving SLKT. Inverse probability of treatment weighted (IPTW) survival analyses were used to analyze posttransplant mortality outcomes. Sensitivity Analysis (SA) performed using 2 alternative definitions of RD for LT candidates: SA(1), either received dialysis or having creatinine ≥2.0 mg/dL at listing for LT, and SA(2), either received dialysis or having eGFR<35 mL/min/1.73 m2 at listing for LT.

Results: Among candidates not listed for SLKT at the time of listing for LT, females had ≥50% lower likelihood of receiving SLKT compared to males (Figure 1). Females continued to have reduced access despite being listed for SLKT. Once transplanted, we found no statistically significant difference in post-transplant survival by sex for SLKT or LT alone recipients (Figure 2).

Conclusions: Prior to the implementation of the SLKT allocation policy, gender disparities were found in access to SLKT but not in post-transplant survival. A tighter gender difference in access to SLKT was found amongst patients listed for SLKT compared to those not listed simultaneously.

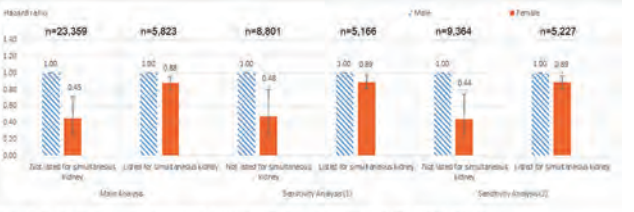

Figure 1: Multivariable-adjusted hazard ratios for receiving SLKT, 2002-2013*

**Covariates included age, race (non-Hispanic white, non-Hispanic black, Hispanic, or other), body mass index, year (2002-2013), ever had dialysis, estimated glomerular filtration rate, serum albumin, creatinine, bilirubin, MELD score, international normalized ratio, insurance, education, income, OPTN region, ascites, pathogenesis of liver disease, and diabetes status at the time of waitlisted.*

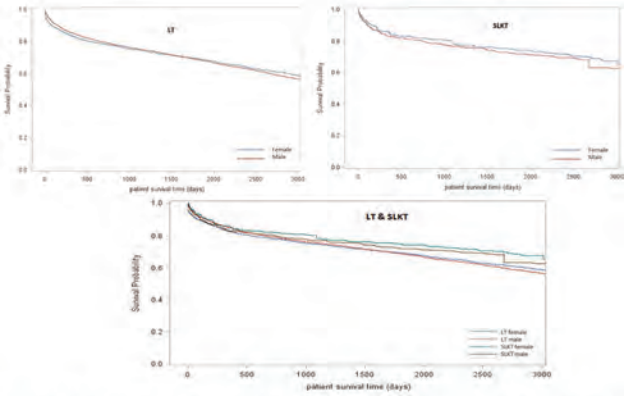

Figure 2: IPTW survival curves by gender comparing overall survival between patients receiving SLKT and LT alone.

PO2147

Development Following Paediatric Kidney Transplantation

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Background: This study aims to assess quality of life, mental health, motor development, executive functioning and medication adherence in paediatric patients following kidney transplantation

Methods: In a cross-sectional study we used standardised tools (FABEL, KINDL, PedsQL, CBCL, M-ABC, WISC-V, BAASIS) to assess the relevant parameters and analyse them against the background of selected medical data.

Results: We included 53 kidney transplanted children age 0-18 (♂32 ♀21). Parents reported increased financial burden and fear of the future. Half of the patients showed some symptoms of mental distress. 13/40 (32.5%) patients fulfilled DSM-criteria for mental health problems. Most frequent symptoms linked to depression and anxiety. Participants who started renal replacement therapy in their first three years of life mainly expressed symptoms of the externalising spectrum. Motor-development could be assessed in 47 patients. Developmental deficits could manly be observed in the field of fine motor skills and dexterity as well as body-balance. In total 11/47 (23.4) patients had fine-motor-skills below the 2nd percentile, 14/47 (29.9%) had deficits in body-balance scoring below the 2nd percentile. Processing speed was assessed in a subgroup of 36 patients without cognitive developmental delay. Mean score was 84 (45-112; sd 16.0). 5/36 (13.9%) patients had results below the 2nd percentile.

Conclusions: Even after successful transplantation chronic kidney disease seams to impact on the overall health and development of the affected child. While nowadays allograft survival is considered to be acceptable, it is time to shift focus on quality of survival and non-renal consequences of a renal disease. Besides further research clinical programs are needed to offer tailored assessments and support.

PO2148

Long-Term Outcomes of Kidney Transplantation in a Disadvantaged Population in Mexico

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Background: Access to kidney transplantation in Mexico was limited to patients with social security. Since 2010 at the Dr. Eduardo Liceaga General Hospital of Mexico, a kidney transplant program was established for patients with terminal chronic kidney disease living in extreme poverty or without social security. We aim was to analyzed patient survival, graft survival, post-kidney transplant complications, and modification of work status before and after transplantation were analyzed.

Methods: Case-control study nested in a cohort. Kidney transplant recipients who were in disadvantaged conditions from 2010 to 2020 were analyzed.

Results: During the study period, 345 transplants were performed. The median age was 31.5 ± 11.58 years, 58.6% were men and 74% of the transplants were from living donors. Ninety patients (26%) with social security (With SS) and 255 patients (74%) without social security (Without SS) at the time of transplantation were analyzed. The With SS patients presented mainly peritoneal dialysis as renal replacement therapy, while the Without SS patients on intermittent hemodialysis (p≦0.05). There were significant differences in immunosuppressive induction and maintenance schedules between groups. Patients Without SS more frequently received only steroids as induction therapy and cyclosporine as maintenance therapy (p≦0.05). A higher frequency of acute rejection and chronic rejection was observed in patients Without SS (p≦0.05). No differences were observed in metabolic, cardiovascular or infectious complications after transplantation. With an average follow-up of 6.23 ± years, not difference was identified in graft survival (With SS: 84.7% vs Without SS: 85.9%, p=0.222); nor in patient survival (88.5% versus 84.3%, p=0.105). When comparing the work status of patients without social security, a significant increase was observed in the work status at baseline and after kidney transplantation (23.7% vs 45.8%, p=0.001).

Conclusions: Access to kidney transplantation in Mexico is uneven and this is due to the fragmented health system in Mexico. A national kidney transplant program without inequities is required where the entire population has access to health services and their post-transplant follow-up.

PO2149

De Novo Inflammatory Bowel Disease in Kidney Recipients: A Single-Center Experience

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Background: Recipients of solid organ transplantation (SOT) receive immunosuppressants (IM) such as calcineurin inhibitors and steroids, both of which are also used for inflammatory bowel disease (IBD). However, the incidence of IBD following SOT (de novo IBD) is 5 to 10 times higher than that among the general population. Although reports of de novo IBD have been mostly reported in liver transplants, and that after kidney transplantation (KT) remains scarce.

Methods: Of the patients who underwent KT from 1998 to 2021 at St. Marianna University Hospital (N=241), we included those diagnosed by colonoscopy with de novo IBD including ulcerative colitis (UC) or Chron's Disease (CD). We retrospectively described the symptoms, time course, HLA typing, IM, and treatment of de novo IBD.

Results: Of 241 recipients, 6 developed de novo IBD posttransplant (incidence: 2.5%): 5 were diagnosed with UC and 1 with CD. The median time from KT to IBD diagnosis was 6 years (range, 2–12). Allograft function did not worsen after IBD in any recipients. The initial presentation was bloody stool in 5 recipients and mild diarrhea in 1. In the recipient with CD, severe and continuous abdominal pain, and bloody stool with moderately elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were present (3.53 mg/dL and 71 mm/h, respectively). In recipients with UC, bloody stool or mild diarrhea without abdominal pain, and mild to moderate inflammation markers such as median CRP [0.28 mg/dL (range: 0.07–6.38 mg/dL)] and median ESR [26.5 mm/h [range: 9–81 mm/h] were present. Three recipients with UC had HLA B52, DR2, or DR15, which are known to associate with UC. All recipients received a triple maintenance IM for KT including tacrolimus and steroids. Regarding treatment for de novo IBD, infliximab for the recipient with CD and 5-aminosalicylate for recipients with UC were used as a primary treatment. One recipient with UC affected the whole colon was resistant to prednisolone, infliximab, and vedolizumab. He eventually underwent total colectomy at 1-year after diagnosis. The others achieved the remission of IBD after initial therapy.

Conclusions: De novo IBD should be a differential diagnosis of bloody stool after KT in spite of low or only mildly elevated inflammation markers. De novo IBD can present even without bloody stool.

PO2150

Renal Transplant Biopsy Outcomes: A Nephrology and Radiology Standpoint in an Academic Center

Rhea Patil,[1] Camilo Cortesi,[1] Mai Sedki,[1] Franco H. Cabeza Rivera,[2] Karla G. Carias Martinez,[1] Phillip Ruiz,[1] Jason T. Salsamendi,[1] Giselle Guerra,[1] Adela D. Mattiazzi.[1] *[1]University of Miami School of Medicine, Miami, FL; [2]The University of Mississippi Medical Center, Jackson, MS.*

Background: Renal transplant biopsies are the gold standard for evaluating allograft dysfunction. Studies comparing biopsy safety outcomes between transplant nephrologist and interventional radiologist are lacking. We describe our academic center experience and identify their risk factors.

Methods: This is a retrospective study of patients who underwent percutaneous ultrasound-guided renal transplant biopsy (US-RTB) at a single center between January 2013 to August 2016. This cohort was stratified into two groups according to the team that performed the biopsy: interventional radiology(IR,n=447) and transplant nephrology(TN,n=231). The predictors of post-biopsy complications were assessed by multivariate logistic regression.

Results: A total of 678 US-RTB were performed in 573 patients. There was no significant difference in the rate of total complications, blood transfusion, or perinephric hematoma between the IR and TN groups. The regression analysis showed that the team that performed the biopsy was not a significant predictor for total complications, blood transfusion or perinephric hematoma. The significant predictors of total complications were uncontrolled blood pressure and anticoagulation therapy. The predictors of blood transfusion were female sex, antiplatelet therapy, anticoagulation therapy, and blood urea nitrogen. The predictors of perinephric hematoma were female sex, black race, uncontrolled blood pressure, and anticoagulation therapy(Figure).

Conclusions: Kidney transplant biopsies are safe when performed by transplant nephrologists and interventional radiologists in an academic center. Blood pressure control and management of anticoagulation are fundamental to decrease the risk of complications. Studies need to be done to understand why sex and race were predictors for blood transfusion and perinephric hematoma.

Figure. Post-Transplant Renal Biopsy Complications

	Interventional Radiology (n=447)	Transplant Nephrology (n=231)	p value
Total number of complicated biopsies	37 (8.27)	18 (7.79)	0.94
Blood transfusion	15 (3.35)	8 (3.46)	1.00
Perinephric hematoma	16 (3.57)	10 (4.32)	0.78

	Odds Ratio	95% Confidence Interval	p value
Predictors of Total Complications			
Uncontrolled blood pressure	2.50	1.24-5.04	0.009
Anticoagulation therapy	4.47	1.33-14.24	0.01
Predictors of Blood Transfusion			
Female sex	5.34	1.71-18.85	0.005
Antiplatelet therapy	3.29	1.12-10.81	0.03
Anticoagulation therapy	12.14	2.01-73.38	0.005
Blood urea nitrogen	1.03	1.001-1.06	0.03
Predictors of Perinephric Hematoma			
Female sex	5.48	1.94-17.26	0.002
Black race	3.29	1.18-9.80	0.02
Uncontrolled blood pressure	2.85	1.002-8.29	0.04
Anticoagulation therapy	6.34	1.10-34.55	0.03

Uncontrolled blood pressure defined as blood pressure ≥ 160/90 mmHg at the time of biopsy.

PO2151

Outcomes of Kidney Referrals from Donors with High Infection Risk in the Most Populous Donor-Specific Antibody

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Background: Overdose-death donors (ODD) increased from 1.1% of donors in 2000 to 13.4% in 2017. Kidneys from ODDs were discarded at a higher rate than trauma-death donors. US Public Health Service defines organs from individuals with opioid abuse as being at increased risk of infection with HIV, HepB and HepC. CAOP is the most populous DSA in the country and improving utilization of organs within the DSA is of great importance. We aimed to study the utilization of kidneys from High-Infectious Risk Donors in this DSA.

Methods: We obtained data from UNOS and the Organ Procurement Organization (OPO), One Legacy between January 2015 and September 2020. We calculated the organ decline rate, organ refusal rate and rate of organs refused under the UNOS organ refusal code Donor age/quality and Donor Social History. We also compare these results to the trauma-death donors.

Results: Out of 2686 kidneys that were considered for recovery, 382 kidneys were from ODDs between 2015 and September 2020. 109 ODD kidneys (22.6%) were shared and successfully transplanted. 51 ODD kidneys were discarded locally in the DSA (22.2%). 47.5 % were refused by centers due to "Donor Age, Quality and Social History" before being either transplanted or being discarded. 103 kidneys of the ODDs were not recovered or offered for transplant. 82 kidneys were recovered from Hepatitis C positive donors, out of which 52 (66.7%) were shared and transplanted outside the DSA and 15 were discarded locally.

Conclusions: Higher infectious risk increased risk donors were being shared and discarded at a high rate. Given we have more evidence that these higher infectious risk kidneys are transplantable efforts to improve their utilization are needed.

Funding: Private Foundation Support

PO2152

Lack of Insurance Predicts with Follow-up Deficiencies After Living Kidney Donation

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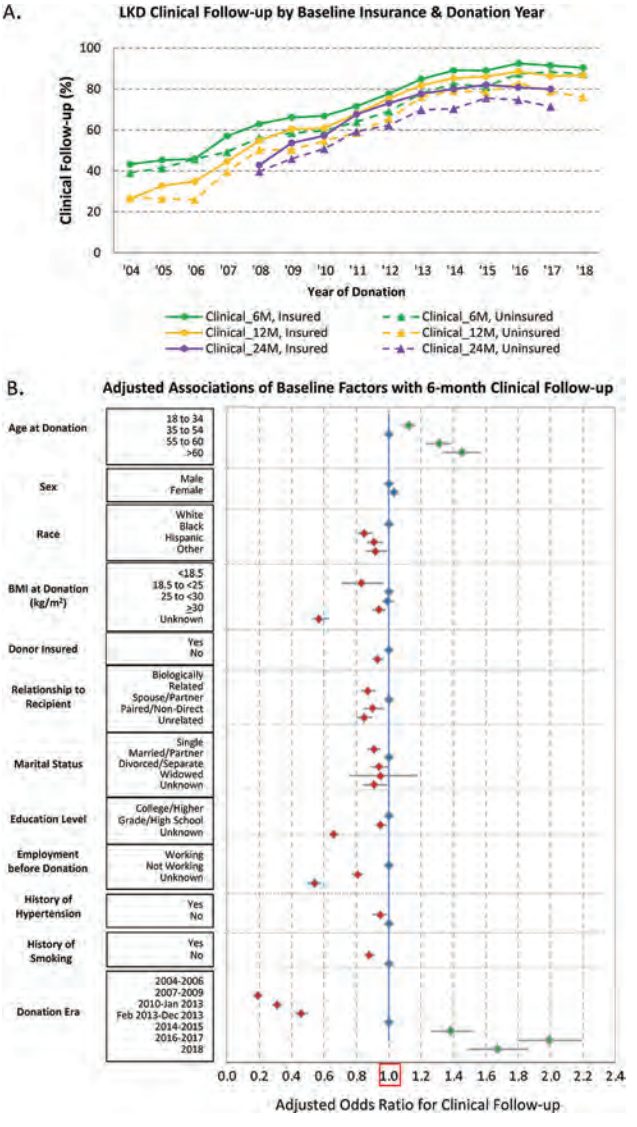
Background: Follow-up after living kidney donation in the United States has improved with recent policy mandates. We hypothesized that lack of insurance at donation may be a barrier to postdonation follow-up.

Methods: We examined Scientific Registry of Transplant Recipients (SRTR) data for 90.460 living kidney donors (LKD) in 2004-2018 to examine associations (adjusted odds ratio, aOR) of insurance status and other baseline factors with clinical and laboratory follow-up after donation.

Results: Follow-up increased over time, and was especially high in older LKD. Follow-up was lower in uninsured compared to insured LKD over time, including in the era of the Affordable Care Act (**Fig. A**). In 2018, for uninsured vs insured LKD, respectively, clinical follow-up was 87.5% vs 90.4% at 6-months, and 76% vs 86.7% at 12-months, while 12-month lab follow-up was 55.4% vs 68.4%. In multivariate regression including adjustment for donation year and other baseline factors, uninsured status was associated with 7% lower odds of 6-month clinical follow-up (aOR, 0.93) and 14% lower odd of lab follow-up (aOR, 0.86). Follow-up was also significantly (P<0.05) lower for LKD who were African American (aOR 0.85) or Hispanic (aOR 0.91), unrelated to their recipient (aOR 0.85), not working (aOR 0.81) and with less than college education (**Fig. B**).

Conclusions: While follow-up after living kidney donation is improving, uninsured LKD and those who are non-white, unemployed, and with lower education are less likely to receive follow-up. Novel initiatives are needed to provide access to follow-up care for at-risk LKD, including the uninsured and under-insured, to minimize the risk of socioeconomic disparities in long-term postdonation outcomes.

Funding: Other U.S. Government Support



PO2153

Visualizing Waitlist Outcomes for Kidney Transplant Candidates Whose Centers Have Declined Deceased Donor Offers

Cory Schaffhausen,[1,5] Jon Miller,[3] Arthur J. Matas,[4] Ajay K. Israni,[1,5] Andrew Wey,[2] Allyson Hart.[5,1] *[1]Hennepin Healthcare Research Institute, Minneapolis, MN; [2]Scientific Registry of Transplant Recipients, Minneapolis, MN; [3]Chronic Disease Research Group, Minneapolis, MN; [4]University of Minnesota Department of Surgery, Minneapolis, MN; [5]University of Minnesota Department of Medicine, Minneapolis, MN.*

Background: While transplant centers closely monitor posttransplant outcomes for each transplant recipient, centers currently lack data to monitor waitlist outcomes of individual candidates. Waiting candidates may receive multiple deceased donor organ offers. Centers may decline offers on behalf of the candidate in order to wait for a better offer. These decisions may impact waitlist outcomes because a better offer may not arrive, and dialysis-related morbidity may worsen. We sought to develop waitlist outcome reports to facilitate monitoring of candidates receiving donor offers.

Methods: A report mockup used patient-level data from the Scientific Registry of Transplant Recipients (SRTR). Data included a deidentified random sample of 200 kidney waitlist candidates from across the United States who had received at least one offer between May 7, 2019 and May 6, 2020. For each candidate, offers were identified from match runs from January 1, 2014 to May 6, 2020. Match run data included any offer that was ultimately accepted somewhere and resulted in a transplant. Offers in the match run after the last accepted offer and multi-listed candidates were excluded.

Results: The report visually identifies several outcomes: candidates who died after receiving offers, additional time on dialysis, and changes to quality and frequency of donor offers over time. Figure 1A depicts multiple patients on a waitlist. Each horizontal row represents one candidate, and each colored cell represents the highest-quality donor offer for each month, indicated by Kidney Donor Profile Index (KDPI).

Conclusions: The waitlist reports are a potential method for centers to self-monitor candidates and may supplement posttransplant outcome monitoring and existing decision support tools such as statistical outcomes calculators. The reports illustrate how offer frequency and KDPI change while candidates wait, as well as candidates' dialysis burden. Additional research is warranted to evaluate additional relevant candidate and donor data for reports (eg, offer number) and understand the utility of visual representations of the impact of offer decisions made on behalf of waitlist candidates.

Funding: Other NIH Support - AHRQ R01 HS 24527, AHRQ and PCORI K12HS026379

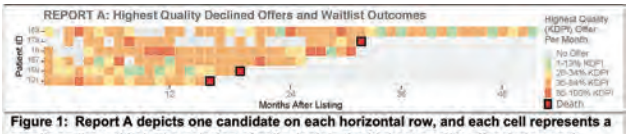


Figure 1: Report A depicts one candidate on each horizontal row, and each cell represents a month on the waitlist. The coloring of cells depicts the highest-quality offer during each month, in which low-KDPI donor organs (green and yellow cells) are highest quality.

PO2154

Guiding Kidney Transplant Candidates for Effective Weight Loss

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Background: Acceptance criteria at most transplant centers for waitlisting include BMI. The best approach to weight loss to facilitate active listing is unknown.

Methods: We aimed to determine the weight loss, listing, and transplant rates in 28 candidates with a mean BMI of 44.4 (4.6) and diabetes treated conservatively for obesity for 1-year post weight loss consultations, where the surgical and non-surgical weight loss options were discussed. A comparator group (n= 15) included patients with the mean BMI of 43.1 (4.4) who had bariatric surgery by 1 year post consultation.

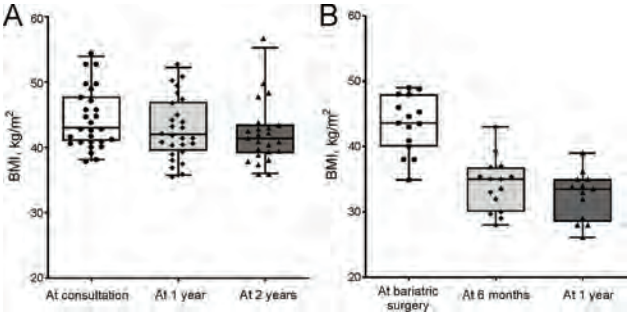
Results: The mean BMI at 1-year follow-up in the studied group (n=28) was 43.0 (4.8), and total body weight loss was 4.4 (8.2) kg (3.6% (6.5). BMI has not improved at 2 years (p=0.8; **Figure 2A**). Eighteen patients (64%) remained ineligible for a transplant due to excess weight and/or comorbidities over a mean follow-up of 4.0 (2.9) years. Most patients (75%) did not achieve an acceptable BMI for transplant. In contrast, total body weight decreased by 22.18 (10.1) kg (19% (7%)) at 6 months post-bariatric surgery with the BMI of 34.2 (4) and 32.5 (3.7) at 6 and 12 months, respectively (**Figure 2B**). Bariatric surgery was associated with subsequent kidney transplantation (HR = 5.75; CI [1.49, 22.14]; p = 0.01).

Conclusions: A conservative weight loss approach was ineffective in most kidney transplant candidates with diabetes to improve access to transplantation. These data suggest the need for larger controlled trials.

Baseline characteristics

Factor	No bariatric surgery	Bariatric surgery	p value	All
Age at evaluation	52.3 (11.9)	53.0 (9.2)	0.83	52.5 (11)
Male gender	15 (53.6%)	5 (33.3%)	0.20	20 (46.5%)
BMI at weight loss consultation	44.4 (4.6)	43.1 (4.4)	0.37	43.9 (4.5)
Dialysis	14 (51.9%)	9 (60.0%)	0.61	23 (54.8%)
Diabetes type 2 (vs. type 1)	23 (82.1%)	14 (93.3%)	0.31	37 (86%)
Follow up (years)	4.5 (3.1)	3.6 (2.2)	0.29	4.1 (2.8)

Data presented as Mean (SD), or N (%). BMI=body mass index.



PO2155

Risk Factors and Outcomes of Post-Transplant Erythrocytosis Among Adult Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

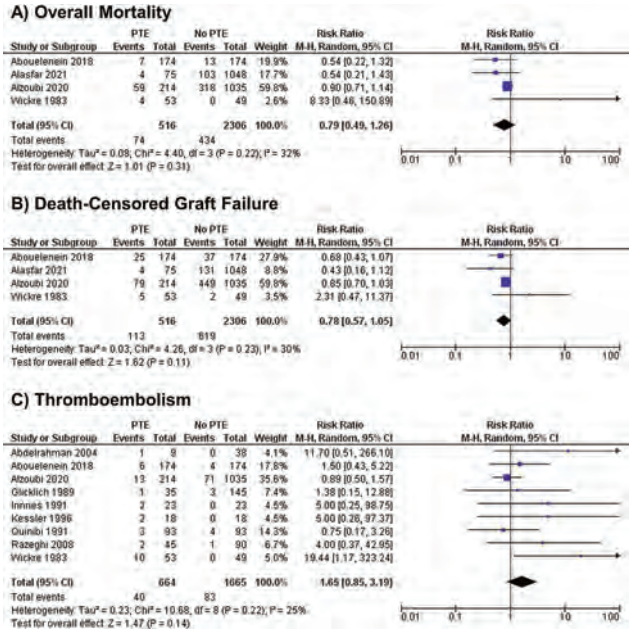
Poemlarp Mekraksakit,[1] Boonphiphop Boonpheng,[2] Natnicha Leelaviwat,[1] Samapon Duangkham,[1] Anasua Deb,[1] Kenneth Nugent,[1] Wisit Cheungpasitporn.[3] *[1]Texas Tech University Health Sciences Center, Lubbock, TX; [2]University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; [3]Mayo Clinic Minnesota, Rochester, MN.*

Background: Post-transplant erythrocytosis (PTE) can occur in up to 10-16% after kidney transplant (KT). However, the post-transplant outcomes of recipients with PTE in the literature were conflicting. We performed systematic review and meta-analysis of published studies to evaluate risk factors of PTE as well as outcomes of recipients who developed PTE compared to controls.

Methods: A literature search was conducted evaluating all literature from existence through February 2, 2021, using MEDLINE and EMBASE. Data from each study were combined using the random-effects model. (PROSPERO: CRD42021230377)

Results: Thirty-nine studies from July 1982 to January 2021 were included (7,099 KT recipients). The following factors were associated with PTE development: male gender (pooled RR=1.62 [1.38, 1.91], I^2=39%), deceased-donor KT (pooled RR=1.18 [1.03, 1.35], I^2=32%), history of smoking (pooled RR=1.36 [1.11, 1.67], I^2=13%), underlying polycystic kidney disease (PKD) (pooled RR=1.56 [1.21, 2.01], I^2=44%), and pretransplant dialysis (pooled RR=1.6 [1.02, 2.51], I^2=46%). However, PTE was not associated with outcomes of interest including overall mortality, death-censored graft failure, and thromboembolism.

Conclusions: Our meta-analysis demonstrates that male gender, deceased donor, history of smoking, underlying PKD, and pretransplant dialysis were significantly associated with developing PTE. However, with proper management, PTE has no impact on the prognosis of KT patients.



Forest plots of the included studies assessing the association between PTE in KT patients and outcomes of (A) Overall mortality, (B) DCGF, (C) Thromboembolism

PO2156

Efficacy of Sodium Zirconium Cyclosilicate for Treatment of Acute Hyperkalemia in Solid Organ Transplant Recipients

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Background: Hyperkalemia is a common electrolyte abnormality following solid organ transplant (SOT). Limited data are available to support the use of sodium zirconium cyclosilicate (ZS-9), a novel gastrointestinal potassium (K^+) binder, in SOT recipients. The purpose of this study was to evaluate short-term efficacy and safety of ZS-9 in SOT recipients.

Methods: We conducted a retrospective single center study of adult hospitalized SOT recipients who received ZS-9 from 05/20-04/21. The primary endpoint was change in K^+ from baseline to within 50 hours of the first dose of ZS-9 among persons not receiving renal replacement therapy (RRT). Data were analyzed using descriptive statistics and multivariable linear models.

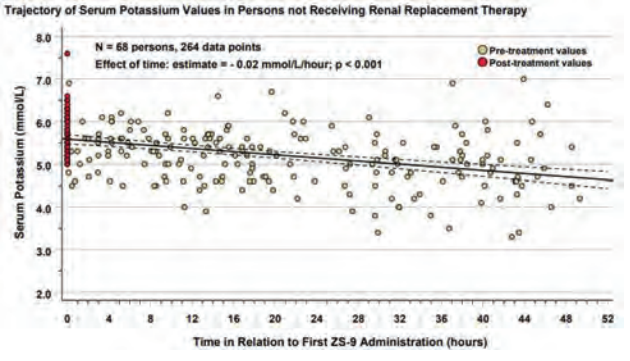
Results: The sample included 95 SOT recipients (Table), 68 of whom were not receiving RRT within 50 hours of ZS-9 administration. After adjusting for differences in follow-up time (34±11 hours), serum K^+ decreased by 0.88±0.81 mmol/L (p=0.002). The fully longitudinal downward trajectory of K^+ through up to 49 hours (p<0.001) is depicted (Figure). Adverse events were infrequent and mild as shown in the Table.

Conclusions: ZS-9 for treatment of acute hyperkalemia in hospitalized SOT recipients was efficacious and safe in this single center study. These findings are important in understanding the utility of ZS-9 broadly in SOT recipients.

Funding: Other NIH Support - REDCap use funded by UL1 TR000445 from NCATS/NIH

Patient Characteristics (n=95)	
Age (years)	55.7 +/- 12.5
Male Gender	73 (76.8)
Race	-
Caucasian	54 (56.8)
African American	34 (35.8)
Asian	5 (5.3)
Other	2 (2.1)
Time from transplant to first dose of ZS-9 (years)	4.6 +/- 6.3
Transplanted Organ	-
Kidney	57 (60.0)
Liver	13 (13.7)
Pancreas	1 (1.1)
Heart	5 (5.3)
Lung	9 (9.5)
Multiorgan	10 (10.5)
Renal Replacement Therapy	27 (28.4)
Hemodialysis	21 (22.1)
Continuous renal replacement therapy	6 (6.3)
Adverse Events	
Median number per person	1 (range 0 to 6)
Hypokalemia	6 (6.3)
Hypoglycemia	8 (8.4)
Nausea	2 (2.1)
Vomiting	1 (1.1)
Constipation	1 (1.1)
Diarrhea	5 (5.3)
Pulmonary edema	1 (1.1)
Bowel perforation	0 (0)

Unless noted, table entries are frequency (%) or mean +/- SD.



PO2157

Clinical Characteristics and Outcomes of FSGS in Kidney Transplant Recipients: A Single-Center Experience

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Background: Focal segmental glomerular sclerosis (FSGS) is a common etiology of chronic kidney disease in adults. Many progress to end stage renal disease requiring dialysis initiation and/or renal transplantation. It is also known to recur in transplantation, however there is limited literature addressing treatment options and outcomes in these patients. The purpose of this study is to evaluate clinical characteristics and post-transplant outcomes in kidney transplant recipients (KTRs) with primary and secondary FSGS.

Methods: This is a single-center retrospective study where data was collected from November of 2014 to December of 2020 on all KTRs with the diagnosis of FSGS within the Henry Ford Health System in Detroit, MI.

Results: A total of 39 KTRs were studied. 28% had primary FSGS and 71% had secondary. Baseline characteristics of KTRs can be found in table 1. 5 had recurred and all had primary disease. Recurrence was suggested by worsening proteinuria (>3.5g/day), and/or albumin <3.5 g/dL, and confirmed by renal biopsy. Median time of recurrence was 24 months post-transplant. Median proteinuria at time of diagnosis was 5.6 g. 3 that recurred were African American, 1 was Caucasian and 1 was Indian. A total of 4 out of 5 were treated with plasmapheresis. 2 had complete remission which was defined by reduction in proteinuria to <300 mg/day. One who did not achieve remission continues to have stable allograft function with ongoing proteinuria and the other had allograft loss at 96 months. None experienced adverse effects from treatment.

Conclusions: Recurrence of FSGS is more prevalent in patients with primary disease. Response to treatment is associated with significantly better outcomes and complete remission was achieved in 50% of cases.

Table 1

Baseline Characteristics	Primary	Secondary
Number of patients (total)	11 (28.2%)	28 (71.7%)
Recurrence (# pt)	5	0
Age at diagnosis (yr)	33 (22-62)	34 (19-72)
Age at transplantation (yr)	35.5 (25-65)	45 (24-77)
Male sex	7 (63.6%)	22 (75.8%)
BMI	30 (20-37)	30 (20-42)
African American	5 (12.8%)	8 (20.5%)
Caucasian	4 (10.2%)	15 (38.4%)
Time of diagnosis to ESKD (mo)	48 (0-144)	48 (0-228)

PO2158

Glomerulonephritis After Kidney Transplantation: Prevalence, Clinical Characteristics, and Outcomes

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Background: The Glomerulonephritis after kidney transplantation (GNKT) is an unknown disease, being the third cause of kidney allograft loss. It is defined as the development of glomerulonephritis (GN) in the allograft and is classified in: recurrent, novo and with unknown primary disease. The prevalence varies to 2-12%, the majority report figures to 6-8%. Recurrent GN have a higher risk of kidney allograft failure (KAF), the most frequent reported are IgAN (9.7%), FSGS (12.7%), MPGN (14.4%) and MN (12.5%).

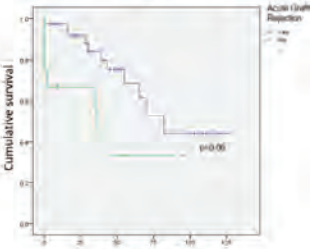
Methods: We conducted a single-center, retrospective cohort study during 10 years in a tertiary hospital in Mexico City. We included 50 patients with biopsy-proven GN in the kidney allograft. We examined the relationship between clinical, biochemical and histologic parameters to predict the KAF in GNKT. We used age and sex adjusted Cox proportional hazards models.

Results: 50 patients were included, median age 39 years, 50% were female, mean creatinine and proteinuria at biopsy were 2.6± 3.0 mg/dL and 2.8± 2.9 g/day respectively. The main biopsy indications was allograft dysfunction in 46%. The mean follow-up was 41.7±33.1 months. KAF occurred in 18 patients (36%). Of the total cases 7 corresponded to recurrent GN and 5 cases to de novo GN. The main etiologies were IgAN 12 (24%), MN 10(20%), DKD 9 (18%) and PGN 5 (10%). 12 patients had acute rejection and was not associated with kidney allograft loss (p= 0.06).

Conclusions: In the present study we found that the incidence of GNKT is similar to that reported in other series, with primary GN being the ones with the highest incidence, in our series IgAN was the most frequent. There were 7 cases of recurrent GN and only 5 cases of de novo GN, the rest GNKT with unknown primary disease. It is noteworthy that in our series we identified 5 cases of ANCA-associated vasculitis. The KAF was 36%, similar to that reported in the literature and MN was the main etiology.

Baseline Characteristics of Patients with glomerulonephritis in kidney allograft (n=50)	
Demographic data	
Age (yr)	39.4 (13.3)
Male (n, %)	25 (50)
Medical history	
DM pretransplant	5 (10)
DM post-transplant	10 (20)
Hypertension post-transplant	8 (16)
Glomerulonephritis kidney allograft etiology	
Primary	
IgA Nephropathy (IgAN)	12 (24)
Membranous Nephropathy (MN)	10 (20)
Focal and Segmental Glomerulosclerosis (FSGS)	4 (8)
Membranoproliferative Glomerulonephritis (MPGN)	4 (8)
Secondary	
Diabetic Kidney Disease (DKD)	9 (18)
Pauciimmune glomerulonephritis (PGN)	5 (10)
Lupus nephritis (LN)	3 (6)
Others	3 (6)
Baseline laboratory findings	
Serum creatinine (mg/dL)	2.6 (3)
Albumin (mg/dL)	3.6 (0.8)
Hemoglobin (g/dL)	12.6 (2.4)
Proteinuria/24 h (g/g)	2.8 (2.9)
UNB (mg/dL)	34.4 (20.5)
Haematuria	22 (44)
Immunosuppressant treatment	
Mycophenolate mofetil	42 (84)
Calcineurin inhibitor	42 (84)
Azathioprine	4 (8)
Prednisone	49 (98)

Classification of glomerulonephritis after kidney transplantation (n=50)	
De novo GN	**5**
MN	2
IgAN	1
DKD	1
Amyloidosis	1
Recurrent GN	**7**
IgA	2
FSGS	2
LN	2
MPGN	1
Unknown primary disease	**38**



PO2159

Outcomes of Renal Transplantation in Patients with AL Amyloidosis: An International Collaboration Through the International Kidney and Monoclonal Gammopathy (IKMG) Research Group

Andrea Havasi,[1] Cihan Heybeli,[2] Nelson Leung,[2] Avital Angel-Korman,[1] Vaishali Sanchorawala,[1] Oliver C. Cohen,[7] Ashutosh D. Wechalekar,[7] Frank Bridoux,[4] Insara Jaffer Sathick,[5] Victoria Gutgarts,[5] Paolo Milani,[6] Giovanni Palladini,[6] Giampaolo Merlini,[6] Ute Hegenbart,[3] Stefan O. Schönland,[3] Heather Landau.[5] The International Kidney and Monoclonal Gammopathy (IKMG) Research Group *[1]Boston University, Boston, MA; [2]Mayo Clinic Minnesota, Rochester, MN; [3]Amyloidosis Center, Heidelberg University Hospital, Heidelberg, Germany, Heidelberg, Germany; [4]Department of Nephrology, CIC INSERM 1402, CHU Poitiers, Poitiers, France; Centre national de référence Amylose AL & autres maladies par dépôts d'immunoglobulines monoclonales, CHU Poitiers, Poitiers, France; Centre National de la Recherche Scientifique UMR CNRS 7276/INSERM U1262, Université de Limoges, Limoges, France, Limoges, France; [5]Memorial Sloan Kettering Cancer Center, New York, NY; [6]Amyloidosis Research and Treatment Center, University ofFoundation "Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo" and Department of Molecular Medicine, University of Pavia, Pavia, Italy, Pavia, Italy; [7]National Amyloidosis Centre, London, United Kingdom*.

Background: New systemic therapies that successfully suppress toxic light chain production have led to an increase in the number of patients with AL amyloidosis who survive longer albeit with end stage renal disease. There is a critical need to identify patients in this specific population who can have good outcomes with renal transplantation.

Methods: We evaluated renal transplant outcomes in 237 patients from 5 countries with AL amyloidosis who underwent renal transplantation between 1987 and 2020. Cox regression analysis and Kaplan–Meier method were used.

Results: The majority of the patients (62%) underwent high dose melphalan and autologous stem cell transplantation (HDM/SCT). Overall survival (OS) from renal transplantation was 8.6 years with a median follow-up of 8.5 years. One-, three- and five-year OS from renal transplantation was 95%, 83% and 73%, respectively. The median time of graft survival was 7.8 years. Death censored graft survival at one-, three- and five-years was 92%, 79% and 69%, respectively. Survival outcomes were analyzed based on degree of hematologic response to therapy at the time of renal transplantation. Overall and graft survival were better in patients with complete hematologic response and very good partial response (CR+VGPR) compared to partial response, no response or treatment naive (PR+NR+TN). Amyloid recurrence rate in the graft was lower (16% vs 37%, p=0.01) and the time to amyloid recurrence was significantly longer in the CR+VGPR group (median time not achieved vs 10 years, p=0.001). Comparing CR vs. VGPR there was no difference in OS and graft survival. A total of 69 patients (29%) experienced hematologic relapse requiring treatment post renal transplantation. Graft survival for those who had a hematologic relapse was not statistically different from that of patients without relapse. Successful hematologic treatment prevented graft loss in 87% of patients who had amyloid recurrence in the graft.

Conclusions: Our results show that selected patients with AL amyloidosis undergoing kidney transplantation have good outcomes.

PO2160

Primary Hyperoxaluria Type 2: Is Combined Liver Kidney Transplant the Answer?

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Introduction: Primary Hyperoxaluria (PH) is a group of rare inborn errors of glyoxylate metabolism characterized by overproduction of oxalate. Oxalate is poorly soluble and is deposited as calcium oxalate in various organs, with the kidneys being the prime target leading to ESRD.

Case Description: 60-year-old female with a history of diabetes, hypertension and ESRD 2/2 obstructive uropathy from staghorn calculi in 2017. Patient underwent bilateral native nephrectomies in 2018 for staghorn calculi and was started on hemodialysis. Pathology showed extensive intratubular calcium oxalate crystals. Patient underwent a living donor kidney transplant in 2019 in India with allograft dysfunction by 2 months. Transplant biopsy showed oxalate deposition and severe ATN. 24-hr urine oxalate level was 182 mg. Genetic testing showed homozygosity for pathogenic variant in GRPHR gene, consistent with PH type-2. Repeat biopsy in 2020 confirmed oxalate nephropathy. Patient was started on daily dialysis for oxalate clearance. Pre-transplant plasma oxalate level on dialysis was 38mg. She underwent simultaneous liver-kidney transplant in 2021. Post-operatively, patient was maintained on CRRT for 4 days and transitioned to daily dialysis thereafter for delayed graft function and anuria. Renal allograft biopsy showed ATN and oxalate crystals. Patient was discharged on daily dialysis with serum oxalate level of 15. Patient finally recovered her kidney function almost 4 months later with current 24-hour creatinine clearance 25ml/min and 24-hour oxalate level of 55mg.

Discussion: PH type-2 was thought to have a more favorable prognosis than PH type-1 however, recent studies have found this disease has significant morbidity. While it was thought that a renal transplant may be the treatment for this 'milder' disease as oxalate deposition may take longer than the life of the allograft, reports have shown that recurrent PH type-2 has led to early post-transplant renal function loss. Dhondup and Del Bello each reported a case of successful treatment of PH type-2 with simultaneous liver-kidney transplantation. Similarly, while our patient remained dialysis dependent for almost 4 months post combined liver-kidney transplant, she is now successfully off dialysis. These 3 cases support the idea of a combined liver-kidney transplant as a better option for PH type-2.

PO2161

Early Post Renal Transplant Hypertension: Incidence of Masked Hypertension and Hemodynamic Correlates

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Background: Hypertension following renal transplantation is prevalent and impacts long term graft survival. Masked and white coat hypertension have been reported in patients with renal allografts. The onset and mechanism of masked hypertension in these patients is poorly understood. We report preliminary data from an ongoing prospective observational study of HTN in the early post-transplant period.

Methods: 40 patients with ESRD who undertook renal transplantation at Baystate Medical Center from June of 2019 to April of 2021 consented to participate in a prospective observational study assessing office BP and ambulatory blood pressure monitoring (ABPM). ABPM was performed at 1 month and at 3-4 months post-transplant. At the same time periods, bioimpedance measures including cardiac index (CI), total peripheral resistance (TPR) and total body water (TBW), were obtained using a whole body bioimpedance technology (NiCAS^{tm}). Patient demographics, office blood pressures (BP), ABPM and bioimpedance data were analyzed to determine rate of masked and white coat hypertension (HTN).

Results: 33 of 40 patients completed ABPM at 1 month and 16 completed the 3-4 month ABPM. Mean office BP at visit 1 and 2 were 133/79 and 132/78, respectively. There was an increase in percentage of patients with masked hypertension at the 3-4 month time period and a decrease in nondipping pattern. We did not identify significant differences in hemodynamic parameters between the 1 and 3 month time periods and between those with and without masked HTN.

Conclusions: In this preliminary analysis of a prospective observational study, we observed an increase in the rate of masked hypertension as patients get beyond 3 months post transplant. A significant percentage of these post transplant patients have non-dipping hypertension. Using whole body bioimpedance technology, we did not identify differences in CI, TPR and TBW between those with and without masked hypertension

	Visit 1	Visit 2
Office BP	N=40	N=21
Normal	6(15%)	4(19%)
HTN	34 (85%)	17 (81%)
Masked HTN	6/33 (18%)	7/17 (44%)
White Coat HTN	5/33 (15%)	2/35 (12%)
Non Dipping HTN	24/33 (85%)	10/17 (63%)

PO2162

AKI Caused by Early Post-Kidney-Transplant Nephrocalcinosis Related to Severe Tertiary Hyperparathyroidism

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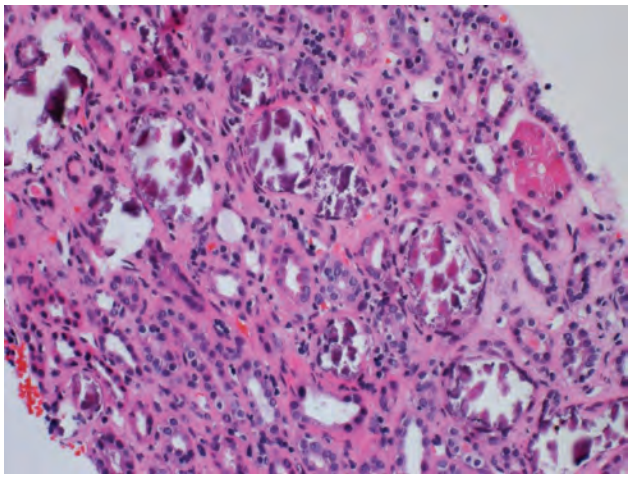
Introduction: Persistent hyperparathyroidism is a common condition in post-kidney transplantation. We present a case of acute kidney injury (AKI) caused by nephrocalcinosis due to tertiary hyperparathyroidism in an early post-renal transplant patient, which was managed and improved with parathyroidectomy.

Case Description: A 42-year-old man with history of diabetes mellitus, hypertension and a deceased donor kidney transplant 3 months prior was evaluated for hypercalcemia. Medications included nifedipine, insulin, mycophenolic acid, tacrolimus and prednisone. Cinacalcet was started but calcium (Ca) level continued to rise. He was later hospitalized for AKI, cinacalcet was discontinued. Blood work showed creatinine (Cr) 2.6 mg/dL (baseline Cr 1.29 mg/dL), corrected Ca 9.9 mg/dL and tacrolimus 6.2 ng/mL. Images of the kidney graft were negative for obstruction. Kidney biopsy revealed no acute rejection or BK infection. However, there were findings of acute tubular injury with frequent calcium phosphate deposits, interstitial fibrosis and tubular atrophy involving 30-40% cortical surface. Interestingly, kidney biopsy obtained 2 months prior was unremarkable. Further workup showed parathyroid hormone 1220 pg/mL, 1,25 di-OH vitamin D 20.1 pg/mL. Given the rapid decline in kidney function and biopsy changes, subtotal parathyroidectomy was performed during the same admission. At 2-week follow-up visit, Cr improved to 1.5 mg/dL.

Discussion: Persistent hyperparathyroidism in post-kidney transplantation can lead to hypercalcemia with nephrocalcinosis, increased mortality and graft loss. These patients usually failed medical therapies. Our case demonstrates that early parathyroidectomy might be the treatment of choice for patients with severe hyperparathyroidism and symptomatic hypercalcemia.



Kidney biopsy in Nephrocalcinosis - Acute tubular injury with calcium phosphate deposits, interstitial fibrosis and tubular atrophy

PO2163

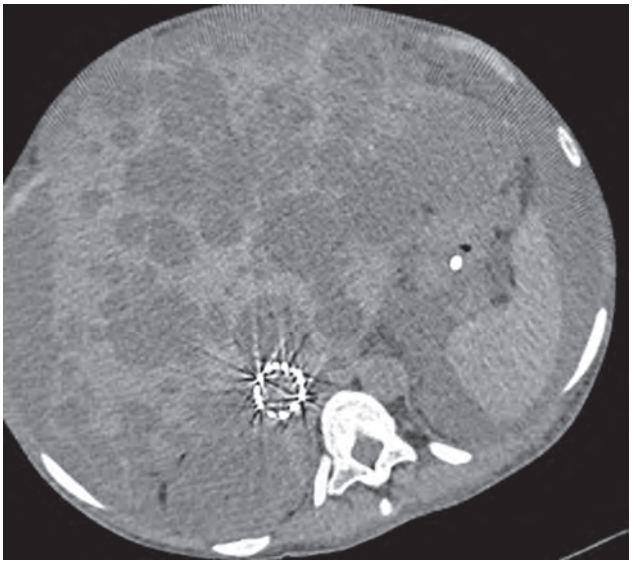
A Rare Case of Liver Failure in a Kidney Transplant Recipient with Polycystic Kidney Disease

Laila S. Lakhani, Payaswini Vasanth. *Emory University School of Medicine, Atlanta, GA.*

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) patients usually have great outcomes post kidney transplant. We describe a rare case (none reported in literature), where kidney transplantation led to progressive enlargement of liver cysts and liver failure physiology.

Case Description: A 51 year old female with end-stage kidney disease from ADPKD, underwent a deceased donor kidney transplant in July 2020. She was induced with basiliximab and maintained on Belatacept, Tacrolimus, mycophenolate and prednisone, with a baseline creatinine of 1 mg/dL. In October 2020, she presented with gross anasarca when CT imaging revealed large ascites, worsening of liver cyst burden, splenic enlargement and IVC compression. Ascitic fluid analysis indicated portal hypertension. Trans-jugular liver biopsy demonstrated nodular regenerative hyperplasia and vascular flow abnormality. MR Venogram showed severe narrowing of the IVC, hepatic and portal veins from mass effect of liver cysts. She underwent IVC stent placement; however, post procedure course was complicated by klebsiella bacteremia, that progressed to developing septic lung emboli and anuric acute kidney injury. She developed multi-organ failure requiring vasopressors, intubation, renal replacement therapy and worsening hepatic encephalopathy. This complex hospitalization culminated into her demise secondary to cardiac arrest.

Discussion: This is a very challenging yet fascinating case that highlights progressive liver failure from rapidly enlarging liver cysts within 3 months of kidney transplantation. Did immunosuppression contribute to accelerating the growth of liver cysts? Should a select group of patients with ADPKD be evaluated for combined liver and kidney transplant? Multi-disciplinary discussions between transplant nephrology and hepatology can guide decision making in these complex patients.



PO2164

Association Between Recipient-Donor HLA Genotypes and Recurrent Membranous Nephropathy After Kidney Transplantation

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Background: Recurrent membranous nephropathy (MN) occurs in up to 40% of kidney transplant recipients (KTRs) and is a major cause of graft loss. Recipient with alleles at the HLA-D loci were found to have an increased risk of disease recurrence in KTRs with primary MN. However, the association between recipient-donor HLA characteristics and disease recurrence has not been explored.

Methods: We integrated data from two registries: United Network for Organ Sharing, and Australian and New Zealand Dialysis and Transplant registries between 1963 and 2020. Least Absolute Shrinkage and Selection Operator (LASSO) regression was used for variable selection. The penalization parameter was chosen by cross-validation and the covariates with non-zero coefficients were included in a logistic regression, together with class, and fitted using maximum likelihood. The model performance was evaluated using C-statistics.

Results: 8058 KTRs with primary MN were included and 232 had recurrent MN. Of the 266 variables, group LASSO selected 59 variables considered as variables of importance and were included in the adjusted logistic regression model. Recipient HLA genotype at DR11 (odds ratio, 95% confidence interval) (1.81, 1.30-2.51, p<0.001), B38 (1.93, 1.00-3.43, p=0.04), and B46 (6.75, 1.55-26.30, p=0.007) and donor-recipient HLA-B65 match (3.38, 1.07-8.85, p=0.02) were associated with an increased risk of recurrent MN, adjusted for recipient sex, ethnicity, comorbidities (diabetes, hepatitis C and cancer), immunosuppression regime (T cell depletion induction therapy, B cell depletion induction therapy, tacrolimus, corticosteroid, or other maintenance therapy), donor type, biopsy-proven rejection, and country of origin. The overall performance of the model was good (C-statistic 82%).

Conclusions: Recipient HLA-DR11, B38, B46 and donor-recipient HLA-B65 match were associated with an increased risk of recurrent MN in KTRs.

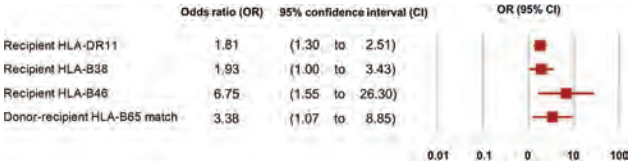


Figure 1. Recipient-donor HLA characteristics associated with recurrent membranous nephropathy in kidney transplant recipients

PO2165

The Cumulative Dose-Dependent Benefit of Metformin in Kidney Transplantation Recipients

Soie Kwon,[1] Yong Chul Kim,[1] Chan-Duck Kim,[5] Jang-Hee Cho,[5] Hyung Eun Son,[2] Jong Cheol Jeong,[2] Jeonghwan Lee,[3] Kyung Don Yoo,[6] Jong Soo Lee,[6] Hajeong Lee,[1] Yon Su Kim,[1,4] Jung Pyo Lee.[3,4] *[1]Seoul National University Hospital Department of Internal Medicine, Jongno-gu, Seoul, Republic of Korea; [2]Seoul National University Bundang Hospital Department of Internal Medicine, Seongnam, Gyeonggi-do, Republic of Korea; [3]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [4]Seoul National University College of Medicine, Seoul, Republic of Korea; [5]Kyungpook National University, Daegu, Daegu, Republic of Korea; [6]Ulsan University Hospital, Ulsan, Republic of Korea.*

Background: The status of metformin as a primary choice is concrete, moreover it has recently been recommended for advanced chronic kidney disease. Although, the evidence of metformin usage in kidney transplant recipients (KTRs) is lacking. We investigated the effect of metformin in KTRs.

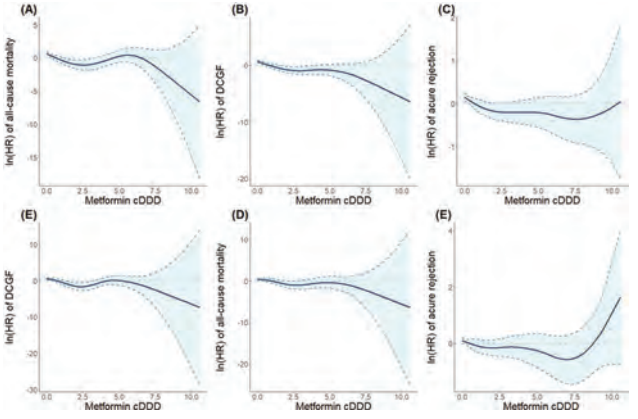
Methods: The primary outcomes were all-cause mortality and death censored graft survival (DCGS) and secondary outcome was biopsy proven acute rejection (BPAR). Cox analysis and propensity score matching were used. Time-varying and marginal structural cox was conducted for HbA1c. A defined daily dose (DDD) of WHO and a penalized spline curve were used to evaluate cumulative effect of metformin.

Results: In 2,048 diabetic KTRs, 1,199 patients were metformin user and 849 patients were non-metformin user. Pre-existing DM patients before transplantation were majority (78.7%) and tend to be less prescribed metformin than NODAT (DM 56.0%; NODAT 68.0%; *P*<0.001). The metformin user had a lower risk of all-cause mortality, DCGS and BPAR. Even after time varying adjustment of HbA1c, metformin usage was associated with significant reduction in all outcomes. (Table 1) Also, the more cumulative metformin exposure was correlated to the less risk of whole outcomes. (Figure 1)

Conclusions: In conclusion, metformin can be also considered as first-line anti-diabetic treatment in KTRs, not only from the benefit of lower mortality, graft survival and acute rejection, but also cumulative dose dependent protective effect.

Survival analysis

	All-cause mortality			Death Censored Graft Failure			Biopsy Proven Acute Rejection		
	aHR	95% CI	P-value	aHR	95% CI	P-value	aHR	95% CI	P-value
Univariate	0.2865	0.1939–0.4232	<0.001	0.3050	0.2171–0.4231	<0.001	0.6352	0.5203–0.7754	<0.001
Model 1	0.3425	0.2288–0.5127	<0.001	0.3165	0.2231–0.4489	<0.001	0.5793	0.4712–0.7122	<0.001
Model 2	0.4761	0.3066–0.7395	0.001	0.4611	0.3109–0.6839	<0.001	0.6426	0.5114–0.8073	<0.001
Model 3	0.5675	0.3429–0.9393	0.028	0.4472	0.2908–0.6879	<0.001	0.5694	0.4438–0.7306	<0.001
Model 4	0.7697	0.4524–1.3100	0.300	0.4795	0.2821–0.8149	0.007	0.6073	0.4448–0.8291	0.002
Model 5	0.5819	0.3578–0.9464	0.029	0.4438	0.2803–0.7027	0.001	0.5627	0.4339–0.7297	<0.001
Model 6	0.5509	0.3340–0.9087	0.020	0.4428	0.2782–0.7047	0.001	0.5539	0.4272–0.7183	<0.001



PO2166

Successful En Bloc Liver Kidney Transplant in a Morbidly Obese Patient

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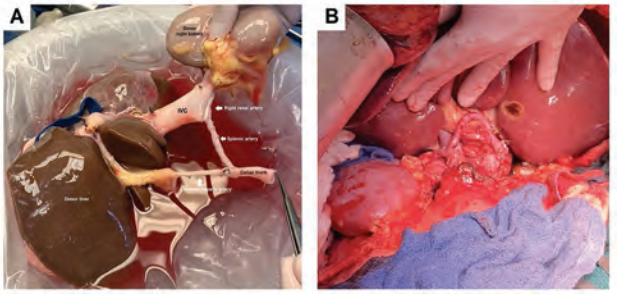
Introduction: *En bloc* liver and kidney transplant is a variant for the traditional simultaneous liver kidney transplant (SLKT) technique that, with simultaneous reperfusion of both grafts through a common vascular anastomosis, can decrease operative time, cold ischemia time and risk of surgical site infections.

Case Description: A 50-year-old morbidly obese (BMI >50) male with history of ESRD due to hypertension, on hemodialysis for 4 years, decompensated NASH cirrhosis, Factor V Leiden, previous episodes of venous thromboembolism and obstructive sleep apnea presented for SLKT. The donor was brain dead with a KDPI 22%, anatomy was normal. On backtable, the donor right renal artery and splenic artery were anastomosed end-to-end to leave these arterial systems in continuity and perfused from the celiac trunk. The infrahepatic IVC cuff was sutured using an endovascular stapler to close the left renal vein orifice and distal IVC (Fig. 1A). The liver transplant was done with a piggyback technique with a side-to-side cavocavostomy. Reperfusion occurred simultaneously in both allografts from the arterial inflow followed by the venous inflow (Fig. 1B). Direct flow assessments by doppler was excellent. The ureter was anastomosed to the recipient's right native ureter in an end-to-side fashion followed by a double J ureteral stent. Total operative time was 7 hrs, 10 min, CIT 7 hrs and WIT 46 min. The postoperative course complicated by DGF for 3 weeks. He was discharged home on POD 6 and the ureteral stent was removed on POD 48. At 3 months follow-up, the portal vein and renal artery remain patent and both allografts have excellent functioning without evidence of complications.

Discussion: This case illustrates that *en block* liver kidney is a feasible and effective option for well-selected patients. This technique should be considered in obese patients or those with extensive iliac arteries atherosclerosis who have increase morbidity with transplant and could benefit from single surgical incision. Close post transplant monitoring is key to surveil for potential complications.



PO2167

Little Goes a Long Way: Is Kidney Donor Profile Index (KDPI) a Good Predictor for Pediatric Kidneys from Donors Less Than 10 kg?

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Introduction: Pediatric deceased donor kidneys (DDK) constitute 10-12% of the DDK supply and are allocated using the same criteria as adult kidneys. Kidney Donor Profile Index (KDPI) is designed to predict kidney graft performance in adult recipients based on 10 donor characteristics. A KDPI scale goes from 1 (best) to 100 (worst). Most child donor kidneys classified as KDPI-C (≥35% but ≤85%) and KDPI-D (>85%) which makes them less desirable. In addition, few programs use kidneys from donors less than 1 year.

Case Description: We report a case of pediatric en bloc kidney (EBK) transplantation procured from a 7-month-old female donor, with a bodyweight of 7.7 kg. KDPI is 87%. The recipient is a 39-year-old female with a bodyweight of 54 kg and a diagnosis of ESKD secondary to biopsy-proven FSGS. The recipient had been on PD for 37 months, baseline sCr of 12-15 mg/dL and was oliguric. Cold ischemic time of the kidneys was 8 h 33 mins, warm ischemic time - 24 mins, estimated blood loss - 200 mL. Intraoperative challenges included tedious organ preparation and extremely small vessels requiring complex reconstruction along with the creation of 2 ureteral anastomoses. A postoperative complication included delayed graft function required 2 hemodialysis sessions. Thereafter graft function improved and sCr trended from 15.48 mg/dL to 1.46 mg/dL at 4 weeks follow-up.

Discussion: KDPI is a valuable tool for adult donors but takes an oversimplified approach to the pediatric donor population. KDPI calculation includes donor age, weight, and height does not lead to a proportional scaling of the hazard in pediatric donors. It leads to misclassification and underestimation of a sizable number of kidneys from small pediatric donors. In addition, although it was found en bloc to be a significant factor and shown EBK versus SKT as an important predictor for graft performance, it was decided not to include this criterion in KDPI. Pediatric EBKs had the lowest acute rejection and delayed graft function rates in comparison with SKT. Furthermore, the eGFR for pediatric EBKs improves due to the continuous growth of pediatric kidneys after transplant. In summary, modified KDPI tailored to the pediatric donors is warranted to accurately represent pediatric donor kidney survival, attract recipients and surgeons to address the problem of organ shortage.

PO2168

Pickering Syndrome in a Kidney Transplant Recipient

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Introduction: Pickering syndrome (PS) refers to hypertensive urgency with recurrent flash pulmonary edema (FPE) due to bilateral renal artery stenosis (RAS) or unilateral RAS in patients with a solitary kidney or kidney allograft. We report a case of PS in a kidney transplant recipient.

Case Description: A 68-year-old gentleman with a history of end-stage kidney disease secondary to diabetic nephropathy treated with deceased donor kidney transplantation (on Belatacept, Mycophenolate Mofetil, and Prednisone) and a history of recurrent admissions for FPE presented 3-months post kidney transplantation with hypertensive urgency, acute kidney injury (AKI) and FPE. Blood pressure was 170/85 mmHg and serum creatinine was 2.5 mg/dL (baseline 1.8 mg/dL). Echocardiogram showed preserved left ventricular function. Kidney transplant ultrasonography (US) showed patent vasculature with no hydronephrosis. Kidney biopsy showed no evidence of acute rejection. Duplex ultrasound showed a high proximal peak systolic velocity (PSV) 622 cm/sec and a low renal arterial resistive index (RI = 0.55) with severe (60-99%) transplant RAS. An intravascular-ultrasound (IVUS) guided stent placement facilitated safe renal artery revascularization using only 2 mL of contrast agent subsequently leading to a complete resolution of AKI and no further episodes of FPE.

Discussion: Transplant RAS causes 1-5% of post-transplant hypertension, and usually occurs within the first 6 months post-transplantation. Activation of the renin-angiotensin-aldosterone system leads to worsening hypertension, allograft dysfunction and fluid retention with FPE. Although duplex US is used for screening, angiography with simultaneous percutaneous angioplasty is often needed for definitive diagnosis and treatment. IVUS guided stenting is beneficial in patients with AKI to minimize contrast exposure and further worsening of graft function. Early diagnosis and prompt treatment of PS are the key to minimize morbidity and mortality in these patients.

PO2169

Treatment of Transplant Renal Vein Thrombosis in a Pediatric Patient Using an EkoSonic Endovascular System (EKOS) Catheter

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Introduction: Transplant renal vein thrombosis (tRVT) is a critical complication after renal transplant with reported prevalence of 0.1% to 4.2% leading mostly to graft loss. Thrombolytic therapy and surgical thrombectomy has been described previously to treat tRVT. EKOS is a modern and innovative ultrasound-facilitated catheter directed thrombolysis technique that is approved primarily for treatment of pulmonary embolism, deep vein thrombosis and arterial occlusion. It requires ultrasound core wire and infusion catheter for delivery of fibrinolytic agent such as Tissue plasminogen activator (tPA).

The ultrasound core wire or transducer generates ultrasound waves that help accelerate fibrinolysis, decrease the treatment time and decrease the risk of bleeding. The use of EKOS for tRVT has not been reported in pediatric literature and we describe one such case.

Case Description: We describe a 17-year-old boy with history of congenital nephrotic syndrome who received living donor renal transplant in 2005. His post-transplant course was complicated by multiple episodes of deep venous thrombosis in right lower extremity, chronic right inguinal venous thrombosis with collaterals in lower extremities, maintained on anticoagulant therapy. He presented with serum creatinine elevation of 3.7 mg/dL (baseline of 1.4 mg/dL) and anuria. On renal US Doppler, the transplant renal vein was not seen and there was concern of lack of flow/RVT. CT venogram performed showed acute lumen occluding thrombus in left lower extremity venous system extending from left popliteal and femoral vein all the way to the left transplant renal vein in the left iliac fossa. He received tPA as per hematology without any improvement. Active discussions between hematology, nephrology and vascular surgery led to a trial of EKOS device to salvage the allograft. The patient then underwent thrombolysis using EKOS catheter with peripheral access to the left transplant renal vein, without any complications. The repeat renal US Doppler showed patent left renal transplant vein, with continued occlusion in the left external iliac vein. The serum creatinine returned to baseline 1.4-1.5 mg/dL one week after procedure.

Discussion: We describe a novel report of successful treatment of transplant renal vein thrombosis using EKOS catheter. Further studies are needed to provide more insight in this therapy.

PO2170

Reversal of Prolonged Delayed Graft Function Following Kidney Transplantation with a Belatacept-Based Regimen

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Introduction: Delayed graft function (DGF) following kidney transplantation is associated with adverse graft and patient outcomes. Many factors contribute to the development of DGF including ischemia-reperfusion injury. There is concern that calcineurin inhibitors such as tacrolimus can perpetuate DGF through tubular injury and vasoconstriction. The non-nephrotoxic co-stimulation blocker belatacept could potentially be beneficial in improving allograft function in such scenario. We present a patient who experienced prolonged DGF following kidney transplantation that reversed following switching immunosuppression from a tacrolimus-based to belatacept-based regimen.

Case Description: A 73-year old non-sensitized female with a history of coronary artery disease, hypertension, and type 2 diabetes mellitus on maintenance hemodialysis underwent kidney transplantation from a 63-year old brain-dead donor with acceptable procurement kidney biopsy and kidney donor profile index (KDPI) of 88%. Cold ischemia time was 27.5 hours. She received induction with Thymoglobulin followed by tacrolimus/mycophenolic acid maintenance with early steroid withdrawal. In the peri-operative period, she experienced hemodynamic instability from cardiogenic shock requiring prolonged ICU stay. She developed DGF requiring dialysis support. Despite clinical improvement, she remained dialysis-dependent. Allograft biopsies at 2 weeks and 2.5 months post-transplant showed acute tubular injury and no rejection. Four months from transplant, immunosuppression was changed from tacrolimus-based to belatacept-based regimen. One week after this change, the urine output started improving and 10 days later the patient came off dialysis. Her serum creatinine continues to improve with a most recent value of 2.4 mg/dl and excellent urine output 3 weeks since stopping dialysis.

Discussion: The patient experienced very prolonged DGF after receiving a high KDPI kidney. We believe that replacing tacrolimus with belatacept facilitated the reversal of prolonged DGF and freedom from dialysis in this patient. Conversion of tacrolimus to belatacept in kidney transplant recipients experiencing prolonged DGF and utilization of de novo belatacept-based maintenance regimen in patients at high risk for developing DGF should be considered in order to improve graft and possibly patient outcomes.

PO2171

Disease-Specific Tissue RNAs as Diagnostic Tool for Kidney Transplant Pathology

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Background: MicroRNAs (miRNAs) play an important role in the development of renal diseases as epigenetic regulators of gene expression. However, there are limited data to date on tissue miRNA expression in transplantation-related kidney disease.

Methods: Study enrolled fifty-six transplant kidney patients with surveillance/indication kidney transplant biopsy including pretransplantation biopsies, which were divided into four (four + control) groups. The control group (CG, n = 12) consisted of patients without patohistological changes on surveillance biopsy. Patients with indication biopsy due to an increase in serum creatinine and nonspecific chronic changes in patohistological analysis were in the nonspecific group (NS, n = 6). The other three groups consisted of histologically proven antibody-mediated rejection (ABMR, n = 13), recurrent glomerulonephritis (rGN, n = 15), and acute tubular injury/necrosis (ATN, n = 10). We analyzed the expression of 6 selected miRNAs (miR-29c, miR-126, miR-146a, miR-150, miR-155, miR-223) and compared them with the respective disease process.

Results: When comparing mRNA expression before and after transplantation, there was no statistically significant difference in the expression of the analyzed miRNAs in CG, NS and rGN, but we observed a statistically significant change in the expression profile of miR-146a and miR-155 after transplantation in patients with ATN and ABMR. Post-transplant biopsies showed differential expression of miR-146a and miR-155 in ABMR and NS compared to CG, miR-155 in rGN compared to CG, miR-146a in ATN compared to CG and miR-223 in NS compared to CG. All but miR-146a showed differential expression in pretransplantation biopsies before transplantation of either NS, rGN, ABMR or ATN compared to CG, but the difference in expression after transplantation was more pronounced.

Conclusions: Our results suggest that miR-146a and miR-155 play an important role in pathological processes after kidney transplantation and also support the hypothesis that there are differences at the molecular level of the donor kidney that may predispose the kidney to certain types of patohistological damage.

PO2172

Trajectory of Gene Expression Profile and Donor-Derived Cell-Free DNA Before and After Subclinical Acute Rejection

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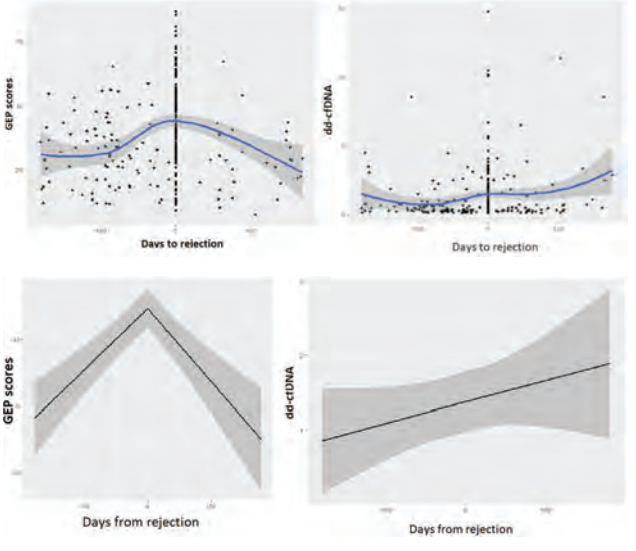
Background: Subclinical acute rejection (subAR) is associated with poor kidney allograft outcomes. Blood gene expression profile (GEP) and donor-derived cell-free DNA (dd-cfDNA) have been used to exclude or diagnose kidney allograft rejection non-invasively. However, the trajectory of GEP and dd-cfDNA are unknown after subAR. We investigated the changes in GEP and dd-cfDNA after subAR.

Methods: We analyzed 100 subjects with GEP and 87 with dd-cfDNA, with some subjects in both groups. GEP and dd-cfDNA were performed before, at, and after the time of subAR. The cohort was extracted from a previously reported prospective, multicenter observational study. GEP was performed using a microarray-based 120 gene expression profile. The study reported dd-cfDNA as a percentage of donor cell-free DNA over total cell-free DNA. Locally estimated scatterplot smoothing (LOESS) and linear mixed effect models were used to analyze longitudinal changes of GEP and dd-cfDNA scores.

Results: A total of 1,314 blood samples were assessed. The longitudinal changes of GEP scores at a sample level are shown in Figure 1. GEP scores peaked at the time of subAR and decreased after. The slope of GEP scores was significantly different after subAR (slope difference = -0.201 p-value <0.001) (Figure 2). On the other hand, dd-cfDNA continued to rise even after subAR (Figure 1). There were no significant changes to the slope of dd-cfDNA between pre-subAR and post subAR (0, p-value = 0.98) (Figure 2).

Conclusions: GEP scores significantly dropped, while dd-cfDNA persistently increased after subAR. How this may inform the biology of gene expression vs. dd-cfDNA after treatment of rejection requires additional study.

Funding: Commercial Support - Viracor-Eurofins



PO2173

Early Experience with TruGraf in Kidney Transplant Recipients: The University of Maryland Medical Center Experience

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Background: TruGraf, an assay based on PBMC gene expression profile, has been recently introduced as a non-invasive screening tool for subclinical rejection in kidney transplantation. Its utility as a screening tool is currently not well defined. In this preliminary study we examined the predictive value of TruGraf for subclinical acute rejection, and its concordance with dd-cfDNA and DSA results.

Methods: In this small, retrospective cohort study, we examined the results of TruGraf in 48 kidney transplant recipients with stable graft function (median 12.9 mo posttransplant, IQR 5.9-19.8). Patients were maintained on TAC/MMF+/-prednisone. We collected data on 11 biposies, 17 dd-cfDNA, and 16 DSA assays performed within 1 mo of TruGraf.

Results: There were 34 'TX" and 14 'Not-TX" results. 3 pts in former (1 with TCMR) and 8 in latter group (1 TCMR, 3 ABMR) had biopsies. Among those with DSA testing, out of 7 "Not-TX" cases 2 had DSA, compared with 4 out of 9 with "TX" (p=0.45). Combining biopsy results with DSA, "rejection or DSA" was present in 5/8 of "Not-TX" and 4/9 of "TX" groups (p=0.4). dd-cfDNA >1% was seen in 1/6 of "Not-TX" and 2/17 of "TX" cases, and 2/6 and 8/17, respectively, had values >0.5% (p=0.46). Comparing dd-cfDNA >0.5% and TruGraf, the former had 3/6 vs 4/6 negative results in absence of "rejection or DSA"; while positive results in presence of "rejection or DSA" was seen in 4/6 vs 2/6, respectively.

Conclusions: These preliminary observations in our cohort suggest that TruGraf could be a useful non-invasive tool for monitoring of allograft status in kidney transplant recipients. With implementing protocolized use of this test in our center along with dd-cfDNA and DSA screening at various time points, we will continue to prospectively collect data, and will be able to better define its utililty in our center toolbox.

Funding: Clinical Revenue Support

PO2174

Sparse Intragraft Molecular Classifiers for Antibody-Mediated and T Cell-Mediated Kidney Transplant Rejection: Development, Validation and Clinical Value

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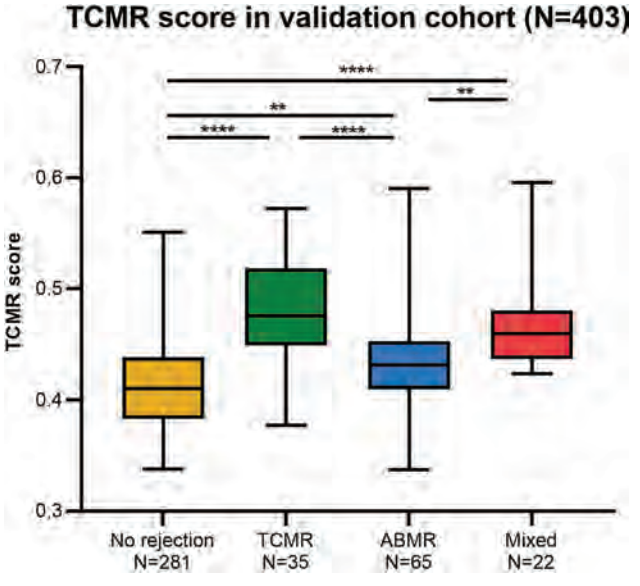
Background: Although the transcriptional landscapes of antibody-mediated rejection (ABMR) and T-cell mediated rejection (TCMR) have been largely elucidated, applying these gene signatures in transplant clinics is hampered by the large number of features and difficult integration with histological findings. We aimed to develop and validate a sparse molecular classifier for ABMR and TCMR.

Methods: In a discovery cohort of 224 kidney transplant biopsies, microarray gene expression was applied to build two separate prediction models for presence of ABMR or TCMR. Variable selection for logistic regression was performed by lasso regularization. The diagnostic accuracy and prognostic value of the obtained ABMR and TCMR classifiers were assessed in two external validation cohorts.

Results: From the discovery cohort, a 2-gene ABMR classifier (*PLA1A, GNLY*) and 2-gene TCMR classifier (*IL12RB1, ARPC1B*) were derived. In the first validation cohort (N=403 biopsies), diagnostic accuracy was retained for both ABMR (ROC-AUC 0.80, 95% CI 0.75-0.85) and TCMR (ROC-AUC 0.83, 95% CI 0.77-0.89), also allowing discrimination between pure and mixed phenotypes. In the second validation cohort (N=282 biopsies), molecular ABMR and TCMR scores predicted graft failure (respective time-integrated AUC of 0.82 and 0.83) and identified kidneys at risk for graft failure which were not picked up by routine histology.

Conclusions: We identified and validated an intragraft 2-gene ABMR classifier and 2-gene TCMR classifier that can be used as diagnostic and prognostic tools. Robust variable selection models can yield parsimonious molecular classifiers for kidney transplant rejection, facilitating their interpretation and clinical implementation.



PO2175

Evolving Experience with TruGraf® Gene Expression Profile and TRAC™ Donor-Derived Cell-Free DNA Testing in Kidney Transplantation: First Year Post Transplant and Beyond

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Background: Non-invasive validated rejection biomarkers are available to monitor kidney transplant recipients (KTR). Our program has replaced 3 and 12 month protocol biopsies (BX) with biomarker surveillance using TruGraf (TG) gene expression profile (GEP) validated to rule out subclinical acute rejection (subAR) and TRAC donor derived cell free DNA (dd-cfDNA) as a marker of allograft injury. This is the evolving single center experience of TruGraf-TRAC surveillance for KTR within the 1st year post-transplant (post-txp) and beyond

Methods: Our immunosuppression (IS) protocol is alemtuzumab with tacrolimus maintenance, mycophenolate mofetil added in high risk KTR. TG and TRAC were done at 3, 12 months post-txp, and with IS changes (mTORi/belatacept conversion, IS decrease). Additionally, all KTR to be tested at least once to determine baseline status (immune quiescence). A positive (pos) TG, TRAC, or dynamic changes in post-op course prompts further evaluation and/or repeat TG/TRAC testing PRN. BX were done in cases with equipoise. Donor specific antibodies (DSA) tested in all patients.

Results: To date, 115 KTRs surveilled with TG and/or TRAC (149 TG and 90 TRAC tests). 30/41 KTR spared 3-month BX. Of 11 BX, 6 were for delayed/slow graft function (negative (neg) TG (Transplant eXcellence (TX)) and neg for acute rejection/DSA) and 5 were for pos TG (not-TX) with 3 neg for DSA/acute rejection. 12/16 KTRs avoided 1-year BX. 45 KTRs were > 1 year post-txp at testing (16 KTR > 10 years, 8 KTR >20 years). Table 1: TG/TRAC concordance (n=82). 45% concordant neg, confirming IS adequacy. 50% discordant (TG or TRAC pos) prompting eval and correlation with findings (DSA, proteinuria, renal function). 5% concordant pos prompting BX, diagnosis, and/or subAR treatment.

Conclusions: Non-invasive TruGraf GEP with TRAC dd-cfDNA spares protocol BX in KTR at 3 and 12 months, while providing enhanced monitoring >1 year post-txp by ruling out subAR and assuring IS adequacy. Combined TruGraf and TRAC testing is promising, warranting larger studies for optimal synergy/frequency of serial testing, especially as subAR persists beyond the 1st year post-txp.

TruGraf-TRAC Concordance

KTR (n=82)	TruGraf neg (TX)	TruGraf pos (not-TX)
TRAC neg (<0.7%)	37	16
TRAC pos (≥0.7%)	25	4

PO2176

LIMS1 Risk Genotype and Clinicopathological Features of Kidney Transplant Recipients

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Background: LIM Zinc Finger Domain Containing 1 (*LIMS1*) homozygous risk genotype (rs893403 GG) is associated with increased risk of T-cell mediated rejection (TCMR) after kidney transplantation (KTx). However, prior studies lack detailed histopathological data. We examined the association of *LIMS1* genotype with histopathology of allograft rejection.

Methods: A total of 110 KTx recipients underwent allograft biopsy were genotyped for *LIMS1* rs893403 variant by Sanger sequencing followed by PCR confirmation of the deletion. The 2013 Banff scores from allograft biopsies were compared between recipients homozygous for *LIMS1* rs893403 genotype GG (n=24) versus AA/AG genotypes (n=86).

Results: There were no differences regarding demographic, clinical and laboratory features between the genotype groups (Table 1). Allograft biopsies were performed after a median 6.2 years after KTx. Serum creatinine, proteinuria and donor specific antibody levels at the time of biopsies were similar between groups. Banff median tubulitis score was significantly higher in GG group compared to AA/AG group (1.42±0.65 vs 1.12±0.66, p=0.03) (Figure 1). There were also no significant differences regarding histopathological diagnosis between the groups (Table 1).

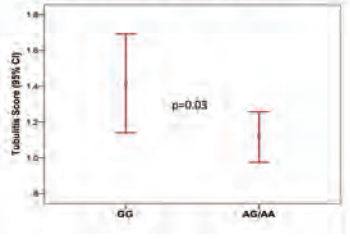
Conclusions: Kidney transplant recipients with homozygous *LIMS1* deletion had higher tubulitis scores. Our data supports the role of *LIMS1* locus in the pathophysiology of allograft rejection and motivates ongoing work to elucidate mechanisms of association of *LIMS1* risk genotype and allograft injury.

Table 1. Demographic, clinical and histopathological characteristics of study groups based on *LIMS* gene rs893403 genotype.

	GG genotype (n=24)	AA/AG genotype (n=86)	p value
Age (years), mean±SD	30 ± 12	32 ± 12	0.41
Gender (M/F), n (%)	18 (75%) / 6 (25%)	49 (57%) / 37 (43%)	0.11
Donor gender (M/F), n (%)	16 (67%) / 8 (33%)	47 (55%) / 39 (45%)	0.29
Donor type (living/deceased), n (%)	17 (71%) / 7 (29%)	70 (81%) / 16 (19%)	0.26
HLA mismatches, mean±SD	3.4 ± 1.1	3.0 ± 1.2	0.07
Biopsy time after KTx (years), median (IQR)	7.6 (4.0-12.8)	5.4 (1.9-12.8)	0.35
Serum creatinine (mg/dL), median (IQR)	2.2 (1.5-2.5)	2.2 (1.68-2.8)	0.84
Proteinuria (g/day), median (IQR)	0.25 (0.03-1.43)	1 (0-2.5)	0.33
DSA, n (%)	11 (45.8%)	30 (34.9%)	0.33
Baseline biopsy results			
Tubulitis score ≥1, n (%)	24 (100%)	77 (89.5%)	0.09
Tubulitis score, median (IQR)	1 (1-2)	1 (1-1)	0.03
Interstitial inflammation ≥1, n (%)	21 (87.5%)	70 (91.9%)	0.51
Interstitial inflammation, median (IQR)	1 (1-2)	1 (1-2)	0.42
Microcirculation inflammation (glomerulitis + ptc) score, median (IQR)	2 (1-4)	1 (0-3)	0.26
Transplant glomerulopathy ≥1, n (%)	9 (37.5%)	33 (38.4%)	0.94
Transplant glomerulopathy, median (IQR)	0 (0-1)	0 (0-1)	0.77
Rejection types and categories			
Acute/active TCMR, n (%)	10 (42%)	22 (26%)	0.13
Acute/active ABMR, n (%)	10 (42%)	33 (38%)	
Chronic/active ABMR, n (%)	4 (17%)	11 (14%)	0.79
C4d positive AMBR, n (%)	11 (46%)	24 (28%)	0.09
Banff borderline lesion, n (%)	3 (13%)	16 (19%)	0.48
TCMR + ABMR, n (%)	4 (17%)	7 (8%)	0.22

Abbreviations: F: female, HLA: human leukocyte antigen, IQR: interquartile range, M: male, ptc: peritubular capillaritis, SD: standard deviation

Figure 1. Banff tubulitis scores of patients with *LIMS1* rs893403 genotypes



PO2177

Association of Vascular Endothelial Growth Factor Gene Polymorphism with Allograft Survival in Renal Transplant Recipients

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Background: Endothelial cell dysfunction is a primary cause for late allograft loss in renal transplantation recipients. Vascular Endothelial Growth Factor (VEGF) is a pro-angiogenic factor that has an important role in the development and maintenance of physiological function of endothelium cell thus may determines the allograft function.

Methods: We did genotyping of VEGF SNPs among 320 renal allograft recipients(non-rejecters (160) and rejecters (160)) and 160 donors by PCR- RFLP technique. Intragraft VEGF mRNA and protein expression were analyzed by RT-PCR and immunohistochemistry. Serum VEGF level were analyzed by ELISA.

Results: On comparison between donors and recipients genotypes of VEGF +936 C>T [CT (OR=7.16; 95% CI=4.33- 11.84; P=0.00) and TT (OR=49.30; 95% CI=11.84-205.29; P=0.00)], -1154 G>A [AG (OR=2.22; 95% CI=1.40-3.50; P=0.00)], -1190G>A [GG (OR=2.21; 95% CI=1.22-4.01; P=0.00)], -634C>G [GG (OR=2.34; 95% CI=1.34-4.10; P=0.00)], -2549 18bp Insertion/Deletion [ID (OR=1.58; 95% CI=1.01- 2.46; P=0.04) were significantly associated with risk of rejection. On comparing mutant genotypes between non-rejecters and rejecters we found that genotypic frequencies of +936 C>T [TT (OR=2.43; 95% CI=1.33-4.44; P=0.004)], -1154 G>A [GG (OR=1.94; 95% CI=1.03-3.67; P=0.04)], -1190G>A [GA (OR=1.83; 95% CI=1.07-3.13; P=0.02)], -2549 18bp Insertion/Deletion [ID (OR=2.35; 95% CI=1.38- 3.99; P=0.002) and -1455T>C [TT (OR=3.13; 95% CI=1.07-9.10; P=0.03)] shown risk of allograft rejection whereas mutant genotypes of -2578 C>A [CA (OR=0.45; 95% CI=0.26-0.79; P=0.005) and CC (OR=0.23; 95% CI=0.11-0.46; P=0.000)] and +405 C>G [GG (OR=0.43; 95% CI=0.20-0.91; P=0.02)] have shown protective association with rejection. The VEGF mRNA expression was also significantly higher in rejecters compared to non-rejecters which both were higher compared to healthy donor. Mean serum VEGF levels was higher in rejecters compared to non-rejecters, which both were higher than those of donors. On IHC percentage of VEGF staining in glomerular capillaries and cortical peritubular capillaries was higher in rejecter as compared to non-rejecter.

Conclusions: The present study signifies genetic associations of all the mutant genotypes of VEGF +936 C>T, -1190G>A, -2549 18bp Insertion/Deletion, and -1455T>C SNPs to be at increased risk for renal allograft rejection.

Funding: Government Support - Non-U.S.

PO2178

Machine Learning and Bioinformatics Approaches to Discover Urine Gene Expression Biomarkers for Kidney Transplant Rejection

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Background: While transplant biopsies are safe and accurate way for monitoring transplant progress, they are associated with defined risks and significant costs. Using the mRNA from urine, we proposed a non-invasive approach to diagnose acute rejection. The multi-step approach involved collection and mRNA analysis of urine samples, application of a machine learning algorithm to select an initial set of gene markers, adding known markers from prior work, and using the combined set for developing a final classifier. The classifier was developed on a training data consisting of 42 samples (17 rejection and 15 control) and a validation data set of 43 samples (13 rejection and 30 control).

Methods: RNA from urine samples was hybridized to customized NanoString panel, consisting of 796-gene Immune Profiling gene panel and 26 genes representing graft rejection or the development of fibrosis from published works. The RNA samples were processed on the nCounter GEN2 using the high sensitivity protocol and high-resolution data capture. Raw data were imported into nSolver4.0 (NanoString) followed by $\log_2$ gene counts and normalized data generation that was used in further analyses.

Results: Using Random Forest on NanoString data we first obtained a set of eight gene as our initial pool of markers. We combined them with the 20 gene markers from our previous work and developed a seventeen gene classifier (after removing duplicates and non-important genes). The combined signature of 17 genes had high AUC (0.875), accuracy (0.881), sensitivity (0.765), specificity (0.96), PPV (0.929) and NPV (0.857) on training data. Although the PPV dipped to 0.714 in the validation data, it still performed well resulting in high accuracy (0.84), sensitivity (0.77), specificity (0.87) and NPV (0.90).

Conclusions: This initial hybrid modeling approach has shown its significance and we plan to further strengthen its reliability and test robustness by incorporating more samples. The final classifier, a non-invasive approach to classify kidney graft heath, could help improve serial monitoring of graft recipients while reducing the cost and safety risks associated with biopsies.

Funding: Other NIH Support - NIAID, Commercial Support - Eurofins-Viracor

PO2179

Discovery of Cellular and Genetic Signatures of Immune Tolerance in Kidney Transplant Recipients Through Single-Cell RNA Sequencing Analysis

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Background: Immune tolerance, defined by maintaining stable allograft function without immunosuppression after transplantation, is the ultimate goal of kidney transplant. Unlike bulk transcriptional analysis, single cell RNA sequencing (scRNA-seq) allows us to profile gene expression at the heterogeneous individual cell level. We aimed to investigate the difference of cellular and genetic signatures of immune tolerance in kidney transplant recipients (KTRs) through scRNA-seq analysis.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 13 KTRs with immune tolerance (Tolerance, n=5), biopsy-proven allograft rejection (Rejection, n=4), and stable allograft function on maintenance immunosuppression (Stable, n=4) at 4 different transplantation centers. We used 20 cell surface marker antibody sequencing to cluster cell subsets, and 399 immune response panel to identify genetic expression difference at a single cell level. Single-cell distribution was visualized on UMAP plot.

Results: We generated 16,784, 10,180 and 7,280 single-cell transcriptomes of PBMCs from Tolerance, Rejection, and Stable groups, respectively. Ten known immune cell subsets were identified using cell surface marker antibody. Heatmap hierarchical clustering showed distinct differential cell surface marker expression in Tolerance group in comparison with other groups. The fractions of B cells and regulatory T cells in peripheral blood were increased in Tolerance group. B cell subsets showed that *Ybx3 (Y-BOX binding protein 3)* was downregulated in Tolerance group, compared with Rejection (fold change 0.12) and Stable group (fold change 0.30). *S100A9 (S100 calcium binding protein A9)* was highly expressed in Regulatory T cell subset of Tolerance group, compared with Rejection group (fold change 0.05).

Conclusions: It is the first study to identify difference in cellular distribution and genetic expression of immune tolerance in KTRs at single-cell resolution so far. Taken together with further scRNA-seq analysis of immune tolerance, it would provide us a better understanding of the mechanism and offer biomarkers to develop immune monitoring strategy, and allow cessation of immunosuppression.

PO2180

Can a Combination of Blood Gene Expression and Donor-Derived Cell-Free DNA Improve Detection of Acute Rejection in Stable and Unstable Kidney Allograft Recipients?

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Background: Non-invasive biomarkers for the detection of acute clinical rejection or subclinical acute rejection (subAR) have shown modest diagnostic performance. Therefore, we hypothesized that a combination of gene expression profile (GEP) and donor-derived cell-free DNA (dd-cfDNA) would improve the diagnostic performance.

Methods: We analyzed 559 blood samples paired with kidney biopsies from CTOT-08 study. GEP probability scores were analyzed as both binary and continuous variables. GEP probability scores >50 were considered positive. dd-cfDNA results > 0.7 % were considered as positive for binary analysis. We calculated the area under the receiver operating characteristics (AUROC) for each test and the combination of both tests. We conducted a logistic regression to assess the performance of combined GEP and dd-cfDNA scores as continuous variables.

Results: 153 rejections consisted of 50 clinical and 103 subclinical rejection cases. Among 406 non-rejection cases, 81 cases had an acute elevation of creatinine, and 325 cases had stable kidney function. For binary analysis, dd-cfDNA showed better positive predictive value (PPV, 0.58, 95% CI 0.48-0.67) than GEP alone (0.49, 95% CI 0.41-0.58). When both tests were positive, PPV went up to 0.75 (95% CI, 0.61-0.88). GEP (0.82, 95% CI 0.78-0.86) and dd-cfDNA alone (0.81, 95% CI 0.77-0.85) had similar NPV. The NPV improved to 0.88 (95% CI, 0.84-0.92) when both assays were negative (Table 1). The logistic regression combining both continuous assay scores achieved an AUROC of 0.80 significantly higher than 0.75 (GEP alone, p-value <0.001) and 0.72 (dd-cfDNA alone, p-value <0.01).

Conclusions: Combining the GEP and dd-cfDNA can improve the ability to distinguish acute rejection in both stable and unstable patients.

Funding: Commercial Support - Viracor-Eurofins

Table 1) Diagnostic performance of GEP and dd-cf DNA for acute rejection including subAR

	GEP alone (>50)	dd-cfDNA alone (>0.7%)	Positive = GEP+ or dd-cfDNA	Positive = GEP+ AND dd-cfDNA+
Sensitivity (95% CI)	0.54 (0.44-0.63)	0.45 (0.35-0.55)	0.75 (0.66-0.83)	0.24 (0.17-0.31)
Specificity (95% CI)	0.79 (0.74-0.84)	0.88 (0.84-0.91)	0.70 (0.65-0.75)	0.97 (0.95-0.99)
PPV (95% CI)	0.49 (0.41-0.58)	0.58 (0.48-0.67)	0.49 (0.41-0.56)	0.75 (0.61-0.88)
NPV (95% CI)	0.82 (0.78-0.86)	0.81 (0.77-0.85)	0.88 (0.84-0.92)	0.77 (0.73-0.81)

PO2181

Lymphocyte Subpopulations in Clinical Practice After Kidney Transplantation: B Cell Levels Predict Renal Function at 1 Year

Giorgia Comai, Valeria Corradetti, Gisella Vischini, Federica Maritati, Claudia Bini, Gaetano La Manna. *Nephrology, Dialysis and Kidney Transplantation Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*.

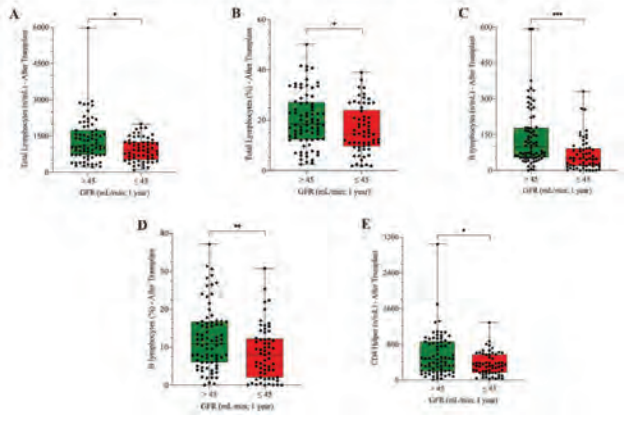
Background: Lymphocytes subpopulations play a key role in the immune response after kidney transplantation. Many different T-lymphocyte have been studied for their suitability to monitor allograft rejection. B cells have been associated with acute and chronic antibody mediated rejection and with poor outcome after transplant but are associated with tolerant kidney transplant recipients.

Methods: We retrospectively analyze the lymphocyte subpopulation (total lymphocyte, CD3+, CD4+, CD8+, NK, CD20+) pre transplant, after 1 week, at discharge and after 2 months post transplant in a cohort of kidney tranpslant recipients and we evaluate the impact of this subsets on kidney outcome.

Results: 187 kidney transplant recipients were included in the study and a total of 748 samples were analyze. We didn't find any association between lymphocyte subsets and delayed graft function, primary non function and graft rejection. We found an association between low level of B lymphocyte at 2 months and 1-year GFR less than 45 ml/min (Figure 1 and 2). Multivariate analysis including donor age, cold ischemia time, rejection, recipient age, induction theraphy and steroid withdrawal confirm these finding.

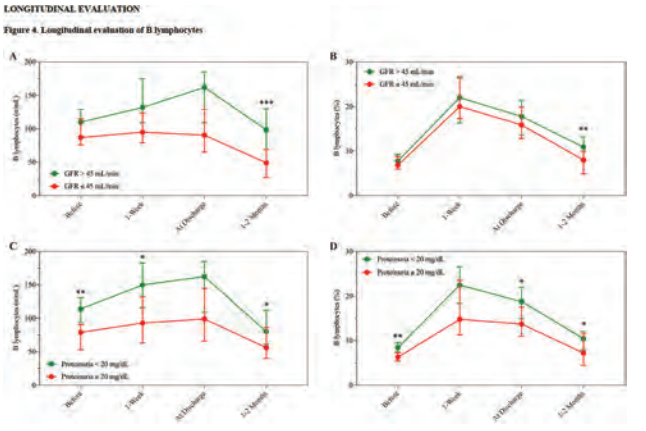
Conclusions: Low level of B lymphocyte at 2 months post transplant is associated with poor graft oucome suggesting that these finding may predict a worse renal function at 1 year. The changes in lymphocyte subset after transplant could represent an early outcome marker usefull to personalized immunosuppressive therapy.

Figure 1 – Analysis of lymphocyte subpopulations after stratification for GFR at 1 year



LONGITUDINAL EVALUATION

Figure 4. Longitudinal evaluation of B lymphocytes



PO2182

Inflammatory Profile Associated with Non-HLA Antibodies to G-Protein Coupled Receptors in Pediatric Kidney Transplant Recipients

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Background: The inflammatory profiles associated with non-HLA antibodies to G-protein coupled receptors in kidney transplant recipients (KTRs) are unknown. We have recently shown that angiotensin II type 1 receptor antibody (AT1R-Ab) and Endothelin-1 Type A receptor antibody (ETAR-Ab) are prevalent and associated with poor clinical outcomes and elevations in TNF-α, IL-1β, IL-8, IFN-γ, IL-17, and IL-6 in pediatric KTRs. We aimed to expand this analysis by examining the association between these non-HLA antibodies and a broad panel of inflammatory markers in a different cohort of pediatric KTRs.

Methods: 157 blood samples from 35 pediatric KTRs followed for 2 years post-transplant were analyzed. ETAR-Ab (ELISA), AT1R-Ab (ELISA), and 38 cytokines (Luminex, Table 1) were measured in blood samples taken at 6 months (m), 12m, and 24m post-transplant and during episodes of rejection. Based on previous receiver operating curve analysis, > 10 and >17 units/ml was considered positive for ETAR-Ab and AT1R-Ab. Patients were serially monitored for viral infections (CMV, EBV, and BK Virus), HLA DSA (Luminex), and rejection (protocol and indication biopsies).

Results: Blood samples positive for AT1R-Ab and ETAR-Ab had elevations in 28 of 38 cytokines (Table 1). On principal component (PC) analysis, AT1R-Ab and ETAR-Ab positivity was highly associated with differences in PC1. This relationship remained significant even when controlled for potential confounders, including age, sex, rejection, viral infections, and HLA DSA status ($p<0.001$, Figure 1).

Conclusions: AT1R-Ab and ETAR-Ab positivity is associated with a distinct inflammatory profile in pediatric KTRs in the first 2 years post-transplant. This distinct profile may help inform mechanistic studies and potentially identify new therapeutic targets to treat non-HLA associated allograft injury.

Funding: Other NIH Support - NIAID, Private Foundation Support

Cytokine (pg/mL) Median [IQR]	AT1R and ETAR-Ab Antibody Positive (n=67)	Antibody Negative (n=90)	P-value
IL-6	213.3 (52.5-422.8)	13.2 (5.6-40.2)	<0.001
IL-1beta	6.9 (3.4-10.7)	0.6 (0.3-1.6)	<0.001
IFN-gamma	13.6 (7.2-24.4)	5.4 (2.5-9.6)	<0.001
IL-8	47.2 (22.0-81.2)	8.3 (4.8-17.9)	<0.001
FGF2	163.3 (116.2-221.4)	88.5 (62.6-117.3)	<0.001
TGFA	4.7 (2.9-10.6)	2.0 (1.2-3.8)	<0.001
GCSF	77.1 (23.0-151.8)	9.4 (3.4-40.7)	<0.001
GM-CSF	19.2 (12.1-31.0)	7.5 (2.6-12.8)	<0.001
IFNA2	14.3 (6.4-29.1)	1.0 (1.0-4.2)	<0.001
IL-10	36.7 (20.4-54.3)	23.1 (17.0-33.4)	<0.001
MCP3	176.4 (132.6-234.9)	49.5 (23.0-81.8)	<0.001
IL-12p40	29.5 (18.1-43.1)	13.8 (7.8-22.2)	<0.001
IL-12p70	10.8 (4.8-28.3)	2.0 (0.4-4.1)	<0.001
IL-13	50.3 (8.5-110.9)	2.8 (0.7-9.2)	<0.001
IL-15	9.6 (7.1-14.0)	5.4 (3.9-7.7)	<0.001
IL-17a	5.1 (3.0-9.6)	1.0 (0.0-2.5)	<0.001
IL-1ra	113.6 (60.3-196.3)	49.6 (32.1-100.9)	<0.001
IL-1a	197.3 (91.1-380.8)	4.8 (0.5-24.4)	<0.001
IL-9	31.1 (10.2-71.3)	2.8 (1.9-6.9)	<0.001
IL-2	1.0 (0.0-3.7)	0.0 (0.0-0.0)	<0.001
IL-4	1503.0 (208.7-3613.5)	15.8 (2.1-221.7)	<0.001
IL-5	22.1 (8.5-47.3)	2.6 (1.3-5.0)	<0.001
IL-7	13.5 (7.4-19.5)	3.0 (1.0-6.8)	<0.001
TNF-b	306.2 (56.0-717.2)	12.1 (0.7-54.1)	<0.001
VEGF	129.4 (84.4-157.1)	89.0 (5.9-70.5)	<0.001
Fractalkine	224.4 (89.6-279.9)	67.0 (32.4-105.3)	0.002
MIP-1a	3.1 (1.1-4.0)	0.1 (1.1-3.1)	0.009
MIP-1b	21.9 (16.5-34.3)	15.7 (10.5-27.2)	0.015
GRO	780.9 (416.0-1391.0)	1075.5 (579.0-1839.5)	0.071
TNF-alpha	25.9 (17.1-42.3)	24.3 (18.2-33.1)	0.166
FLT3L	47.7 (37.0-75.0)	51.7 (36.1-55.1)	0.274
EGF	39.5 (24.5-72.3)	46.7 (24.8-72.4)	0.548
MCP1	620.3 (394.6-957.9)	657.7 (467.1-848.5)	0.799
IP10	503.5 (375.7-992.1)	550.0 (427.4-911.2)	0.864
Eotaxin	258.5 (199.6-340.8)	241.5 (184.5-290.5)	0.885
SCD40L	765.0 (378.7-1182.5)	629.2 (376.3-1062.5)	0.892
MDC	553.5 (409.6-872.7)	579.8 (443.5-881.7)	0.997
IL-3	1.3 (1.3-1.3)	1.3 (1.3-1.3)	1.000

Table 1: Median Cytokine Levels in Blood Samples AT1R and ETAR Antibody Positive vs. Negative. 28 of 38 cytokines were elevated in antibody positive samples. P-value for mixed effects models controlled for patient shown.

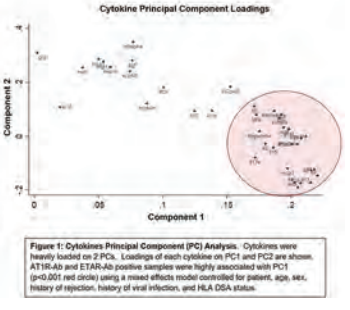

Figure 1: Cytokines Principal Component (PC) Analysis. Cytokines were heavily loaded on 2 PCs. Loadings of each cytokine on PC1 and PC2 are shown. AT1R-Ab and ETAR-Ab positive samples were highly associated with PC1 ($p<0.001$ red circle) using a mixed effects model controlled for patient, age, sex, history of rejection, history of viral infection, and HLA DSA status.

PO2183

Immunoglobulin G (IgG) Glycosylation, Renal Function, and Antibody-Mediated Rejection in Renal Transplant

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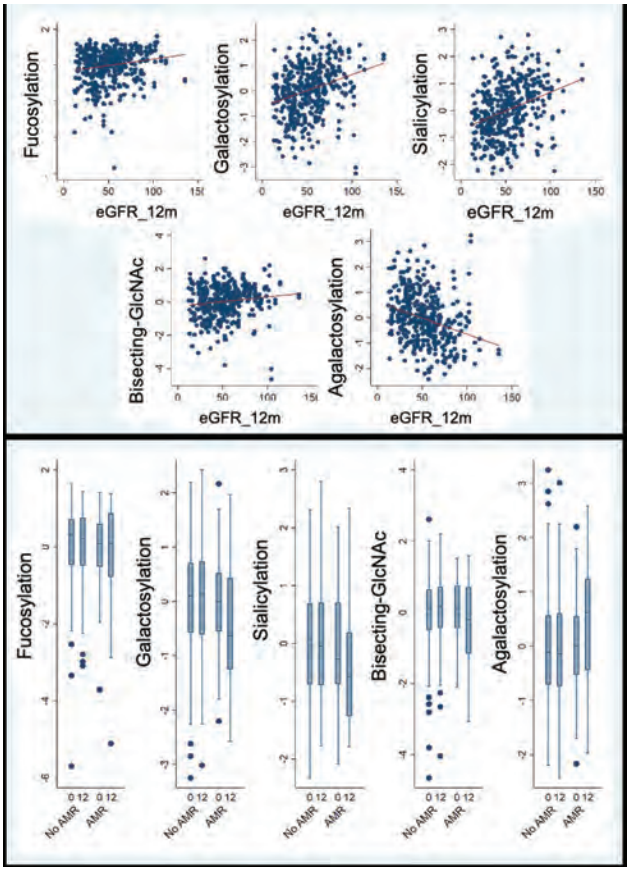
Background: IgG glycome composition is a key regulator of immune system modulating inflammation at multiple levels. It has been associated to aging, infections response, autoimmune diseases or early kidney failure. Its role in KT has not been studied. Our aim was to analyze the prognostic and diagnostic value of IgG_glycans in renal function after 1year of KT and in antibody-mediated rejection (AMR)

Methods: We analyzed 24 essential IgG glycans by Highperformance LiquidChromatography grouped them by biological function, according to the proportion of Galactosylated, Agalactosylated, Sialicylated, Fucosylated and Bisecting-GlcNAc structures. We measured baseline IgG_glycans and one year after KT in 248 recipients (62%M:38%M) of 55.9±13.6 years, 36 with AMR. Association models were adjusted by donor characteristics, baseline renal function, age/sex, BMI, ATN-postKT and comorbidities

Results: Differences between IgG_glycans at baseline and 1year values were associated with the achieved renal function: Higher Sialization (Coeff [95% CI] 2.07 [0.23-0.3.9]) and Galactosylation (1.84 [0.0-3.6]), the better renal function and higher proportion of agalactosylated glycans associated worse renal function -2.02 [-4.1- -0.34]. AMR occurred more frequently in patients with a higher proportion of Agalactosylated glycans (OR [95% CI]) 1.7 [1.15-2.51] and less in those with a greater proportion of Galactosylates 0.59 [0.4-0.87], Sialicylates 0.67 [0.45-0.9] and Bisecting-GlcNAc 0.66 [0-45-0.99] (*Figure*)

Conclusions: Glycans, that modulate the IgG function, are a potential prognostic tool for renal function in KT and as a diagnostic support in the identification of patients who develop AMR



PO2184

A Possible Effect of Glucagon-Like Peptide 1 Receptor Enhancement on Graft Kidney Function

Tetsuhiko Sato, Yoshinori Azuma, Yasuhiro Otsuka, Norihiko Goto, Shunji Narumi, Asami Takeda, Takahisa Hiramitsu, Manabu Okada, Kiyomi Osako, Yoshihiko Watarai. *Nagoya Daini Sekijuji Byoin, Nagoya, Japan.*

Background: Successful kidney transplantation (KTX) has revolutionary improved comorbidities related to diabetic kidney disease in type 2 diabetic patients. Enormous evidence has accumulated that incretin enhancer, glucagon-like peptide 1 receptor agonists (GLP-1RAs) have potential to boost native kidney function. However, little is known about a possible protective effect of its use on graft kidney function.

Methods: We conducted an observational cohort study to investigate the association between the use of GLP-1RA versus other antidiabetic medications (Non-GLP-1RA), and the 4-year risk of sustained eGFR decline (4 straight month-40% decrease from baseline) in consecutive kidney transplant recipients (KTRs) with type 2 diabetes who underwent KTX in our center from January 2012 through December 2018. Included were all KTRs with type 2 diabetes who were followed forward in time from month 1 post-transplant for 24 months or longer at the time of December 31, 2020. We calculated the propensity score of initiating GLP-1RA versus Non-GLP-1RA as a function of baseline covariates using logistic regression. Inverse probability of treatment weighting was generated from the propensity score and treatment-weighted odds ratio was estimated between the two treatment groups to better control for baseline confounding variables including presence or absence of protocol biopsy-proven interstitial fibrosis/tubular atrophy 1 month after KTX. Sodium-glucose cotransporter 2 inhibitors medication was treated as competing event.

Results: Seventy three were identified as GLP-1RA users, 73 were on Non-GLP-1RA medications, and no deaths with graft function were observed during the study period. There were 6 sustained eGFR decliners in Non-GLP-1RA group whereas 1 in GLP-1RA group. According to multivariate analysis, GLP-1RA use after KTX was associated with a lower risk of sustained eGFR reduction (weighted odds ratio, 0.105; 95% confidence interval, 0.012-0.961).

Conclusions: GLP-1RA initiation and continuous use had a lower eGFR decline compared with other antidiabetic medications and may contribute to better kidney graft survival after KTX.

PO2185

Impact of Low-Normal vs. High-Normal Baseline Donor-Derived Cell-Free DNA Levels on Two-Year Allograft Function Following Kidney Transplantation

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Background: Donor derived cell free DNA (dd-cfDNA) is a biomarker that helps to predict acute rejection in kidney allografts. Baseline dd-cfDNA levels are <1% in 96% of kidney transplant recipients (KTRs) and a value ≥ 1% suggests allograft injury usually from acute rejection. dd-cfDNA levels <1% are considered as normal. We tested whether low-normal vs. high-normal baseline dd-cfDNA values would have differing impact on longitudinal allograft function.

Methods: We identified patients who underwent kidney transplantation at our center between September 2017 and June 2020 and had dd-cfDNA (AlloSure, CareDx, Brisbane, CA) levels under the surveillance protocol at or around 8 weeks post-transplantation. Those KTRs with dd-cfDNA levels <1.0% were included in the analysis. Patients were divided into 2 groups based on the dd-cfDNA levels : group 1 with dd-cfDNA <0.5% (low-normal) and group 2 with dd-cfDNA 0.5-0.99% (high-normal). Estimated glomerular filtration rates (eGFR) between the groups at 3 month intervals were compared using box plots and longitudinal eGFR up to 2 years post-transplant were compared between the groups using lineal mixed model.

Results: There were 111 patients included in the analysis including 62 males and 49 females. Among the study group, 39 had living and 72 received deceased donor kidneys. There were 96 patients in group 1, and 15 patients in group 2. We observed no differences either in 3-month interval cross-sectional eGFRs (fig 1A) or 2 -year longitudinal eGFRs (fig 1B) between the groups.

Conclusions: Our analysis found no differences between early post-transplant low-normal and high-normal baseline dd-cfDNA levels in terms of the impact on eGFR up to 2 post-transplant years in KTRs. These findings support the use of 1% cut off as a threshold to separate normal from abnormal dd-cfDNA levels.

Funding: Commercial Support - CareDx

Figure 1A: Box plots of eGFR at 3 month intervals for ddcfDNA <0.5% vs 0.5-0.99%

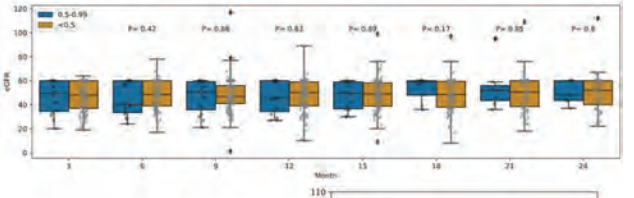
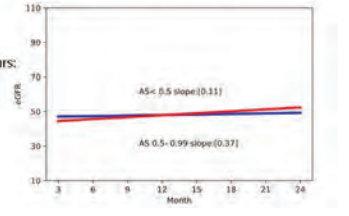


Figure 1B: eGFR (ml/min) slopes over 2 years: 8 wk ddcfDNA <0.5__ vs 0.5-0.99__



PO2186

Baseline Trends in Tacrolimus Intrapatient Variability in Pediatric Kidney Transplant Patients

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Background: High tacrolimus intrapatient variability (IPV) is a known risk factor for inferior graft outcomes in kidney transplant patients. Baseline trends in tacrolimus intrapatient variability have not been well-defined in pediatric kidney transplant patients.

Methods: Pediatric patients who received a kidney-only transplant from 2010-2018 at a single center were considered for inclusion. Patients with follow-up time of at least 1 year were included. Tacrolimus IPV was determined using the mean coefficient of variation over the immediate 6-month time period prior to each tacrolimus level at each year post-transplant. All available tacrolimus levels were included in the analysis. Patients were stratified by age at time of transplantation (ages 1-6, 7-12, 13-18 years). A paired t test was performed to evaluate the IPV change with increasing time post-transplant, with a specific post-transplant year tested against the prior year for each age group.

Results: 220 pediatric kidney transplant patients met inclusion criteria. Median age was 12.8 years. 117 patients (53.2%) were male, and 54 (24.5%) underwent living donor kidney transplant. IPV trends varied by age group, but IPV was high for all groups during the first year. After the first year, IPV decreased over time for patients in the 1-6 years group while it increased for those in the 7-12 and 13-18 years groups (Figure 1).

Conclusions: Tacrolimus IPV patterns differ in pediatric kidney transplant patients based on age at time of transplantation. It is likely that in the youngest group of patients, factors other than nonadherence explain their initial prolonged high IPV. More research is needed to quantitate and better understand the factors influencing variability in children given the association between IPV and adverse graft outcomes.

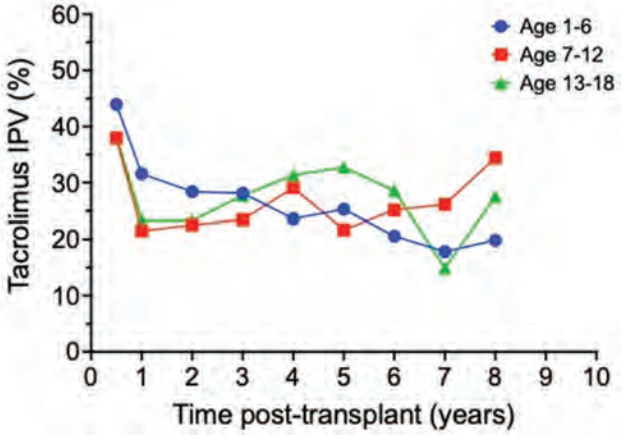

Figure 1. Tacrolimus intrapatient variability (IPV) trends over time post-transplant for different age groups

PO2187

The Impact of Intrapatient Tacrolimus Trough Level Variability over 2 Years Post Transplant on the Long-Term Allograft Outcomes in Kidney Transplant Recipients

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Background: The current study aimed to determine the impact of tacrolimus (TAC) trough level (C0) intra-patient variability (IPV) over 2 years after kidney transplantation (KT) on allograft outcomes.

Methods: In total, 1,143 patients with low immunologic risk were enrolled. The time-weighted coefficient variability (TWCV) of TAC-C0 was calculated, and patients were divided into tertile groups (T1: <24.6%, T2: 24.6–33.7%, T3: ≥33.7%) according to TAC-C0-TWCV until post-transplant 1st year. Moreover, they were classified into the low/low, low/high, high/low, and high/high groups based on a TAC-C0-TWCV value of 33.7% during post-transplant 0–1st and 1st–2nd years. We compared the allograft outcomes among the three tertile and four TAC-C0-TWCV groups.

Results: The T3 group had the highest rate of death-censored allograft loss (DCGL), and T3 itself was an independent risk factor for DCGL (adjusted hazard ratio (HR) 1.853, P = 0.029). In addition, sustained TWCV ≥33.7% until 2 years after KT showed the highest risk for DCGL (HR 2.395, P = 0.013). Moreover, the changes in TWCV during the 1st–2nd post-transplant year significantly affect to DCGL occurrence (HR of low/high 2.086, P = 0.045, HR of high/low 1.813, P = 0.021). Patients with an average TAC-C0 of ≥5 ng/mL in the high/high group were at highest risk for DCGL as well.

Conclusions: In conclusion, TAC-IPV is an important factor that can significantly affect comprehensive allograft outcomes. TAC-IPV after 1st year of KT was also considered an important factor for allograft outcomes. Moreover, TAC-IPV can significantly affect allograft outcomes even with a high average TAC-C0.

Funding: Other NIH Support - This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI20C0317).

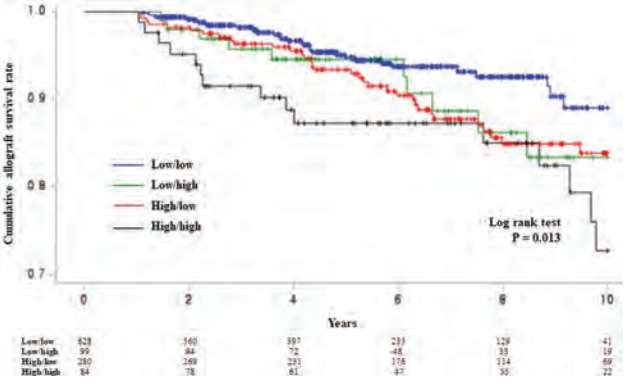

Figure 1. Kaplan–Meier survival analysis of allograft survival according to TAC-C0-TWCV during post-transplant 0–1st and 1st–2nd years

PO2188

The Balance Between Memory and Regulatory Cell Populations in Kidney Transplant Recipients with Operational Tolerance

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Background: Donor-reactive memory cells represent a barrier to long-term kidney graft survival. A better understanding of regulatory mechanisms that counterbalance alloreactive memory responses may help to identify patients with operational tolerance.

Methods: The prospective, bicentric BALANCE study investigated the equilibrium between memory T cell subsets and regulatory T or B cells (Tregs, Bregs) in peripheral blood of kidney transplant recipients with operational tolerance (N=8), chronic rejection (N=8), and different immunosuppressive treatment regimens (N=81). Patients on hemodialysis and healthy individuals served as controls (N=50). In addition, the expression of Treg- and Breg-associated molecule genes was analyzed.

Results: Patients with chronic rejection showed a disrupted memory T cell composition with a significantly increased frequency of circulating $CD8^+$ terminally differentiated effector memory (TEMRA) T cells than in patients with operational tolerance, patients on hemodialysis, or healthy controls ($P<0.001$). Compared to all other transplant recipients, the lowest ratios between $CD8^+$ TEMRA and naïve or effector T cells and the highest frequency of Tregs and transitional Bregs were found in operationally tolerant patients (for all $P=0.001$). Consequently, operationally tolerant patients showed, as compared to all other transplant recipients with different immunosuppressive regiments, the lowest ratios between $CD8^+$ TEMRA T cells and Tregs or Bregs (for both $P<0.001$). A specific peripheral blood transcription pattern was found in operationally tolerant patients with an increased expression of Breg- and Treg-associated genes *CD22* and *FoxP3* and a decreased *FcγRIIA/FcγRIIB* transcript ratio (for all $P<0.001$, as compared to all other transplant recipients).

Conclusions: Monitoring the balance between circulating $CD8^+$ TEMRA T cells and regulatory cell subsets and their transcripts may help to distinguish transplant recipients with operational tolerance from recipients at risk of graft loss.

PO2189

Steering of Immunosuppression by Virus-Specific T Cells After Pediatric Kidney Transplantation (KTx) in the Randomized Controlled IVIST Trial

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Background: Pharmacokinetic monitoring alone is insufficient to estimate the intensity of immunosuppression after KTx. Levels of virus-specific CD4 T cells(CD4Tvis) have been shown to identify overimmunosuppression. The IVIST trial has demonstrated that additional steering of immunosuppressive therapy by CD4Tvis levels is safe and reduces exposure to immunosuppressants with significantly lower trough levels but without increasing the risk of acute rejections.

Methods: In the randomized controlled IVIST trial, 64 pediatric KTx recipients were randomized 1:1 to a control group with trough level monitoring of immunosuppressants or to an intervention group with additional steering by CD4Tvis levels against adenovirus(ADV), cytomegalovirus(CMV) and herpes simplex virus(HSV). The immunosuppression consisted of cyclosporine A, everolimus and glucocorticoids. CD4Tvis were quantified by cytokine flow cytometry in 20 visits during the two-year study period. In the intervention group we have analyzed the CD4Tvis levels and the number of Tvis-based dose adjustments of immmunosuppressants.

Results: At time of transplantation, ADV-CD4Tvis were detectable in 30/31 patients (intervention group), CMV-CD4Tvis and HSV-CD4Tvis only in 12/31. No significant ADV- or HSV-DNAemia was found; only two patients showed transient CMV-DNAemia based on CMV-reactivation. Five primary CMV-infections with seroconversion and boost of CMV-CD4Tvis were observed without significant CMV-DNAemia. The mean level of ADV-CD4Tvis was 1.63(SD1.25), 2.03(SD1.8), 2.18(SD2.51) and 1.97 cells/µl(SD1.34) 1,6,12 and 24 months after KTx. In case of CD4Tvis <2cells/µl 125 dose reductions of immunosuppressants (96% based on ADV-CD4Tvis) were performed in 28/31 children with a median of 4 Tvis-based dose reductions (range 0-10) per patient. 48% of these were carried out in the first six months.

Conclusions: Under the intensified immunosuppression during the initial post-KTx period low ADV-CD4Tvis levels were observed with subsequent increase after dose reduction of the immunosuppression. ADV-CD4Tvis are most suitable for immune monitoring because of their high prevalence (even in children) and stability combined with absence of ADV-DNAemia. Routine monitoring of ADV-CD4Tvis is recommendable especially in the first post-KTx year to prematurely identify overimmunosuppression.

Funding: Government Support - Non-U.S.

PO2190

Regulatory T Cells, BK Virus Infection, and Long-Term Outcomes in Kidney Transplant Recipients

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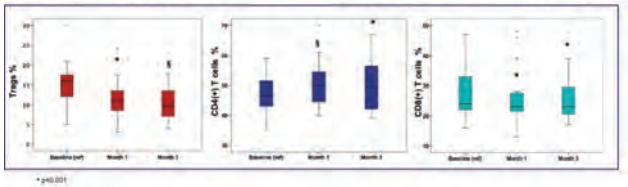
Background: Regulatory T cells (Tregs) may inhibit pathogen-specific immunity in infectious disorders. We monitored Treg levels during BK virus (BKV) viremia/viruria, examined pattern of Tregs that might contribute BKV infection, and assessed their prognostic value for the KTx outcomes.

Methods: We evaluated 20 KTx recipients (male:13, mean age:41±12 years, living donor 15) in whom BKV viremia/viruria was detected at a median 12.6 (IQR, 4.6-31.2) months after KTx. Serum and urine BKV DNA were measured by real-time PCR at baseline, 1 and 3 months after detection of BKV viremia/viruria. Lymphocyte profile and CD4(+)CD25(+)FoxP3(+) Tregs were measured by flow cytometry concurrently at these time points. Graft outcomes over 8 years were examined in relation to BK viremia, viruria levels, and lymphocyte profiles.

Results: At the time of diagnosis of BKV viremia/viruria, 17 (85%) patients were on calcineurin inhibitor (CNI)-based triple immunosuppression. CNI was discontinued in 9 patients, sirolimus was started in 3 of them. Mycophenolic acid was switched to azathioprine or the dose was decreased in all patients. Reduction in overall immunosuppression was associated with a decrease in serum and urine BKV DNA levels. Tregs and CD8(+) T lymphocytes were significantly decreased and CD4(+) T lymphocytes were increased during this period (Figure 1). After a median follow-up of 8.1 years (IQR, 3.3-8.5), 6 (30%) patients lost their allografts. There were no significant differences in mean Tregs levels between patients with and without graft failure (p=0.63). Serum and urine mean BKV DNA levels were similar between patients with and without graft failure (p=0.38 and p=0.20, respectively).

Conclusions: Tregs may play a role in BKV infection, reduction in the overall amount of immunosuppression is associated with improvement of BKV viremia/viruria accompanied by a decrease in Treg levels. Future work is needed to discriminate predictors of allograft failure in patients with BK nephropathy.

Figure 1. Tregs, CD8(+) lymphocytes were significantly decreased and CD4(+) T lymphocytes were increased during follow up.



PO2191

Expansion and Characterization of Regulatory T Cell Populations from Korean Kidney Transplant Recipients

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Background: The development of immunosuppressants has enabled remarkable progress in kidney transplantation (KT). However, current immunosuppressants cannot achieve induction of immune tolerance and their nonspecific immunosuppressive effects result in many adverse effects. Regulatory T cells (Tregs) play crucial roles in controlling allospecific immune responses. This study evaluated the distribution of Tregs and their effects on kidney allograft function in Korean KT recipients.

Methods: We enrolled 144 KT recipients with stable graft function between 1989 and 2018. Differentiation and expansion of Tregs were studied by flow cytometry to compare the Tregs subpopulations. Tregs were defined as $CD4^{+}CD25^{high}CD127^{low/-}FoxP3^{+}$ cells.

Results: Among the 144 patients, 75 patients (65.8%) were males and mean follow-up period was 144.3 ± 111.5 months. All patients received calcineurin inhibitors as maintenance immunosuppressants. Patients with follow-up period more than 144.3 months tended to have more gating Tregs numbers than that in shorter follow-up period (92.3 ± 142.4 vs. 50.1 ± 76.4, p = 0.061, respectively). There were no significant differences in Tregs subpopulations between patients with serum creatinine more than 1.5 md/dL and patients with serum creatinine less than 1.5 mg/dL. In terms of the number of Tregs, when the trough level of tacrolimus was at an appropriate level, the number of Tregs tended to be higher than that of Tregs when the trough level of tacrolimus was low or high, and the organ function of the transplant was also stable.

Conclusions: Tregs counts may be associated with transplant outcomes considering that there is a relationship between these cells and kidney graft function.

Table 2-1. Regulatory T cell subpopulation according to the patient's characteristics.

	Gating cell number	P value	Gate
Male (n=73)	76.7 ± 129.5	0.295	29.1
vs. Female (n=40)	vs. 56.6 ± 73.5		vs. 3
LDKT (n=85)	75.6 ± 121.5	0.113	32.0
vs. DDKT (n=23)	vs. 44.5 ± 72.1		vs. 3
Follow-up duration ≤ 147.5 months	50.6 ± 76.9	0.073	36.4
(n=87)	vs. 89.0 ± 138.5		vs. 2
vs. Follow-up duration > 147.5 months (n=56)			
Tacrolimus (n=70)	49.3 ± 69.4	0.095	34.3
vs. Cyclosporine (n=39)	vs. 94.7 ± 158.1		vs. 2
MMF (n=73)	65.0 ± 121.7	0.558	33.2
vs. No MMF (n=40)	vs. 78.1 ± 95.8		vs. 3
PDN (n=79)	58.1 ± 89.6	0.181	34.1
vs. No PDN (n=34)	vs. 96.3 ± 152.4		vs. 2
Tacrolimus/MMF/PDN (n=49)	44.0 ± 66.4	0.427	36.8
vs. Cyclosporine/MMF/PDN (n=9)	vs. 88.9 ± 158.8		vs. 2
Median tacrolimus level ≤ 5.7 ng/ml	56.9 ± 72.7	0.363	31.7
(n=38)	vs. 41.7 ± 66.1		vs. 3
vs. Median Tacrolimus level > 5.7 ng/ml (n=35)			
Mean tacrolimus level ≤ 5.8 ng/ml	57.6 ± 73.3	0.266	30.9
(n=39)	vs. 38.9 ± 63.8		vs. 3
vs. Mean Tacrolimus level > 5.8 ng/ml (n=31)			
Median tacrolimus dose ≤ 2.5 mg	46.6 ± 62.5	0.963	37.6
(n=36)	vs. 45.7 ± 80.2		vs. 3
vs. Median tacrolimus dose > 2.5 mg (n=22)			
Mean tacrolimus dose ≤ 2.6 mg (n=36)	46.6 ± 62.5	0.963	37.6
vs. Mean tacrolimus dose > 2.6 mg (n=22)	vs. 45.7 ± 80.2		vs. 3
Median cyclosporine level ≤ 87.7	53.5 ± 111.1	0.095	32.0
ng/ml (n=20)	vs. 138.1 ± 189.3		vs. 2
vs. Median cyclosporine level > 87.7 ng/ml (n=19)			
Mean cyclosporine level ≤ 98.1 ng/ml	52.9 ± 105.5	0.078	30.7
(n=23)	vs. 154.8 ± 201.1		vs. 2
vs. Mean cyclosporine level > 98.1 ng/ml (n=16)			

Regulatory T cell subpopulation according to the patient's characteristics.

PO2192

Diagnosis of Early Delayed Graft Function (DGF) Using TIMP-2*IGFPB-7 Product in Transplant Recipients: Preliminary Results

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Background: DGF is acute kidney injury (AKI) defined as need for dialysis within one week of renal transplant. AKI is defined by a change in serum creatinine (SCr), however early recognition is limited by delay in creatinine rise. Accurate early biomarkers may lead to prevention or treatment of established AKI. The product of two novel biomarkers of cell cycle arrest, tissue Inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein (IGFBP-7) have shown promise in predicting AKI. In prior studies, TIMP-2*IGFPB-7 ≤0.3 had high negative predictive value, and ≥2 high positive predictive value for AKI. **Aims** - 1) Investigate the early diagnostic value of TIMP-2*IGFPB-7 for DGF; 2) Correlate TIMP-2*IGFPB-7 with long term graft function.

Methods: This is a prospective, double-blinded single center observational study with goal enrollment of 150 transplant recipients. Urine TIMP-2*IGFBP-7 was measured in $(ng/mL)^2/1000$ with a commercial kit, Nephrocheck (Astute Medical, San Diego, CA) at 4-12 hours, 48-72 hours and 72-96 hours post-transplant. SCr was measured just prior to transplant, 1 week post-transplant, and at 1, 3, 6, 9 and 12 months post-transplant.

Results: Thus far, 64 patient samples have been collected, 11 with DGF. Mean TIMP-2*IGFPB-7 were 3.08 ± 0.63 vs 0.54 ± 0.23 (p-value <0.001) at 4-12 hours, 3.39 ± 0.93 vs 0.38 ± 0.13 at 24-48 hours (p-value <0.001), and 1.73 ± 0.76 vs 0.62 ± 0.27 (p-value =0.09) at 72-96 hours in DGF vs non DGF patients respectively. Mean SCr at 1 week were 6.14 ± 0.71 mg/dL in DGF vs 2.13 ± 0.26 mg/dL (p-value <0.001) in non-DGF. Correlation between peak TIMP-2*IGFPB-7 at 24-48 hours and sCr at 1, 3, 6, 9, and 12 months, was nonsignificant.

Conclusions: These preliminary results confirm the use of TIMP-2*IGFBP product measured by Nephrocheck in the diagnosis and prediction of DGF in the post-kidney transplant period as early as 4-12 hours, and peaking at 24-48 hours. The non-DGF TIMP-2*IGFBP-7 means were higher than prior reports, suggesting mild renal injury in the peritransplant period in those patients without DGF. The current sample size is too small and underpowered as of yet to draw conclusions on prediction of long-term renal dysfunction.

Funding: Commercial Support - Astute Medical Inc

PO2193

Kidney Injury in Hematopoietic Stem Cell Transplant (HCT) Recipients: Transcriptome Profiling and Development of Urinary Biomarkers

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Background: In kidney biopsies of HCT recipients, thrombotic microangiopathy with/without tubulointerstitial/microvascular inflammation suggest the possibility of kidney being a target of graft versus host disease. We tested the hypothesis: (i) kidney inflammation/injury in HCT recipients is immune mediated, (ii) urinary mRNA profile may be used as a noninvasive biomarker.

Methods: (i) RNA-sequencing of native kidney from 6 HCT recipients with kidney injury was performed. We compared the transcriptome profile to that of allograft kidney. (ii) Urine samples from 9 HCT recipients were collected. We calculated the CTOT-04 signature score for each recipient. We compared the score to that of kidney allograft recipients.

Results: Of the 4188 genes (26% of 16375) that were different (FDR-P<0.05) between HCT and Normal, 2152 were shared among HCT, ACR, and AMR; 1442 were unique to HCT **(Figure 1)**. Shared genes revealed enrichment of innate and adaptive immune system pathways. Urinary cell CTOT-04 signature score was higher in AKI/tubulitis and interstitial inflammation in the native kidney and resembled ACR of kidney allograft recipients **(Figure 2)**.

Conclusions: In recipients of HCT: (i) kidney inflammation/injury is immune mediated, (ii) urinary cell mRNA profiling is useful for diagnosing kidney injury

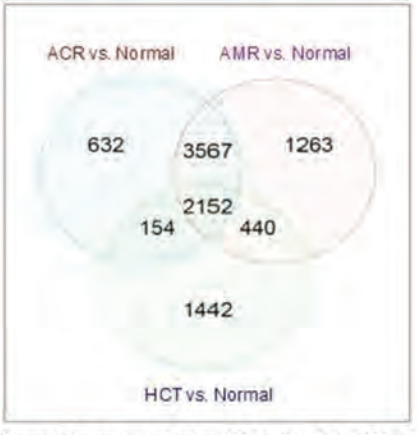

Figure 1. Differential expression of mRNAs. We did mRNA transcriptome profiling of kidney tissue by RNA sequencing (6HCT recipients with kidney injury and 51 allograft recipients [16 ACR, 17 AMR and 18 Normal]). Venn diagram depicts the number of mRNAs that were statistically significant (FDR-P <0.05) between HCT versus Normal, ACR versus Normal and, AMR versus Normal. Probability values were adjusted for false discovery rate using the Benjamini-Hochberg method and is the expected proportion of false positives among all the statistically significant P-values (<0.05)

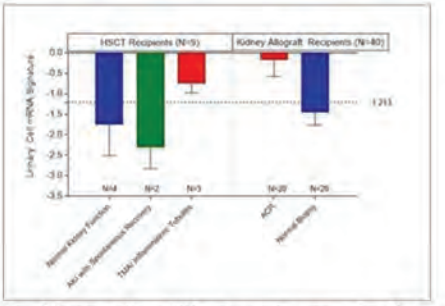

Figure 2. Urinary cell mRNA signature score in HCT recipients and kidney transplant recipients. CTOT-04 signature (Suthanthiran et al. N Eng J Med 2013) is a score derived from urinary cell mRNA profiling of kidney transplant recipients for the noninvasive diagnosis of acute rejection of kidney allograft. The score is a liner combination of urinary cell levels of CXCL10 mRNA, CD3e mRNA, and 18S rRNA, quantified by RT-PCR assay and expressed as copies/µg of total RNA. The dotted line in the figure is the cut point value (-1.213) for the diagnosis of ACR in kidney transplant recipients. We collected urine from HCT recipients and kidney allograft recipients, isolated total RNA from urinary cells, reverse transcribed to cDNA, measured the absolute quantity of urinary cell transcripts, and calculated the CTOT-4 signature score for each patient. Figure depicts the mean ± SE of the CTOT-04 signature score.

PO2194

The Role of Hyperleptinaemia and Low Values of Interleukin 10 in De Novo Donor-Specific Antibody Production After Kidney Transplantation

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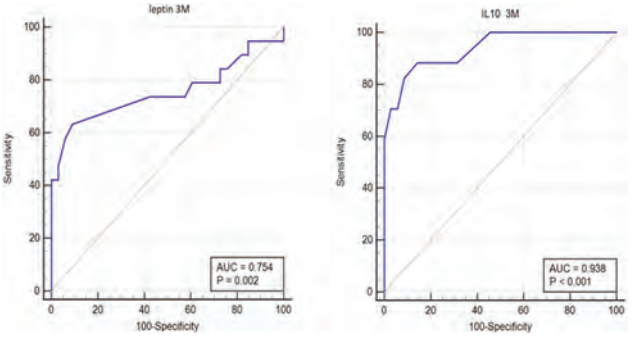
Background: White adipose tissue secretes a number of peptide hormones, including leptin, adiponectin, and several cytokines. The aim of this paper was to determine the role of selected adipocytokines (leptin and adiponectin) and interleukins (IL-10 and IL-6) on the development of graft rejection in protocol biopsy after kidney transplantation.

Methods: In a prospective analysis (n=104), we monitored the values of leptin, adiponectin, IL-6, and IL-10 prior to the transplantation and in the 3rd month after the transplantation. The protocol biopsy of the graft was performed in the 3rd month after the transplantation. The group was divided into the following according to the biopsy result: negative result, IFTA 1, borderline, and DSA positive.

Results: After adjusting for the differences in the baseline recipient and donor characteristics, we identified the hyperleptinaemia baseline (HR=2.0444, P=0.0341) and month 3 (HR=49.8043, P<0.0001) as independent risk factors for borderline changes in the protocol biopsy. The hyperleptinaemia baseline (HR=7.4979, P=0.0071) and month 3 (HR=9.7432, P=0.0057) are independent risk factors for de novo DSA positivity. A low value of IL-10 month 3 is a risk factor for de novo DSA positivity (HR=3.0746, P=0.0388).

Conclusions: Higher leptin levels might play a role in rejection and de novo DSA production. We also confirmed the influence of low values of IL-10 on the development of de novo DSA. We assume that values of adipocytokines in context of other risk factors can predict the immunological risk of patients after kidney transplantation.

Funding: Government Support - Non-U.S.



ROC curve. Leptin 3M and IL-10 3M for the endpoint of de novo DSA and borderline

PO2195

Diagnostic Performance of Donor-Derived Cell-Free DNA Assay (AlloSure®) in Kidney Transplant Recipients with Graft Dysfunction: A Single-Center Study

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Background: Circulating donor-derived cell-free DNA (dd-cf-DNA) is a non-invasive biomarker of kidney allograft injury with a high negative predictive value for ruling out active rejection in patients with evidence of graft dysfunction. At our center, we

compared the AlloSure® test (CareDx®) for the dd-cfDNA assays using >1% as the cut-off value suggested by the DART study or an increase of >30% from the previous value against the gold standard biopsy results and calculated its performance metrics.

Methods: From Dec 2019 to Oct 2020, we found 16 patients who had their 21 AlloSure® assays drawn which were within 4 weeks of for-cause biopsy sampling. In assessing the cause of 21 biopsy samples, 20 had AKI, 5 had proteinuria, and 3 had clinical symptoms of volume overload.

Results: AlloSure® and biopsy results were concordant in 14/21 (66.7%) samples [*Table 1*]. Of the 21 for-cause biopsies, 8 biopsies were positive for rejection (2 borderline, 1 TCMR, 3 AMR, 1 mixed AMR/TCMR, 1 chronic). AlloSure® was positive in 2 of these rejections (1 TCMR, 1 mixed AMR/TCMR). However, it was false-negative in the other 6 rejections (2 borderline, 3 AMR, 1 chronic). Out of the 13 negative biopsy results, AlloSure® was negative in 12 samples and false-positive in one sample. The performance metrics in this patient population were: sensitivity 25%, specificity 92.3%, positive and negative predictive values of 66.7%, and accuracy of 66.7%.

Conclusions: Although we had a sample size, it can be concluded from this study that AlloSure® has a high specificity to diagnose active graft rejection in kidney transplant recipients.

Table 1: 2 x 2 Table

		Biopsy		
		Positive	Negative	Total
AlloSure®	Positive	2	1	3
	Negative	6	12	18
	Total	8	13	21

PO2196

Extremely Elevated Donor-Derived Cell-Free DNA Fractions in Kidney Transplant Recipients Are Strongly Indicative of Allograft Rejection

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Background: Donor derived cell-free DNA (dd-cfDNA) is an established non-invasive biomarker for the identification of kidney allograft rejection. The Prospera™ test utilizes a single-nucleotide polymorphism (SNP)-based massively multiplexed-PCR (mmPCR) methodology to quantify dd-cfDNA as a fraction of total cfDNA in kidney transplant recipients. dd-cfDNA fractions ≥1.0% indicate high-risk for rejection and in a small fraction of patients, dd-cfDNA fractions can be elevated significantly over this threshold. Here we present a case series of 18 kidney transplant patients with extremely elevated dd-cfDNA fractions >10% along with clinical data, when available.

Methods: To better understand the relationship between highly elevated dd-cfDNA fractions with allograft health, we identified cases from quality assurance data with dd-cfDNA fractions >10% and corresponding clinical follow-up data.

Results: Among the 18 cases with dd-cfDNA levels >10%, the median dd-cfDNA fraction was 14.73% (range: 10.8-20.7%). Biopsy data was available for 83.3% (15/18) of the patients indicating mixed rejection in 40% (6/15), TCMR in 40% (6/15), ABMR in 7% (1/15) and chronic ABMR in 13% (2/15). In the remaining 3 patients, 1 patient had chronic complicated JC viremia with history of JC nephropathy, 1 had allograft loss associated with diffuse vasculopathy and 1 was admitted and treated for rejection without a biopsy. A 60-year-old female underwent surveillance testing with Prospera and dd-cfDNA results came back at 19.3%. SCr was 1.2 mg/dL compared to a baseline value of 1.1 mg/dL six weeks post-KT. Detailed patient follow up revealed constitutional symptoms of malaise and general discomfort and low grade fever. The patient underwent kidney allograft biopsy and was diagnosed with TCMR 1a rejection. Patient was subsequently treated with IV methylprednisolone 250 mg x 2 days with a rapid steroid taper. Follow-up Scr levels were 0.9 mg/dL accompanied by a decline in the dd-cfDNA fraction during a subsequent Prospera test.

Conclusions: These results suggest that highly elevated dd-cfDNA fraction in the absence of comorbidities can be a strong indicator of allograft rejection. Further investigation is needed to determine whether there is a relationship between elevated risk for rejection and dd-cfDNA levels elevated significantly above 1%.

PO2197

Can Donor-Derived Cell-Free DNA or Gene Expression Profile Be Used to Monitor Response to Treatment After Subclinical Acute Rejection?

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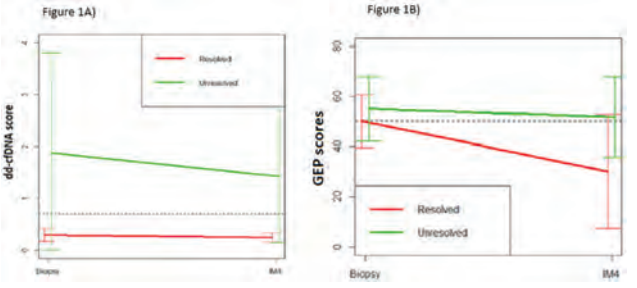
Background: Subclinical acute rejection (subAR) is defined as acute rejection with stable kidney allograft function. Creatinine is not sensitive enough to detect subAR. Donor-derived cell-free DNA (dd-cfDNA) and gene expression profile (GEP) have been used for acute rejection detection in kidney allograft. We hypothesized that dd-cfDNA and GEP could be used to monitor response to treatment of rejection after subAR.

Methods: We analyzed dd-cfDNA and GEP results from 14 unique subjects in the CTOT08 study with subAR who had 8 weeks follow-up biopsy after treatment. Blood samples were paired with kidney biopsies, and collected after subAR during the intensive monitoring periods. We calculated the mean and standard deviation (SD) for each group at the same time points. A paired T-test was used to generate p-values. We conducted locally estimated scatterplot smoothing (LOESS) and linear mixed effect models for the analysis of serial changes of dd-cfDNA scores.

Results: Of 14 patients, subAR resolved in 5 patients (36%) but 9 (64%) patients had persistent rejection after treatment. The slope of dd-cfDNA scores was not significantly different between the resolved and the unresolved group (p-value = 0.43) (Figure 1A). The slope of GEP scores in the resolved group tended to be steeper than unresolved group one after treatment but was not statistically significant between the two slopes (p-value = 0.06) (Figure 1B).

Conclusions: GEP scores showed a greater decrease after successful treatment compared to dd-cfDNA scores. Repeating GEP after subAR might be useful to monitor treatment of rejection.

Funding: Commercial Support - Viracor-Eurofins



PO2198

Immunosuppression Could Influence De Novo Angiotensin II Type Receptor Antibodies Development Early After Kidney Transplantation

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Background: Angiotensin II type I receptor antibodies (AT1R-Ab) are non-HLA autoAb associated with graft rejection and detrimental effects on graft function in kidney transplantation (KT). Nevertheless, the data regarding risk factors associated with AT1R-Ab development is scanty. To our knowledge, immunosuppression (IS) has not yet been reported as a potential risk factor. We sought to evaluate the incidence of de novo AT1R-Ab at 1 year after KT and risk factors associated with their formation.

Methods: We performed a prospective study on 58 KT recipients, transplanted between October 2018 and October 2019, who were followed for 1 year. Exclusion criteria: age <18 years and preformed AT1R-Ab. AT1R-Ab were evaluated at 1 year after KT using an ELISA technique and the cut-off value for detection was >10 U/ml. Logistic regression analysis was used to identify risk factors associated with AT1R-Ab formation.

Results: Twelve out of 58 patients (20.6%) had de novo AT1R-Ab at 1 year of follow-up. Mean age of the study cohort was 40.8±10.5 years, 60.3% were males and 17.2% had a preemptive KT. Glomerular diseases was the main cause for CKD (27.6%). Donors mean age was 48.6±15.6 years, 62.1% were cadaveric donors and 31% of patients had ≥4 mismatches. Monoclonal Ab directed against IL-2 receptor (84.5%) was the main induction IS used. Immediate-release tacrolimus (TAC) was used in 53.4% and mycophenolate sodium was preferred in 89.7% of cases. Patients with de novo AT1R-Ab had a significantly decreased BMI (21.4±1.8 vs 23.2±2.9 kg/m^2, p=0.04), received significantly more frequently IS with rabbit globulin anti-thymocyte (rATG) (41.7 vs 8.7%, p=0.01), immediate-release TAC (83.3 vs 45.7%, p=0.01) and had a significantly higher mean TAC level at 3 months after KT (13.8±5.6 vs 11.4± 3ng/ml, p=0.04). By multivariate logistic regression we found that rATG was an independent risk factor for de novo AT1R-Ab development (OR= 5.62; 95%CI: 1.11- 28.34, p=0.03) and immediate-release TAC had a trend of association with Ab (OR= 5.02; 95%CI: 0.93- 27.06, p=0.03) at 1 year after KT.

Conclusions: The incidence of de novo AT1R-Ab was 20.6% and rATG induction IS was an independent risk factor for Ab development at 1 year after KT. Our results suggest that IS could influence de novo AT1R-Ab formation.

PO2199

The Histological Fingerprint of Kidney from High Kidney Donor Profile Index Diabetic Donors Transplanted in Non-Diabetic Recipients

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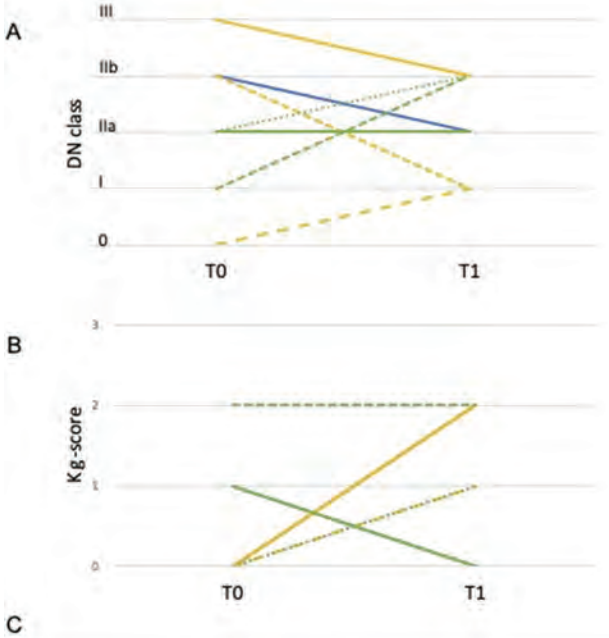
Background: To face the persistent organ shortage and the increasing age and comorbidities of donors, criteria to donation have been expanded. Diabetic donors are recognized as a reliable source of organ, few data are available on the histological evolution of these organs for these reasons we compare the pre implantation biopsy of high-KDPI diabetic donor with a protocol biopsy of non diabetic recipients.

Methods: We performed a retrospective analysis of deceased donors from 2004 to 2015. We selected those with a diagnosis of diabetes and with available pre implantation kidney biopsy (T0) that was scored for diabetic and Karspinski score. Then we selected those recipients whose at time of analysis (T1) were still on follow up, had not a history of diabetes and executed at least one biopsy which has been compared with the previous one.

Results: A total of 10 cadaveric kidney donors (mean KDPI 95.7%) were selected. Diabetic lesions of all classes present already at pre-implantation biopsies associated with mild IF/TA and vascular damages. At follow-up the lesions showed variable modifications of DN class (fig.1) and moderate evolution of IF/TA and vascular damages. eGFRs were stable and proteinuria was mild.

Conclusions: In the ten patients and at the different follow-ups there was not a uniform trend of DN lesions, we demonstrated an amelioration in 3 cases, stability in 4 and worsening in 3, and did not find a relationship between these changes and the follow up time. Our data suggest that the diabetic kidneys keep after transplantation the histologic stigma that denote their origin and even in this very marginal extended criteria donation the diabetes status in the donor may not represent a limitation to transplantation in favorable conditions as euglycemia.



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Follow up time	1 year			5 years				10 years		
ID	1	2	3	4	5	6	7	8	9	10
GBM thickness (nm)	468± 311	350±50	NA	430±80	NA	279±65	460±50	470±50	NA	766± 100

PO2200

Utility of Noninvasive Rejection Biomarkers to Assess the Risk of Rejection in Kidney Transplant Recipients with Post COVID-19 Infection

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Introduction: COVID-19 infection is associated with 25% mortality in kidney transplant recipients (KTRs). Treatment of Coronavirus Disease 2019 (COVID-19) infection in KTRs has involved reduction of immunosuppressants (IS). This potentially increases the risk of allograft rejection in the setting of reduced immunosuppression. We reported 6 cases of kidney allograft rejection post COVID infection

Case Description: Total 123 kidney transplant recipients had COVID-19 infection between March 2020 and February 2021. Immunosuppression was reduced routinely in patients who had symptomatic COVID-19 infection. We implemented. We implemented the protocol of screening tests to assess for rejection which included dd-cfDNA, gene expression profile (TruGraf), donor specific antibody (DSA). Elevated serum creatinine greater than 25% over baseline, dd-cfDNA value greater than 1%, TruGraf value of Non-Tx (NT) or up-trending DSA prompted to allograft biopsy to rule out rejection.

Discussion: Twelve patients out of 123 KTRs received kidney biopsy for above mentioned indications Only 4.8% had kidney rejection (6 out of 123 patients) : 3 patients with acute cellular rejection (ACR) Banff 1B rejection, 2 patients with borderline ACR, and 1 patient with antibody mediated rejection (AMR). Of these 6 patients with rejection 5 patients have elevated dd-cf DNA peri COVID infection, 3 patients with elevated Cr and 1 patient had Non-Tx. Three patients with rejection were transplanted within 1 years. The patients with Banff 1B rejection were treated with anti- thymocyte globulin (ATG) and 1 patient with AMR due to AT1R antibody was treated with methylprednisolone, IV Ig and Losartan. Only 4.8% had kidney rejection post COVID infection. Despite reduction in IS, COVID infection did not increase the risk of allograft rejection and can monitor the risk of rejection by using non-invasive rejection biomarkers.

PO2201

Donor-Derived Leukocyte Chemotactic Factor 2 Amyloidosis in Renal Allografts

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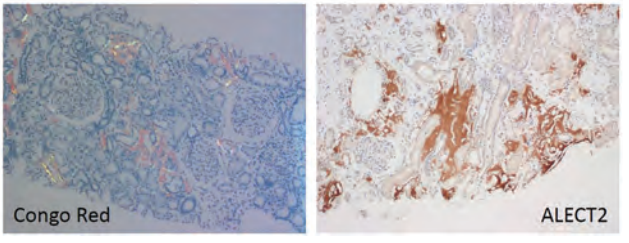
Introduction: Leukocyte chemotactic factor 2 amyloidosis (ALECT2) is a relatively common form of amyloidosis with strong ethnic predilection in the Hispanic population. Patients tend to be older and present with chronic kidney disease with variable proteinuria. Histologically, ALECT2 has a unique preference for interstitial accumulation. We report two cases of donor-derived ALECT2 in renal allografts.

Case Description: Case 1: 69-year-old (yo) Hispanic man with type II diabetes and end-stage renal disease (ESRD) received an 86% Kidney Donor Profile Index (KDPI) deceased donor renal transplant (DDRT) from a 52-yo Hispanic man who died of a stroke. The recipient had delayed graft function and suboptimal nadir serum creatinine (SCr) of 2.6 mg/dL. Proteinuria initially peaked at 2.3 g/g, which decreased to <1 g/g at 4-mo post-transplant (tx). Both time-0 and 3-mo protocol biopsies (bx) revealed widespread interstitial amyloid positive for ALECT2 on immunohistochemistry and mass spectroscopy. **Case 2:** 45-yo Hispanic female with ESRD of unknown etiology received a 78% KDPI DDRT from a 60-year-old female with no medical history who died from head trauma. The recipient experienced immediate graft function with new baseline SCr of 1.2-1.6 mg/dL. She had persistent proteinuria following tx and underwent bx at 2-, 3-, and 6-mo post-tx. The bx showed mostly interstitial amyloid, later confirmed to be ALECT2. Additionally, the patient developed focal segmental glomerulosclerosis (FSGS) as well as CMV infection of the allograft. She eventually lost her graft ~2 years post-tx, likely from FSGS rather than ALECT2.

Discussion: Rare cases of donor-derived ALECT2 have been reported in the literature and suggest that kidney allografts with limited and localized donor-derived ALECT2 involving <10% of the renal parenchyma have good outcomes. Our cases represent more severely affected donor kidneys. Although the clinical course for our patients were suboptimal, other factors aside from ALECT2 were likely the major contributing factors. Thus, donor-derived ALECT2 is likely of low consequence in the recipient allograft.



PO2202

Regardless of Donor-Specific Antibody, Do Not Forget Non-HLA

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Introduction: Antibody-Mediated Rejection (AMR) remains an important cause of allograft rejection and loss of transplant. This is mainly attributed to donor-specific antibodies (DSA) directed against human leukocyte antigen (HLA). In patients with biopsy findings of AMR and undetectable DSA, non-HLA antibodies must be considered. Here we present two cases of AMR mediated by Angiotensin II type 1 receptor (AT1R) antibody, one of the most widely studied non-HLA antibodies.

Case Description: A 46 yo AA HIV-positive male underwent deceased donor kidney transplant, induced with Basiliximab and methylprednisolone, and maintained on tacrolimus, mycophenolate mofetil and prednisone. His post-op course was complicated by delayed graft function with biopsy performed on day 11 showing acute vascular rejection and severe microcirculation inflammation, highly suspicious for AMR. DSA was negative, but non-HLA panel resulted positive for anti-AT1R at 22 U/ml. He was treated with steroids, PLEX, IVIG, Rituximab, and started on ARB therapy with recovery and most recent creatinine 1.59 mg/dl. To our knowledge, this is the first reported case of an HIV-positive patient with anti-AT1R AMR. A 50 yo AA female underwent deceased donor kidney transplant induced with Alemtuzumab and methylprednisolone and maintained on tacrolimus, mycophenolate mofetil and prednisone. She had immediate graft function, but 5 days after discharge, presented with anuric AKI. Biopsy on day 10 showed thrombotic microangiopathy and diffuse C4d positivity, suggestive of AMR. DSA panel showed MFI values that correlated with high levels of anti-B18 and anti-B25. Non-HLA panel was positive for anti-AT1R at 29 U/ml. She was treated with steroids, PLEX, IVIG, Rituximab, and started on ARB therapy with recovery and most recent creatinine 1.23 mg/dl.

Discussion: Non-HLA antibodies including anti-AT1R have been recognized as possible mediators of allograft injury. They should be suspected in AMR with no identifiable DSA, or in early AMR regardless of DSA. Although no standardized treatment exists for non-HLA antibodies, early recognition may have implications for treatment, particularly with AT1R antibodies in which angiotensin receptor blockade effectively reduces anti-AT1R activity. Along with other AMR therapies, this may improve allograft function as seen in these two cases. To our knowledge, this is the first reported case of an HIV-positive patient with anti-AT1R AMR.

PO2203

Autoimmune Encephalitis with Concurrent Epstein-Barr Virus Infection in a Renal Transplant Patient

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Introduction: Epstein-Barr virus (EBV) infection following renal transplant is typically associated with post-transplant lymphoproliferative disorder (PTLD). Autoimmune encephalitis (AE) is caused by antibodies against N-methyl-D-aspartate receptor (NMDAR), a ligand-gated ion channel with a crucial role in synaptic transmission. We describe a patient who developed encephalitis 1 year after renal transplant with cerebral spinal fluid (CSF) analysis positive for NMDAR antibodies and evidence of EBV infection on brain biopsy without PTLD or malignant processes. To our knowledge, this is the 1st case with tissue evidence of EBV infection on brain biopsy in renal transplant.

Case Description: A 70 year-old female with end stage renal disease from Type 2 Diabetes mellitus who received a deceased donor renal transplant one-year prior was admitted for 3 weeks of progressively worsening mentation. Immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone. Brain MRI did not reveal any acute findings. EEG showed generalized slowing consistent with diffuse encephalopathy. CSF analysis showed lymphocytic pleocytosis and elevated protein level. The infectious workup was negative except for positive EBV PCR in CSF. Cytometry did not reveal any evidence of PTLD. CSF autoimmune panel demonstrated NMDAR1 antibody. Brain biopsy showed a chronic inflammatory process with features of EBV infection. EBV-infected cells were detected in tissue specimen via in-situ hybridization with EBV-encoded small RNA. Patient initially received ganciclovir, amBisome, and broad-spectrum antibiotics. Treatment then changed to steroids, IVIG and plasmapheresis for autoimmune encephalitis, all of which were stopped and ganciclovir was restarted when brain biopsy was positive for EBV. Unfortunately, patient did not show any clinical improvement possibly due to delayed diagnosis and went home with hospice care.

Discussion: EBV Encephalitis without PTLD following renal transplant is uncommon. Only a few cases have described renal transplant patients with encephalitis and concomitant findings of NMDAR antibodies and EBV DNA in CSF study. The relationship between EBV infection and AE remains unclear; however, EBV infection may play a role in the pathogenicity of NMDAR antibodies. AE can occur in the setting of chronic immunosuppression and should not be overlooked to avoid delay in diagnosis and treatment.

PO2204

2,8-Dihydroxyadenine Crystalline Nephropathy in Transplanted Kidney

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Introduction: 2,8-dihydroxyadeninuria (DHA) disease is a rare autosomal recessive disorder caused by adenine phosphoribosyltransferase (APRT) deficiency, that typically manifests with nephrolithiasis, but rarely can cause chronic kidney disease (CKD). Recurrence of DHA nephropathy after kidney transplant can cause persistent allograft dysfunction with increased risk of early graft failure if diagnosis and treatment are delayed. We describe a case of APRT deficiency which remained undiagnosed until evaluation of a poorly functioning kidney allograft due to DHA nephropathy, successfully managed with allopurinol and conversion to Belatacept.

Case Description: 72-year-old Caucasian male with ESRD secondary to diabetes mellitus type 2 and obstructive uropathy. The patient received a living donor kidney transplant from his daughter on 10/15/2020 with Thymoglobulin and steroid induction followed by maintenance immunosuppression with tacrolimus, mycophenylate, and prednisone. It was a one haplotype mismatch with no pre-formed donor specific antibodies. He had slow graft function with a creatinine of 4 mg/dL on discharge. At 6 weeks post-transplant, his creatinine remained elevated at 2.1 - 2.3 mg/dl with no clear cause for persistent allograft dysfunction. An allograft renal biopsy showed numerous polarizable pigmented brown intratubular crystals, in the absence of triamterene-based diuretics. A diagnosis of 2,8 DHA crystalline nephropathy was made and he was started on allopurinol and a low purine diet. To minimize tubular injury, Belatacept was added to maintenance immunosuppression and tacrolimus dose was reduced with a goal to wean over 9 months. To further confirm the diagnosis, a kidney gene panel was performed confirming homozygous ARPT deficiency with an autosomal recessive inheritance pattern. Kidney function continued to improve with creatinine of 1.5 mg/dl (eGFR 45 ml/min/1.73m2) at 7 months post-transplant.

Discussion: DHA nephropathy due to APRT deficiency is a rare but preventable cause of CKD and can remain undiagnosed until its recurrence after kidney transplant. To prevent allograft failure, high index of suspicion and early biopsy is important. In addition to allopurinol, low purine diet, and increased hydration, CNI minimization and utilization of Belatacept is an effective strategy to minimize vascular and tubular injury and prevent further precipitation of crystals.

PO2205

Anti-MDA5 Dermatomyositis as a Paraneoplastic Syndrome of Myelodysplastic Syndrome After Kidney Transplant in Autosomal Dominant Polycystic Kidney Disease

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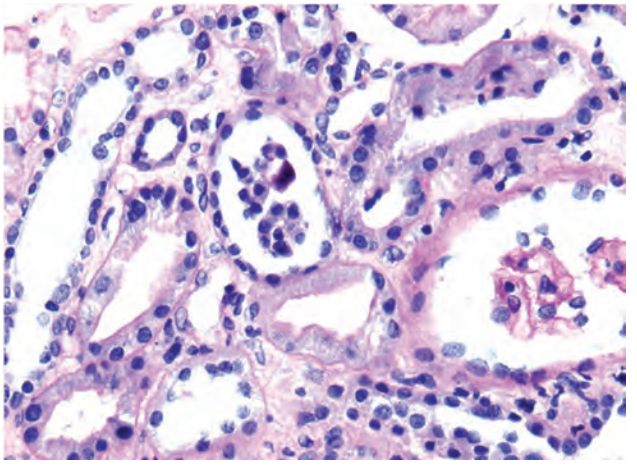
Introduction: Malignancy after solid organ transplantation is increasing, there is 3 to 5-fold greater incidence than in general population. Major risk factors for non-cutaneous neoplasms are male sex, older age and Caucasians, there are no data on the prevalence of hematologic malignancies after kidney transplantation. We report a case of kidney allograft infarctions causing acute dysfunction secondary to myelodysplastic syndrome and amyopathic dermatomyositis as a paraneoplastic syndrome (PS).

Case Description: A 40-year-old man with chronic kidney disease (CKD) secondary to autosomal dominant polycystic kidney disease (ADPKD) was programmed for preemptive kidney transplant (KT); basiliximab induction and mycophenolate mofetil (1 year), tacrolimus and steroid was the maintenance therapy. Three years after KT he was admitted to the hospital with AKI (SCr 4.7mg/dL, baseline 1.7mg/dL), unexplained weight loss (17kg) and rash in face, hands and feet. Kidney biopsy showed cortical segmental infarction, focal hypoperfusion with negative C4d. MDA-5, Anti-Jo-1 and PL-7 were positive and Gottron papules were reported in skin biopsy, myopathy was excluded. PS was our conclusion, so PET-CT and BMA were done, with no metabolic activity and hypoplastic myelodysplastic syndrome with high risk for acute myeloid leukemia, respectively.

Discussion: Kidney infarctions were the etiology of AKI as a expression of a hypercoagulable state secondary to amyopathic dermatomyositis (paraneoplastic syndrome) presents and precedes hematologic malignancies in almost 50% cases, awarding poor prognosis at 1, 3 and 5 year with 96.9%, 78.1% and 51.4% overall survival, respectively. Dermatomyositis coexistence with kidney transplant has been described, nevertheless, ADPKD and dermatomyositis is anecdotal. In any case, the diagnosis of Anti-MDA5 dermatomyositis requires ruling out neoplasms.



PO2206

Bilateral Pyomyositis in a Kidney Transplant Patient

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Introduction: Immunocompromised hosts are susceptible to infectious complications including pyomyositis, a purulent bacterial infection of deep skeletal muscle that most commonly affects lower extremities (LE) and is acquired through hematogenous spread, trauma or injections.

Case Description: A 30-year-old man who received a kidney transplant in 2015 for ESRD due to congenital obstructive uropathy presented to an outside hospital with dysuria, bilateral LE pain, leukocytosis to 18.9 k/uL, and an elevated serum creatinine of 4.7 mg/dL. He was treated with intravenous (IV) antibiotics and his dysuria resolved but bilateral LE pain persisted and he was unable to ambulate. He denied recent vigorous exercise, trauma to his calves or history of IV drug use. Leukocytosis persisted at 20.2 k/uL and he had elevated CRP at 7.5 mg/dL. Ultrasound showed no venous thrombi but was notable for avascular fluid collections in the bilateral medial calves. MRI showed a 2.1 x 3.6 x 7.1 cm fluid collection centered in the gastrocnemius with marked muscle edema, and a similar fluid collection in the contralateral LE at the same location (Figure 1). On further questioning, the patient admitted that two months prior he injected B12, that he had purchased online, into his bilateral calves. Incisions and drainage yielded turbid-looking fluid. Bacterial and fungal cultures showed no growth. Acid-fast stain was negative. The patient's antimicrobial treatment was broadened and he rapidly improved leaving the hospital shortly thereafter.

Discussion: This is a rare case of bilateral pyomyositis in a kidney transplant patient. The inability to culture an organism is likely due to preceding IV antibiotic treatment. This case underscores the importance of keeping a broad differential diagnosis and obtaining a detailed history when treating immunosuppressed patients.

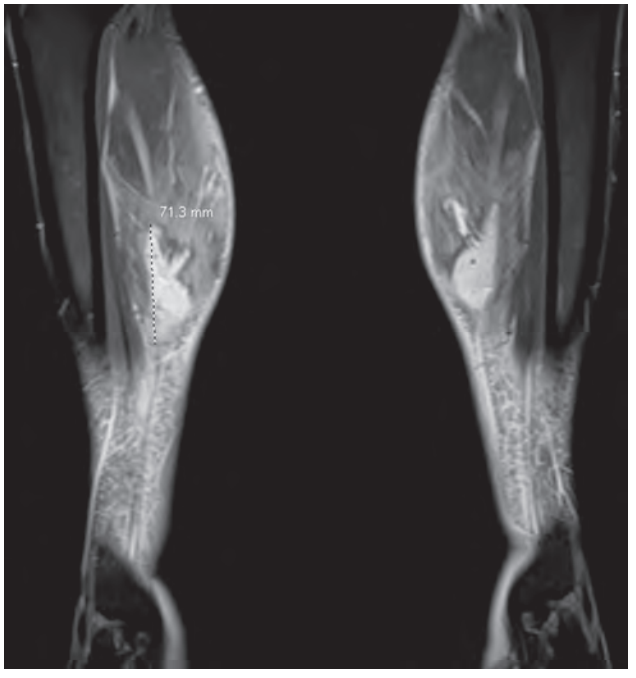


Figure 1

PO2207

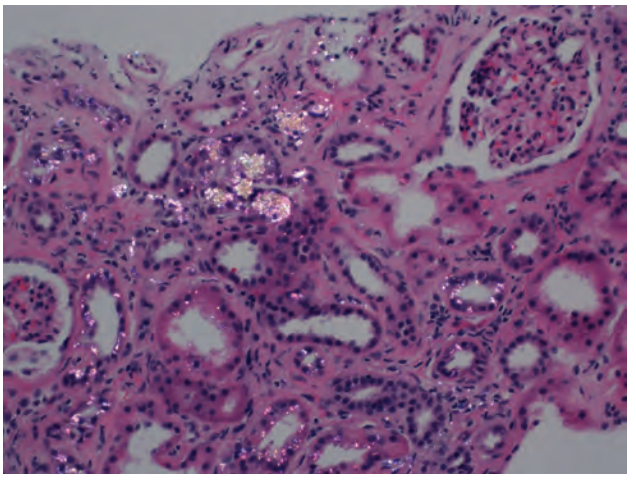
Dihydroxyadenine Crystals Leading to Renal Graft Loss

Niraj K. Yadav, Janame J. Kottey, Rama Kethineni, Zachary Drury, Marc Barry, Divya Raghavan, Josephine Abraham, Fuad S. Shihab. *University of Utah Health, Salt Lake City, UT.*

Introduction: Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive disease which leads to excessive production and renal excretion of poorly soluble 2,8-dihydroxyadenine (DHA). This causes crystal-induced acute kidney injury and progressive chronic kidney disease (CKD). We describe a case of DHA nephropathy in a renal transplant recipient leading to graft failure.

Case Description: A 69 year old female with ESRD secondary to recurrent nephrolithiasis underwent a deceased donor kidney transplant. The stone composition was previously unknown but she underwent genetic testing and was found to be homozygous for APRT c.81-3C>G mutation which was reported as a variant of uncertain significance. Following transplantation, she was started on allopurinol for stone prevention and an APRT activity level was checked and was within normal range. As a result, allopurinol was stopped. Her serum creatinine which was 1.6 mg/dl started to gradually increase to 5.5 mg/dL. She underwent a kidney biopsy which showed extensive tubular cytoplasmic and luminal 2,8-DHA crystal deposits. Despite restarting allopurinol, renal function continued to worsen and she developed uremic symptoms. She was initiated on hemodialysis.

Discussion: APRT deficiency is a rare condition and novel mutations are being reported. It is likely that the mutation of unknown significance which our patient has might be another novel mutation associated with APRT deficiency. DHA stone formation can occur even when APRT levels are normal or detectable. It is of utmost importance to continue allopurinol in patients with known DHA stones as genetic testing and APRT level may be misleading and stopping allopurinol will result in irreversible kidney damage



Intratubular and cytoplasmic DHA crytals.

PO2208

Hypercalcemia in Immunocompromised Host: Beware of Zebras

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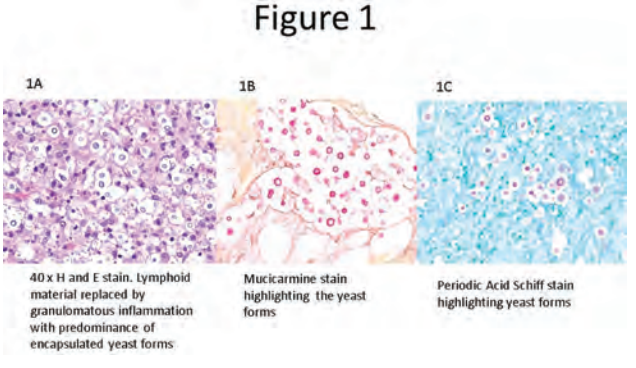
Introduction: Hypercalcemia has varied etiology with treatment dictated by underlying cause. We present an immunocompromised host with weight loss, lymphadenopathy and hypercalcemia masquerading as malignancy.

Case Description: A 74 year old male construction worker with deceased donor liver transplant 4 months earlier on tacrolimus/mycophenolic acid (MPA) maintenance and stage 4 chronic kidney disease presented with constitutional symptoms and 20 pound weight loss. Serum creatinine was 2.5 mg/dl and corrected calcium 11.9 mg/dl. CT scan showed mediastinal and bilateral axillary lymphadenopathy. Serum EBV and CMV PCR were negative. Work up for hypercalcemia revealed: intact PTH 6.8 picogram/ml (11.0-68.0), 25 OH vitamin D 44.6 ng/ml (30-100), κ:λ ratio 1.45 (0.26-1.65) and absent M-spike on serum protein electrophoresis. Blood culture grew Cryptococcus neoformans and serum Cryptococcal antigen titer was positive at 1:4096. Lumbar puncture revealed CSF lymphocytic pleocytosis and positive cryptococcal antigen titer at 1:32. Axillary lymph node biopsy showed cryptococcal lymphadenitis with diffuse involvement by encapsulated yeast forms within non-necrotizing granulomatous inflammation (fig 1). Patient was started on induction treatment with intravenous liposomal amphotericin B and oral flucytosine till 2 weeks after negative blood cultures followed by 8 weeks of consolidative therapy with oral fluconazole. MPA was stopped and tacrolimus continued. Hypercalcemia resolved a week after initiating antifungal therapy. Patient doing well 4 months later on maintenance fluconazole.

Discussion: Hypercalcemia is a rare manifestation of disseminated fungal infection. The exact etiology is unclear but 1, 25 di (OH) vitamin D and PTHrp are implicated. Weight loss and lymphadenopathy in our immunosuppressed patient raised concern for malignancy. However, blood culture and lymph node histology clinched the diagnosis enabling prompt therapy with resolution of the symptoms and hypercalcemia.



PO2209

A Rare Case of Collapsing Focal Segmental Glomerulosclerosis Caused by Cytomegalovirus in a Renal Transplant Recipient

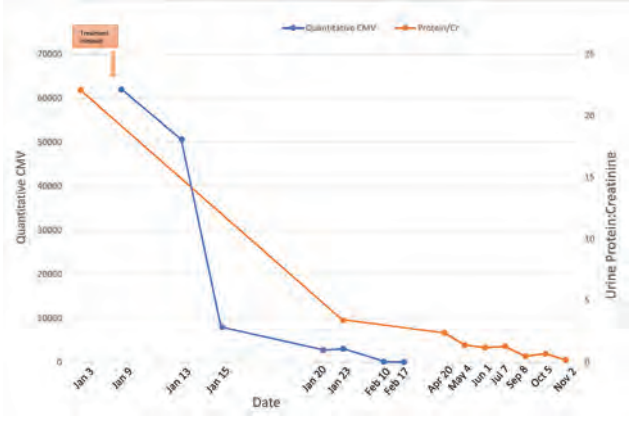
Abdelwahab Ahmed, Abdel-Rhman Mohamed, Abdullah Naji, Anita K. Patel, Rohini Prashar. *Henry Ford Hospital, Detroit, MI.*

Introduction: Cytomegalovirus (CMV) is a DNA virus that is associated with several clinical manifestations in renal transplant recipients (RTR), presenting often with asymptomatic viremia, CMV syndrome, and tissue invasive disease in the lungs, colon,

esophagus, and retina. CMV infection may occur in the renal allograft presenting as interstitial nephritis. We present a rare case of CMV nephritis in a RTR that presented as a collapsing focal and segmental glomerulosclerosis (FSGS).

Case Description: A 55 year old caucasian male with a history of end-stage renal disease due to hypertension on hemodialysis for 4 years received a living donor renal transplant with immediate graft function. Induction was with Thymoglobulin, maintenance immunosuppression was with MMF, Prednisone, and Tacrolimus. He completed valganciclovir prophylaxis for CMV, and soon after presented to an outside hospital with hypotension, lower extremity swelling, and diarrhea of 2 weeks duration. He had a proteinuria value of 22.1gm with hypoalbuminemia and an acute kidney injury. A presumptive diagnosis of FSGS was made and he received IV Solumedrol. Chart review revealed CMV viremia 4 weeks prior to presentation. He was transferred to a tertiary center for management, where a kidney biopsy was done that revealed interstitial inflammation, widespread collapse of glomerular tufts, podocyte hyperplasia and hypertrophy, extensive podocyte foot process effacement, microthrombi and CMV staining in tubular epithelial cells. He was treated with IV ganciclovir, and both viremia and proteinuria resolved (Figure 1).

Discussion: The patient's de novo collapsing-FSGS is a rare manifestation of CMV infection. While CMV is the most common opportunistic viral infection in RTR, renal involvement is unusual. This may be a cytokine related injury to podocytes in the setting of a viral infection. Our patient had complete recovery following treatment with renal function returning to baseline.



PO2210

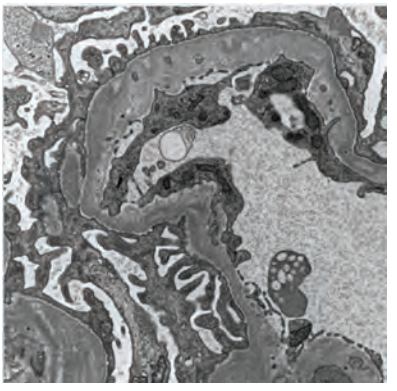
Use of Lipoprotein Apheresis in Recurrent Focal Segmental Glomerulosclerosis Following Transplant

Ruth E. Campbell, Monica Grafals. *University of Colorado, Denver, CO*.

Introduction: Primary focal segmental glomerulosclerosis (FSGS) recurs in 20-50% of transplanted kidneys and has a high rate of transplant failure. We report a case of recurrent FSGS treated with lipoprotein apharesis (LDL-A)

Case Description: A 27 year-old male with primary FSGS underwent a DBD kidney transplant. He was ESRD on PD and anuric. ATG and steroids were given for induction. On post-op day (POD) 2, his spot urine protein was > 2000 mg (unable to calculate urine protein/creatinine ratio (UPCR)). Serum creatinine was 1.47 mg/dL (pre-transplant: 9.65 mg/dL). With concern for recurrent FSGS, emergent therapeutic plasma exchange (TPE) and losartan were started. On POD 3 and 4, proteinuria was > 2,000 mg; TPE was done daily and adrenocorticotrophic hormone (ACTH) and rituximab started. Despite 5 days of TPE and medical therapy, proteinuria was > 2,000 mg. On POD 8, LDL-A was started. Prior to second LDL-A run, his proteinuria was 1990 mg but 294 mg afterwards. Proteinuria rebounded between treatments, but steadily decreased: by week 3, UPCR was 686 mg/g and by final LDL-A, was 200 mg/g. Renal function was stable and biopsy had no podocyte effacement. He completed LDL-A biweekly for 3 weeks, then weekly for 6 weeks. ACTH and rituximab were continued. Currently, his UPCR is 9 mg/g.

Discussion: Treatment of recurrent FSGS centers on plasma exchange and immunosuppression. By lowering LDL levels, LDL-A is thought to reduce proteinuria by reducing vascular permeability and improving response to immunosuppressive agents. Case reports indicate efficacy, but currently the use of LDL-A is designated as a humanitarian device exemption for drug resistant recurrent FSGS in transplanted kidneys by the FDA. Although this modality is uncommon, our case suggests that patients with recurrent FSGS may benefit from early initiation of LDL-A.



PO2211

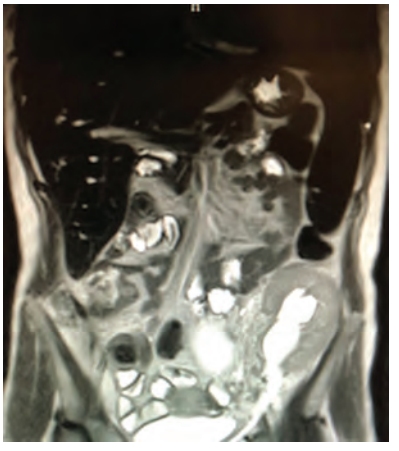
Iron Overload Syndrome and Primary Focal Segmental Glomerulosclerosis Recurrent with Monthly Plasma Exchange Therapy: Long-Term Second Kidney Allograft Survival

Belen Martinez-Vazquez, Pedro Gudiño Bravo, Octavio R. Garcia-Flores, Francisco Rodríguez. *Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico*.

Introduction: Patients who lose their allograft due to recurrent FSGS are usually not retransplanted since the risk of recurrence (80–100%). Proteinuria as a result of glomerular damage is linked to tubulointerstitial injury, which is associated with increased filtration of transferrin-bound iron and can lead to tubular accumulation.

Case Description: A 32-year old female with a history of collapsing FSGS, living related kidney transplant with loss of the allograft function due to recurrent disease underwent a 2nd kidney transplantation in October 2018. At 2 months post transplantation elevated levels of proteinuria (6 g/g), kidney biopsy (KB) demonstrated recurrent FSGS. She received treatment with high-dose steroids, CsA and an intensive course of plasma exchanges (PEs) due to persistent proteinuria. There is no history of blood transfusions, iron treatment and diseases with ineffective erythropoiesis. Ferritin levels (15000 ng/ml) and a MRI with liver and spleen iron deposition pointed to the diagnosis of Hereditary Hemochromatosis (HH), common mutations (C282Y, H63D and G320V genes) were negative. KB of 2020 demonstrated iron deposition (ID) in tubular epithelial cells.

Discussion: Histological evidence of ID in the tubulointerstitium can be related to persistent proteinuria. The negative genetic testing is common in the Hispanic race in which there is a lesser prevalence for the most frequent mutation, C282Y homozygosity (0.03% compared to 0.44% in Whites). We assume that this patient has a genetically unknown type of HH. To our knowledge this is the first reported case in which an Iron Overload Syndrome (IOS) is associated with FSGS. PEs is a therapeutic option in patients with recurrent FSGS, also used in IOS.



PO2212

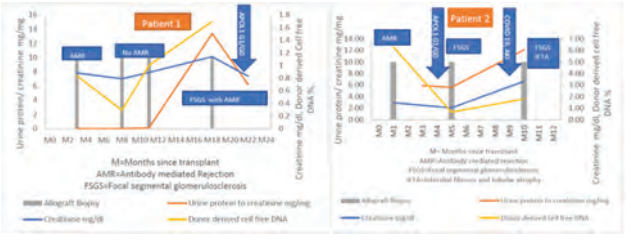
Is One Allele Enough to Cause APOL1-Associated Nephropathy?

Peace Johnson, Sindhura Bobba, Sravanthi Paluri, Gaurav Gupta. *Virginia Commonwealth University Health System, Richmond, VA.*

Introduction: The high risk APOL1 genotype are associated with an increased risk of developing non-diabetic kidney disease. In the post-kidney transplant setting, a high-risk donor APOL1 genotype (but not recipient genotype) is associated with an increased risk of graft failure and proteinuria, indicating that it is local glomerular APOL1 gene expression that confers disease rather than systemic gene expression. Here, we present 2 patients that developed post-transplant focal segmental glomerulosclerosis (FSGS) after an initial diagnosis and treatment of Antibody-mediated rejection (AMR).

Case Description: Two patients with end stage kidney disease, highly sensitized, received deceased donor kidney transplants from African American donors (one in 2019 and the other a regraft in 2020). Donors were without discernable proteinuria on urine dipstick. Initial post tranasplant courses were complicated by AMR treated as per center protocol. Tissue-based whole biopsy gene expression studies on kidney biopsy specimens (MMdx, using Molecular Microscope, Alberta, Canada) confirmed AMR along with grossly elevated interferon-γ gene expression. Subsequently each developed nephrotic range proteinuria with biopsy-confirmed FSGS and ongoing AMR . In both patients, in the absence of a prior history of FSGS and a delayed development of proteinuria in the first case (2019, patient1), an absence of recurrence in the first allograft in the second case (2020, patient2), a diagnosis of donor-derived APOL-1 nephropathy was considered and retrospective donor genotyping revealed the intermediate G1/G0 genotype. See Figure for more details.

Discussion: We hypothesize that extreme local interferon-γ activation due to AMR was the primary trigger that could have resulted in local APOL-1 gene activation and subsequent podocytopathy. Similar data was recently reported by Shetty et al, in a kidney transplant patient with COVID associated collapsing nephropathy and G1/G0 donor genotype. Based upon these data we hypothesize that the G1/G0 genotype may represent intermediate risk for podocytopathies. Further research is needed in this area to confirm these initial associations.



PO2213

Early Recurrence of Fibrillary Glomerulonephritis After Kidney Transplantation

Nicholas S. Niazi, Yanli Ding, Suverta Bhayana. *The University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerulonephritis characterized by glomerular congo red negative nonbranching fibrils on electron microscopy (EM). The optimal treatment for FGN is unclear and the renal prognosis is poor, with up to half of patients progressing to end-stage kidney disease (ESKD) by four years. Kidney transplantation has a variable recurrence rate after transplant ranging from 9 to 50%.

Case Description: A 57-year-old-male with a history of cirrhosis secondary to nonalcoholic fatty liver disease and ESKD secondary to FGN was hospitalized for acute kidney injury. The patient underwent simultaneous liver and kidney transplantation four weeks prior to presentation. The patient underwent induction with basiliximab and started on tacrolimus, mycophenolate mofetil, and prednisone for maintenance immunosuppression. The patient's serum creatinine had increased from the previous nadir of 2.0 mg/dL to 2.7 mg/dL. Given worsening allograft function, a transplant kidney biopsy was performed. The patient's biopsy showed evidence of recurrent fibrillary glomerulonephritis, including positive immunohistochemical staining for DNAJB9 and ultrastructural findings of mesangial nonbranching fibrils averaging 21.5 nm in diameter. The biopsy also showed acute tubular necrosis, secondary global and focal segmental glomerulosclerosis, and tubular atrophy and interstitial fibrosis in 20-30% of the cortex. There was no evidence of acute T-cell mediated rejection or antibody-mediated rejection. The patient's allograft function improved and ranged from 1.5 -1.7 mg/dL at the time of discharge. The patient is now six months from transplant and has stable allograft function and minimal proteinuria.

Discussion: FGN recurrence after kidney transplantation has been described in case reports and case studies. In the most recent and largest study, utilizing DNAJB9 and protocolized post-transplant biopsy, the authors showed a recurrence rate of 21% and a median time to recurrence of 10.2 years. Additionally, all biopsies before five years were negative in their cohort. Allograft failure was seen in 33% of patients with recurrent FGN. To our knowledge, this case is the earliest reported recurrence of FGN after transplantation. In patients with a history of FGN, recurrent disease should be considered in the differential of early allograft dysfunction.

PO2214

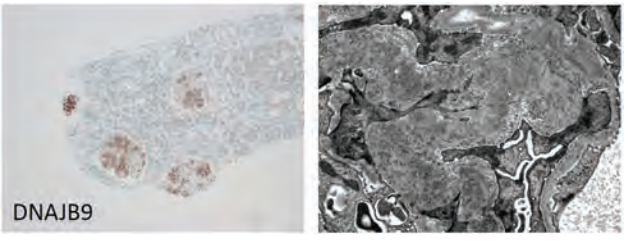
Donor-Derived Fibrillary Glomerulonephritis in a Renal Allograft

Tiana Jespersen, Yihung Huang, Muna Alnimri, Kuang-Yu Jen. *University of California Davis, Sacramento, CA.*

Introduction: Fibrillary glomerulonephritis (FGN) is a rare progressive renal disease that is defined by the presence of randomly oriented non-branching fibrils showing positive immunostaining for DnaJ homolog subfamily B member 9 (DNAJB9). Recurrent FGN in renal allografts have been described with an indolent course. We report a case of donor-derived FGN in a renal allograft.

Case Description: A 73-year-old female with history of end-stage renal disease (ESRD) due to anti-myeloperoxidase antibody-associated pauci-immune glomerulonephritis received a preemptive deceased donor renal transplant from a 62-year-old 79% Kidney Donor Profile Index female. The patient experienced slow graft function and nadir serum creatinine (Cr) of 1.7 mg/dL at 4 months post-transplant with subsequent Cr stabilizing in the 2.0-2.3 mg/dL range. Proteinuria mainly fluctuated between 1-2 g/g. Time-0 biopsy demonstrated mild mesangial widening/hypercellularity with rare glomerular capillary double contours. Ancillary studies revealed positive staining for DNAJB9 and kappa light chain-restriction, consistent with donor-derived FGN. 4-month surveillance biopsy showed similar findings. Background renal parenchyma showed moderate chronicity with prominent chronic vascular disease. At 10-months post-transplant, Cr remains at ~2 mg/dL and proteinuria remained in the 1-1.6 g/g range.

Discussion: FGN carries a poor prognosis with nearly half of patients progressing to ESRD within a few years. A case series of recurrent FGN after kidney transplantation suggests a relatively benign clinical course including a single report of donor-derived FGN (from a living related donor) without proteinuria in the recipient. Our case shows a more severely afflicted allograft that resulted in persistent low-grade but stable proteinuria in the recipient. Suboptimal Cr was also observed following transplant as well, although the allograft had other factors such as chronicity and chronic vascular disease.



PO2215

A De Novo Case of C1q Nephropathy in a Renal Allograft

Zachary Appelbaum, Muralidharan Jagadeesan, Joseph K. Melancon, Divya Shankaranarayanan. *George Washington University Medical Faculty Associates, Washington, DC.*

Introduction: C1q nephropathy (C1qN) is a rare idiopathic glomerulopathy that is characterized by mesangial C1q deposition in the absence of systemic lupus erythematosus or membranoproliferative glomerulonephritis. Clinical manifestations vary, but can include proteinuria, hematuria, and renal dysfunction. C1qN is not usually responsive to corticosteroids and outcomes are poor for most patients. We describe a de novo, but clinically silent case of C1qN in a renal allograft incidentally detected on surveillance biopsy.

Case Description: A 20 year old male, with history of end stage renal disease secondary to congenital renal hypoplasia, on maintenance tacrolimus, mycophenolate mofetil, and oral prednisone, underwent a surveillance biopsy 1 year after a deceased donor kidney transplantation. Laboratory studies revealed a baseline serum creatinine of 1.7 mg/dL and a spot urine protein to creatinine ratio of 258 mg/g. Urinalysis did not show hematuria and the rheumatologic workup was unremarkable. Light microscopy revealed minimal mesangial hypercellularity without endocapillary proliferation. Immunofluorescence microscopy demonstrated granular mesangial staining for C1q with positive staining for IgG, IgM, C3, C4, and kappa and lambda light chains. Electron microscopy revealed mesangial and paramesangial electron-dense immune deposits.

Discussion: Unlike other C1qN cases described in the literature, our patient did not have evidence of an underlying autoimmune disease or viral infection. Renal biopsy demonstrated positive immunofluorescence staining of IgG, IgM, C3, C4, and kappa and lambda light chains, in addition to C1q. Moreover, there was no evidence of proteinuria, hematuria, or renal dysfunction. One question that arises is whether this patient, with a history of congenital renal hypoplasia, was susceptible to developing an autoimmune process that was otherwise being masked by immunosuppression. This case emphasizes the following: (1) further research is needed to determine the frequency and length of monitoring of de novo C1qN in renal transplant recipients, and (2) further research is needed to determine the optimal therapeutic regimen.

PO2216

Repository Corticotropin (Acthar®) in Treating De Novo C3 Glomerulonephritis Post Transplantation

Muhammad S. Naseer, Ayush Singh, Neeraj Singh. *Willis Knighton Medical Center, Shreveport, LA.*

Introduction: De-novo C3 glomerulonephritis (C3GN) post-transplant is uncommon. Although eculizumab has been used successfully in several cases, the response is heterogeneous and treatment strategies remain undefined. The use of repository corticotropin in C3GN has not been described in the literature.

Case Description: A 48-year-old African American male with kidney transplantation secondary to diabetic nephropathy presented 6 years post-transplant with lower extremity edema and nephrotic range proteinuria of 8.2 g/g of creatinine. His renal allograft biopsy confirmed the diagnosis of C3GN (*Figure 1).* He was treated with eculizumab (Solaris®) 900 mg IV once weekly for 4 weeks and repository corticotropin (H.P. Acthar® gel) 80 units subcutaneous twice weekly for 6 months with complete resolution of proteinuria within 3 months of the treatment. However, the patient presented again after 6 months of completing therapy with a recurrence of proteinuria which peaked at 11.6 g/g of creatinine. The kidney allograft biopsy was consistent with C3GN. He was started on Acthar® 80 units subcutaneous twice weekly and the proteinuria was reduced to >50% within 2 months of therapy. When eculizumab 900 mg IV once weekly for 4 weeks was added with Acthar®, the proteinuria fully resolved within 10 weeks of treatment. Since then, the patient has been maintained on Acthar® monotherapy of 40 units subcutaneous twice weekly and has stayed in complete remission of proteinuria for more than a year till his last follow-up.

Discussion: In conclusion, this is the first case report describing the role of repository corticotropin as an effective therapy in reducing proteinuria and maintaining patients with C3GN in complete remission.

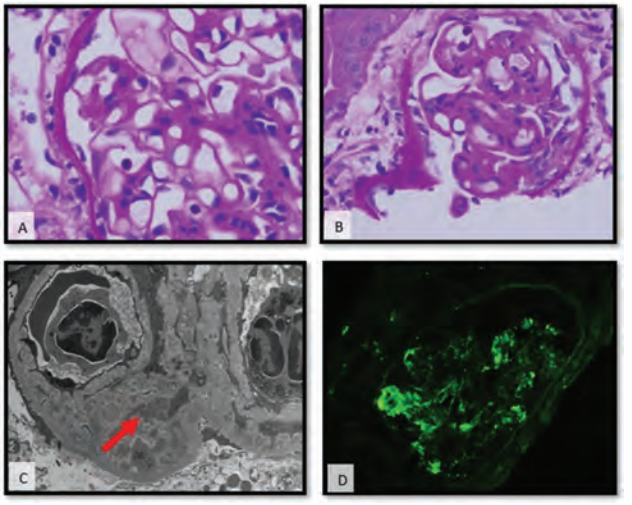


Figure 1. *Kidney Allograft Biopsy*

A & B: PAS shows a membranoproliferative pattern

C: EM shows large subendothelial deposits (red arrow)

D: IF shows a strong C3 reaction of mesangial and capillary walls

PO2217

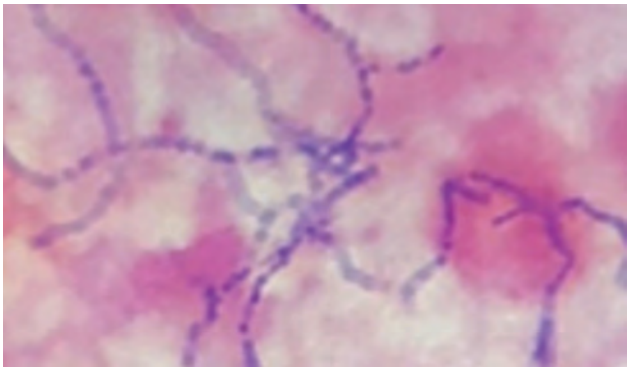
Rare Presentation of Disseminated Nocardia as Syndrome of Inappropriate Antidiuretic Hormone (SIADH) in Renal Transplant

Iskra Myers, Joseph C. Parker, Scott Richardson. *East Carolina University, Greenville, NC.*

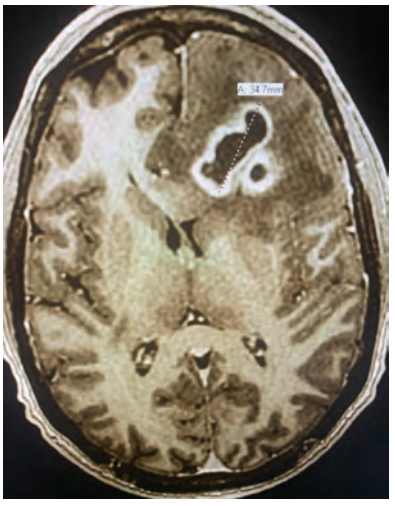
Introduction: Nocardia is a rare opportunistic pathogen that typically affects the immunocompromised host. Recently, Williams et. al. reported a third of patients have disseminated cerebral nocardiosis at presentation with most common isolate Farcinica species. SIADH has been reported in association with disease progression.

Case Description: A 31-year-old renal transplant recipient presented 4 years post-transplant with dyspnea and left upper extremity jerking. Immunosuppressives (IS) included Mycophenolate, Tacrolimus and Prednisone. He had non focal exam. Blood work showed Na 129, Uosm 500 mosm/kg, UNa 92. MRI brain showed multiple lesions, largest in left frontal area. CT chest revealed right pleural effusion. Biopsy of resected brain abscess and pleural fluid analysis both confirmed Nocardia Araoensis and Bejingensis. Imipenem and Bactrim were started, IS regimen was tapered down. Repeat scans month later showed resolution of vasogenic edema, pleural effusion and SIADH.

Discussion: Cerebral nocardiosis is life-threatening opportunistic infection that often presents with no specific clinical signs to guide diagnosis. High index of clinical suspicion is the key to early diagnosis. Presence of SIADH should prompt search for Nocardia which needs to be identified down to its species for targeted antibiotic treatment.



Branching g+ rod on gram stain, Nocardia.



Left frontal ring-enhancing lesion.

PO2218

Disseminated Mycobacterium Avium Complex in a Renal Transplant Patient with Subsequent Immune Reconstitution Inflammatory Syndrome Post Transplant Nephrectomy

William G. Middleton, Sridevi Govindarajulu. *Toowoomba Health Service, Toowoomba, QLD, Australia.*

Introduction: *Mycobacterium avium* Complex (MAC) are a group of pathogenic mycobacteria present in soil and water. Infection can present with respiratory symptoms, but in immunocompromised patients disseminated disease with fevers, weight-loss or diarrhoea is more common. Immune Reconstitution Inflammatory Syndrome (IRIS) is an excessive but protective inflammatory response against an existing pathogen when immune function is restored. It is usually seen in patients with Human Immunodeficiency Virus but has been described in renal transplant patients with MAC infection. It can lead to hypercalcaemia via increased macrophage 1α-hydroxylase activity, causing increased $1,25(OH)_2D_3$ production.

Case Description: A 54-year-old male presented 3 years post renal transplant with recurrent fevers, night sweats and pancytopenia with a haemoglobin of 76 g/L, leucocytes of $1x10^9$/L and platelets of $72x10^9$/L. He was on Tacrolimus, Mycophenolate and Prednisolone, and was previously treated with anti-thymocyte globulin for cellular rejection. Bone marrow and blood cultures were positive for MAC at 8 weeks. He was started on clarithromycin, ethambutol and rifampicin, with reduction in immunosuppression. Blood cultures were negative 1 month post anti-MAC therapy. He represented 7 months later with fevers and 22lb weight loss. Extensive bloodwork was negative. Computerised Tomography showed cervical lymphadenopathy and mesenteric stranding. Non-necrotising granulomas were demonstrated on fine needle aspirate of both a cervical lymph node and bone marrow, in keeping with disseminated MAC. Transplant nephrectomy was performed to allow cessation of immunosuppression. Renal histology showed granulomatous interstitial nephritis. He had ongoing fevers and hypercalcaemia for 1 month post nephrectomy with albumin corrected calcium of 3.32 μmol/L. Septic screen was negative. He was treated with oral prednisolone for suspected IRIS with resolution of symptoms.

Discussion: Disseminated MAC is a rare but life-threatening infection in renal transplant recipients that can require nephrectomy for cessation of immunosuppression. Non-tuberculous mycobacteria can take 6 weeks to culture and require specific culture media. Differentiation of IRIS vs drug resistance as a cause of persistent fevers is important.

PO2219

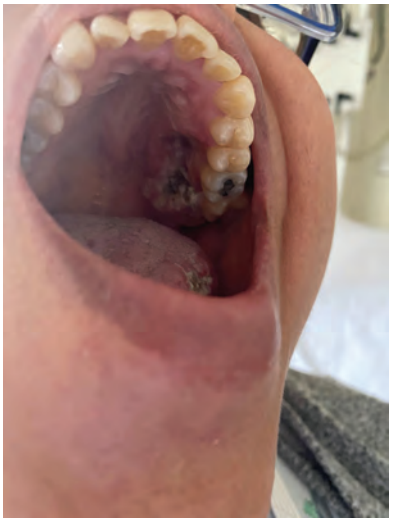
A Very Rare Presentation of Oral Invasive Aspergillosis Immediately Post Kidney Transplant

Walaa S. Dabbas, Zahraa F. Hajjiri, Prerna Kumar, Sajid Q. Ansari, Ruchi H. Naik. *University of Illinois at Chicago, Chicago, IL.*

Introduction: Although oral candida infection is very common opportunistic infection after kidney transplant, there are incidences of other fungal infections like aspergillosis, cryptococcosis, histoplasmosis, coccidioidomycosis, Blastomyces dermatiti etc. that are also important to be considered. Here we are reporting a very rare presentation of oral aspergillosis in very early phase post Kidney transplant.

Case Description: 38 years old Hispanic female with history of systemic lupus erythematosus and lupus nephritis since 2005, last lupus flare in June 2020 was treated with rituximab and high dose prednisone followed by maintenance with azathioprine and hydroxychloroquine. She received preemptive directed deceased donor kidney transplant in November 2020 with thymoglobulin induction followed by Tacrolimus and Mycophenolate mofetil maintenance therapy. 1 month post-transplant she received pulse dose intravenous Methylprednisone for acute T cell mediated rejection and prednisone was added to her maintenance immunosuppressive regimen. 2 months later she presented with a necrotic lesion with pain over the hard palate with a couple of more oral lesions with similar characteristics. she underwent debridement with excision and biopsy that confirmed oral aspergillosis. She was treated with isavuconazole for 3 months. The oral lesions eventually recovered after 12 weeks of treatment.

Discussion: Oral aspergillosis is very rare but associated with high morbidity and mortality if not treated timely. The diagnosis is based on tissue culture and histopathologic findings. The treatment is surgical combined with systemic fungal therapy for at least 3-6 months. Our patient developed the infection early post kidney transplant due to her recent extensive immunosuppression before and after kidney transplant.



PO2220

Simultaneous Occurrence of Actinomyces Gastritis and Severe Rejection in a Kidney Pancreas Transplant Recipient

Ravi K. Thimmisetty, Zohreh S. Soltani, Catherine G. Staffeld-Coit, Jorge C. Garces. *Ochsner Medical Center - New Orleans, New Orleans, LA.*

Introduction: We are presenting a 33 year old lady with history of Kidney Pancreas transplant admitted for rejection treatment and found to have co infection, actinomyces and CMV in gastric mucosa. Patient was managed well with modified net immunosuppression and discharged safely on long term antibiotics.

Case Description: 33 year old woman with h/o stage V CKD from type I diabetes mellitus had Simultaneous kidney pancreas transplant in 2018 admitted directly from clinic for rejection treatment. admission vitals were temperature 97 f, blood pressures of 151/99, heart rate 83, respiratory rate 18, on room air. exam unremarkable. home Immunosuppression is cyclosporine, sirolimus and prednisone. baseline creatinine

is 1.1-1.3 mg/dl. Admission creatinine is 5.0, BUN 33, lipase 290, amylase 124, cyclosporine level is 52, sirolimus level < 2, immuknow cylex 332, HbA1C is 5.3, c peptide is 3.13. renal biopsy showed acute cellular rejection, moderate microvascular inflammation, C4d positive, acute antibody mediated rejection. Class I and II DSA were positive. she got 3 doses of solumedrol, 3 doses of thymoglobulin, 2 sessions of plasmapheresis. She was found to have group B streptococcal bacteremia. Removed central line. CT scan of abdomen and pelvis was done for chronic abdominal pain showed diffuse gastritis or infiltrative disease such as gastric lymphoma. EGD showed gastric ulcer with Actiomyces colonization. Biopsy of gastric mucosa showed reactive gastropathy, purulent exudate, ample Actinomyces colonies, No lymphoma or cancer. CMV viral inclusions also seen. Serum CMV PCR negative. Further rejection treatment was placed on hold. Scheduled 2 doses of IV IG outpatient and resume mycophenolate mofetil as an outpatient after finishing antibiotics. Discharged with cyclosporine, prednisone, long term IV ampicillin, valcyte and follow up EGD in 4 weeks. Outpatient renal transplant biopsy was scheduled after completion of antibiotics to assess rejection. creatinine was plateud around 3.4. lipase and amylase were normalized.

Discussion: Actinomycosis is considered an endogenous, opportunistic infection of immunocompromised patients. Incidence is about one per 500 000 (0.0002%) in developed countries. Prevalence of actinomycosis was around 0.02% in transplant recipients. Infections alter the management and outcome of graft rejections.

PO2221

Recurrent Renal Allograft Torsion After Simultaneous Kidney and Pancreas Transplantation: Is Still Possible to Salvage the Graft?

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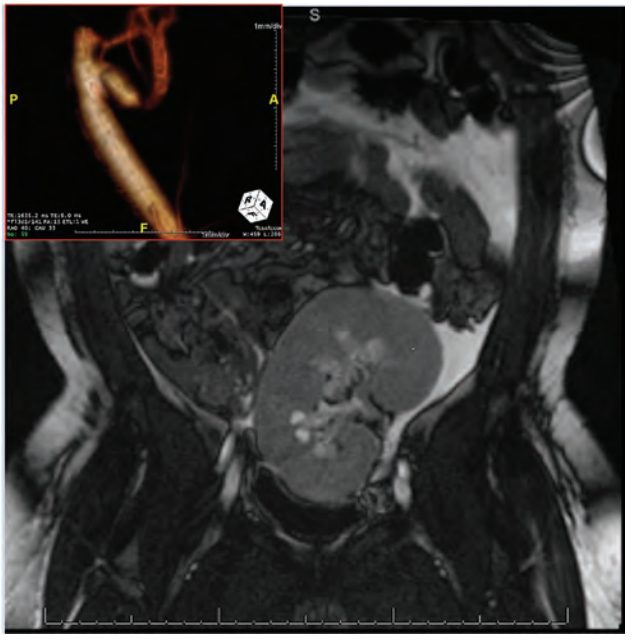
Introduction: Kidney Allograft Torsion (KAT) is defined as a rotation of the renal allograft around its vascular pedicle. It is a rare complication with high rate of graft loss. The nonspecific presentation and inability to provide a definitive diagnosis by imaging, mainly in cases of partial torsion, often delay the diagnosis and treatment. We report a case of recurrent complete torsion of the renal allograft after simultaneous kidney and pancreas transplantation (SKPTx), requiring two emergency exploratory laparotomies.

Case Description: A 38-year-old woman with a history of intraperitoneal SKPTx underwent two separate emergency exploratory laparotomies secondary to complete renal allograft torsion, respectively seven and eleven months after the transplant. In both episodes, no adhesions were encountered. During the first operation, nephropexy was performed. During the second operation, an abdominal wall mesh was placed and fixed to the abdominal wall. Acute kidney injury (AKI) related to KAT recovered in both occasions with a creatinine of 1.3 mg/dl at four months follow-up.

Discussion: Renal torsion should be always suspected in intraperitoneally placed kidneys presenting with nonspecific symptoms, abdominal pain, oliguria and worsening kidney function. Surgical exploration should be considered to salvage the renal graft. This case illustrates the reversibility of a severe injury related to this vascular complication with an adequate return to baseline kidney function even when diagnosis and surgical treatment of KAT might be delayed secondary to its misleading clinical presentation.



PO2222

New-Onset Antibiotic Anaphylaxis Post Kidney Transplant: A Role of Calcineurin Inhibitors?

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Introduction: Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporin, are a mainstay of post-transplant immunosuppression. Immunosuppressive medications typically suppress type I allergic reactions, however, there have been reports of allergic sensitization post-transplantation, despite no known drug allergies.

Case Description: We report two cases of antibiotic-related anaphylaxis post kidney transplant. In case one, a 63-year-old male was admitted for an elective transurethral prostate resection having received an NDD renal allograft two-months prior and maintained on tacrolimus, mycophenolate and prednisone. Preoperatively, cefazolin was given for antibiotic prophylaxis, but he developed an anaphylactic reaction leading to hemodynamic collapse requiring ICU admission. Serum tryptase (37.6ug/L, normal <11.4ug/L) and histamine (20.4ng/mL, normal <1ng/mL) levels were markedly elevated confirming anaphylaxis. In case two, a 56-year-old male received a DCD renal allograft (on immunosuppression with prednisone, mycophenolate and tacrolimus), eleven months prior to admission for suspected sepsis. He was empirically treated with ceftazidime and vancomycin but developed an anaphylactic reaction, requiring intubation and ICU admission. Serum tryptase and histamine levels were not assessed. A comprehensive medication review revealed that both patients had received the offending antibiotics without issues prior to transplantation. In both cases, neither donor had a documented allergy to these medications.

Discussion: In these clinical vignettes, we describe two patients with anaphylaxis post transplantation, despite previously tolerating the offending medications without issue. Furthermore, these reactions were not donor derived. Type I allergic reactions are typically suppressed post-transplant, yet there is literature to suggest that allergic sensitization maybe mediated by CNIs. The rates of sensitization are cited to be as high as 10% in liver and kidney recipients. Risk factors for sensitization are not described, although we note both of our patients had anaphylactic events within one-year post transplant. Given the importance of CNIs in allograft immunosuppression balanced against the morbidity of anaphylaxis, these cases highlight the need to better identify high risk patients for such events.

PO2223

Immunosuppression Cessation During Chemotherapy for Post-Transplant Lymphoproliferative Disorders in Kidney Transplant Recipients

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Introduction: Kidney transplant patients have a 20-fold higher risk to develop Post-Transplant Lymphoproliferative disorder (PTLD). PTLD requires reduction in immunosuppression (IS) medications to the lowest dose that prevents rejection. Here we report the safe withdrawal of IS in three kidney transplant recipients with PTLD receiving chemotherapy.

Case Description: Case 1: A 44-year-old male received a deceased donor renal transplant with alemtuzumab induction. He developed cellular rejection that was treated with steroids and thymoglobulin. He was maintained on cyclosporine, mycophenolate, and prednisone. Later on, he developed resistant EBV viremia and a retroperitoneal mass with diffuse lymphadenopathy. Biopsy revealed a high-grade, EBV-negative, monomorphic diffuse large B cell lymphoma (DLBL). IS medications were stopped except for low-dose prednisone. Creatinine remained stable post six cycles of chemotherapy, with complete response after three cycles. Case 2: A 59-year-old male with a history of membranous nephropathy (MN) treated with rituximab. Received a living-related donor renal transplant (LRDRT), with alemtuzumab induction. MN recured three years after transplantation and was treated with modified Ponticelli protocol. He was maintained on cyclosporine and mycophenolate. Ten years post-transplant, he had a large mesenteric soft tissue mass with lymphadenopathy. Biopsy showed EBV-negative, monomorphic high-grade DLBL. IS medications were stopped. The patient received six cycles of chemotherapy and achieved a complete response. Creatinine remained at baseline. Case 3: A 36-year-old male with a history of IgA nephropathy, received a LRDRT with alemtuzumab induction. He was maintained on tacrolimus and mycophenolate. Five months later, he was diagnosed with stage IIIB, EBV-positive, monomorphic DLBL via tonsillar mass biopsy. IS medications were stopped and he went into complete remission after eight cycles of chemotherapy. He was started on sirolimus monotherapy post-chemotherapy. Creatinine remained at baseline for five years.

Discussion: IS withdrawal seems to be a safe option during chemotherapy for PTLD. Chemotherapy causes prolonged immunosuppression or immune tolerance to the allograft. The safe cessation of IS while receiving chemotherapy for PTLD has been described, with reinstitution of low-dose IS post-remission.

PO2224

Sirolimus and Chyloperitoneum: A Rare Pair

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Introduction: The mammalian target of rapamycin inhibitors (mTORi) are associated with complications like hyperlipidemia, lymphoceles, lymphedema and rarely chylous ascites (CA), characterized by a milky colored, triglyceride (TG) rich fluid leading to dehydration, electrolytes imbalances and immunosuppression. We present a case of sirolimus induced chyloperitoneum in an ESKD patient.

Case Description: 44 year old woman with heart failure reduced ejection fraction (HFrEF) secondary to transposition of great vessels and orthotropic heart transplant in 2007, NASH cirrhosis and ESKD from calcineurin inhibitor toxicity, switched to sirolimus in 2018. Renal function declined requiring initiation of peritoneal dialysis (PD) in December 2020. 3 months prior patient presented with right upper extremity (RUE)/ipsilateral breast swelling, erythema and dull pain. US doppler ruled out DVT. Lymphangitis/cellulitis was suspected, started antibiotics with some improvement. Lymphoscintigram showed diffuse skin/right breast soft tissue edema. PD catheter was placed, incidentally found mild clear ascites, liver cirrhosis and bilateral ovarian cysts, work up for malignancy was negative and discharged. She trained for PD and effluent for KT/V had milky appearance. Fluid anlaysis showed nucleated cell count 1151mcL, RBCs 1391mcL, total protein 2.4g/dl, albumin 1g/dL, amylase <30u/L, glucose 160mg/dL, LDH 248IU and TG level 141mg/dl consistent with CA. Sirolimus was held and 2 weeks after PD fluid cleared and RUE lymphedema slowly improved with right breast enlargement to date.

Discussion: CA results from disruptive lymphatic system and posterior leakage of lymph into the abdominal cavity. Diagnosis requires TG levels >110mg/dl and gold standard imaging test is lymphangiography. Multiple etiologies are proposed: malignancy, traumatic surgical injury, liver cirrhosis and cardiovascular disease. Less common, mycobacterium infections and medications (mTORi, calcium channel blockers). Sirolimus causes disruption in proliferative signals required to seal perivascular lymphatics leading to high rates of lymphedema/lymphoceles. This explains RUE/ipsilateral breast swelling in our case. As the PD fluid cleared after stopping the sirolimus, it was deemed the cause. Cornerstone of therapy is correcting underlying cause. Presence of CA warrants immediate attention and targeting underlying cause, crucial for rapid recovery and avoiding complications.

PO2225

Renal Transplant Recipient with Large Periorbital Basal Cell Carcinoma (BCC) Cured Nonsurgically with Vismodegib

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Introduction: Renal transplant recipients (RTR) live a delicate balance between preserving allograft function with immunosuppression medications (IS) and the side effects (e.g malignancies), Skin cancers are prevalent with Squamous (SCC) & BCC (SCC), comprising 90% of skin cancers. These tumors are aggressive, exhibiting unique pathophysiologic characteristics. We present a case of a RTR who developed invasive periorbital BCC; successfully treated with novel chemotherapeutic Vismodegib

Case Description: A 66-year-old man with history of kidney transplant had a stable graft function with Cr 1.6 on IS for 35 years, on Prednisone and Tacrolimus. with a history of recurrent SCC and BCC treated with surgical and radiation therapy, During clinic, he was found to have a large tumor in the lateral canthus of the left eye. Patient was referred to dermatology, biopsy evealed BCC. Tumor grew rapidly, further invading the eye within a few weeks. Given the proximity to visual organs; ENT, Ophthalmology, Dermatology, and Transplant team decided to treat the BCC non-surgically with Vismodegib. Patient achieved complete remission in 6 months of treatment with successful preservation of eyesight.

Discussion: Surgical excision is considered first line therapy in BCC. Patients with periocular BCC can place visual organs at risk with surgical and/or radiotherapy. Vismedogib is indicated for metastatic BCC or locally advanced BCC that has recurred following surgery. Vismedogib binds and inhibits the smoothened receptor, leading to hedgehog signaling pathway inhibition and decreased tumor cell proliferation. Recent studies assessing Vismodegib benefit recruited patients with median tumor size of 22mm. Our case highlights that Vismedogib is efficacious in preserving essential visual structures and eyesight even in much larger tumor burden; 55mm. In conclusion, Vismodegib is now emerging in critical management of large and fast growing BCC affecting vital facial structures, especially in RTR on long term IS meds.

PO2226

Psychosis as a Neurotoxic Manifestation of Extended-Release Tacrolimus

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Introduction: Tacrolimus is a calcineurin inhibitor used in renal transplant to reduce the risk of rejection. Common side effects include infection, nephrotoxicity, and neurotoxicity (7). The neurotoxic effects can manifest as psychosis, paranoia, and bipolar mania (4, 2). The unpredictable nature of tacrolimus pharmacokinetics has led to the development of extended-release tacrolimus such as Envarsus XR (8, 9, 12). While data is lacking, Envarsus XR is thought to have a lower incidence of neurotoxic side-effects (10, 1, 11). To our knowledge, there are no recorded cases in the literature of psychosis related to Envarsus XR (3,6). We present a case of acute paranoia secondary to Envarsus XR.

Case Description: Ms. H is a 62 year old woman who underwent allogenic renal transplant and was placed on immediate-release tacrolimus 0.5 mg twice daily. Due to high tacrolimus levels (average 9.6 ng/dl) she was switched to Envarsus XR 0.75 mg daily and subsequently reported new onset emotional disturbance. She was initially treated with fluoxetine then switched to citalopram without relief. She then developed paranoid ideation and refused to sleep. The patient and family felt this behavior correlated with starting Envarsus XR. This was discussed with her transplant team and Envarsus XR was continued as her tacrolimus levels were within goal (average 5.3 ng/dl). Her paranoia worsened and she was seen by psychiatry and placed on risperidone 2 mg daily. She continued to experience paranoid delusions and behavioral disturbance. She was then switched from Envarsus XR back to immediate-release tacrolimus and had complete resolution of symptoms. Her current average tacrolimus level is 5.05 ng/dl.

Discussion: This case presents a unique instance of extended-release tacrolimus induced psychosis. While immediate-release tacrolimus is well known to cause neurotoxicity (5, 13), extended release is generally felt to be safer (12, 9). This case illustrates that while extended-release Tacrolimus formulations may have a reduced incidence of neurological side effects, they are not devoid of them. The SIMPLE trial is currently ongoing and its data may shed more light on tacrolimus induced neurotoxicity (10). Regardless of the outcome of this research, the treatment for tacrolimus induced neurotoxicity should always be to decrease the dose or withdraw the medication (14).

PO2227

Deep Learning Identifies Pathological Abnormalities Predictive of Graft Loss in Kidney Transplant Biopsies

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Background: Interstitial fibrosis, tubular atrophy, and inflammation are major contributors to renal allograft failure. Here we seek an objective, quantitative pathological assessment of these lesions to improve predictive utility.

Methods: We constructed a deep-learning-based pipeline recognizing normal vs. abnormal kidney tissue compartments and mononuclear leukocyte (MNL) infiltrates from Periodic acid-Schiff (PAS) stained slides of transplant biopsies (training: n=60, testing: n=33) that quantified pathological lesions specific for interstitium, tubules and MNL infiltration. The pipeline was applied to 789 whole slide images (WSI) from baseline (n=478, pre-implantation) and 12-month post-transplant (n=311) protocol biopsies in two independent cohorts (GoCAR: 404 patients, AUSCAD: 212 patients) of transplant recipients to correlate composite lesion features with graft loss.

Results: Our model accurately recognized kidney tissue compartments and MNLs. The digital features significantly correlated with Banff scores, but were more sensitive to subtle pathological changes below the thresholds in Banff scores. The Interstitial and Tubular Abnormality Score (ITAS) in baseline samples was highly predictive of 1-year graft loss (p=2.8e-05), while a Composite Damage Score (CDS) in 12-month post-transplant protocol biopsies predicted later graft loss (p=7.3e-05). ITAS and CDS outperformed Banff score or clinical predictors with superior graft loss prediction accuracy. High/intermediate risk groups stratified by ITAS or CDS also demonstrated significantly higher incidence of eGFR decline and subsequent graft damage.

Conclusions: This deep-learning approach accurately detected and quantified pathological lesions from baseline or post-transplant biopsies, and demonstrated superior ability for prediction of post-transplant graft loss with potential application as a prevention, risk stratification or monitoring tool.

Funding: Other NIH Support - NIH 5U01AI070107-03

PO2228

Dual Diagnosis of Thrombotic Thrombocytopenic Purpura and Atypical Hemolytic Uremic Syndrome in Pregnancy

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Introduction: Thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) are thrombotic microangiopathy (TMA) disorders which may initially occur in pregnancy. TTP, caused by severe ADAMTS13 deficiency, is treated with plasma exchange (PEX); whereas aHUS, caused by uncontrolled complement activation, is treated with complement inhibition (e.g., eculizumab). Because TTP and aHUS have different causes, the term TTP-HUS is no longer used. However, we describe a patient diagnosed and treated for both TTP and aHUS in pregnancy.

Case Description: A 38-year-old female at 9 weeks' gestation presented with hematuria. Labs revealed severe thrombocytopenia (platelets 5 k/μl), hemolytic anemia, and acute kidney injury. TTP was suspected, so PEX was initiated, but she did not fully respond (Fig 1). ADAMTS13 activity was low (11%) but with negative inhibitor, arguing against acquired TTP; genetic testing ruled out congenital TTP. Complement-mediated TMA (aHUS) was considered given low C3, C4, and proteinuria; Lupus and Anti-Phospholipid Syndrome were ruled out. Complement genetic testing revealed a rare C3 variant and polymorphisms in CFH and MCP, which are enriched in aHUS patients. After multidisciplinary review, the diagnosis of aHUS was made. PEX was stopped, and eculizumab was started with good response. At 35 weeks' gestation she presented with hypertension and petechiae, and labs showed recurrence of hemolytic anemia and thrombocytopenia (platelets 7 k/μl). She had cesarean delivery, after which PEX was initiated given renewed concern for TTP. ADAMTS13 activity was <5% with positive inhibitory antibody, now confirming acquired TTP. Eculizumab was stopped, and she received 14 cycles of PEX, prednisone, and rituximab for refractory TTP (Fig 1). Treatments were stopped after 6 weeks, and she remains in remission after 1 year.

Discussion: This case illustrates dual diagnosis of TTP and aHUS in pregnancy. Key points: a) Rarely, TTP and aHUS may coexist; b) ADAMTS13 activity and complement genetic testing may help identify TMA etiology; and c) Treatment of TMA in pregnancy with PEX or complement inhibition should be clinically-based.

Clinical course

PO2229

Pregnancy-Associated Atypical Hemolytic Uremic Syndrome in the Setting of a Rare THBD Mutation and Successful Treatment with Eculizumab

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Introduction: Pregnancy-associated atypical hemolytic uremic syndrome (PaHUS) is a rare but fatal thrombotic microangiopathy that results from uncontrolled complement activation during the peripartum and postpartum periods. Underlying complement gene mutations are found in a majority of cases. THBD, the gene responsible for encoding thrombomodulin, is a known risk variant associated with PaHUS. We present a case of PaHUS complicated by intrauterine fetal demise and acute renal failure in the setting of a rare THBD gene variance which was successfully treated with the terminal complement inhibitor eculizumab.

Case Description: 20-year G1P0 female presented at 30w4d with severe abdominal pain and diffuse vaginal bleeding. An emergent cesarian section revealed a placental abruption with intrauterine fetal demise. Hospital course was complicated by anuria with a maximum serum creatinine 8.43 mg/dL, hemoglobin 5.5 g/dL, platelets 15 x10^3/uL, lactate dehydrogenase 9051 U/L, and schistocytes seen on peripheral smear. She was initiated on renal replacement therapy, daily plasma exchange, and steroids. Despite this, she experienced persistent hemolysis, dialysis dependence, and worsening respiratory failure ultimately requiring intubation. ADAMTS13 activity was normal at 83%. Eculizumab was initiated, and after one week, hematologic parameters normalized with evidence of renal recovery. Outpatient genetic testing revealed a rare variant in THBD. Six months following discharge, the patient remains in remission on maintenance eculizumab.

Discussion: The diagnosis of PaHUS is very challenging; however, prompt recognition and subsequent genetic testing for complement variants are crucial given association with more severe outcomes, progression to ESRD, and increased risk of relapse. Pathologic variances in THBD account for 5% of aHUS cases and have been associated with earlier onset and higher mortality, however, risk of disease relapse with mutations in this gene is unknown. Although eculizumab has been shown effective in PaHUS, there is little data on treatment duration and recurrence rate with therapy in subsequent pregnancies. Further expansion of genetic testing is required to enhance our knowledge of all PaHUS susceptibility factors and improve management of patients similar to the presented case.

PO2230

Efficacy of Eculizumab Therapy in Delayed-Diagnosed, Hemodialysis-Dependent, Pregnancy-Triggered, Complement-Mediated Thrombotic Microangiopathy

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Introduction: Pregnancy associated atypical hemolitic uremic syndrome (p-aHUS) is provoked by pregnancy and affects 1/25,000 pregnancies in the general population. The delivery is vital for halting the disease process. The course of complement-mediated thrombotic microangiopathy(C-TMA) is not affected by delivery, but condition improves with anti-complement therapy. We are presenting a rare case of delayed diagnosed, pregnancy provoked C-TMA with significant improvement in blood pressure, stabilization of anemia, and resolution of thrombocytopenia after treatment with Eculizumab.

Case Description: A 25-year-old Hispanic woman with history of CKD stage IIIB presented with syncope. She developed renal failure, required hemodialysis(HD) and HTN during her first pregnancy. During postpartum, HD was stopped and HTN resolved. Two years later she was admitted with worsened renal function, severe anemia (Hb 4 g/dl), thrombocytopenia (36K/ul), and poor controlled HTN, needing 6 different classes of drugs to control her blood pressure. Blood smear showed schistocytes. Our extensive work up ruled out: TTP, HUS, DIC, lupus, scleroderma, and other disorders. Complement 3 was low. Renal ultrasound excluded post-renal obstruction and renal artery stenosis, but showed echogenic kidneys. Given echogenic kidneys and increased bleeding risk, renal biopsy was not performed. The diagnosis of C-TMA was established. Regular HD was resumed. She was started on Eculizumab and with maintenance treatment her HTN became well controlled with only two medications.

Discussion: Timely diagnosis and management are the key points to improve C-TMA prognosis. It may be a difficult diagnosis and mimic eclampsia, HELLP syndrome, or p-aHUS. Although it is related to inherited defects of complement alternative pathway or the proteins that regulate it, lack of linked gene mutations cannot exclude C-TMA. In this patient, the diagnosis of C-TMA was not made until two years after onset. Our case report showed that even though Eculizumab cannot completely reverse the renal injury at the late stage of C-TMA, it may still improve the blood pressure control, normalize platelets, help anemia, and prevent further injury.

parameters	before Eculizumab	Eculizumab induction dose (900mg/week)				Eculizumab maintenance dose (1200mg/ every 2 weeks)		
	Day 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Hb (g/dl)	7.6	7.3	7.9	8.2	9.1	7.7	9.1	10.1
PLT	91	91	85	68	108	73	183	156

PO2231

Therapeutic Plasma Exchange Improved Pregnancy Outcomes in a Patient with Triple Positive Anti-Phospholipid Antibody Syndrome

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Introduction: Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by antibodies directed at platelet, monocyte, endothelial cell, and trophoblast moieties potentially causing venous and arterial thromboses. The placental vasculature is particularly vulnerable to these antibodies resulting in a marked increased risk of fetal growth restriction, placental infarction, abruption, stillbirth, and preterm severe preeclampsia. APS is diagnosed by clinical criteria in conjunction with laboratory findings, and the circulating anti-phospholipid antibodies commonly tested are lupus anticoagulant, anti-cardiolipin, and anti-beta-2-glycoprotein-1. The simultaneous presence of all three antibodies is associated with the highest risk of thrombotic complications in APS.

Case Description: A 29-year-old nulligravida with medical history was significant for APS on lifelong coumadin. Her APS labs at the time of preconception visit showed elevated lupus anticoagulant ratio, anticardiolipin and anti-beta2-glycoprotein-1antibodies (Triple- positive antibodies). Medications included twice daily LMWH 60 mg and hydroxychloroquine 200 mg. Fetal anatomic survey at 20 weeks demonstrated normal fetal growth, however, by 21 weeks 6 days ultrasound showed absent-end diastolic flow of the umbilical artery Doppler waveform. She was admitted to the hospital. A pre-eclampsia workup was completed due to hypertension and new onset proteinuria. LDA daily, pravastatin 20mg was added. Due to the diagnosis of preeclampsia with severe features, the decision was made to treat with therapeutic plasma exchange.

Discussion: High-risk obstetric APS profiles are linked to specific serological markers such as triple antibody positivity, clinical features such as a history of thrombosis, and the presence of pregnancies result in a liveborn infant, with that rate dropping to 30% in patients who are triple systemic autoimmune diseases. Therapeutic plasma exchange every 48 hours successfully prolonged the pregnancy for 11 weeks, resulting in an optimal pregnancy outcome for both mother and infant given the initial dire clinical situation at a pre-viable gestation. The rationale for TPE every 48 hours was based on the experience in plasmapheresis use in Catastrophic Antiphospholipid Syndrome (CAPS)

PO2232

Lupus Nephritis Kidney Biopsy Characteristics and Preterm Birth

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Background: Lupus nephritis (LN) in pregnancy is associated with high rates of preterm birth (PTB). Hypocomplementemia, elevated creatinine, proteinuria and hypertension serve as risk factors. Outside of pregnancy, class IV LN and interstitial fibrosis at initial biopsy associate with progressive disease. We performed a retrospective chart review to assess if timing of kidney biopsy and histologic features increased PTB.

Methods: We included women with LN enrolled in the Glomerular Disease Collaborative Network registry who delivered at University of North Carolina (UNC) Hospital from 2001-2019. Delivery data came from the UNC perinatal database. Fishers exact test assessed biopsy characteristics and PTB (< 37 weeks).

Results: There were 36 deliveries in 32 women. Figure 1 describes the cohort. Among preconception biopsies (n=25), pregnancy occurring ≤ 24m after biopsy was more likely to result in PTB than if biopsy was performed > 24m prior to conception (82% vs 29% p =0.02). A UPCR > 0.5 mg/g in the first trimester was also associated with PTB (81% vs 36% p=0.04). PTB occurred in 69% with proliferative LN vs 50% without (ie primary diagnosis class II or V), p=0.44. Class IV LN was not significantly associated with PTB; neither was the presence of crescents (n=21/36), activity ≥ 6 (n=16/25), chronicity ≥ 3 (n=12/27), or more than mild interstitial sclerosis (n=6/33).

Conclusions: Biopsy occurring within 2 years of conception and first trimester proteinuria were significantly associated with PTB. While this presumes greater LN activity, no specific biopsy characteristic impacted the outcome. This data may aid in preconception counseling for optimal timing of conception. Calcineurin inhibitors were not used in the first trimester in this cohort; their antiproteinuric qualities and effect on PTB requires evaluation.

Characteristic by delivery (n=36)	%
Maternal race	
African American	56%
Caucasian	19%
Hispanic/Latino	16%
Other	9%
Multigravida	56%
Singleton gestation	94%
Biopsy timing	
Preconception	69%
During pregnancy	6%
Postpartum	25%
Biopsy primary classification	
Class II	3%
Class III	22%
Class IV	50%
Class V	25%
First trimester	
Creatinine* (mg/dl) (n=28)	0.63 (0.55-0.89)
Urine protein-to-creatinine ratio* (mg/g) (n=27)	0.86 (0.20-2.40)
Low C3 (n=27)	48%
Chronic hypertension (n=30)	50%
Hydroxychloroquine (n=32)	75%
Prednisone (n=32)	47%
Azathioprine (n=32)	25%
Calcineurin inhibitor (n=32)	0%
Delivery (n=36)	
Maternal age† (years)	26.8 ± 4.8
Cesarean section	47%
Preterm birth (< 37 weeks)	64%
Gestational age† (weeks)	33.8 ± 4.6
Birth weight† (grams) (n=38)	2047 ± 864

*Median (interquartile range); †Mean ± standard deviation

PO2233

Second Trimester eGFR and Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus

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Background: Adverse pregnancy outcomes are more common in women with SLE.2nd trimester eGFR was shown to predict adverse pregnancy outcomes in a general population cohort. We sought to evaluate 2nd trimester eGFR as a predictor of adverse pregnancy outcomes in women with SLE.

Methods: We evaluated 684 women with SLE(22% of Black race)who received care in North America and Europe from 1995-2017.2nd trimester eGFR was stratified based on studies demonstrating women with an eGFR 120-135 ml/min/1.73m^2 had the lowest odds of adverse outcomes. Outcomes of interest included preterm birth, preeclampsia, fetal loss and poor pregnancy outcome(composite outcome). 2nd trimester GFR was computed using the CKD Epi equation without adjustment for race. In sensitivity analysis, 2nd trimester GFR computed using the conventional race-based equation. Polynomial and logistic regression models used to evaluate 2nd trimester eGFR and adverse outcomes.

Results: Very low eGFR(eGFR<90ml/min/1.73m^2)and very high eGFR (>135ml/min/1.73m^2)were associated with higher adverse outcomes. In univariate and multivariable regression models adjusted for age, race, and SLE disease activity, very low eGFR was associated with preterm birth, preeclampsia, fetal loss and poor pregnancy outcome. Very high eGFR was associated with poor pregnancy outcome and preterm birth. In sensitivity analyses using race based GFR estimates, very low eGFR remained associated with adverse outcomes observed. No association was observed between very high eGFR and adverse outcomes.

Conclusions: We found a U-shaped relationship between 2nd trimester eGFR and adverse pregnancy outcomes. Women with eGFR <90ml/min/1.73m^2 and >135ml/1.73m^2 had higher odds of adverse outcomes. 2nd trimester eGFR may be a helpful tool to identify women with SLE at greater risk for adverse outcome. Our results further suggest that kidney hyperfiltration may become pathologic during pregnancy. There were notable differences using non-race based and race-based GFR estimating equations. These differences may have clinical implications when utilizing GFR estimating equations to predict health outcomes.

Funding: Private Foundation Support

Association of 2nd Trimester eGFR and Adverse Outcomes

eGFR strata	Preterm Birth Unadjusted OR (95%CI)	Preeclampsia Unadjusted OR (95%CI)	Fetal Loss Unadjusted OR (95%CI)	Poor Pregnancy Outcome Unadjusted OR (95%CI)
Very Low eGFR<90	3.16 (1.63, 6.12)	2.91 (1.32, 6.37)	5.82 (2.28, 14.86)	3.79 (2.00, 7.19)
Low eGFR90-120	1.01 (0.67, 1.51)	0.83 (0.46, 1.52)	0.55 (0.19, 1.60)	0.92 (0.62, 1.35)
Normal eGFR 121-135	1.0	1.0	1.0	1.0
Very High eGFR>135	2.80 (1.55, 5.06)	1.69 (0.75, 3.81)	0.50 (0.06, 3.92)	2.19 (1.22, 3.92)

PO2234

Comparison of Clinical Features of Pregnant and Non-Pregnant Women with Primary Hyperoxaluria

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Background: Primary hyperoxaluria (PH) is a rare monogenic disease characterized by oxalate overproduction in the liver, hyperoxaluria, and risk of kidney stones and chronic kidney disease. Data about the effects of pregnancy on women with PH are lacking. We aimed to compare clinical features and risk of incident kidney failure in women with PH with and without pregnancy.

Methods: Women with PH were identified from the Rare Kidney Stone Consortium registry, and pregnancy was identified by phone interview and medical record review. Kidney survival and risk of time-dependent kidney failure were estimated using the Kaplan-Meier method and adjusted proportional hazard Cox's model.

Results: We identified 47 women with PH and a history of pregnancy and 39 women without pregnancy. PH was diagnosed later in women with pregnancy vs. women without pregnancy (median age 32.4 vs. 13.4 years, p<0.001). Other clinical characteristics such as PH type, eGFR and 24-hour urine oxalate excretion ($U_{[ox]}$) at PH diagnosis did not differ between the 2 groups. **Fig 1A** shows the time course of the PH diagnosis, pregnancy and kidney failure in 29 women with known delivery date. In women with pregnancy versus non-pregnancy, the hazard ratio for incident kidney failure was 0.81 (95% CI 0.25-2.6, p=0.73) when adjusted for PH type, age, and eGFR and $U_{[ox]}$ at PH diagnosis. Among patients with PH1 who did not have kidney failure by the time of the 1st pregnancy (n=20), kidney survival estimates at 10, 20, and 30 years after delivery were 79%, 60%, and 45%, respectively (**Fig 1B**).

Conclusions: These results suggest that pregnancy did not greatly impact renal prognosis in women with PH.

Funding: Other NIH Support - NIH grant U54KD083908, Commercial Support - The Oxalosis and Hyperoxaluria Foundation, a non-profit patient advocacy group

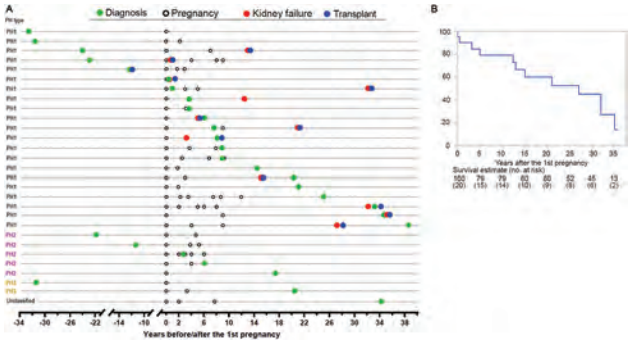

Fig 1. Time from first and last pregnancy to PH diagnosis and kidney failure in 29 women **(A)** and Kaplan-Meier plots of renal survival in PH1 patients who did not have kidney failure by the time of the 1st pregnancy **(B).**

PO2235

Narrowing Communication Gaps to Optimize Patient-Centered Pregnancy Counseling for Women with CKD

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Background: Women with chronic kidney disease (CKD) face unique pregnancy decision-making challenges. Although there is an increased risk of adverse pregnancy outcomes in women with CKD, many women report strong pregnancy desires. There is little evidence on how to support pregnancy communication and decision-making needs in women with CKD.

Methods: We performed semi-structured interviews with women 18-45 years of age who have CKD stages I-V (n=30), and their practicing nephrologists (n=12) at one academic medical center. The average age of patients was mean(SD) 32.4(6.9) years; 50% already had children. 50% (n=15) identified as white, 26.7% (n=8) as Black, 13.3% (n=4) as Hispanic, 6.7% (n=2) as Asian, and one declined to answer. CKD etiologies included lupus nephritis (n=7, 23.3%), other nephrotic/nephritic syndromes (n=9, 30%), diabetes (n=4, 13%), hypertension (n=3, 10%), other (n=4, 13%), and unknown (n=3, 10%). Interview questions probed patients about counseling experiences and reproductive health in CKD, approaches to pregnancy decision-making, barriers and facilitators to effective counseling, and desires for future support. A codebook was iteratively developed, with double coding of transcripts and discrepancies resolved via consensus.

Results: Most women with CKD preferred their nephrologist introduce the concept of reproductive planning to elicit their values in care and reduce barriers to pregnancy counseling. Specific information about individual pregnancy risks and risks to potential offspring were desired. Women with strong reproductive intentions more often sought pregnancy information and indicated a higher risk tolerance especially when compared to physicians. Among women considering pregnancy, discussion of risks alone without discussion of strategies to manage or mitigate risks was perceived as alienating. Nephrology providers acknowledged importance of patient pregnancy desires, however, prioritized decision-making communication about absolute numerical risks to patients, and expressed high risk-aversion.

Conclusions: Patient-provider pregnancy communication and decision-making are critical for women who have CKD. Further research is needed to ensure nephrologists have tools to support pregnancy decision-making that incorporates patients' needs, values and goals in care.

Funding: NIDDK Support

PO2236

Maternal Hypertension and Hypertensive Disorders of Pregnancy Are Associated with Increased Risk of Hypertension in Offspring

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Background: Hypertensive disorders of pregnancy (HDP) have significant effects on perinatal outcomes for offspring. Although there is increasing evidence of adverse effects of HDP exposure on long-term health outcomes in offspring, the impact of maternal hypertension beyond HDP is limited.

Methods: We performed a population-based cohort study of 7544 women with 8755 pregnancies from 1976 to 1982. HDP during each offspring's birth was identified using a previously validated algorithm. Diagnosis of hypertension in mothers (before or after the pregnancy) and in offspring was determined using diagnostic codes through 2019. Associations were evaluated using Cox proportional hazards models adjusted for maternal age at delivery, child's sex, fetal weight percentile and gestational age.

Results: Among offspring, the cumulative incidence of hypertension was 5.7% (95%CI 5.1-6.4%) by the offspring's age of 30, 9.5% (95% CI 8.7-10.3%) by age 35, and 16.2% (95% CI 15.0-17.5%) by age 40. HDP exposure at birth (HR 1.49, 95%CI 1.19-1.87) and maternal hypertension as a time-dependent covariate (HR 1.73, 95%CI 1.48-2.02) were associated with an increased risk of hypertension in offspring. Maternal hypertension was associated with a 1.6-fold (95%CI 1.37-1.92) increased risk of hypertension among offspring without HDP exposure compared to a 2.3-fold (95%CI 1.40-3.78) increased risk among offspring with HDP exposure; however this difference was not significant (p-interaction=0.18). We also performed a landmark analysis to evaluate maternal hypertension prior to age 55 as a static covariate. Compared to offspring without HDP exposure and without maternal hypertension prior to age 55, HDP exposure was not associated with risk of hypertension in offspring (HR 0.58, 95%CI 0.27-1.22) whereas maternal hypertension (HR 1.65, 95%CI 1.34-2.03) or the presence of both (HR 2.44, 95%CI 1.59-3.15) conferred an increased risk.

Conclusions: HDP exposure at birth and maternal hypertension are independently associated with an increased risk of hypertension in offspring. Our results suggest the possibility of an interaction effect for offspring exposed to HDP at birth and maternal hypertension, however this requires further research.

Funding: Other NIH Support - NIH Grant funding: Hypertensive pregnancy disorders and future cardiovascular risk

PO2237

Complement Genetic Variants and Hypertensive Diseases of Pregnancy

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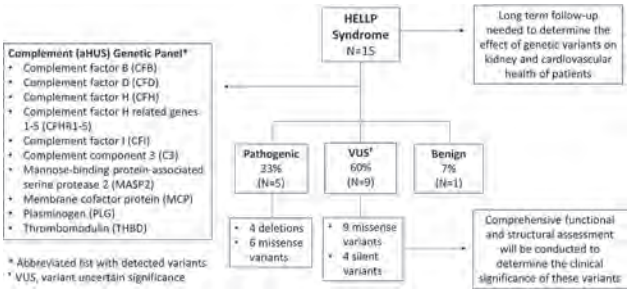
Background: Complement genetic variants are associated with thrombotic microangiopathy (TMA). Atypical hemolytic uremic syndrome (aHUS) is a classic complement-mediated TMA characterized by hemolytic anemia, thrombocytopenia and acute kidney injury. Clinical features of aHUS resemble those of preeclampsia and HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome. Therefore, we sought to determine if complement genetic variants also predispose to these hypertensive diseases of pregnancy.

Methods: We conducted genetic testing for 20 complement genes in a cohort of 15 women with HELLP syndrome (Fig 1). Patients were evaluated between April 2018 and September 2019 at our institution; those with a diagnosis of aHUS were excluded. Variants were classified on the basis of clinical significance, according to published American College of Medical Genetics guidelines. Based on these standards, variants are classified as, Level 1: pathogenic; Level 2: likely pathogenic; Level 3: variant of uncertain significance (VUS); Level 4: likely benign; Level 5: benign.

Results: At the time of index pregnancy with HELLP syndrome, patients were 36 ± 5 years old; twelve of 15 (80%) were nulliparous, and delivery occurred at 34 ± 5 weeks gestation. Five of 15 patients (33%) had a pathogenic variant, 9 (60%) had a variant of uncertain significance (VUS), and one (7%) had a benign variant. Homozygous deletion of CFHR1-CFHR3 was detected in four patients. Fifteen unique missense variants were detected in various genes, including C3, CFD, CFH, CFHR2, CFHR5, CFI, MASP2, and PLG. One patient with a pathogenic variant developed recurrent severe preeclampsia and one patient with a VUS developed recurrent HELLP syndrome.

Conclusions: These results reveal that overactivity of the complement system, due to an underlying genetic variant, may define a subset of patients that develop preeclampsia and HELLP syndrome. Long term follow-up of these patients is needed to evaluate the risk for future cardiovascular and kidney disease.



Flow Diagram

PO2238

Pregnancy Outcomes in C3 Glomerulopathy

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Background: C3 Glomerulopathy (C3G) is a glomerular disease characterized by underlying dysregulation of the alternative complement pathway. Most patients approach ESKD within ten years of diagnosis. Recurrence in renal transplants is high. Little is known of the role of pregnancy in the natural history of C3G or whether a coincident diagnosis affects comorbidities or maternal-fetal outcomes.

Methods: Female subjects in the University of Iowa's C3G Natural History Study who met consensus biopsy criteria (n=76) and had at least one pregnancy (n=17) were included in the cohort. Clinical and lab data, including genetic and/or acquired drivers of disease studies were assessed. Standard peri-pregnancy outcomes were considered.

Results: 44 pregnancies and 34 deliveries were identified. Non-live birth pregnancy outcomes included eight miscarriages, one ectopic pregnancy and one elective abortion. The presumed driver of disease was known for eight patients; gene variants of unknown significance (n=3), nephritic factors (n=4), and a monoclonal protein (n=1). Six patients presented first C3G symptoms during pregnancy. Preeclampsia developed in 11. Six infants were premature. Five were born with low birthweight. One infant suffered a stroke. One infant presented with AKI. [Maternal nephritic factor was identified in neonatal sera.]

Conclusions: We provide a summary of maternal-fetal outcomes in C3G mothers. Our data supports an increased risk of preeclampsia in C3G mothers as compared to healthy mothers. There was no excess risk of miscarriage, cesarean section, ectopic pregnancy, prematurity, or low birth weight. This data indicates a relatively higher risk of preeclampsia and lower risk of cesarean section compared to women with IgA Nephropathy. A similar risk of miscarriage, prematurity, and low birth weight as other glomerular diseases was evident. Our data supports a reasonable maternal-fetal risk profile for C3G patients.

Figure 1- Peri-Pregnancy Outcomes in C3G Mothers

	# of Pregnancies	# of Live Births	Average Age at Conception	First C3G Symptoms Before Pregnancy	First C3G Symptoms During Pregnancy	First C3G Symptoms After Pregnancy
n=	44	34	26	6	6	5
	n=	Sample %	Healthy %	p value	IgA Nephropathy %	p value
# of Preeclamptic Pregnancies	11	32.4%	4.0%	<.0001	9.0%	<.0001
# of Premature Infants	6	17.6%	9.8%	0.062	14.2%	0.290
# of Low Birth Weight Infants	5	14.7%	8.0%	0.075	13.1%	0.391
# of C-Sections	5	14.7%	17.0%	0.640	49.1%	<.0001
# of Miscarriages	8	18.2%	13.0%	0.276	15%	0.350

PO2239

Maternal Health in Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: Autosomal dominant tubulointerstitial kidney disease due to *MUC1* mutations (ADTKD-*MUC1*) and *UMOD* mutations (ADTKD-*UMOD*) are becoming increasingly recognized as causes of chronic kidney disease (CKD). Genetic testing allows women to determine if they are affected with these conditions, and data on the outcomes in pregnancy in ADTKD would be of great interest to them as they prepare for future pregnancies.

Methods: We surveyed women with ADTKD and genetically unaffected family regarding past pregnancy outcomes. We also analyzed survival to end-stage kidney disease (ESKD) according to number of pregnancies.

Results: We received completed standardized questionnaires surveys from 52 women with ADTKD-*MUC1* (113 pregnancies), 74 women with ADTKD-*UMOD* (136 pregnancies), and 35 genetically unaffected women (64 pregnancies). At the time of pregnancy, only 16.5% of genetically affected women were aware that they had ADTKD. Results are summarized in Table 1. There was a nonstatistical increase in HTN and hospitalization for HTN. 10% of births to affected mothers were premature vs. 0% in unaffecteds (p<0.01); 12% of babies required a NICU stay vs. 6% in unaffecteds (p=0.06), but child outcomes were good. Survival analysis showed no statistical differences in age to ESRD based on number of pregnancies for affected women.

Conclusions: Patients with ADTKD had an increased prevalence of hypertension, anemia, and early delivery than controls, but overall pregnancy outcomes were good for mother and child. More information is needed on changes in glomerular filtration rate with pregnancy in ADTKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

Characteristics and Pregnancy Complications Reported.

Characteristic	ADTKD-*MUC1*	ADTKD-*UMOD*	ADTKD-*MUC1* and ADTKD-*UMOD*	Unaffected	p-value with individual as cluster
Individuals (n)	35	50	85	23	
Pregnancies (n)	74	90	164	50	
Age during pregnancy	28.3±4.8 (n=73)	27.0±4.8 (n=88)	27.6±4.8 (n=161)	29.3±4.1 (n=50)	0.032
High blood pressure during pregnancy	8 (11%)	22 (24%)	30 (18%)	6 (12%)	0.54
New onset high blood pressure	6 (8%)	17 (19%)	23 (14%)	6 (12%)	0.71
Hospitalized for hypertension	3 (4%)	9 (10%)	12 (7%)	1 (2%)	0.13
Anemia	10 (14%)	9 (10%)	19 (12%)	1 (2%)	0.058
New anemia	8 (11%)	4 (4%)	12 (7%)	1 (2%)	0.10
Premature (<37 weeks)	8 (11%)	10 (11%)	16 (10%)	0	< 0.0001
Cesarean section	14 (19%)	17 (19%)	31 (19%)	19 (38%)	0.061
Neonatal intensive care admission	9 (13%)	10 (11%)	19 (12%)	3 (6%)	0.25

PO2240

Effect of Reproductive History on Kidney Structure and Function in Women

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Background: Varying estrogen levels from menarche to menopause and physiological changes of pregnancy may impact kidney health in women.

Methods: Female kidney donors from 2000 to 2017 were sent a survey on reproductive health, including menarche, pregnancy, and menopause. At the time of donation, donors had a medical evaluation, measured GFR, 24h urine albumin, CT angiography of kidneys, and a kidney biopsy. Kidney volumes were calculated from CT images. Non-sclerosed and globally sclerosed glomeruli counts and % interstitial fibrosis/tubular atrophy (IFTA) were assessed via kidney biopsy. Kidney function and structural findings at the time of donation were assessed by differences in reproductive factors prior to donation adjusting for age.

Results: There were 673 women studied with a mean (SD) age at donation of 47.4 (11.4) and 74% had at least one pre-donation birth. As compared to non-parous women, parous women had a higher total cortical volume (6.1%, p=0.009) and medullary volume (6.7%, p=0.038). However, among parous women, additional parity was not associated with further increases in kidney volumes. Among the 218 post-menopausal women, each year since menopause was associated with a higher likelihood of IFTA > 0% on biopsy independent of age (OR=1.052, p=0.027). With each 5-year increase in reproductive lifespan (years from menarche to menopause), there was a lower likelihood of having IFTA > 0% (OR=0.81, p=0.048). We did not find any significant association between past reproductive factors on GFR, urine albumin, glomerulosclerosis, or nephron number at the time of donation.

Conclusions: Past pregnancy is associated with larger kidneys among healthy women suggesting that the enlargement of kidneys with pregnancy does not fully resolve after delivery. Among healthy post-menopausal women, longer duration of menopause and shorter reproductive lifespan associated with detectable IFTA on kidney biopsy consistent with a protective effect of estrogen on preventing subclinical kidney injury.

Funding: NIDDK Support, Clinical Revenue Support

PO2241

Kidney Disease Prevalence in Transgender Individuals

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Background: Kidney disease in the transgender population is understudied which precludes the ability to derive appropriate care guidelines for promoting kidney health. The term transgender includes individuals for whom their assigned sex at birth doesn't align with their gender identity. Transgender individuals often choose gender-affirming hormone therapy (GAHT) to achieve greater alignment. The impact of this necessary treatment on their kidney health has not been studied.

Methods: We performed a cross-sectional study of 360 transgender individuals, using medical records from 2009-2019. Diagnosis codes were used to identify individuals with acute kidney injury (AKI) and chronic kidney disease (CKD), and comparisons were performed between the groups.

Results: The mean age of the population was 42 (SEM 0.91) and 40% were of black race. Black individuals made up a greater proportion of the transfeminine population who received GAHT but a lower proportion of transmasculine individuals who received GAHT. The transfeminine population receiving GAHT had a higher proportion of non-white/non-black populations than in the overall transfeminine population. There was a statistically significant difference in the prevalence of AKI in transfeminine individuals who received GAHT as compared to transfeminine individuals who did not receive exogenous GAHT; no such difference was found with CKD. In the transmasculine population, there was no statistically significant association of exposure to GAHT with prevalence of AKI or CKD. Transfeminine individuals who received GAHT showed a statistically lower prevalence of CKD than transmasculine individuals.

Conclusions: This single-center study of prevalence of kidney disease in the transgender patients demonstrates significant differences in kidney disease conditions in those who did vs. did not use GAHT. These studies highlight the need for further research to define the health and disease manifestations seen in the transgender population.

Funding: NIDDK Support

PO2242

Dietary Inflammatory Potential and the Risk of Incident ESKD in the Women's Health Initiative

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Background: Inflammation is implicated in the pathogenesis and progression of chronic kidney disease (CKD). Diet is an important modulator of chronic inflammation, and possibly kidney health. We evaluated the association of diet-associated inflammation with risk of incident end-stage kidney disease (ESKD) in the Women's Health Initiative (WHI) study.

Methods: Participants enrolled between 1993-1998 in the Observational Study and Dietary Modification Trial of the WHI with completed food frequency questionnaires (FFQs), Medicare enrollment data, and serum creatinine (sCr) measurements were included in our study. Dietary inflammatory potential was assessed from FFQs using the dietary inflammatory index (DII®). The index has been previously validated in the WHI. Medicare claims data were used to ascertain ESKD status. Analyses used DII® scores adjusted for energy-intake (E-DII®), which were categorized into quartiles (Q): scores in Q1 (reference group) having the lowest dietary inflammatory potential and Q4 being the most pro-inflammatory. We performed multivariable Cox proportional hazards models adjusted for important covariates of interest to compare dietary quartiles for risk of incident ESKD. Participants were censored at the time of study withdrawal, loss-to-follow-up, or death.

Results: Of the 15,722 women included in our study, the mean age was 64.2 years (standard deviation 7.01); 35% self-identified as African American, 12% as Hispanic/Latinx, and 50% as White; 40% had hypertension and 9% had diabetes mellitus at baseline. The mean baseline sCr and estimated glomerular filtration rate were 0.74 mg/dL and 89 ml/min/1.73m2, respectively. African American and Hispanic women compared to White women (30% vs 19%) were more likely to report consuming diets with scores in Q4. Over mean follow-up of 11.5 years, 515 women developed ESKD. Women with dietary patterns in Q4 compared to those in Q1 had a 20% higher risk of developing ESKD (hazard ratio 1.20 [95% confidence interval 1.05 – 1.38]; P=0.02) after adjusting for age, race/ ethnicity, comorbidities, body mass index, education, medications, trial vs cohort study status, and region.

Conclusions: A pro-inflammatory dietary pattern is associated with a higher risk of new-onset ESKD among Medicare-eligible post-menopausal women without baseline CKD.

PO2243

Age-Stratified Sex Differences in the Risk of Cardiovascular Disease in Patients with CKD

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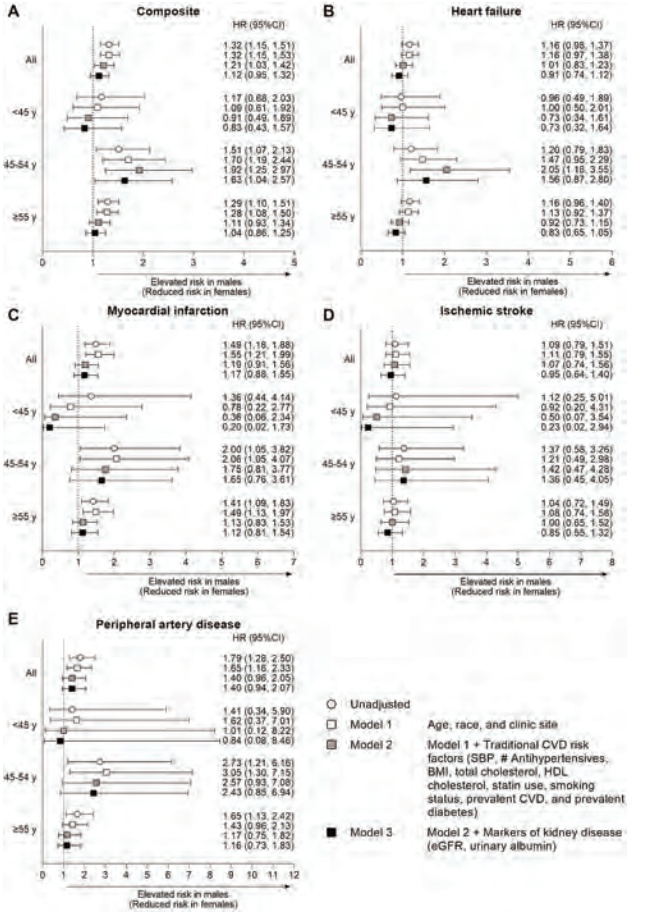
Background: In the general population, females (vs. males) and younger individuals have a lower cardiovascular risk. However, little is known whether this age- and sex-specific risk pattern of cardiovascular disease (CVD) translates to individuals with chronic kidney disease (CKD). The purpose of this study was to examine if sex-specific risk of CVD differed across the age groups approximating premenopause (<45 y), perimenopause (45-54 y), and postmenopause (≥55 y) in patients with non-dialysis CKD who participated in the Chronic Renal Insufficiency Cohort (CRIC) observational study.

Methods: Cox proportional-hazards models were used to examine the age-stratified (<45 y, 45-54 y, and ≥55 y) association between sex and time to a composite of CVD events (heart failure, myocardial infarction, ischemic stroke, and peripheral artery disease). Secondary outcomes were individual components of the CVD composite.

Results: The median follow-up time was 7 years. In the entire cohort, males had a 32% higher risk of incident CVD (95% CI: 15-53%; Figure) than females after adjusting for age, race, clinic site, and traditional CVD risk factors, but not after further adjustment for markers of kidney disease (fully adjusted model). In the 45-54 y group, there was a 63% higher risk for CVD (95% CI: 4-157%) in males than females in the fully adjusted model. However, no sex-specific CVD risk was observed in the <45 y and ≥55 y groups in the fully adjusted model.

Conclusions: Our findings suggest that CKD may be a strong risk factor for CVD in females. Moreover, females may have a lower risk of CVD than males, particularly in the perimenopausal, but not premenopausal and postmenopausal ages.

Funding: NIDDK Support



PO2244

Elevated Triglyceride-Glucose Index Predicts Renal Hyperfiltration in Young Adults

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Background: Insulin resistance increases the risk for renal hyperfiltration (RHF), a proposed mechanism for kidney injury in diabetes. However, the association between triglyceride-glucose (TyG) index, a novel marker for insulin resistance, and RHF is not well established in young adults. This study aimed to investigate the association between TyG index and RHF in Korean young adults.

Methods: Data were retrieved from the Korean National Health and Nutrition Examination Surveys (2010-2019). A total of 15,764 participants aged 19~39 years with normal kidney function were enrolled. The participants were divided into tertile based on TyG index [ln(fasting triglyceride[mg/dL] x fasting glucose [mg/dL]/2)]. RHF was defined as eGFR with residuals >90th percentile after adjusting for sex, age, weight, and height.

Results: The mean age of the study participants was 30.4± 6.1 years, and 43.8% were male. The mean levels of TyG index were 7.70±0.25, 8.28±0.15 and 9.07±0.45 in tertile 1,2, and 3 respectively. The prevalence of RHF was significantly higher tertile (9.1%, 10.0%, and 10.9%, respectively, *P* for trend= 0.03). When the association between TyG index and the risk for RHF was evaluated by multivariable logistic regression analysis, the higher tertiles showed increased risks for RHF compared to lowest tertile. (odds ratio [OR],1.24; 95% confidence interval [CI],1.08-1.41, *P*=0.002 in tertile 2 and OR,1.64; 95%CI, 1.41-1.90, *P*<0.001 in tertile 3). This association was consistent when TyG index was treated as continuous variable (OR, 1.53; 95% CI, 1.39-1.38; *P*<0.001). When subgroup analysis stratified by hypertension or diabetes were performed, no significant interactions were found, suggesting TyG index is an independent predictor for RHF regardless of hypertension or diabetes.

Conclusions: This study showed that higher TyG index is associated with increased risk of RHF in Korean young adults with normal kidney function. Longitudinal studies are need to investigate whether elevated TyG index levels associated RHF is an early risk factor for kidney injury in young adults.

Table 1. Risk of RHF according to TyG index group

Group	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
TyG index*	1.20[1.11-1.30]	<0.001	1.43[1.31-1.55]	<0.001	1.53[1.39-1.68]	<0.001
T1			(Reference)			
T2	1.11[0.97-1.26]	0.120	1.22[1.07-1.39]	0.003	1.24[1.08-1.41]	0.002
T3	1.22[1.07-1.38]	0.003	1.55[1.35-1.77]	<0.001	1.64[1.41-1.90]	<0.001

Note: Model 1: Unadjusted model
Model 2: Adjusted for age, sex
Model 3: Adjusted for age, sex, hemoglobin, BMI, HTN, alcohol, education, income, smoking
Abbreviations: BMI, body mass index; HTN, hypertension; OR, odds ratio; CI, confidence interval
*TyG index as continuous variable.

PO2245

Screening for Early CKD in School Children in Kano, Nigeria

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Background: There has been an ongoing debate on the benefits of CKD screening in general especially as it relates to cost effectiveness and absolute relevance. However, screening for CKD in children will make a huge impact especially in low- and middle-income countries (LMIC) where treatment for End Stage CKD is not readily available due to high cost, shortage of skilled personnel and donor organs. This NIH/VECD Fogarty Funded research aimed to determine the burden of early CKD among school children in Kano, Nigeria.

Methods: The study screened 228 school children (5-15 years) within Kano metropolis for CKD from February 2020 to February 2021. Information of participants' socio-demographic profile and medical history was obtained through questioning. Participants' height, weight and blood pressure were measured. They also had their spot urine assessed for albumin creatinine ratio (ACR), and blood for serum creatinine and estimated glomerular filtration rate (eGFR). Participants with abnormal findings had a a repeat assessment after three months for BP, ACR and eGFR

Results: The median age of the children was 13.0 (11.1-14.0) years, with a male:female ratio of 1.1:1. Seventy-eight of the children (34%) had at least one abnormality in the form of hypertension, decreased eGFR (<90 ml/min/1.73m^2) or increased ACR (>30 mg/g) at recruitment. Following re-assessment, 43 of the 78 children had persistent abnormal findings suggestive of early CKD (19%). Factors such as age, sex, type of school, parent's education, history of family member with kidney disease, and nutritional status were not significantly associated with early CKD.

Conclusions: The outcome of this study indicates that a significant number of school children had persistent abnormal findings suggestive of early CKD. Thus, further emphasising the need for large scale CKD screening programmes in our setting. A long-term follow-up of these children will help determine the clinical significance of these findings and provide more information on the epidemiology of CKD. Abdullahi Mudi was supported by a VECD Global Health Fellowship, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Fogarty International Center (FIC) of the NIH (D43 TW009337). The views expressed are solely those of the authors and do not necessary represent the views of the NIH.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Fogarty International Center (FIC) of the NIH (D43 TW009337).

PO2246

Advanced Liver Fibrosis Predicts CKD Development in Patients with Nonalcoholic Fatty Liver Disease

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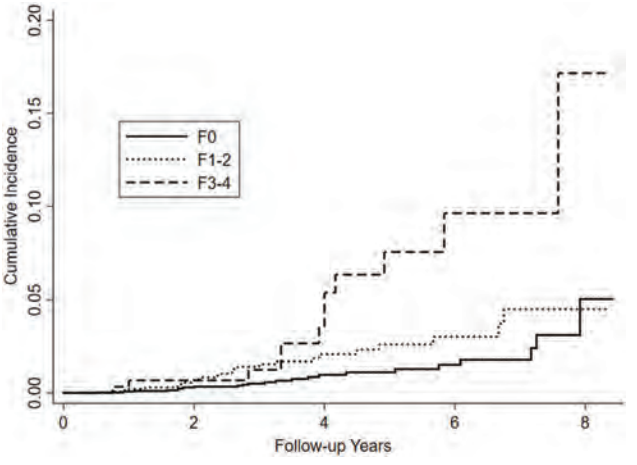
Background: Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are progressive chronic conditions that share important cardiometabolic risk factors and pathogenic mechanisms. We investigated the association between liver fibrosis and the risk of incident CKD in patients with NAFLD.

Methods: A total of 5,983 participants with NAFLD (defined as controlled attenuation parameter >222 dB/m) but without CKD who underwent transient elastography (TE) between March 2012 and August 2018 were selected. The primary outcome was incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or proteinuria (≥1+ on dipstick test) on two consecutive measurements during follow-up. The secondary outcome was a 25% decline in eGFR measured on two consecutive visits.

Results: The mean age was 51.8 years and 3,756 (62.8%) participants were male. During 17,801 person-years of follow-up (mean follow-up of 3.0 years), 62 participants (1.0%) developed incident CKD. When stratified into TE-defined fibrosis stages, multivariable Cox models revealed that risk of incident CKD was 3.63-fold (95% CI, 1.64-8.06, *P*<0.001) higher in the F3-4 group (≥9.5 kPa), compared to the F0 group (<5.5 kPa). During 17,577 person-years of follow-up (mean follow-up of 3.0 years), 201 participants (3.4%) experienced the secondary outcome, for which the F3-4 group had a 2.69-fold increased risk (95% CI, 1.70-4.27, *P*<0.001), compared to the F0 group.

Conclusions: In this large cohort of NAFLD patients without baseline CKD, advanced liver fibrosis measured by transient elastography was significantly associated with a higher risk of incident CKD.



PO2247

Association Between Rates of In-Hospital Decongestion Among Patients with Heart Failure with Reduced Ejection Fraction with Longer-Term Kidney Outcomes

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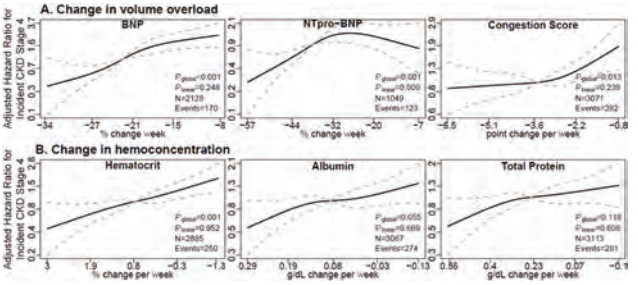
Background: Achievement of decongestion in acute heart failure (AHF) is associated with improved cardiovascular outcomes, but can be associated with acute declines in estimated glomerular filtration rate (eGFR). We aimed to examine whether rate of in-hospital decongestion is associated with longer term kidney function decline among patients with heart failure with reduced ejection fraction (HFrEF).

Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, we used multivariable Cox regression models to evaluate the association between in-hospital change in assessments of volume overload, including b-type natriuretic peptide (BNP), N-terminal prob-type natriuretic peptide (NT-proBNP) and clinical congestion score (0-12), as well as change in hemoconcentration including hematocrit, albumin and total protein with risk of incident chronic kidney disease (CKD) Stage≥4 (as defined by a new eGFR <30 ml/min/1.73m^2) and eGFR decline of >40%.

Results: Among 3500 patients over 10-month follow-up, faster decreases in volume overload and more rapid increases in hemoconcentration were associated with decreased risk of incident CKD Stage≥4 and eGFR decline of >40%. In adjusted analyses, for every 6% faster decline in BNP per week, there was a 32% lower risk of both incident CKD Stage≥4 (HR=0.68, 95% CI 0.58, 0.79) and eGFR decline by >40% (HR=0.68 [0.57, 0.80]). For every 1% faster increase per week in hematocrit, there was a lower risk for both incident CKD Stage≥4 (HR=0.73 [0.64, 0.84]) and eGFR decline by >40% (HR=0.82 [0.71, 0.95]), with results consistent for other biomarkers.

Conclusions: These results provide reassurance that more rapid rates of decongestion in patients with AHF do not increase the risk of adverse kidney outcomes in patients with HFrEF, and may in fact be associated with better kidney function in the long term. The ability to rapidly decongest may also serve as a valuable proxy for better kidney outcomes.



PO2248

Hearing Impairment Among Patients with CKD

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Background: Kidney and cochlear have similar physiologic mechanisms involving fluid and electrolytes. Impaired kidney function may affect cochlear function leading to hearing impairment (HI). Nevertheless, the association between chronic kidney disease (CKD) and hearing impairment is not clear. Moreover, the prevalence of HI among CKD patients has not been well-established.

Methods: We conducted a cross-sectional study among 8,105 US adults aged 20-69 years old in the National Health and Nutrition Examination Survey (NHANES) 2011-2012 and 2015-2016. CKD was defined as eGFR < 60 ml/min/1.73m^2. We calculated the prevalence of HI among CKD population by using analytic survey weights and design factors. We also examined the association between CKD and HI using weighted multivariable logistic regression.

Results: The prevalence of speech frequency HI among patients with CKD was 33.1% vs 14.0 % among control (p<0.001). The prevalence of high-frequency HI among patients with CKD was 74.9% vs 38.7% among control (p<0.001) **(Table 1).** The prevalence of speech frequency HI was 31.5% among CKD stage 3, 47.0% among CKD stage 4 and 53.6 among CKD stage 5 (p-trend = 0.26). The prevalence of high frequency HI was 74.8% among CKD stage 3, 75.9% among CKD stage 4 and 75.2% among CKD stage 5 (p-trend = 0.99). After adjusting for age, sex, race, income, diabetes, hypertension, history of smoking, alcohol drinking, history of cardiovascular diseases, and loud noise exposure, CKD was significantly associated with higher odds of overall speech frequency HI (OR = 1.94, 95% CI [1.03, 3.64]; p=0.04) and overall high-frequency HI (OR = 3.03, 95%CI [1.83, 5.02]; p<0.001).

Conclusions: Nearly one-third of CKD patients have speech frequency HI and about 75% have high frequency HI. Both speech frequency and high-frequency HI are common even in the early stage of CKD. CKD is independently associated with speech frequency and high frequency HI. Early screening and intervening on HI among CKD patients may enhance speech communication, prevent social isolation and improve quality of life.

Table 1 The prevalence of speech frequency and high frequency hearing impairment

	CKD (n = 256)	Controls (n = 7,382)	P-value
Speech frequency HI			
Overall	33.1 [25.4, 41.8]	14.0 [12.5, 15.7]	<0.001
Unilateral	13.6 [9.2, 19.8]	7.03 [6.2, 8.0]	0.001
Bilateral	19.4 [11.7, 30.5]	7.0 [5.9, 8.2]	0.001
High frequency HI			
Overall	74.9 [66.9, 81.5]	38.7 [36.0, 41.4]	<0.001
Unilateral	24.2 [18.3, 31.2]	14.3 [13.2, 15.4]	0.001
Bilateral	50.7 [41.1, 60.3]	24.4 [22.4, 26.5]	<0.001

PO2249

Genetic Determinants of Interleukin-6 Levels and Risk of ESRD

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Background: Multiple observational studies indicate an association between circulating levels of interleukin-6 (IL-6) and end-stage renal disease (ESRD). However, these studies are prone to confounding and reverse causation, limiting their utility in identifying causal relationships. Mendelian Randomization (MR) studies can provide evidence for causality by examining the relationship between genetically-determined biomarker levels and outcomes. We used MR to evaluate whether genetically predicted higher IL-6 levels are associated with the risk of ESRD.

Methods: We performed two-sample MR of the relationship between IL-6 and ESRD. We selected 5 single nucleotide polymorphisms (SNPs) robustly associated with IL-6 levels at genome-wide significance among 30,931 individuals in the SCALLOP consortium as instrumental variables and examined their association with the odds of ESRD in the Million Veteran Program (MVP) among 5,503 ESRD cases and 6,354 controls.

Results: A genetically-driven increase in IL-6 levels was associated with a 30% higher odds of ESRD (95% confidence interval [CI] 1.01 to 1.67; p = 0.04). In race stratified models, among 3,112 Caucasians and 3,170 controls, there was a weaker association (OR 1.17, 95% CI 0.86 – 1.59) compared to 2,062 African Americans (OR 1.30, 95% CI 0.83 – 2.04).

Conclusions: IL-6 levels might be causally associated with the risk of ESRD. This association was stronger among African Americans, although was underpowered. Additional studies are needed to clarify the role of IL-6 in ESRD, and if inhibition of this cytokine could be a target for delaying kidney disease progression to ESRD. **Co-seniors: Robinson Cohen & Hung**

Funding: Veterans Affairs Support

PO2250

Association Between Serum Metabolites and Adverse Renal Outcomes: The Atherosclerosis Risk in Communities (ARIC) Study

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Background: Few metabolomic studies have characterized associations between metabolites and end-stage renal disease (ESRD) and kidney failure. Better characterization of the biological underpinnings may help identify at-risk individuals.

Methods: A total of 3,799 participants with serum samples collected at ARIC visit 1 (1987-1989) were included in this analysis. Starting with 318 individual metabolites, we formed clusters of metabolites using Netboost. We then examined longitudinal associations with ESRD and kidney failure using Cox regression. For significant clusters, we also assessed associations of component metabolites with the outcomes. Because the metabolomic profiling was performed in two studies, analyses were performed within each study and then meta-analyzed.

Results: There were 160 ESRD events and 357 kidney failure events during a median follow-up of 23.5 and 23.3 years, respectively. Overall, mean age was 53.5 years, 59.9% were women, and 61.4% were African American. Mean GFR was 107.5 (SD 16.7). We classified metabolites into 43 clusters. Four clusters were significantly associated with ESRD, and all were associated with kidney failure in a directionally consistent manner. Cluster 26 was primarily sugars involved in glycolysis and anaerobic metabolism. Cluster 5 included amino acids involved in liver metabolism using glutathione and gamma glutamyl transferases. Cluster 34 was an assortment of lysolipids involved in creating phospholipid components of cell membranes. Significant component metabolites included: mannose and glucose from cluster 26; gamma-glutamyl tyrosine, gamma-glutamyl threonine, and 5-oxoproline from cluster 5; and 6 lipids in the phosphocholine family from cluster 34. With the exception of mannose and glucose, higher levels of these metabolites were significantly related to lower risk of ESRD and kidney failure.

Conclusions: We identified several related metabolites associated with ESRD and kidney failure. Additional work is needed to determine whether the relationship is causal.

Funding: NIDDK Support

Table 1. Association between Significant Clusters and Adverse Renal Outcomes.[a,b,c]

Cluster	Meta-Analyzed (N=3799; ESRD=160)			Meta-Analyzed (N=3799; KF=357)		
	HR	95% CI	*P* values	HR	95% CI	*P* values
26	1.31	[1.15-1.51]	<0.001	1.26	[1.14-1.39]	<0.001
5	0.77	[0.67-0.88]	<0.001	0.79	[0.72-0.87]	<0.001
34	0.77	[0.66-0.88]	<0.001	0.81	[0.73-0.90]	<0.001
1	0.78	[0.68-0.89]	<0.001	0.85	[0.77-0.94]	0.0015

[a]HR: hazard ratio; CI: confidence interval
[b]Clusters achieved Bonferroni-corrected threshold (0.05/43 clusters = 0.0012)
[c]Model adjusted for age, sex, race-center, systolic blood pressure, anti-hypertensive medication, diabetes, history of coronary heart disease, smoking, eGFRcr, and high-density lipoprotein cholesterol

PO2251

Plasma Oxalate and Risk of Adverse Outcomes in CKD

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Background: Oxalate is a novel risk factor for CKD but data on plasma oxalate (POx) and outcomes are limited to primary hyperoxaluria. We studied the associations of POx with CKD progression and death in common forms of CKD using the Chronic Renal Insufficiency Cohort (CRIC).

Methods: We measured POx in 1,800 randomly selected CRIC participants at the year 1 visit using the Broad's high-throughput liquid chromatography-mass spectrometry untargeted metabolomics panel. Multivariable Cox proportional hazards regression tested the associations of POx with CKD progression (50% eGFR decline/ESKD) and death. We also tested whether eGFR modified these associations.

Results: Mean eGFR decreased with higher POx quartiles. eGFR modified the associations of POx with CKD progression (P=0.01) and death (P=0.02). In participants with eGFR≥45, higher POx quartiles were associated with CKD progression after adjusting for demographic factors, comorbidities, medications, lab values (including hemoglobin, serum albumin, urine protein-to-creatinine ratio), and eGFR (Q3 vs Q1: HR 2.07, 95% CI 1.12-3.82; Q4 vs. Q1: HR 2.23, 95% CI 1.24-3.99). Higher POx was associated with death in participants with eGFR≥45 after multivariable adjustment (Q4 vs. Q1, HR 1.94, 95% CI 1.10-3.44). POx doubling was associated with a 34% increased risk of CKD progression and 28% increased risk of death (Table 1A). In those with eGFR<45, higher POx was associated with CKD progression after adjusting for demographic factors, comorbidities, medications, and lab values. Adjusting for eGFR attenuated these associations, with higher POx trending towards being protective of CKD progression. Associations of POx and death were not significant after adjusting for covariates and trended towards being protective after adjusting for eGFR (Table 1B). Sensitivity analyses adjusting for 24-hour urinary oxalate did not change these associations.

Conclusions: Higher plasma oxalate may be an independent risk factor for CKD progression/ESKD and death in persons with eGFR≥45.

Funding: NIDDK Support, Private Foundation Support

Table 1A: Plasma Oxalate and Outcomes in the Chronic Renal Insufficiency Cohort Participants with eGFR>45 mL/min/1.73 m²

Model	Continuous*	Q1	Q2	Q3	Q4
Outcome: CKD Progression (50% decline in eGFR) or ESKD					
Unadjusted	1.27 (1.03, 1.57)	Ref	0.87 (0.53, 1.76)	1.79 (1.04, 3.06)	2.14 (1.27, 3.63)
Model 1	1.36 (1.07, 1.72)	Ref	0.78 (0.46, 1.50)	2.11 (1.15, 3.85)	2.28 (1.26, 4.05)
Model 2	1.34 (1.06, 1.70)	Ref	0.78 (0.46, 1.50)	2.07 (1.12, 3.82)	2.23 (1.24, 3.99)
Outcome: Death					
Unadjusted	1.35 (1.09, 1.68)	Ref	1.17 (0.67, 2.04)	1.22 (0.70, 2.14)	2.03 (1.20, 3.43)
Model 1	1.31 (1.05, 1.64)	Ref	1.33 (0.75, 2.35)	1.30 (0.72, 2.34)	2.04 (1.15, 3.59)
Model 2	1.28 (1.02, 1.60)	Ref	1.31 (0.74, 2.32)	1.26 (0.70, 2.27)	1.94 (1.10, 3.44)

Table 1B: Plasma Oxalate and Outcomes in the Chronic Renal Insufficiency Cohort Participants with eGFR<45 mL/min/1.73 m²

Model	Continuous*	Q1	Q2	Q3	Q4
Outcome: CKD Progression (50% decline in eGFR) or ESKD					
Unadjusted	1.16 (1.08, 1.25)	Ref	1.11 (0.85, 1.44)	1.39 (1.07, 1.79)	1.65 (1.28, 2.13)
Model 1	1.10 (1.02, 1.18)	Ref	1.32 (1.00, 1.74)	1.25 (0.93, 1.65)	1.49 (1.13, 1.96)
Model 2	0.89 (0.82, 0.97)	Ref	1.14 (0.86, 1.50)	0.81 (0.61, 1.09)	0.78 (0.58, 1.05)
Outcome: Death					
Unadjusted	1.21 (1.13, 1.30)	Ref	1.09 (0.84, 1.41)	1.32 (1.03, 1.71)	1.89 (1.48, 2.41)
Model 1	1.10 (1.02, 1.19)	Ref	0.94 (0.72, 1.23)	1.04 (0.80, 1.35)	1.16 (0.90, 1.54)
Model 2	0.98 (0.91, 1.07)	Ref	0.87 (0.66, 1.13)	0.85 (0.65, 1.11)	0.84 (0.64, 1.12)

Model 1: Stratified by site and adjusted for age, sex, race/ethnicity, systolic blood pressure, diabetes, and body mass index, medications (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretics, beta-blockers, statins, antiplatelet, and phosphorus binders), and laboratory values (hemoglobin, serum albumin, and natural-log-transformed urine-protein-creatinine ratio)
Model 2: Adjusted for model 1 plus estimated glomerular filtration rate
*HRs are per doubling of plasma oxalate

PO2252

Relationship Between 24-Hour Urinary Oxalate and Incident CKD Among Patients with and Without Underlying Gastrointestinal Disease

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Background: Hyperoxaluria may result from intake of high oxalate foods or enhanced intestinal absorption of dietary oxalate caused by gastrointestinal (GI) disorders with underlying malabsorption, including Crohn's disease, short bowel syndrome, gastric bypass surgery, and chronic pancreatitis. Hyperoxaluria has been associated with negative outcomes, including kidney stones and chronic kidney disease (CKD), but larger studies are needed.

Methods: This is a longitudinal retrospective observational cohort study of patients in the US who have completed at least one 24-hr urine collection analyzed by a central laboratory during the study period of January 2013 through December 2020. Outcome and covariate data were drawn from a multi-source data cloud containing deterministically linked, de-identified, individual-level healthcare claims and electronic medical records (EMR) data. Malabsorption was defined by the presence of a relevant ICD 9/10 or CPT code. The association between categories of urine oxalate (UOx) and incident CKD was modeled using logistic regression.

Results: 762,537 individuals age ≥ 18y with at least one 24-hr urine collection were identified. At least 6 months of baseline and 6 months of follow-up data (median follow-up time: 36.7 months; IQR: 20.4, 56.0) were available for 447,958. Of these, N=12,522 (2.8%) had an underlying malabsorptive condition preceding the index urine test. 426,896 patients had no evidence of CKD at baseline and were eligible for analysis of incident CKD. After adjusting for baseline urine calcium, urine citrate, age, sex, race, BMI, tobacco use, hypertension, diabetes, malabsorption, and CVD, a significant association between baseline UOx and the development of incident CKD was observed. Compared with patients with UOx <20 mg/d, the odds of developing incident CKD increased for 20-29 mg/d (OR: 1.22, 95% CI: 1.15, 1.30) through 80+ mg/d (OR: 1.67, 95% CI: 1.51, 1.86) and was statistically significant for each UOx category.

Conclusions: In this large population of patients with hyperoxaluria, the risk of incident CKD increased with increasing 24-hr urine oxalate excretion. Future studies should examine whether reducing urine oxalate diminishes the risk of developing CKD.

Funding: Commercial Support - Synlogic Inc.

PO2253

Associations of CKD Risk Factors and Longitudinal Changes in Urine Biomarkers of Kidney Tubules Among Women Living with HIV

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Background: Among women with HIV (WWH), urine biomarkers of tubule dysfunction and injury allow detection of antiretroviral toxicity and prediction of CKD risk and mortality. However, risk factors for changes in urine biomarkers are unclear.

Methods: We assessed traditional and infection-related CKD risk factors and measured 14 urine biomarkers at baseline and at follow-up (median 2.5 years) among WWH in the Women's Interagency HIV Study. We used simultaneously adjusted multivariable linear regression models to evaluate the associations of CKD risk factors with changes in biomarker levels concurrently.

Results: Of the 647 women in this analysis, 67% were Black, median age at baseline was 45 years and eGFR was 104 ml/min/1.73m². Each CKD risk factor associated with distinct changes in urine biomarkers (**Figure**). For example**,** baseline hemoglobin a1c (HbA1c) associated with worse tubular injury (higher interleukin-18 [IL-18]), proximal tubular reabsorptive dysfunction (higher alpha-1 microglobulin), tubular reserve (lower umodulin) and heightened immune response to injury (higher chitinase-3-like protein [YKL-40]). Higher HbA1c at follow-up was associated with further worsening of tubular injury (higher kidney injury molecule-1 [KIM-1] and IL-18), and immune response to injury (higher YKL-40). Hepatitis C virus co-infection associated with worsening proximal tubular reabsorptive dysfunction (higher beta-2 microglublin [β2m]), and immune response to injury (higher YKL-40), whereas HIV viremia associated with worsening markers of tubular and glomerular injury (higher KIM-1 and albumin, respectively).

Conclusions: CKD risk factors associated with unique patterns of biomarker changes among WWH, suggesting that longitudinal biomarker measurements may help in detecting and monitoring kidney disease in WWH.

Funding: NIDDK Support

Simultaneous multivariable adjusted associations of baseline and follow-up CKD risk factors with longitudinal changes in urine biomarker levels among HIV-positive women

	Urine Biomarkers							
	▲albumin	▲α1m	▲β2m	▲KIM-1	▲IL-18	▲UMOD	▲EGF	▲YKL-40
CKD risk factors	Estimate (95%CI)							
Hemoglobin a1c		0.06 (0.01, 0.11)			0.06 (0.02, 0.11)	-0.10 (-0.16, -0.03)		0.10 (0.04, 0.17)
▲Hemoglobin a1c				0.04 (0.00, 0.08)	0.05 (0.01, 0.10)			0.13 (0.06, 0.19)
Systolic blood pressure	0.06 (0.01, 0.12)						-0.08 (-0.13, -0.03)	
Serum albumin				-0.08 (-0.13, -0.03)			0.090 (0.04, 0.14)	-0.17 (-0.25, -0.10)
▲Serum albumin		-0.10 (-0.16, -0.04)	-0.08 (-0.14, -0.02)			0.13 (0.05, 0.20)		
Hepatitis C virus			0.31 (0.19, 0.43)					0.23 (0.08, 0.37)
CD4 count			-0.08 (-0.12, -0.03)		-0.09 (-0.13, -0.04)	0.09 (0.02, 0.16)		
▲CD4 count		-0.09 (-0.14, -0.03)				-0.08 (-0.15, -0.00)		
HIV RNA	0.06 (0.01, 0.11)			0.05 (0.00, 0.09)				
▲HIV RNA			0.11 (0.07, 0.16)		0.18 (0.14, 0.22)			
TDF duration			0.11 (0.05, 0.16)					-0.07 (-0.13, -0.02)

We modeled biomarkers in combination using the multivariable sparse group least absolute shrinkage and selection operator (MSG-LASSO) method for variable selection. Red shading indicates worsening marker of kidney markers, while green shading indicates improving kidney biomarkers. Blank boxes indicate variables that were not selected by the MSG-LASSO method. Estimates are reported as standardized regression coefficients (e.g 1 standard deviation (SD) increase in hemoglobin a1c is associated with a 0.06 SD increase in α1m). ▲: change in risk factor or biomarker level; α1m: α1-microglobulin; β2m: β2-microglobulin; KIM-1: kidney injury marker-1; IL-18: interleukin 18; UMOD: uromodulin; EGF: epidermal growth factor; YKL-40: chitinase-3-like protein-1; TDF: Tenofovir Disoproxil Fumarate.

Showing 7 risk factors and 8 biomarkers selected based on prior literature.

PO2254

Correlation Between Urinary Sodium and Protein Excretion in CKD

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Background: Urinary protein excretion often fluctuates in patients with chronic kidney disease (CKD). We aimed to establish a correlation between spot urine sodium (Na) measurement as a surrogate marker of 24hr urine excretion based on Kawasaki formula, and therefore, sodium intake, and urinary protein excretion. We hypothesize that urinary Na excretion may affect urinary protein excretion.

Methods: This was a retrospective study involving 213 US veterans with CKD followed in the Albany VAMC nephrology clinic for the period of 2 years. Patients with cirrhosis, end-stage renal disease, and renal transplant were excluded. Simultaneous measurements of serum Na, Creatinine (Cr) and urine Na, Cr and protein were performed on 2 separate visits. Kawasaki formula was used to estimate 24-hour urine Na excretion. Proteinuria was calculated using urine protein to creatinine ratio (UPCR). Correlations among percent change in estimated 24h urine Na and UPCR were determined with linear regression model.

Results: The mean age ± SD of the cohort was 74.4 ± 9.5 years. Mean estimated GFR was 47.4 ml/min/1.73 m² and UPCR was 1.0 g/g. About 97% of subjects were male and 51% had diabetes. Using multivariable linear regression, we found that weight, height,

BMI, and percent change in estimated 24h urine Na were significant predictors of percent change in UPCR (all $p < 0.05$). The percent change in UPCR correlated with estimated 24h urine sodium on univariate linear regression ($R^2 = 0.24$, $p < 0.01$). We found that 68% of cases of UPCR rise also had estimated 24h urine Na increase, while 70% of patients with UPCR fall also had estimated 24h urine Na decrease.

Conclusions: Urine sodium and urine protein excretion correlated in patients with chronic kidney disease. Therefore, the role of dietary sodium as a potential influencing factor of urine protein excretion requires further examination.

PO2255

Liver Disease Is a Predictor of Recurrent Hyperkalemia

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Background: Liver disease is not a well-established predictor for recurrent hyperkalemia (HK) independent of mineralocorticoid receptor antagonist (MRA) therapy, which is a common treatment in this population. This study explores the relationship between liver disease and recurrent HK independent of MRA therapy and Renin Angiotensin System Inhibitors.

Methods: In a cohort of 9,894,683 US veterans that had at least one potassium measurement between 0.5-8 mEq/L during year 2004 and 2018, we identified 2,169,401 patients who had a HK event (sK >5.0 mEq/L) and complete data on covariates and examined the association of possible predictors of HK recurrence within 1 year after index HK event. Liver disease was defined according to the presence of mild, moderate, or severe liver disease ICD 9/10 codes using 1 inpatient or 2 outpatient records in one year prior to index HK event. HK recurrence is defined as the 3rd or later potassium measurement after index HK measurement subsequent to one or more normal (≤5 mEqL) potassium measurement. Fine and Gray competing risk regression model was used to evaluate the association between liver disease and HK recurrence, where HK recurrence was the outcome and the competing event was all-cause mortality within 1 year after index HK occurrence. The model was adjusted for demographics, comorbid conditions, eGFR, RASi and MRA treatment and potassium supplementation.

Results: Among the 2,169,401 patients, 376,358 (17%) patients had HK recurrence within 1 year after index HK event. Out of 2,169,401 patients, 93,141 (4%) patients had liver disease within 1 year prior to index HK event and 26,846 (29%) of patients had HK recurrence within 1 year after index HK event. Patients with liver disease had a 39% higher risk of HK recurrence within 1 year after index HK event (hazard ratio [HR] [95% CI]: 1.39 [1.37, 1.42]) in the fully adjusted model and was the 2nd strongest predictor after diabetes. Compared to patients without liver disease, patients with liver disease were younger, more likely to be African American, and had a higher Charlson Comorbidity Index.

Conclusions: In US veterans, liver disease is a predictor of 1 year HK recurrence independently of RAASi therapy. Further studies are needed to understand the possible cause underlying this association.

Funding: Commercial Support - AstraZeneca

PO2256

Associations of Urinary and Dietary Sodium-to-Potassium Ratios with Albuminuria in Community-Dwelling Japanese Adults: A Cross-Sectional Study

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Background: Urinary sodium-to-potassium (Na/K) ratio is an indicator of dietary sodium intake and is associated with reduced kidney function. However, it is not known whether urinary Na/K ratio is also associated with albuminuria, the other key component of CKD, in community-dwelling adults.

Methods: We quantified the association of urinary Na/K ratio with albuminuria in 6,276 Japanese adults (age 40-97 years; 51.0% women) by using spot urine samples. Linear and logistic regression analyses were performed with adjustment for potential confounders. We also evaluated dietary Na/K ratio based on a food-frequency questionnaire.

Results: Median values of urinary and dietary Na/K ratios were 2.70 (interquartile interval: 1.87, 3.83) and 1.50 (1.20, 1.84), respectively, with median albumin-to-creatinine ratio (ACR) of 11.0 (6.0, 24.0) mg/g and mean eGFR of 74.7 (SD 15.7) mL/min/1.73 m^2. In multivariable linear regression analysis, urinary Na/K ratio (per one-unit increment) was significantly associated with log-ACR (e.g., β 0.023 [95% CI 0.008, 0.039] in Model 3) (Table). Similarly, dietary Na/K ratio was independently associated with ACR (Table). The results were consistent with those of multivariable logistic regression analysis with elevated ACR ≥30 mg/g as a dependent variable.

Conclusions: Both urinary and dietary Na/K ratios were associated with elevated albuminuria in community-dwelling Japanese adults. Our findings further support the potential usefulness of urinary Na/K ratio as an indicator of sodium intake and suggest a link between sodium intake and kidney damage.

Funding: Government Support - Non-U.S.

Table: Multivariable linear regression analysis between urinary or dietary sodium-to-potassium ratio and log albumin-to-creatinine ratio. Model 1 was adjusted for age and sex; Model 2 was additionally adjusted for current smoking and drinking habits; Model 3 was further adjusted for body mass index, diabetes, systolic blood pressure, use of any antihypertensive medication, and eGFR.

	Model 1	Model 2	Model 3
	β (95%CI)	β (95%CI)	β (95%CI)
Urinary sodium-to-potassium ratio, per one-unit increment	0.049 (0.033, 0.065)	0.048 (0.033, 0.064)	0.023 (0.008, 0.039)
Dietary sodium-to-potassium ratio, per one-unit increment	0.144 (0.090, 0.198)	0.140 (0.086, 0.194)	0.140 (0.089, 0.192)

PO2257

Urinary Sodium-to-Potassium Excretion Ratio Is Associated with Incident CKD in the General Population

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Background: Previous study suggests that urinary sodium to potassium (UNAK) ratio is associated with cardiovascular event and mortality, but the association of incident chronic kidney disease (CKD) and UNAK ratio in a preserved kidney function adult showed conflict results.

Methods: Data from the Korean Genome and Epidemiology, a prospective community-based cohort study were used to evaluate the between UNAK ratio and CKD development. 24 hour estimated sodium and potassium excretion amounts were calculated by a Kawasaki equation using spot urinary potassium and sodium measurements. A total 4088 participants were analyzed with a primary outcome of incident CKD that defined as estimated glomerular filtration ratio (eGFR) <60 mL/min/1.73m^2 in ≥2 consecutive measurements during the follow-up period.

Results: The mean age was 52.1 ± 88 years and 47.5% were male. The median estimated 24h urinary sodium excretion, potassium excretion, UNAK ratio were 4.9 (4.1-5.8) g/day, 2.1 (1.8-2.5) g/day, and 2.3 (1.9-2.7), respectively. During 37,950 person-year of follow-up (median 11.5 years), the primary outcome developed in 513 participants and corresponding incidence rate was 14.0 (95% Confidence interval [CI], 12.9 to 15.3) per 1000 person-year. When the participants were categorized into quartiles according to UNAK ratio, age, sex and baseline eGFR adjusted hazard ratios (HR) (95% CI) for the Cox proportional hazard model were 0.76 (0.59-0.96), 0.89 (0.70-1.14), and 1.15 (0.91-1.46) from UNAK ratio quartile 1, 2, and 3, respectively as compared with the highest quartile and this finding was consistent even after further adjustment. Similar results were observed when log-transformed UNAK ratio was treated as a continuous variable; for one increase in UNAK ratio, there was a 51% higher risk of adverse kidney outcome (HR 1.51, 1.12-2.04). Spline regression analysis show that HR increased more steeply up to 1 in log transformed UNAK ratio, but there was no significant increase of risk after that.

Conclusions: low UNAK ratio is significantly associated with a decreased risk of CKD development.

PO2258

Time on Patiromer Therapy and Impact on Serum Potassium Levels in Real-World German CKD Patients

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Background: Hyperkalemia (HK) (serum K>5.0 mEq/L) is a frequent condition in patients with chronic kidney disease (CKD) associated with high morbidity and mortality and it is a common reason for RAASi discontinuation and dose limitation. Patiromer is a non-absorbed, sodium-free, potassium (K) binder that has been shown to chronically reduce serum K in patients with HK, enabling RAASi therapy, which is supported by randomized trial evidence in CKD patients. Data on patiromer use in patients with moderate-to-advanced CKD in the real-world setting in Europe is lacking. We describe time to discontinuation and changes in serum K levels among CKD stage 3-5 patients starting patiromer using 2018-21 data from German participants in CKD Outcomes and Practice Patterns Study (CKDopps).

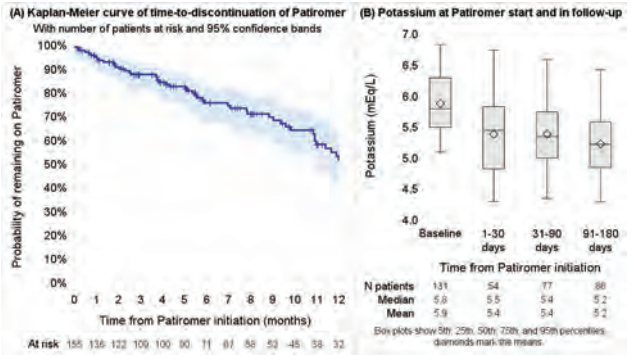
Methods: Duration of patiromer use was estimated by Kaplan-Meier curve, starting at patiromer initiation and censoring for death, dialysis, transplant, or loss of follow-up. Serum K levels are described as mean/median at the baseline and in ranges of 1-30, 31-90 and 91-180 days during the follow up, restricted to patients remaining on patiromer.

Results: Patiromer use was limited to 34 of 90 clinics. We identified 155 Patiromer users, 131 with K measurements at baseline and 110 with at least one follow-up value. 79% of patiromer users were CKD stage 4/5, v. 28% of non-patiromer users in the sample. A large proportion (95%) of patiromer users stayed on treatment past 1 month, with 53%

of surviving users continuing for over a year (Fig 1A). Mean serum K levels decreased after patiromer initiation and remained stable under treatment during follow-up (up to 180 days) (Fig 1B).

Conclusions: Most patients were not observed to discontinue patiromer prior to one year after initiation. Mean levels of serum K were lower after patiromer initiation and remained stable during the follow-up period.

Funding: Commercial Support - Vifor Pharmaceutical



PO2259

Kidney Outcomes in Pediatric Non-Kidney Solid Organ Transplant Patients

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Background: Acute Kidney Disease (AKD) is defined as impaired kidney function for < 90 days with or without an acute kidney injury (AKI) event. Adults with AKD have increased risk for progression to chronic kidney disease (CKD) and mortality. There are no data on the epidemiology of AKD in children after transplant. The aim of this study was to evaluate the incidence and risk factors for AKI, AKD and CKD at a large pediatric transplant center.

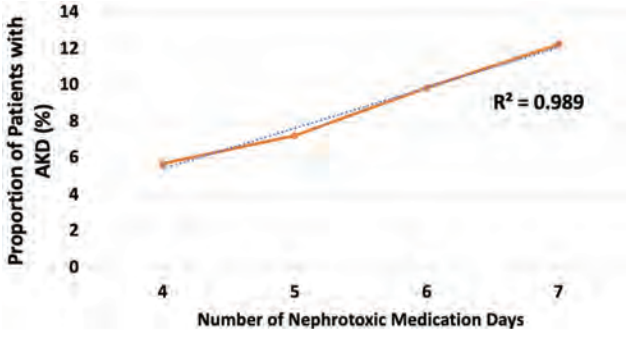
Methods: A retrospective chart review was done in children who underwent non-kidney solid organ transplant between 2011-2019 at UPMC Children's Hospital of Pittsburgh. AKI and AKD are defined using the Kidney Disease Improving Global Outcomes criteria. AKD is defined as serum creatinine >/= 50% times baseline or eGFR < 60 ml/min/1.73m^2 or a decrease in eGFR by >/= 35% times baseline for > 7 days and up to 3 months. Patients with a new eGFR of <60 ml/min/1.73m^2 persisting for > 3 months met criteria for CKD. Variables associated with AKI, AKD and CKD were analyzed.

Results: Among 338 patients 37.9% met criteria for severe AKI, 11.5% for AKD and 8% for a new diagnosis of CKD. Stage 3 AKI was independently associated with AKD (OR: 4.10; 95% CI: 1.64-10.25). AKD but not severe AKI was associated with new onset CKD (Table 1). There was a dose dependent relationship between nephrotoxic medication use and incidence of AKD (Figure 1).

Conclusions: In conclusion, children with AKD after transplant are particularly vulnerable to developing CKD and there are modifiable risk factors that could decrease the risk of progression of AKI to AKD and CKD in this population.

Multivariable logistic regression of risk factors for CKD

Characteristic	OR (95% CI)	P-value
Age (years)	1.00 (0.99-1.01)	0.51
Gender	2.67 (1.00-7.13)	0.05
Race	2.55 (0.88-7.38)	0.09
Severe AKI	0.94 (0.38-2.30)	0.89
All AKI	1.58 (0.62-4.00)	0.33
AKD	20.45 (7.48-55.87)	<0.01



Association between nephrotoxic medication use and AKD

PO2260

Cardiovascular Outcomes in Pediatric CKD: A CKiD Study

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Background: Cardiovascular Disease (CVD) poses high risk to Chronic Kidney Disease (CKD) pediatric patients with existing literature noting decreased mortality and other comorbidities. Here, we use the Chronic Kidney Disease in Children Cohort Study (CKiD), a prospective cohort study of pediatric renal cystic patients, to assess CVD parameters in this vulnerable population.

Methods: We performed control-matched analysis of CKiD patents with renal cystic disease (PKD, MCDK, BOR) compared to a group of aplastic/dysplastic/hypoplastic kidney patients or those with obstructive uropathy. Variables were normalized using the Kolmogorov-Smirnov test; categorical variables were summarized as percentages while continuous variables as medians and inter-quartile ranges. Univariate associations were tested using chi-square statistic or Fischer exact test for categorical variables and Mann-Whitney I test for continuous variables.

Results: 41 patients in the renal cystic group were compared to 294 patients in the non-renal non-cystic group. Renal cystic patients demonstrated statistically significant increases in cystatin-C with no difference in iGFR or serum creatinine. Blood pressure was decreased [103 (97 - 112) vs. 107 (99 - 115) mm Hg; p=0.004] in the renal cystic group but cardiac parameters of ascending aortic stiffness [3.1 (2.11 - 5.21) vs. 2.53 (1.87 - 3.56); p=0.001] and incidence of left-ventricular hypertrophy (LVH) [12 (15.2%) vs. 44 (8.3%); p=0.049] was increased.

Conclusions: CVD mortality is the primary cause of death in patients with CKD, especially ADPKD. Previous literature conceptualized link between renal cystic disease and hypertension leading to poorer CVD outcomes however our analyses show this is an incomplete picture with almost 50% higher incidence of LVH but lower blood pressure in renal cystic group compared to other CKD pediatric patients. This suggests a need for further exploration of cardiac remodeling and structural changes to improve the understanding of CVD development in renal cystic pediatric patients.

PO2261

Biopsy-Proven CKD Etiology and Outcomes: The CKD Japan Cohort (CKD-JAC) Study

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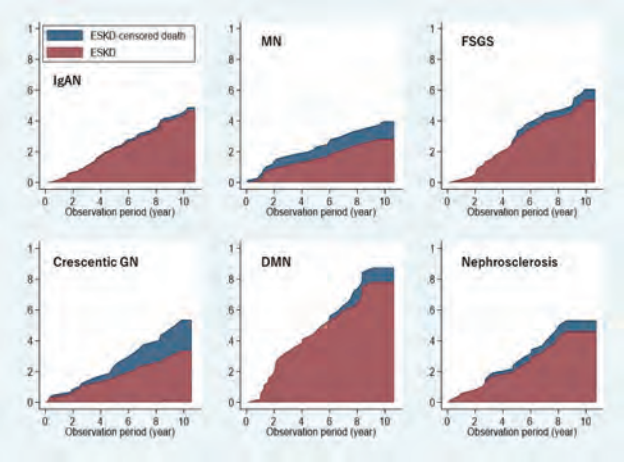
Background: The KDIGO guidelines advocated cause-GFR-albuminuria (CGA) classification for predicting outcomes. However, a dearth of data exists supporting the use of the cause of chronic kidney disease (CKD). This study aimed to address how to incorporate prior biopsy-proven diagnosis in predicting outcomes.

Methods: We compared end-stage kidney disease (ESKD) and all-cause death before ESKD among various biopsy-proven diagnoses (n = 778) in Analysis A. In Analysis B, the same outcomes were compared among biopsy-proven diabetic nephropathy (DN), biopsy-proven other diseases, and no biopsy in those with a history of diabetes mellitus (n = 1117).

Results: In analysis A, adding biopsy-proven diagnoses to GFR-albuminuria (GA) classification significantly improved both net reclassification improvement and integrated discrimination improvement to predict the 8-year incidence of ESKD and all-cause death. Fine-Gray (FG) models with ESKD as a competing event showed significantly higher subdistribution hazard ratios (sHRs) for all-cause death in nephrosclerosis (4.12 [1.11–15.2]), focal segmental glomerulosclerosis (3.77 [1.09–13.1]), and membranous nephropathy (MN) (2.91 [1.02–8.30]) as compared to IgA nephropathy, while Cox model failed to show significant associations. Crescentic glomerulonephritis had the highest risk of all-cause death (sHR 5.90 [2.05–17.0]). MN had a significantly lower risk of ESKD than IgA nephropathy (sHR 0.45, [95% Confidence interval:0.24–0.84]). In analysis B, biopsy-proven other diseases had a lower risk of ESKD as compared to biopsy-proven DN in FG model with death as a competing event (sHR 0.62 [0.39–0.97]).

Conclusions: The Biopsy-proven cause of CKD is of great value in predicting outcomes in CKD adjusting for GA classification.

Funding: Commercial Support - Kyowa-Kirin company



PO2262

Ideal Cardiovascular Health and Risk for Incident CKD: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

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Background: Prior studies have reported that measures of ideal cardiovascular health influence the risk of developing chronic kidney disease (CKD). However, U.S. Hispanic/Latino adults were not well represented in these studies.

Methods: We analyzed data from 8,770 U.S. Hispanic/Latino adults aged 18-64 years enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) who completed a baseline (2008-2011) and a follow-up (2014-2017) visit and did not have CKD at baseline (estimated glomerular filtration rate [eGFR] ≥ 60 ml/min/1.73m^2 and urine albumin-to-creatinine ratio [UACR] <30 mg/g). Cardiovascular health metrics were assessed using the American Heart Association's Life's Simple 7 (LS7, nonsmoker; body mass index <25 kg/m^2; ≥150 minutes/week of physical activity; healthy diet; total cholesterol <200 mg/dL; blood pressure <120/80 mm Hg; and fasting blood glucose <100 mg/dL). Outcomes included incident ACR (defined as UACR ≥30 mg/g) and incident low eGFR (defined as eGFR <60 ml/min/1.73m^2 and a decline in eGFR ≥1 ml/min per year). The association between LS7 and the outcomes was evaluated using Poisson regression with robust variance while accounting for the complex sampling design of HCHS/SOL.

Results: At baseline, the weighted mean age was 42.1 years, 56.3% were female, mean eGFR was 107 ml/min/1.73 m^2, median UACR was 7 mg/g, and 49% had ≥4 ideal health factors. After a median follow-up of 5.9 years, there were 598 incident albuminuria events, and 201 low eGFR events. Compared with the presence of <4 ideal factors, ≥4 ideal health factors was associated with lower risk for incident albuminuria but there was no association with incident low eGFR (**Table).**

Conclusions: Among U.S. Hispanic/Latino adults, the presence of a higher number of ideal health factors was associated with a lower risk of incident albuminuria. These findings may have implications for public health strategies for CKD prevention in this population.

Outcome	Number of Ideal Factors	Rate per 1000 Person Years	Incident Density Ratio (95% CI)
Incident Albuminuria	<4	14.5 (13.2, 16.0)	Referent
	≥4	7.6 (6.6, 8.8)	0.62 (0.46, 0.85)
Incident Low eGFR	<4	5.5 (4.7, 6.5)	Referent
	≥4	1.8 (1.3, 2.4)	1.11 (0.67, 1.84

*Adjusted for center, age, sex, background, education, eGFR, and log(UACR)

PO2263

Inflammatory Biomarkers and Proteinuria Progression in CKD Patients: The CRIC Study

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Background: Proteinuria progression is considered a surrogate endpoint for CKD progression. We studied prospective association of inflammatory biomarkers with proteinuria progression in the Chronic Renal Insufficiency Cohort (CRIC) Study participants.

Methods: The CRIC Study recruited 3939 CKD patients in the US. After excluding those without urine protein measures at baseline or follow-up and those with missing covariables at baseline, 3177 patients were included in this analysis. Proteinuria progression was defined as a ≥ 30% increase in urine protein-to-creatinine ratio (UPCR) from baseline and UPCR ≥150 mg/g at follow-up visits. Incident proteinuria was defined as UPCR ≥150 mg/g among patients without proteinuria at baseline. Cox proportional hazards models were used to examine multivariate association of inflammatory biomarkers with proteinuria progression and incidence, adjusting for age, sex, race, current smoking, body mass index, systolic blood pressure, total cholesterol, hemoglobin A1C, eGFR, baseline UPCR, and use of ACE-Is/ARBs, statins, and aspirin.

Results: Over a mean follow-up of 6.6 years, 1478 participants developed proteinuria progression and 625 participants developed proteinuria. Multivariable-adjusted hazard ratios (95% confidence intervals [CI]) of proteinuria progression for the highest quartile vs. lowest quartile of inflammatory biomarker levels were 1.20 (1.01-1.42; P=0.03) for fibrinogen, 1.21 (1.03-1.43; P=0.02) for interleukin-6 (IL-6), 1.54 (1.30-1.81; P<0.0001) for tumor necrosis factor-α (TNF-α), and 1.22 (1.04-1.42; P=0.01) for CXCL12. Among 1635 patients without baseline proteinuria, similar relationships of fibrinogen, IL-6, TNF-α and CXCL12 with incident proteinuria were identified. C-reactive protein, white blood cells, IL-1β, IL-1 receptor antagonist, fetuin-A, transforming growth factor-β, and fractalkine were not significantly associated with proteinuria progression or incidence.

Conclusions: Our findings suggest that higher levels of fibrinogen, IL-6, TNF-α, and CXCL12 are independently associated with proteinuria progression and incidence. Future studies may test whether targeting specific inflammatory pathways will improve proteinuria and reduce CKD progression.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences (NIGMS)

PO2264

Racial Disparities in Progression to ESRD and Mortality in Rural vs. Urban Veterans

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Background: Little is known about how race and rurality interact to influence progression of CKD to ESRD and mortality in CKD patients.

Methods: We analyzed a national cohort (n=915,039) of veterans with CKD (eGFR < 60 on two or more outpatient serum creatinines >60 days apart) who received care from 1/1/2010-12/31/2015 and who had information on demographics, comorbidities, and residence coding available. ESRD data was obtained by linkage to USRDS. Cox linear regression models were used to relate rural and urban residence defined by RUCA codes with time to incidence of ESRD, as well as time to all-cause mortality. The models were adjusted for age, gender, and comorbidities. The full cohort was examined as well as two subgroups divided by race. Hazard ratios were calculated using the urban (RUCA 1.0 & 1.1) veterans within the full cohort or each subgroup as a reference.

Results: When compared to urban veterans, veterans who reside in rural regions had lower risk of ESRD (HR 0.89, 95% CI 0.87-0.91) but had a slightly higher risk of mortality (HR 1.03, 95% CI 1.02-1.03). Within race subgroups, White rural veterans had lower risk of ESRD compared to White urban veterans (HR 0.88, 95% CI 0.85-0.91) but not in Black rural versus Black urban veterans (HR 0.99, 95% CI 0.93-1.05). While rural White veterans had slightly higher risk of mortality compared to urban White veterans (HR 1.02, 95% 1.01-1.02), the difference in mortality between rural and urban veterans was much larger in the Black subgroup (HR 1.11, 95% CI 1.08-1.14).

Conclusions: Examination of CKD patients cared for by the VA reveals an intersection between race and rurality in which mortality is increased for Black rural veterans with CKD. Interventions to improve preESRD care in rural Black veterans are needed.

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

PO2265

Trends in Prevalence of Comorbid Conditions at Onset of CKD Among US Veterans with Incident CKD, 2004-2018

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Background: Many comorbid conditions are strong risk factors for adverse outcomes in people with CKD. We examined trends in prevalence of major comorbidities at CKD onset in the US Veterans Health Administration (VHA).

Methods: Incident CKD was defined as the first time the estimated glomerular filtration rate (eGFR) decreased to <60 mL/min/1.73 m^2 for >3 months. We excluded veterans recorded in the VHA for <2 years prior to the first eGFR <60, or with CKD stage ≥4 when first identified. We identified 15 comorbidities at CKD onset using ICD-9/ICD-10 codes during the 2 years before and 6 months after CKD onset and calculated the Charlson comorbidity index (CCI), a composite score of total disease burden.

Results: The cohort included 892,005 veterans with new-onset CKD between 2004 and 2018. The mean age (72 years), eGFR (52 mL/min/1.73m^2), and body mass index (30 kg/m^2) at CKD onset were similar in 2004 and in 2018. Among the 8 comorbidities with >20% prevalence (left panel, Table), hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and cancer declined from 2004 to 2018, with the largest decline (21%) for cancer. Diabetes, anemia, depression, and obesity increased in prevalence, with the largest increases for obesity (58%) and depression (30%). The percentage of patients with a CCI ≥6 increased from 9% in 2004 to 14% in 2018.

Conclusions: In US veterans, obesity, depression and the CCI score have significantly increased at CKD onset over the recent 15 years, underscoring the importance of a multifaceted approach to management of CKD and its risk factors.

Funding: NIDDK Support, Other U.S. Government Support

Prevalence of comorbidities at CKD onset among US veterans, 2004–2018

Comorbidity	Prevalence (%)		Percent change*	Comorbidity	Prevalence (%)		Percent change*
	2004	2018			2004	2018	
Hypertension	91.7	89.3	-2.6	Gastrointestinal bleeding disorders	17.9	10.9	-39.0
Cardiovascular disease	77.8	74.0	-4.9	Psychoses	8.9	3.6	-59.0
Diabetes	46.0	51.3	11.6	Alcohol abuse	7.6	11.5	49.8
Chronic obstructive pulmonary disease	34.6	33.9	-1.9	Dementia	5.0	8.0	60.9
Anemia	34.5	35.6	3.3	Drug abuse	4.4	7.3	67.5
Depression	27.8	36.1	29.7	Liver disease	4.0	4.6	16.7
Cancer	25.9	20.6	-21.0	HIV/AIDS	0.4	0.7	101.0
Obesity	22.3	35.3	58.4	Charlson comorbidity index (CCI) ≥ 6	8.9	14.4	62.2

*P-values were all <0.001, controlling for demographics.

PO2266

Association Between Cardiac Autonomic Function and Coronary Artery Calcification in Persons with Type 2 Diabetes with and Without CKD

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Background: Cardiac autonomic neuropathy and cardiovascular disease are concomitant complications to diabetes but the link between these complications are largely unknown, especially in relation to kidney function. We examined the association between measures of cardiac autonomic function and coronary artery calcification (CACS) in persons with type 2 diabetes stratified by presence of chronic kidney disease (CKD).

Methods: Post-hoc analysis of baseline data from a randomized clinical trial including 84 persons with type 2 diabetes. Cardiac autonomic function was evaluated using heart rate variability (HRV) indices and cardiovascular autonomic reflex tests (CARTs). Lower response in CARTs and HRV measures were taken as indicators of impaired cardiac autonomic function. CT based CACS was calculated using Agatston method.

Results: The participants had a mean age of 64.7 (SD 7.8) years, 15% were women, mean eGFR was 83.5 (SD 16.2) ml/min/1.73 m^2, median urinary albumin creatinine ratio 5.5 [IQR 3.5 – 11.8] mg/g and 10 (11.5%) had CKD (eGFR < 60 ml/min/1.73 m^2). In persons without CKD, a higher CACS was associated with a lower 30-to-15 ratio (-1.27, SE: 0.33), *p < 0.0001*), E-to-I ratio (-1.33, SE:0.32, *p < 0.0001*), standard deviation of normal-to-normal intervals (-0.73 ms, SE:0.34, *p=0.03*), high frequency power (-0.49 ms^2, SE:0.24, *p=0.045*) and total power (-0.86 ms^2, SE:0.33, *p=0.01*). All these associations remained significant after adjustment for age, heart rate (only for HRV measures), sex, LDL-cholesterol, HbA_1 c, systolic blood pressure, diabetes duration and weight (except for standard deviation of normal-to-normal intervals and high frequency power). In persons with CKD, no significant associations were demonstrated between measures of cardiac autonomic neuropathy and CACS.

Conclusions: In persons with type 2 diabetes but without CKD, we demonstrated an association between impaired cardiac autonomic function and higher coronary artery calcification. This association could not be demonstrated in persons with CKD.

PO2267

Characterization of Metabolome-Wide Biochemicals Associated with Kidney Function

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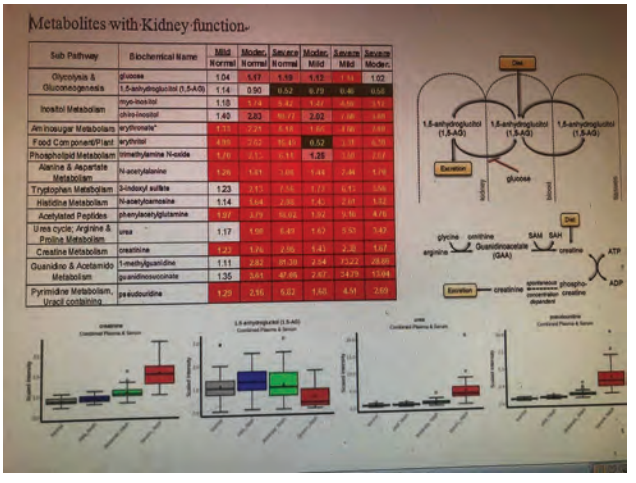
Background: Chronic kidney disease (CKD) is a global public health problem. Identifying sensitive filtration biomarkers is a key diagnostic value contributing to an understanding of CKD at the molecular level. A metabolomics study indicated a snapshot of the biochemical activity of the human body at a particular time in the progression of CKD. This metabolome-wide study verified whether blood metabolite profiles are significantly different in CKD at various stages and characterized potential markers to assess kidney function in Chinese population.

Methods: An analysis of plasma and serum metabolites using ultrahigh-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was performed on 198 participants (53 serum samples and 145 plasma samples) based on their measured GFR (by iohexol plasma clearance).

Results: A large number of metabolomics related to the mGFR were selected as the top 30 metabolites by the random forest method, and we found 15 amino acids, 8 nucleotides, and 2 carbohydrates strongly related to kidney function in the combined group (serum and plasma). Thirteen amino acids, 9 nucleotides, and 3 carbohydrates were identified in the plasma group, while 13 amino acids, 7 nucleotides, and 3 carbohydrates were found in the serum group. We observed that 10 of the top 15 ranked metabolites were concordant between the plasma and serum groups. Major differences in metabolite profiles with increasing stage of CKD were observed.

Conclusions: Our study identified 6 novel and potential metabolites that reproducibly strongly associate with mGFR, including pseudouridine, C-glycosyltryptophan, erythronate, N-acetylalanine, myo-inositol, and N-acetylcarnosine. However, pseudouridine may be an ideal biomarker that is nondependent on race. Specifically, a potential negative biomarker of kidney disease may be 1,5-anhydroglucitol (1,5-AG). Future studies will utilize the potential 3-5 novel biomarkers in estimating the glomerular filtration rate without race input.

Funding: Government Support - Non-U.S.



PO2268

Lipid Accumulation Product Index and CKD

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Background: Obesity, a well-known risk factor for chronic kidney disease (CKD), is generally assessed using body mass index (BMI). However, because BMI does not take body composition into account, it may not reflect the metabolic abnormalities associated with obesity. Recently, lipid accumulation product index (LAP) has been proposed to effectively recognize metabolic syndrome. Therefore, the association between LAP and risk of incident CKD was investigated in a general population cohort.

Methods: A total of 180,268 subjects without CKD, who participated in the Korean Genome and Epidemiology Study from 2001 to 2018, were analyzed. LAP was calculated as [waist(cm)−65] × triglyceride(mmol/l) for males and [waist(cm)−58] × triglyceride(mmol/l) for females. The association between LAP and CKD, defined as eGFR<60mL/min/1.73m^2, was examined in the cross-sectional analysis. In the longitudinal analysis, the risk of incident CKD development was analyzed among 8,427 participants without CKD at baseline which was a subset of the main cohort.

Results: The mean age was 53.1±8.4 years, and 117,321 patients (65.1%) were female. Prevalent CKD was observed in 342 (0.6%), 707 (1.2%), and 1155 (1.9%) participants in the lowest, middle, and highest LAP tertile groups, respectively. In multivariate logistic regression analysis, a logarithmic increase in LAP was associated with a 47% increase

in CKD odds ratio (OR 1.47; 95% CI, 1.35-1.61; *P*<0.001). When stratified into tertiles, the risk of CKD prevalence was significantly higher in the highest tertile (OR 2.05; 95% CI, 1.72-2.45; *P*<0.001), when compared to the lowest tertile. During a mean follow-up of 182 months, CKD occurred in 720 (8.5%) participants. In the multivariable Cox analysis, LAP was significantly related with incident CKD risk (per 1-log LAP, HR 1.20; 95% CI, 1.13-1.27; *P*<0.001). The risk of incident CKD was significantly higher in the highest tertile (HR 1.48; 95% CI, 1.32-1.65) than the lowest tertile.

Conclusions: Increase in LAP was associated with higher prevalence of CKD and elevated risk of incident CKD.

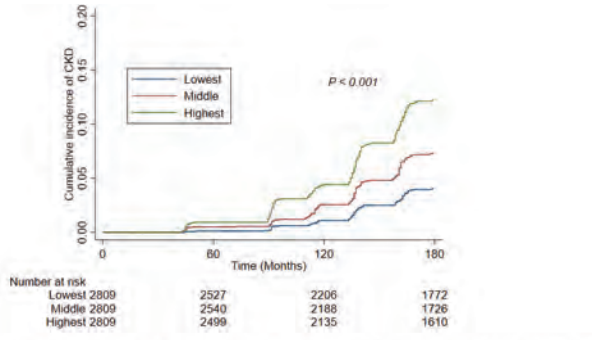

Figure. Cumulative incidence curve for incident chronic kidney disease according to lipid accumulation product index.

PO2269

Comparison of Two Immunoassay Technologies for Plasma Biomarker Measurement

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Background: Anti-double-stranded DNA (anti-dsDNA) antibodies in autoimmune diseases such as systemic lupus erythematosus (SLE) may interfere with immunoassay technologies that use oligonucleotide-based antibodies (Olink) or aptamers (SomaScan). In this study, we compare measurements of plasma kidney injury molecule-1 (KIM-1), a well-known marker of tubular injury, across two different immunoassay technologies in patients with and without SLE.

Methods: We measured plasma KIM-1 levels in 444 individuals enrolled into a prospective, observational cohort study of patients with chronic kidney disease using microbead-based sandwich ELISA and the proximity extension assay (PEA, Olink). The PEA uses oligonucleotide-labeled antibodies that bind to the target protein. We investigated differences in plasma KIM-1 measurements between the two assays in individuals with SLE (n=68) and individuals with other diseases than SLE (n=376) using Bland-Altman plots and Spearman correlation coefficients.

Results: Mean eGFR was 85.2±37 and 52.3±33 ml/min/1.73m^2 and the median proteinuria (IQR) was 1.5 (0.7, 3.2) and 1.7 (0.4, 4.2) g/g creatinine in individuals with and without SLE, respectively. The correlation between paired plasma KIM-1 measurements from both assays was 0.7 (p<0.001) in individuals with SLE and 0.9 (p<0.001) in individuals with other diseases than SLE (Figure 1A). The Bland-Altman plots show the bias between the mean differences in plasma KIM-1 in individuals with and without SLE, indicating that the bias in measurements was significantly greater in those with than without SLE (-2.8 vs. -3 units, p=0.008, Figure 1B).

Conclusions: Anti-dsDNA antibodies in SLE may interfere with measurements by oligonucleotide-labeled antibodies.

Funding: NIDDK Support

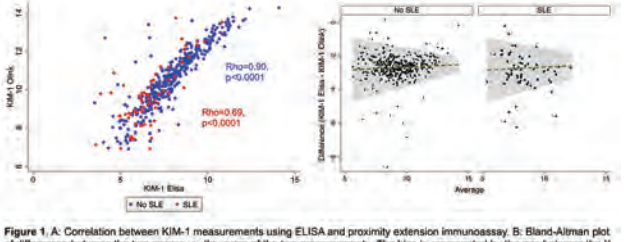

Figure 1. A: Correlation between KIM-1 measurements using ELISA and proximity extension immunoassay. B: Bland-Altman plot of differences between the two assays vs. the mean of the two measurements. The bias is represented by the gap between the X axis, corresponding to a zero difference, and the parallel line to the X axis.

Figure 1.

PO2270

Associations Between eGFR and Brain Atrophy

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Background: The associations between estimated glomerular filtration rate (eGFR) and both cognitive decline and brain atrophy have been less studied in elderly with kidney disease. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is an NIH funded multicenter observational study characterizing progression of dementia in the elderly. Using the ADNI data, we analyzed the association between eGFR and brain volume.

Methods: We used multiple linear regression model to determine the association between eGFR and normalized (brain region divided by intracranial volume) whole brain and hippocampus volume (primary outcomes) and entorhinal cortex, and middle temporal gyrus volumes (secondary outcomes) as determined by brain MRI.

Results: Mean age of the 1596 ADNI participants was 74 ± 7 years; 53% had mild cognitive impairment (MCI), and 19% had dementia. 27% had eGFR <60 ml/min/1.73m^2. Participants with lower eGFR were older and had a higher prevalence of dementia. While increasing age, and female sex were associated with lower brain volumes, lower eGFR was not (table 1). The results persisted in sub analyses divided by tertiles of age in participants with normal cognition, MCI, or dementia.

Conclusions: Low eGFR was not associated with brain atrophy in the ADNI participants with mild-moderate reduction in eGFR.

Funding: Other NIH Support - NIA

Multiple linear regression model predicting brain volumes.

	Whole brain	Hippocampus	Entorhinal	Fusiform	Mid Temporal
Age	-3.0e-03 (<0.001)	-3.7e-05 (<0.001)	-1.3e-05 (<0.001)	-6.7e-05 (<0.001)	-5.7e-05 (<0.001)
Sex (F)	1.1e-02 (<0.001)	2.5e-04 (<0.001)	3.6e-05 (0.19)	1.3e-04 (0.16)	1.7e-04 (0.09)
Education	1.99e-04 (0.64)	5.2e-06 (0.48)	1.6e-05 (0.001)	4.4e-05 (0.01)	2.9e-05 (0.10)
eGFR	1.4e-04 (0.09)	1.07e-06 (0.48)	1.4e-07 (0.89)	-6.6e-07 (0.84)	2.9e-06 (0.44)

eGFR; estimated glomerular filtration rate. Values are represented as B estimate (p value)

PO2271

Correlation of Silent Brain Infarction with the Metabolic Abnormality of CKD Stage 3-5 (Nondialytic) Patients

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Background: Silent brain infarction (SBI) is a hidden comorbidity, mostly unrecognized in CKD patients which increases the risk of symptomatic stroke, dementia and overt neurological mortality. The relationship between SBI and chronic kidney disease (CKD) is unknown. It is supposed that SBI will predict the progression of diseases processes in CKD patients.

Methods: This is a cross-sectional study. A total of 115 subjects were enrolled in this study. 85 patients of CKD stage3-5 (non dialytic) who have no neurological symptoms suggesting stroke were considered as group I and Group-II were 30 healthy controll. Glomerular filtration rate (GFR) was estimated using MDRD-equation. All study subjects underwent MRI.

Results: The proportion of Silent Brain Infarction is 52.9% in CKD patients. SBI was found in 45(52.9%) patients in group I and 4(13.3%) in group II which was significant (p<0.05). The proportion of SBI was also increased in higher CKD stages. (stage-3:8.9%; stage-4:35.6%; stage-5ND:55.6%). In a multivariate logistic regression analysis CKD had independent relationship with SBI along with serum phosphate and parathyroid hormone level (CKD had Odds ratio (OR)=1.847 (95.0% C.I 0.064 to 53.319), serum PO_4 had OR=0.958 (95.0% C.I. 0.885 to 1.038) and serum PTH had OR=0.996 (95.0% C.I. 0.993 to 1.000). Spearman rank correlation coefficient test showed positive correlation between SBI and serum PO4 level (r=0.416; p=0.001) and serum PTH level (r= 0.405; p=0.001) separately.

Conclusions: The proportion of SBI in CKD stage 3-5(non dialytic) patients is high which is 52.9% and serum PO4 and serum PTH level have positive correlation with the development of SBI in CKD stage 3-5(non dialytic) patients.

Funding: Clinical Revenue Support

PO2272

Risk Factors for Incident Pruritus in Patients with CKD Not on Dialysis

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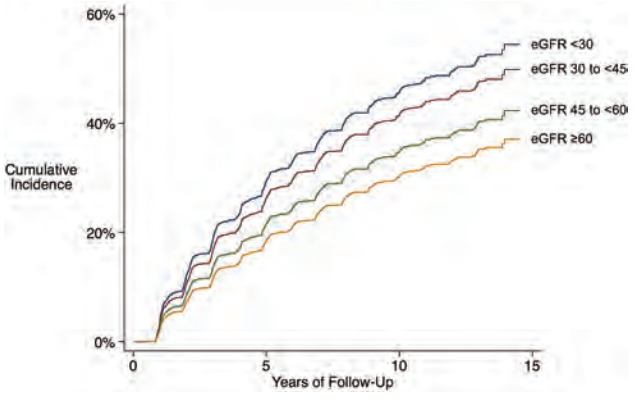
Background: Pruritus is common in patients with CKD not on dialysis, but its incidence and risk factors have not been rigorously evaluated.

Methods: Using data from the Chronic Renal Insufficiency Cohort (CRIC) study, we identified 2,164 participants that were pruritus free at baseline. Pruritus was assessed annually by the Kidney Disease Quality of Life instrument. We used Cox models adjusted for age, sex, race, ethnicity, diabetes, smoking status, and opioid use to analyze the association of pruritus with baseline estimated GFR, categorized as <30, 30 to <45, 45 to <60, and ≥60 mL/min/1.73 m^2. In an exploratory analysis, markers of bone-mineral metabolism and inflammation, possible mediators of the association between eGFR and pruritus, were added to the models to evaluate their association with risk of pruritus.

Results: The mean age of participants was 58 years, 43% were women, and 43% Black. During a median follow-up of 6.0 years, 684 participants developed moderate-to-severe pruritus, with an overall unadjusted incidence rate of 4.6 per 100 person-years. The 5-year unadjusted cumulative incidence of pruritus was: overall 21%, eGFR ≥60 18%, eGFR 45 to <60 20%, eGFR 30 to <45 24%, and eGFR <30 20%. In the fully adjusted model, compared to eGFR ≥60, an eGFR of 30-45 was associated with a 39% (95% CI 1.08 – 1.80) higher risk of pruritus, and an eGFR <30 was associated with a 56% (95% CI 1.15 – 2.11) higher risk of pruritus (Figure 1). Female sex, diabetes, current smoking, and opioid use were associated with increased risk of pruritus, independent of eGFR. Notably, serum albumin and c-reactive protein were independently associated with pruritus, whereas calcium, phosphorous, and parathyroid hormone were not.

Conclusions: A significant proportion of patients with CKD develop pruritus, even at modestly reduced eGFR ≤ 45 mL/min/1.73 m^2. Careful assessment and management of pruritus should be considered as a part of routine CKD care.

Funding: NIDDK Support



Adjusted cumulative incidence of pruritus by eGFR in the CRIC study

PO2273

Subtle Changes in Uremic Symptoms with CKD Progression

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Background: Uremic symptoms are a major contributor to symptom burden in CKD and related to lower quality of life. However, factors associated with uremic symptom progression have not been rigorously examined.

Methods: We included 3,504 participants with CKD not on dialysis from the Chronic Renal Insufficiency Cohort (CRIC) study with at least two assessments of estimated GFR (eGFR) and uremic symptoms. The uremic symptoms fatigue, anorexia, and pruritus were assessed annually by the Kidney Disease Quality of Life instrument. Responses were transformed to a scale from 0-100, with lower scores indicating worse symptom severity. We used multivariate linear mixed effects models with random intercepts and random slopes to estimate the association between eGFR change and the change in uremic symptoms over time.

Results: The mean age of participants was 58 years, 45% were women, 41% Black, and the mean eGFR at baseline was 45 mL/min/1.73m^2. Over a median follow-up of 7 years (IQR 3-11), the average annual decline in eGFR was -1.3 mL/min/1.73m^2/year. The average annual change in the symptom scores for fatigue, anorexia, and pruritus were -0.27 (95% CI: -0.35, -0.19), -0.26 (95% CI: -0.33, -0.19), and -0.49 (95% CI: -0.59, -0.39), respectively. A 10-unit change in eGFR was significantly associated with worsening fatigue, anorexia, and pruritus (Table 1). The association was stronger for those with eGFR <30 than those with higher eGFR.

Conclusions: Decreasing kidney function is associated with worsening fatigue, anorexia, and pruritus; however, the absolute change in symptom severity scores is small and unlikely to be clinically meaningful. Regular symptom assessment should be incorporated into routine CKD care; however, caution should be used when attributing large changes in symptom severity solely to changes in the level of kidney function.

Funding: NIDDK Support

Change in symptom score per 10-unit decrease in eGFR

	Fatigue*	Anorexia	Pruritus	Fatigue	Anorexia	Pruritus
	eGFR < 30			eGFR ≥ 30		
Unadjusted	-3.15 (-4.47, -1.83)	-2.05 (-3.08, -1.02)	-2.12 (-3.53, -0.72)	-1.46 (-1.75, -1.17)	-0.87 (-1.09, -0.66)	-1.43 (-1.72, -1.14)
Adjusted†	-3.36 (-4.60, -2.11)	-1.91 (-2.93, -0.90)	-1.20 (-2.56, 0.17)	-1.20 (-1.47, -0.93)	-0.64 (-0.84, -0.43)	-0.97 (-1.24, -0.70)

*Symptom severity scored from 0-100. Negative sign (-) indicates worsening symptoms

†Model adjusted for age, gender, race/ethnicity, baseline symptom score, BMI, employment, cancer history, total number of medications, ACEi/ARB, NSAIDs, antidepressants, opioids, gabapentin, and time.

PO2274

Conservative Kidney Management Practice Patterns in the United States: A CKDopps Analysis

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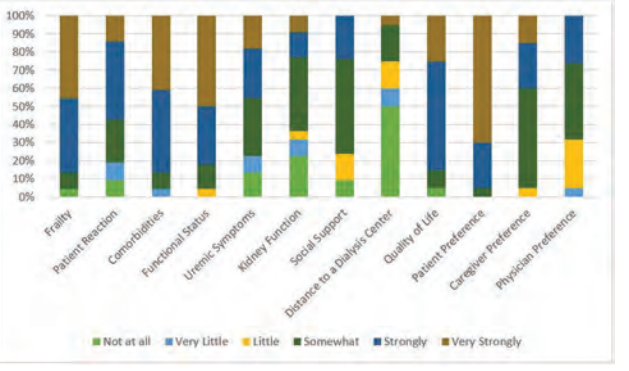
Background: Conservative kidney management (CKM) of kidney failure is an important treatment option for many patients. However, its availability in the United States (US) is not well described. We describe CKM resources and provider practice patterns in US Chronic Kidney Disease (CKD) clinics.

Methods: Cross sectional analysis of provider surveys (n=22) from unique clinics in the US from the CKD Outcomes and Practice Patterns Study (CKDopps) collected between 2014-2017.

Results: Only eight (36%) providers reported involving palliative care in planning for and educating patients about kidney failure. A majority (59%) were extremely comfortable discussing CKM and nearly 100% typically discussed CKM as a treatment option. Nearly all (95%) reported their clinics had the ability to routinely deliver CKM, but only one had a CKM protocol or guideline, and none offered a specific CKM clinic. Most providers said their clinics used the word "conservative" to describe CKM, with 24% choosing "palliative" or "supportive" terminology. Regardless of involvement of PC, most providers estimated that 5% of their patients with or approaching kidney failure were managed with CKM. Patient preference, functional status, frailty, and comorbidities were the most important factors influencing provider decisions in contemplating the suitability of CKM for patients. (Figure 1)

Conclusions: Most providers report feeling comfortable discussing CKM, yet almost no clinics report resources or dedicated infrastructure for CKM delivery. Despite reported high frequency of discussing CKM, few patients were described as choosing this treatment pathway. Factors that influence consideration of CKM are consistent with elements that generally influence well-informed geriatric and end-of-life care. Efforts to improve assessment of those elements may allow for more informed recommendations of CKM.

Funding: NIDDK Support



Factors influencing providers to consider conservative kidney management

PO2275

Association Between Monocyte Counts and All-Cause Mortality in Patients with CKD

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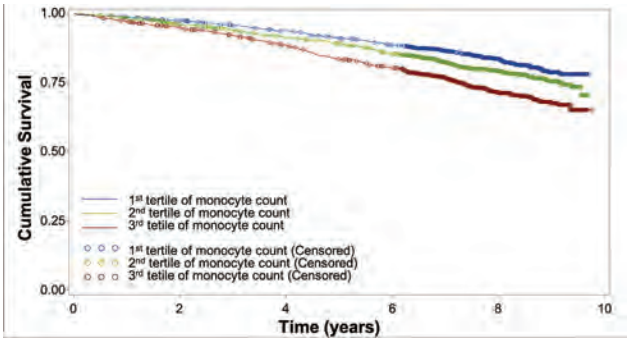
Background: In the general population, monocyte counts are strongly associated with a higher risk of all-cause mortality. However, little is known whether this association translates to individuals with chronic kidney disease (CKD). The purpose of this study was to examine if monocyte counts are associated with the risk of all-cause mortality in patients with non-dialysis CKD who participated in the Chronic Renal Insufficiency Cohort (CRIC) observational study.

Methods: Patients were divided in tertiles according to their monocyte counts at baseline, and survival analysis was performed using Kaplan-Meier curve with statistical comparison by the log rank test. Cox models with time interaction effects were used to examine the association between monocyte counts and all-cause mortality.

Results: Among the 3,939 CRIC participants, a total of 3,391 participants (1,838 males and 1,553 females) were included in the final analytic cohort, with a mean ± SD eGFR of 45 ± 15 mL/min/1.73 m^2 and age of 58 ± 11 years. Participants in the highest tertile of monocyte count had a lower rate of survival than those in the lowest tertile (P<0.001, Figure). At follow-up time of 5 years, there was a 39% higher risk for all-cause mortality (95% CI: 22-59%) with every 2-fold increase of monocyte count after adjusting for age, sex, race, clinic site, traditional cardiovascular risk factors, markers of kidney disease, and c-reactive protein (fully adjusted model).

Conclusions: There may be an elevated risk for all-cause mortality in patients with CKD who have higher monocyte counts.

Funding: NIDDK Support



PO2276

Kidney Disease and Longitudinal Changes in Muscle Strength in Older Adults

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Background: Persons with chronic kidney disease (CKD) experience lower physical function and increased risk of disability, both of which have strong prognostic importance for poor clinical outcomes. To date, functional status studies in populations with CKD have focused on physical activity and/or individuals with end-stage kidney disease, and have largely neglected measures of muscle strength, especially among those with non-dialysis dependent CKD.

Methods: Participants were from the Health, Aging and Body Composition Study, a longitudinal cohort focused on functional decline in adults aged 70-79 years at baseline. Kidney function was defined by estimated glomerular filtration rate (eGFR) using the CKD-EPI Cystatin C Equation at each available visit (up to 5) during 10 years of follow up. Participants were grouped based upon their longitudinal eGFR: no CKD (eGFR ≥60 mL/min/1.73 m^2), prevalent CKD (baseline eGFR <60 mL/min/1.73 m^2), and incident CKD (baseline eGFR ≥60 but <60 mL/min/1.73 m^2 during follow up). Grip and quadriceps strength were also assessed longitudinally (8 and 6 visits, respectively). Linear mixed models stratified by sex tested associations between kidney function groups and grip and quadriceps strength over time.

Results: Of the 2,630 participants with median age 73 years, 64.9% had no CKD, 23.4% had prevalent CKD, and 11.7% developed incident CKD. At baseline, men and women without CKD had higher unadjusted grip and quadriceps strength compared to those with CKD. In adjusted linear mixed models for grip strength, men with CKD had faster decline over time, compared to men without CKD (Table). For women, changes in grip strength were not different across kidney function groups. In adjusted models of quadriceps strength over time, there were no differences among kidney function groups.

Conclusions: Men with CKD had faster decline in grip strength compared to those without CKD. Future studies can determine if recognizing decreased muscle strength and intervening can change this functional trajectory among those with CKD.

Funding: NIDDK Support

		Grip strength		Quadriceps Strength	
		Baseline β (SE)	Change over Time β (SE)	Baseline β (SE)	Change over Time β (SE)
Men	No CKD	REF	REF	REF	REF
	Prevalent CKD	-1.1* (0.54)	-0.12* (0.06)	-0.13** (0.03)	0.006 (0.004)
	Incident CKD	-0.31 (0.69)	-0.14* (0.07)	-0.11*** (0.03)	0.001 (0.004)
Women	No CKD	REF	REF	REF	REF
	Prevalent CKD	-0.65 (0.37)	-0.06 (0.04)	-0.10*** (0.02)	0.0003 (0.004)
	Incident CKD	-0.15 (0.48)	-0.01 (0.05)	-0.07** (0.03)	0.002 (0.003)

SE=Standard error; *P<0.05; **P<0.01; ***P<0.001

PO2277

Health-Related Quality of Life in Patients with Inflammation and Non-Dialysis-Dependent CKD

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Background: Inflammation is common in chronic kidney disease (CKD) and can affect treatment of anemia, which is a common complication of CKD. Both inflammation and anemia in CKD have been linked with poor health-related quality of life (HRQoL), though evidence is limited. We aimed to assess the association between inflammation and HRQoL in patients with non-dialysis-dependent CKD (NDD-CKD).

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a point-in-time survey of physicians and their patients with CKD (stage 3-5D) collected in the United States in 2018. Patients were also invited to complete a questionnaire which included subjective assessment of the impact of CKD, as well as the Kidney Disease Quality of Life-36 questionnaire (KDQoL-36). Patients with NDD-CKD who filled out the KDQoL-36 were included in this analysis. Inflammation was defined as C-reactive protein ≥4.9 mg/L, ferritin ≥700 ng/mL, or albumin ≤3.6 g/L. T-tests were conducted to assess differences in KDQoL-36 scores between patients with and without inflammation.

Results: Inflammation was present in 136/491 (28%) patients. Mean KDQoL-36 scores reported by patients with inflammation were lower than scores reported by patients without inflammation across all 5 domains (all p<0.05; Table 1). Most differences in KDQoL scores between patients with and without inflammation exceeded the distribution-based minimal clinically important difference (MCID).

Conclusions: We found that patients with inflammation in NDD-CKD reported poorer HRQoL compared with those without. Reducing inflammation in CKD may improve HRQoL.

Funding: Commercial Support - FibroGen Inc

Table 1: KDQoL-36 scores* by inflammation status

	Patients with inflammation N, Mean (SD)	Patients without inflammation N, Mean (SD)	p-value	Distribution-based MCID (½ SD)
KDQoL-36: SF-12 Mental Health Composite	76, 44.9 (10.6)	189, 50.1 (8.4)	<0.0001	4.7
KDQoL-36: SF-12 Physical Health Composite	76, 38.0 (10.1)	189, 41.8 (9.3)	0.0032	4.8
KDQoL-36: Effects of kidney disease	77, 70.9 (22.3)	195, 82.7 (19.4)	<0.0001	10.4
KDQoL-36: Symptoms/problems	77, 80.8 (17.5)	194, 87.9 (13.7)	0.0004	7.6
KDQoL-36: Burden of kidney disease	79, 56.1 (29.0)	196, 66.6 (26.2)	0.0039	13.7

KDQoL-36, Kidney Disease Quality of Life-36 questionnaire; SD, standard deviation; SF-12, the 12-Item Short Form Health Survey

*Lower KDQoL-36 scores represent lower HRQoL

Table includes only patients with a KDQoL score, therefore bases may vary from total.

PO2278

Higher Frequency of Physical Activity Reduces the Risk of Kidney Function Loss in a General Non-Diabetic Population

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Background: Physical activity (PA) reduces the risk of diabetes and hypertension, known risk factors for chronic kidney disease (CKD), but there is limited data on the independent association between PA and loss of kidney function. Previous population studies of PA have reported mixed results and relied on estimated glomerular filtration rate (eGFR). All eGFR equations are biased by non-GFR related factors such as muscle mass and inflammation, making confounding likely, particularly in studies of PA. We investigated the association between self-reported PA and the annual change of measured GFR in a general population cohort.

Methods: 1627 subjects aged 50-62 years, without diabetes, cardiovascular disease or CKD were recruited from the general population in Tromsoe, Norway, and included in the Renal Iohexol Clearance Survey (RENIS) in 2007. Participants completed a questionnaire regarding frequency, intensity and duration of leisure-time PA, medication and comorbidities. GFR was measured using iohexol clearance at baseline and follow-up in 2013-15 and 2018-20. Linear mixed regression was used to analyze the association of PA with annual change in GFR, and logistic regression was used to assess the risk of accelerated GFR decline, defined as being those with the 10% steepest GFR decline.

Results: Mean (SD) age was 58 (3.8) years and 51% were female, median follow-up time was 11 years. Relative to participants that never exercise, the annual GFR decline rate for participants with PA once a week, 2-3 times a week or almost every day was slower by 0.40 (95% CI 0.05-0.76, p=0.026), 0.49 (95% CI 0.15-0.84, p=0.005) and

0.52 (95% CI 0.16-0.89, p=0.005) ml/min/1.73m^2/year (linear trend p=0.002), in a fully adjusted model. Increasing frequency of PA was associated with a lower odds ratio (OR) of rapid kidney function decline, with an OR of 0.25 (95% CI 0.1-0.6, p=0.004) for the highest frequency of weekly PA compared to the group that never exercise, in a model adjusted for established risk factors for GFR decline (linear trend across groups p=0.011).

Conclusions: In this population-based study with repeated measurements of GFR during 11 years of follow-up, higher frequencies of leisure-time PA are associated with slower GFR decline.

Funding: Government Support - Non-U.S.

PO2279

Serum Uric Acid Levels and Nephrosclerosis in a Population-Based Autopsy Study: The Hisayama Study

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Background: The information regarding the influence of serum uric acid levels on the pathological changes in kidney is limited. We aimed to examine the association between serum uric acid levels and pathological findings of nephrosclerosis in population-based autopsy samples.

Methods: A total of 923 deceased subjects in a Japanese community underwent autopsy examinations between 1974 and 1994. Of these, 547 cases with available kidney tissues and health examinations data within a median of 3 years before death were eligible for the present study. Serum uric acid levels were categorized into quintiles (Q1, 1.8-3.9; Q2, 4.0-4.6; Q3, 4.7-5.4; Q4, 5.5-6.3; Q5, 6.4-12.7 mg/dL). The presence of the advanced degree of glomerular sclerosis, kidney arteriolar hyalinosis, and kidney arteriosclerosis were determined by the 90th percentile or more of a glomerular sclerosis index and an arteriolar hyalinosis index, and the 10th percentile or less of a wall-lumen ratio, respectively. A logistic regression model was used to evaluate odds ratios and their 95% confidence intervals of serum uric acid levels on each kidney lesions.

Results: Higher serum uric acid levels were associated significantly with greater age- and sex-adjusted glomerular sclerosis index and lesser wall-lumen ratio. Subjects in the Q5 groups had a significantly greater likelihood of advanced glomerular sclerosis and advanced kidney arteriosclerosis than in subjects in the Q1 group after adjusting for potential covariates. There was no evidence of significant associations of serum uric acid levels with arteriolar hyalinosis index and the presence of advanced arteriolar hyalinosis.

Conclusions: Elevated serum uric acid levels were associated significantly with advanced glomerular sclerosis and advanced kidney arteriosclerosis, but not with advanced arteriolar hyalinosis in community based autopsied samples of Japanese.

PO2280

Prescribed Medications for Nausea and Vomiting Symptoms and Incident CKD in US Veterans

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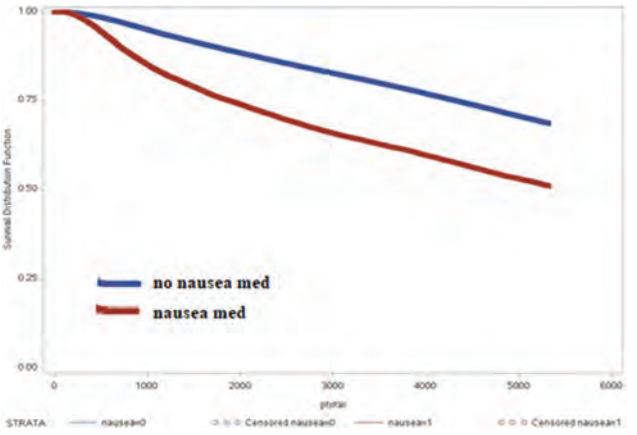
Background: Unpleasant upper gastrointestinal symptoms including nausea and vomiting and prescribed medication for their management may have important clinical implications as prelude to incident of chronic kidney disease (CKD), a hypothesis we sought to examine in US Veterans without reduced kidney function.

Methods: In 2,524,842 US Veterans with normal baseline eGFR (≥60 ml/min/1.73m2) and available data on albuminuria in 2004-2006, we examined the association of de novo prescription of anti-emetic medications during the baseline period with incident CKD over 14 years. Associations were examined in hazard models adjusted for demographics, major comorbidities, baseline eGFR, and albuminuria category.

Results: We identified 14,813 Veterans who were incident new anti-emetic users. Patients were a mean 61±14 years old, 7% female, 16% Black, and 5% Hispanic. Anti-emetic medication users were more likely to be female, White, smokers, with higher frequencies of comorbidities such as chronic obstructive pulmonary disease, cancer, and diabetes. Anti-emetic medication users had an almost 2-fold higher incident rate of CKD compared to non-users [4.7 (95% CI 4.6-4.9) per 100 patient years vs. 2.4/100PY (2.4-2.4), a faster time to incident CKD (Figure 1), and a 73% higher multivariable adjusted hazard (HR: 1.73, 95%CI: 1.69, 1.78) of incident CKD.

Conclusions: De novo prescription of anti-emetic medications in Veterans without reduced kidney function is associated with 73% higher likelihood of incident CKD independent of comorbidities and other potential confounders. Higher incident CKD likelihood may be due to prescribed anti-emetic medications or this relationship may represent the association of the unpleasant upper gastrointestinal symptoms with CKD risk, which warrants additional studies.

Funding: Veterans Affairs Support



PO2281

Polypharmacy and Potentially Inappropriate Medication Use in Patients with CKD Managed in Canadian Primary Care

Mohammed M. Tinwala,[1] Deenaz Zaidi,[1] Feng Ye,[1] Shezel Muneer,[1] Anukul Ghimire,[1] Maryam Khan,[1] Naima Sultana,[1] Ikechi G. Okpechi,[1] Paul E. Ronksley,[3] Neil Drummond,[1] Dee Mangin,[2] Aminu K. Bello.[1] *[1]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [2]McMaster University Faculty of Health Sciences, Hamilton, ON, Canada; [3]University of Calgary Cumming School of Medicine, Calgary, AB, Canada.*

Background: Polypharmacy and the use of potentially inappropriate medications (PIMs) are an increasingly serious public health challenge attributable to aging populations and multimorbidity. This study assessed the prevalence of polypharmacy and use of PIMs in chronic kidney disease (CKD).

Methods: A cross-sectional analysis using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database (January 1, 2010 through December 31, 2018). Polypharmacy was defined as the use of ≥ 5 medications, excessive polypharmacy as ≥ 10 medications, and PIMs as medications recommended to be avoided in CKD.

Results: The cohort was comprised of 70,331 patients (mean [SD] age, 73.1 [11.4] years; 40,502 [57.6%] female) with CKD stages G3a to G5. The most common chronic conditions were hypertension (60.8%), diabetes (29.4%), and osteoarthritis (25.4%). Overall, the prevalence of polypharmacy and excessive polypharmacy was 91.5% and 74.9%, respectively. The median number of medications was 14 (IQR 9-23). The most commonly prescribed medications were atorvastatin (29.8%), amlodipine (28.9%), and rosuvastatin (27.2%). About 45% of patients with CKD had at least one PIM, 11.1% had two PIMs, and 3.6 % had three or more PIMs. The most commonly prescribed PIMs were metformin (21.7%), nitrofurantoin (16.2%), and rivaroxaban (4.5%).

Conclusions: Polypharmacy and use of PIMs are highly prevalent among patients with CKD managed in primary care. These findings highlight opportunities for interventions aimed at improving prescribing practices in the management of CKD.

Funding: Government Support - Non-U.S.

PO2282

Association of SGLT2 Inhibitors and DPP-4 Inhibitors vs. GLP-1 Agonists with Incident CKD in US Veterans

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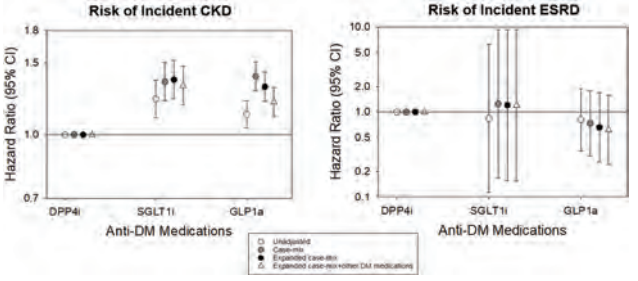
Background: Randomized controlled trials (RCTs) have demonstrated that SGLT2 inhibitors (SGLT2i) reduce the risk of eGFR decline and ESRD as compared with placebo in patients with pre-existing CKD. These RCTs showed an initial dip in eGFR with initiation of SGLT2i that stabilized over time. Little is known about the impact SGLT2i vs. other newer anti-diabetic medications (DPP-4 inhibitors [DPP4i], GLP1 agonists [GLP1a]) upon risk of developing de novo kidney dysfunction in patients without underlying CKD.

Methods: Among US Veterans with diabetes and absence of pre-existing CKD (normal eGFR and no proteinuria) followed over 2004-18, we identified incident (new) users of SGLT2i vs. DPP4i vs. GLP1a therapy, excluding combined users of the examined classes. We examined associations of SGLT2i vs. DPP4i vs. GLP1a use with the risk of incident CKD (primary outcome) and ESRD (secondary outcome) using multivariable Cox models.

Results: Among 39,065 diabetic patients without pre-existing CKD, 15%, 70%, vs. 15% were new users of SGLT2i, DPP4i, vs. GLP1a, respectively. Compared to DPP4i, use of SGLT2i and GLP1a were each associated with higher risk of incident CKD: adjusted HRs (aHRs) (95%CI) 1.32 (1.18-1.47) and 1.20 (1.11-1.31), respectively (**Figure 1A**). However, use of SGLT2i and GLP1a were not associated with higher risk of de novo ESRD: adjusted HRs (aHRs) (95%CI) 1.20 (0.15-9.32) and 0.62 (0.24-1.57), respectively (**Figure 1B**).

Conclusions: In a national cohort of diabetic US Veterans without pre-existing CKD, SGLT2i and GLP1a use were each associated with higher risk of incident CKD as compared with DPP4i use. However, neither medication was associated with incident ESRD, suggesting that early decline with SGLT2i and GLP1a use may be an acute/subacute effect that stabilizes over time.

Funding: Veterans Affairs Support



PO2283

Insulin Use and CKD Are Risk Factors for Mild Cognitive Impairment (MCI) or Dementia in Persons with Type 2 Diabetes

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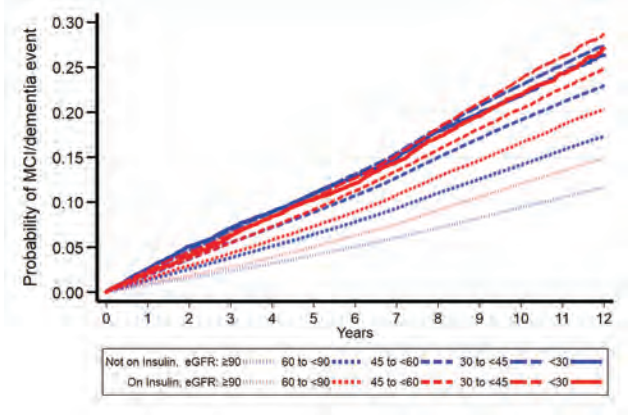
Background: Both insulin use and CKD are risk factors for hypoglycemic episodes in patients with diabetes. Recurrent hypoglycemia is associated with increased risk of dementia. Hence, we examined whether insulin use and CKD are associated with increased risk of MCI/dementia.

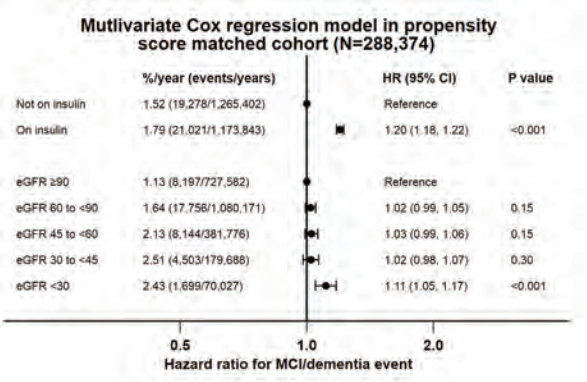
Methods: We analyzed a national VA cohort (N =855,133) with T2DM defined by ICD-9 codes and outpatient serum creat from 1/2008 to 12/2010. Index date was the date of first outpatient serum creatinne measurement. Baseline comorbidities were defined by ICD-9 codes from 10/1999 to the index date. MCI/ dementia were defined by ICD9/10 codes. Those with baseline MCI/dementia were excluded and new onset of MCI/dementia was tracked from index date to 12/31/2020. A multivariate logistic regression model of baseline variables was used to develop propensity scores of baseline insulin use (24% were on insulin at baseline). A propensity score matched cohort (N = 288,374) was used to relate baseline insulin use and CKD stages with subsequent MCI/dementia in Cox regression models.

Results: Baseline mean age was 65 ±11 yrs, 20% black and mean eGFR 72±24. There were 40,299 MCI/dementia events over 2,439,244 years of follow up. There was a graded increase in incidence rate of MCI/dementia by CKD stages and insulin use (Fig1). In a Cox regression model adjusted for propensity scores and covariates, both insulin use and advanced CKD were associated with higher risk of MCI/dementia (Fig2).

Conclusions: Both insulin use and advanced CKD are associated with higher risk of MCI/dementia in persons with T2DM.

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





PO2284

Incidence of CKD Stages 3-5 Among Patients on Lithium Therapy

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Background: The association between lithium use and chronic kidney disease (CKD) is not well understood, and the impact of comorbidities and other factors remains unknown. The aim of this study was to examine the risk of developing CKD stage 3 and above among individuals using lithium.

Methods: This was a retrospective cohort study of all patients in Iceland treated with lithium in the years 2008-2018. A control group was comprised of patients with affective disorders (ICD-10 codes F30-F39) who attended the outpatient clinics of the Landspitali–The National University Hospital Mental Health Services in 2014-2016 and had not been prescribed lithium. CKD stages 3-5 was defined according to the KDIGO 2012 guidelines and eGFR was calculated from serum creatinine (SCr) using the CKD-EPI equation. Individuals with CKD 3-5 prior to 2008 and those with fewer than 2 SCr measurements during the study period were excluded. Risk assessment was performed using logistic regression.

Results: A total of 2682 persons had received lithium treatment, of whom 2051 (76.5%) were included in the study. Of those 221 (10.8%) developed CKD 3-5. Of the 1426 persons in the control group, 1010 (70.8%) were included, of whom 29 (2.9%) developed CKD 3-5. Lithium use was significantly associated with CKD development (OR 1.94, 95% CI 1.25–3115) after adjusting for sex, age and comorbid diseases (Table).

Conclusions: Lithium treatment is a highly significant independent risk factor for the development of CKD in individuals with affective disorders.

Funding: Government Support - Non-U.S.

Factors associated with CKD, multivariable logistic regression.

	Odds Ratio	95% confidence interval
Sex, men	0.87	0.63 - 1.19
Age	1.03	1.02 - 1.04
Initial eGFR	0.93	0.92 - 0.94
Hypertension	1.20	0.81 - 1.77
Diabetes	1.78	1.05 - 2.94
Acute kidney injury	1.68	1.12 - 2.50
Lithium use	1.94	1.25 - 3.11

PO2285

Effect of Serum Testosterone on Kidney Function in Men and Women from the General Population

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Background: Testosterone may prevent kidney function decline, but at population level evidence is sparse in males, and even lacking in females. Therefore, we investigated the association between serum testosterone and kidney function in males and females from a large population-based cohort study.

Methods: Linear regression and linear mixed models were used to assess the associations of serum free and total testosterone with kidney function, including baseline assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcreat) or serum cystatin C (eGFRcys), and the urine albumin-to-creatinine ratio (ACR), and repeated assessments of eGFRcreat. Betas with their 95% confidence intervals (CI) were reported per 1 nmol/L increase in testosterone. Analyses were conducted for males and females separately.

Results: Our study population comprised 9,484 participants (mean age 65.2 years). In males (n=4,162), higher free testosterone was associated with lower eGFRcreat (beta -0.63, 95% CI -1.05;-0.21), but higher eGFRcys (beta 0.56, 95% CI 0.07;1.05), and lower ACR (beta -0.25, 95% CI -0.35;-0.16) at baseline. Higher total testosterone was associated with higher eGFRcreat at baseline and over time, but with lower eGFRcreat when additionally adjusted for sex hormone-binding globulin. In females (n=5,449), higher free testosterone was associated with lower eGFRcreat and eGFRcys at baseline (beta -1.03, 95% CI -1.36;-0.71, beta -1.07, 95%CI -1.44;-0.70) and lower eGFRcreat over time (beta -0.78, 95% CI -1.10;-0.46), but not with ACR. Similar results were obtained with total testosterone.

Conclusions: The association between serum testosterone and kidney function is sex-dependent, with a positive association in males and a negative association in females. The discrepant results with eGFRcreat in males may be explained by the effect of testosterone on muscle mass. Whether treatment with testosterone replacement therapy may be beneficial for kidney function in males with low serum testosterone still needs to be investigated. The association between testosterone and lower eGFR in females requires further study.

PO2286

Assessment of Circulating Inflammatory Cytokines Aids in the Prediction of Progression of CKD

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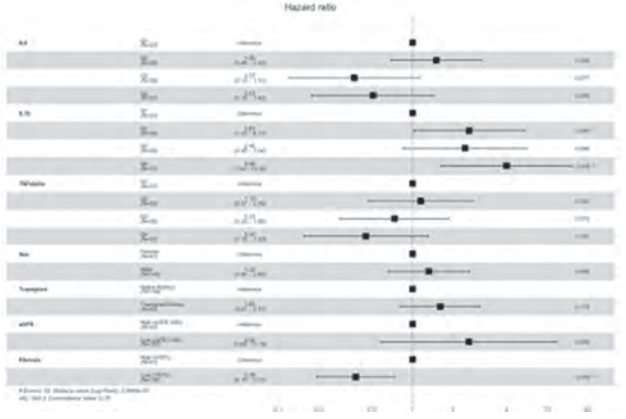
Background: Though Chronic Kidney Disease (CKD) is common, only a small proportion of patients progress towards the need for dialysis or transplantation. Understanding the factors which drive progression of CKD may facilitate better prediction of outcomes for patients and streamline patient care.

Methods: Inflammatory cytokines, IL-6, IL-10 and TNF-α were measured in patients with CKD. Clinical data, including demographic, biochemical, histological, and longitudinal assessments of renal function were collected for these patients. Differences in levels of circulating inflammatory cytokines were examined using independent samples, two-sided T tests, with $\alpha < 0.05$. Linear regression models, using bootstrap resampling were explored to identify the ability of these cytokines to explain future eGFR. Cox proportional hazards models were explored to examine predictors of progression of CKD, defined as the need to commence dialysis or undergo transplantation.

Results: Levels of inflammatory cytokines were assessed in 226 patients with kidney disease. Higher levels were seen in those patients who experienced progression of CKD. 14% of the variance in eGFR at 12 month follow-up was explained by IL-6 levels at baseline (bias -0.0039, SE 0.036). TNF-α levels were predicted to explain 21% of 12 month eGFR (bias -0.005, SE 0.07). In a Cox proportional hazards model, patients with the highest quartile of IL-10 measurements were more likely to experience CKD progression towards the need for dialysis or transplantation (HR 4.99, 95% CI 1.62-15.32) (Likelihood ratio test = 45, on 13 df, $p = 2x10^{-5}$). Patients with lower levels of tubulointerstitial fibrosis (<50% on kidney biopsy) were less likely to experience progression of CKD (HR 0.38, 95% CI 0.19-0.73).

Conclusions: Higher levels of inflammatory cytokines in patients with CKD are predictive of eGFR decline and may be incorporated in models to help predict outcomes for CKD patients.

Funding: Private Foundation Support, Government Support - Non-U.S.



PO2287

Disturbance of Circadian Rhythm and CKD in Korean Adult Population

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Background: Disturbances in circadian rhythm are known to cause a number of health problems (psychosis, metabolic syndrome, cancer, etc.), however their contribution to kidney disease is not well understood. Therefore, this study evaluated the association with chronic kidney disease (CKD), sleep disturbance, and shift work in a Korean adult population.

Methods: A total of 32,429 participants who completed the National Health and Nutrition Examination Survey from 2010 to 2018 were assessed for their sleep patterns, shift work, and renal function. CKD was defined by eGFR ≤60 mL/min/1.73 m^2 or urinary albumin-to-creatinine ratio ≥30 mg/g.

Results: First, sleep disturbances were assessed according to sleep onset time and total sleep duration. We observed that the early bedtime group (starting sleep before 9pm) had a significantly higher CKD prevalence (OR 2.757, $p < 0.001$) compared to the regular bedtime group (9pm-2am), but inadequate sleep duration (<6hr) had minimal effect on CKD (OR 1.052, p=0.745), which suggest that alterations in circadian rhythms due to sleep disturbance are associated with CKD development. In particular, there was a strong association between sleep disturbance and renal dysfunction in patients with comorbidities younger than 65 years of age. Next, work schedules were divided into two types; regular work (day or evening work) and shift work (fixed night shift, 24-hour shift, split-work). The shift-work group also had a higher prevalence of CKD compared to the regular work group (OR 1.32). However, in a multivariate analysis that adjusted for age, sex, BMI, smoking, drinking, diabetes, and hypertension, neither sleep disturbance nor shift work showed an independent association with the occurrence of CKD.

Conclusions: Our results suggest that impaired circadian rhythm may be associated with CKD development and that sleep disturbance can be an important therapeutic target for circadian rhythm.

PO2288

Mortality Risk and Life-Years Associated with CKD for Young and Older Adults

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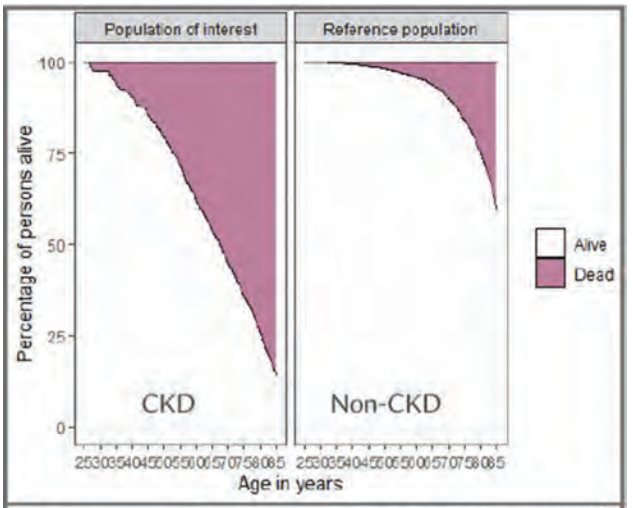
Background: Younger individuals living with CKD face a lifetime at risk for complications, including an increased risk of mortality. There is limited data to inform individual patients with CKD across the lifespan how their risk for mortality compares with equivalently aged individuals without CKD. The objective of this study is to provide age specific contexts to the risk of mortality associated with a diagnosis of CKD.

Methods: We created a pooled study cohort using participants with CKD enrolled in the Chronic Renal Insufficiency Cohort along with participants aged 21-75 years with an eGFR >70mL/min/1.73m^2 included in the 2002-2008 NHANES surveys. Age-stratified mortality rates, along with unadjusted and adjusted hazard ratios (HR) for mortality were generated to compare differences between those with and without CKD. Mean life-years-lost (LYL) relating to CKD were calculated using CDC life tables.

Results: A total of 17,550 participants (3,746 with CKD) were included. The adjusted HR for mortality relating to CKD was highest in the 21-35yr strata (HR [95% CI]: 5.6 [3.5, 9.0]) and lowest in the 65-75yr strata (HR [95% CI]: 1.9 [1.6, 2.1]). Mean LYL secondary to CKD was inversely related with increasing age (**Fig. 1**). An individual aged 21yrs old with CKD could expect a mean of 15.6 LYL compared to age-matched peers without CKD. A similar comparison in a 70-yr-old would translate to 2.9 LYL.

Conclusions: Compared to age-matched peers without CKD, the risk for mortality and LYL associated with a diagnosis of CKD is highest in younger individuals. Further research is needed to elucidate the societal and personal costs of premature mortality in young adults with CKD.

Funding: NIDDK Support



Age	Life years lost (95% CI) due to CKD
21-year-old	**15.6** (13.4, 18.7)
30-year-old	**14.7** (13.2, 16.3)
40-year-old	**12.6** (11.7, 13.8)
50-year-old	**9.8** (9.2, 10.5)
60-year-old	**6.1** (5.7, 6.5)
70-year-old	**2.9** (2.6, 3.1)
80-year-old	**0.7** (0.6, 0.9)

PO2289

Estimated Glomerular Filtration Rate (eGFR) and Myocardial Fibrosis Biomarkers in Hypertensives with and Without CKD

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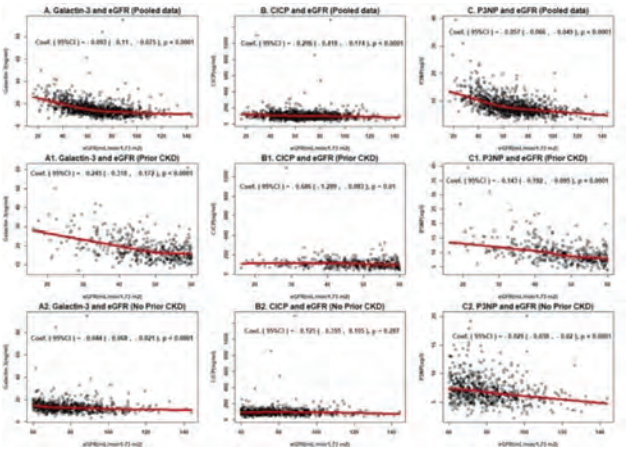
Background: CKD leads to accumulation of fibrotic tissue in the myocardium with subsequent loss of cardiac function. Two circulating biomarkers of collagen type I and III (PICP and P3NP) correlate with the amount of cardiac collagen deposition. Galectin 3 (Gal-3), a predictor of heart failure, is used to stratify patients at increased cardiovascular risk. We aimed to assess the association between eGFR and Gal-3, PICP, and PIIINP levels in individuals with and without CKD enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: A random sample of 1026 SPRINT participants 50 years or older were included in the study. Baseline demographic, anthropometric, co-morbid conditions and laboratory data were examined univariately for association with quartiles of Gal-3, CICP and PIIINP. The statistically significant variables were chosen for the multivariate quantile regressions at median (MQR) to assess the association between baseline eGFR and each biomarker.

Results: The mean age (SD) was 68.3±9.9 years, and 38.4% had CKD. In MQR models, baseline eGFR was negatively associated with Gal-3, PICP and PIIINP levels. (Figure) Similar results were found in participants with CKD, but not in participants without CKD, with significant correlation between eGFR with Gal 3 and PIIINP, but not with PICP. In combination, PIIINP was correlated with PICP (Coef 0.26, 95%CI (0.17, 0.35), p<0.001)), and Gal3 (Coef (0.35, 95%CI (0.26, 0.43), p<0.001) in the CKD subgroup, but not in the non-CKD subgroup (p=0.10, and p=0.07 respectively).

Conclusions: CKD status modifies the association between myocardial fibrosis biomarkers and eGFR, with high serum Gal-3, CICP, and PIIINP levels associated with low eGFR. Future research is needed to elucidate whether there is a causal link between kidney function decline and risk for myocardial fibrosis.

Funding: Other NIH Support - NHLBI



Quantile Regressions for eGFR and Myocardial Fibrosis Biomarkers

PO2290

Renal Biopsy Is Mandatory in Normal Urinary Findings with Unknown Origin Hypertension or CKD

Byoung-Soo Cho. *Dr.Cho's kidney Center, Deoul, Seoul, Republic of Korea.*

Background: One of th most common causes of end stage renal disease are diabetes mellitus, hypertension and chronc glomerulonephritis, however most centers do not try to find the origin of hypertension especially in chronic kideny disease patients. Most chronic glomerulonephritis patients usually associated with hematuria and or proteinuria. Most kidney centers do not recommend renal biopsy if proteinuria is absent even though associated with persistent hematuria. In order to clarify the causes of hypertension or chronic kidney diseases, our center performed renal biopsy who showed unkown origin chronic kidney disease or unknown origin hypertension even though urinalysis findings showed no abnormalities.

Methods: From 2014 to 2020, we performed 1,300 cases of renal biopsy, of which 272 cases showed no urinary abnormalities when performing renal biopsy. We perfomred renal biopsy not only in unknown origin hematuria and unknown origin proteinuria but also we perfomed renal biopsy in unkown origin CKD and unknown origin hypertension even though urinary findindings were normal at that time of renal biopsy.

Results: Of the 1,300 renal biopsy patients, 272(20.9%) showed normal urinalysis findings at that time of renal biopsy. Minor changes were detected in 2 cases among 272 cases. Most cases were serious chronic glomerulonephritis. Biopsy results were as follows: IgA nephrothy 98cases(36%), Mild focal nonspecific glomerulonephritis 43 cases(15.8%), Focal segmental glomerulosclerosis 39 cases(14.3%), Diffuse mesangial proliferative glomerulonephritis 39 cases(14.3%), Podocyte disease 8 cases (2.9%), Membranous nephropathy 6 cases ((2.2%), C1q nephropathy 5 cases(1.8%), Lupus nephritis 4 cases(1.5%), malignant hypertension 3 cases1.1%), obesity related glomerulopathy 2 cases(0.7%), Minor change 2 cases(0.7%), C3GN 1 case(0.3%)

Conclusions: Most patients with CKD /hypertension patients without urinary abnormalities showed serious chronic glomerulonephrits such as IgA nephroapthy, FSGS, diffuse mesangial proliferative glomerulonephritis etc. kidney biopsy is mandatory in unknown origin CKD /hypertension to clarify the original causes before considering antihypertensive medicine.

PO2291

Association Between Diabetes and Major Bleeding Complications of Renal Biopsy: Analysis of 76,304 Patients Using a National Inpatient Database in Japan

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Background: Nephrologists have recently recognized the heterogeneity of kidney diseases in patients with diabetes and actively performed percutaneous renal biopsies (PRBs). However, the association between diabetes and major bleeding complications of PRBs remains unclear.

Methods: In this retrospective observational study using the Japanese nationwide Diagnosis Procedure Combination inpatient database, we identified patients who underwent an elective PRB between July 2010 and March 2018. The primary outcome was the occurrence of major bleeding complications defined as (i) red blood cell transfusion within 7 days after the PRB or (ii) invasive hemostasis after the PRB. Multiple regression analysis was performed to analyze the association between diabetes and major bleeding complications with adjustment for patient and hospital characteristics.

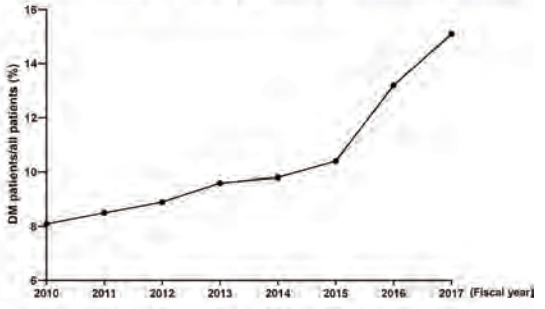
Results: We identified 76,304 patients, including 8,245 patients with diabetes. The proportion of biopsies for patients with diabetes to total biopsies increased year by year (Figure 1). Major bleeding complications occurred in 678 (0.9%) patients, including 622 (0.8%) red blood cell transfusion and 109 (0.1%) invasive hemostasis. Diabetes was significantly associated with major bleeding complications (RR, 2.66; 95% CI, 2.12-3.34)

after adjusted for patient and hospital characteristics. Among patients with diabetes, multi-agent or insulin treatment showed a significant association with major bleeding complications (RR, 1.55; 95% CI, 1.16-2.08), compared with single-agent diabetes treatment.

Conclusions: Diabetes was an independent risk factor for major bleeding complications of PRBs. Moreover, severity of diabetes was associated with increase in major bleeding complications. Nephrologists should carefully judge whether the anticipated benefits counterbalance the relatively high risk of major bleeding complications when considering PRBs for patients with diabetes.

Funding: Government Support - Non-U.S.

Figure 1. Annual transition of renal biopsies for patients with diabetes



	2010	2011	2012	2013	2014	2015	2016	2017
DM patients, n (%)	442 (8.1%)	649 (8.5%)	838 (8.9%)	911 (9.6%)	1053 (9.8%)	1110 (10.4%)	1484 (13.2%)	1758 (15.1%)
Non-DM patients, n (%)	5037 (91.9%)	6969 (91.5%)	8614 (91.1%)	8560 (90.4%)	9651 (90.2%)	9572 (89.6%)	9796 (86.8%)	9860 (84.9%)

PO2292

Application of the Renal Chronicity Score on Native Kidney Biopsies: Results from the FCGG Biopsy Registry

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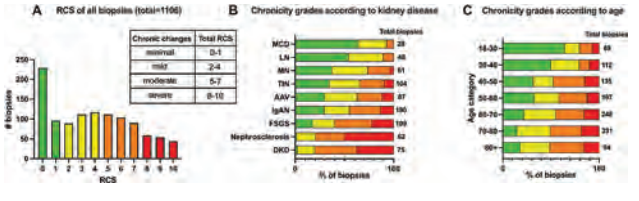
Background: Chronic changes on kidney biopsy strongly predict renal outcome and have important treatment implications. Sethi *et al*. recently proposed the renal chronicity score (RCS), a standardized pathology scoring system which uniformly scores chronic changes on kidney biopsies. We report the RCS of the biopsies included in the FCGG registry in 2018 and 2019.

Methods: The RCS is derived from the sum of the degree of glomerulosclerosis, tubular atrophy, interstitial fibrosis and arteriosclerosis, and ranges from 0 (no/minimal chronic changes) to 10 (severe chronic changes). The FCGG registry is a population-based native kidney biopsy registry in Flanders (Northern part of Belgium) that covers a population of approximately 6.5 million inhabitants.

Results: In 2018 and 2019, the RCS was reported in 1106 of 1403 adult biopsies (78,83%), with a median value of 4 (mild chronic changes, Fig. 1A). Minimal change disease (MCD) and lupus nephritis (LN) showed mostly minimal to mild signs of disease chronicity (Fig. 1B). Membranous nephropathy (MN), tubulointerstitial nephritis (TIN), ANCA-associated vasculitis (AAV) and IgA-nephropathy (IgAN) showed an increasing proportion of moderate to severe chronic changes (26%, 35%, 37%, 45%, respectively, Fig. 1B). Finally, in focal segmental glomerulosclerosis (FSGS), nephrosclerosis and diabetic kidney disease (DKD) the proportion of biopsies with moderate to severe chronic changes exceeded 50% (60%, 79%, 80%, respectively, Fig. 1B). The RCS was also higher in biopsies from older patients (Fig. 1C), although this observation is likely confounded by the etiology of kidney disease in the older age categories (i.e., more nephrosclerosis in older patients).

Conclusions: We report on the first large population-based kidney biopsy registry that systematically scores chronic changes on kidney biopsy in a standardized manner, using the RCS. Future research should validate this score by assessing the correlation with prognosis and treatment outcome in individual kidney diseases and determine whether disease-specific modifications in the chronicity classification should be made.



PO2293

Cystatin C and Creatinine as Biomarkers of Pediatric Sarcopenia

Lokesh N. Shah, Jin Long, Jessica R. Whalen, Paul C. Grimm, Mary B. Leonard. *Stanford University School of Medicine, Stanford, CA.*

Background: Pediatric sarcopenia defines a state of reduced muscle mass and strength in chronically ill children. Since Creatinine is a byproduct of all skeletal muscle cells and Cystatin C is made by all nucleated cells, we hypothesized that a relationship between the two could estimate muscle mass and muscle strength.

Methods: In 217 recruited healthy children and adolescents, data collected included anthropometric measures, whole body DXA composition, handgrip strength, leg extension and leg flexion. Stored sera were sent for Creatinine and Cystatin C measurements. We developed 4 models to estimate muscle mass and strength. Low lean mass based on an NHANES Z-score of appendicular lean mass index < -1 defined sarcopenia.

Results: Univariate analyses demonstrated the following to be associated with muscle mass and strength: age, sex, weight, height, sexual maturity, serum creatinine, differences in eGFR, and ratio of serum Cystatin C to serum Creatinine ($p < 0.01$). When compared against a model of only physical exam biomarkers, adding creatinine and cystatin C did not lead to clinically significant improved estimates. Using a definition of sarcopenia defined by low lean mass, there was minimal added predictive ability in identifying sarcopenia in healthy children.

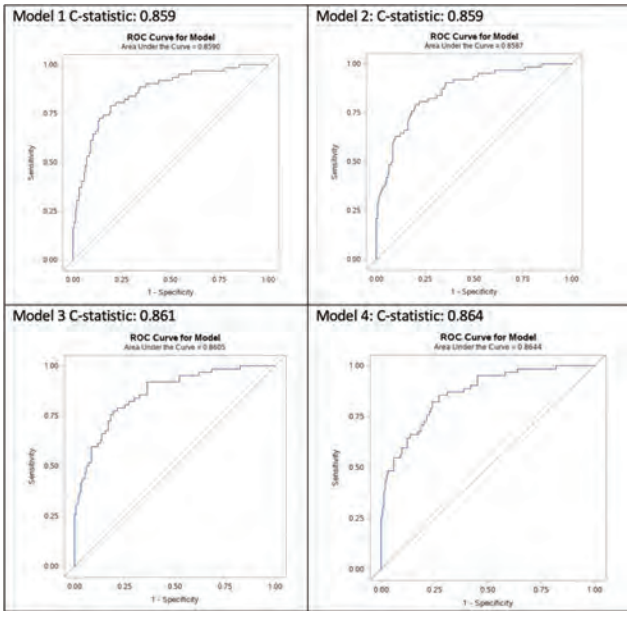
Conclusions: The addition of Cystatin C and Creatinine did not meaningfully improve the estimation of muscle mass or muscle strength in healthy children. Future work remains to evaluate these models in children with chronic kidney disease.

Funding: NIDDK Support, Private Foundation Support

Table 1A. Summary of R^2 values: Model Estimation in Healthy Children

	Appendicular Lean Mass	Whole Body Total Lean Mass	Handgrip Strength	Leg Strength in Knee Extension	Leg Strength in Knee Flexion
Model 1	0.9333	0.947	0.7671	0.7994	0.6689
Model 2	0.9366	0.9508	0.7774	0.8054	0.677
Model 3	0.938	0.9518	0.7803	0.8054	0.6767
Model 4	0.9418	0.9542	0.7953	0.8062	0.6816

Model 1 (Physical Exam Biomarkers Only): Weight, Height, Age, Sex, Tanner Stage, Sex*Tanner Stage (interaction)
Model 2: Model 1 + Difference in eGFR calculated using creatinine (Bedside Schwartz 2009) vs. Cystatin C (2012)
Model 3: Model 1 + Cystatin C to Creatinine Ratio
Model 4: Model 1 + absolute Cystatin C + Creatinine values



ROC Curves of Estimating Equations for Identifying Sarcopenia (ALMI NHANES Z-score < -1).

PO2294

Behavioral Characteristics and Related Factors Among CKD Patients in South Korea During the COVID-19 Pandemic

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Background: The recent novel coronavirus disease (COVID-19) pandemic has led to unprecedented changes in behavior. We evaluated the current status of precautionary behavior and physical activity in chronic kidney disease (CKD) patients during the COVID-19 pandemic.

Methods: A population of CKD patients (n=306) registered in a SKETCH (Study on Kidney disease and EnvironmenTal Chemicals, Clinical Trial No. NCT04679168) cohort recruited from June 2020 to October 2020 was included in the study. We conducted a questionnaire survey related to (1) risk perception of COVID-19, (2) hygienic behavior, (3) social distancing, and (4) physical activity during the past year (before the pandemic) and during the pandemic. To compare behaviors before and during the COVID-19 pandemic, the Wilcoxon-signed rank test was used. Logistic regression analysis was conducted to identify the relative factors related to risk recognition or behavior changes.

Results: There were 187 (61.1%) patients with eGFR <45 mL/min/1.73 m^2. This population showed a higher degree of risk perception for COVID-19 than the general population. During the pandemic, social distancing and hygiene-related behavior was significantly increased (P <0.001). The frequency of exercise was decreased only among those with regular exercise, without diabetes, or with a lower Charlson comorbidity index (CCI) (P <0.001), with no change among the other groups. Socioeconomic status and comorbidities significantly affected behavioral characteristics regardless of the category. Age was the most significant determinant of risk perception among CKD patients. Education and income were significantly associated with precautionary behaviors such as staying at home and hand sanitizer use. Also, patients with higher CCI status significantly increased their frequency of exercise (adjusted OR 2.10, 95% CI 1.01-4.38).

Conclusions: CKD patients showed higher risk-perception with active precautionary behavioral changes than the general population. Healthcare providers should be aware of the characteristics to comprise precautionary behavior without reducing the physical activity.

PO2295

AKI in Rural Workers: Is Mesoamerican Nephropathy in Fact an Agricultural Nephropathy?

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Background: Mesoamerican nephropathy (MN) is a chronic tubule-interstitial nephropathy, originally described in Central America, and whose exact etiology is still unknown. Many inducing factors have been proposed such as severe dehydration, rhabdomyolysis, nephrotoxicity, chronic infections, genetic predisposition, etc. However, similar nephropathies to MN have been described in areas geographically far and ethnically diverse from Mesoamerica but which have a common factor: the intensity of hot weather and rural physical labor. For this reason, we suggest the term "agricultural nephropathy" as more appropriate name for this condition. Then, it was decided to study whether this entity could occur among rural workers of non Mesoamerican region but having similar climatic and working conditions, as is the case of the Colombian Caribbean countryside, and to consider how much repeated dehydration could weigh in its pathogenesis.

Methods: A descriptive, observational, cross-sectional study was carried out, based on field work in a farm in Sitio Nuevo (Magdalena, Colombia) in 28 rural worker volunteers (rice fields), who were measured for weight, blood pressure, blood and urine samples to measure electrolytes and osmolarity, at 2 times of the day (morning and evening).

Results: Of the 28 young men workers evaluated, 5 (18%) presented a significant increase in serum creatinine during the day (0.8±0.15 vs 1.2±0.17, p: 0.001). The volume of water ingested by the workers was highly variable (2,861 ± 1,591 cc). There was a significant increase in serum sodium (p: 0.001), and urinary osmolarity (p: 0.01) values between morning and afternoon values in these 5 patients

Conclusions: Some rural workers developed parameters compatible with AKI and dehydration during their work day in the Colombian Caribbean countryside

PO2296

A New Epidemiologic Methodological Approach Using Machine Learning in Prevalence Estimation of CKD

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Background: Prevalence of chronic kidney disease (CKD), a pandemic condition, is generally estimated at 5-10% of the general population and increases with ageing. With the emergence of artificial intelligence, machine learning approaches could identify patients with such condition, improve our understanding of health, and provide opportunities for intervention. The aim was to automatically identify people with CKD and estimate more precisely its prevalence, which remains a real challenge.

Methods: Two sources of data were used, LPD (Longitudinal Patients Data) and LRx (Lifelink Treatments Dynamics), including data of near 2.5 and 40 million subjects, respectively. LPD, a medical database, included 191,905 patients receiving medications usually defined as specific for CKD from July 1st, 2019 to June 30, 2020. Of these subjects, 1.9% had a firm diagnosis of CKD, dialysis, or kidney transplant status. These patients were followed by 1,210 general practitioners who participated in a permanent longitudinal observatory of ambulatory medicine prescriptions (LPD). LRx contained all anonymized medication dispensing in outpatient care database from a representative panel of 45% of all French metropolitan retail pharmacies. A machine learning algorithm using a gradient boosting model was trained from CKD patients identified in LPD (metrics performance - sensitivity: 68%, specificity: 99%, positive predictive value: 52%, negative predictive value: 99%, F1 score: 59%). The model was implemented in LRx to obtain the overall number of CKD patients in the period of interest. As we will underestimate the true number of CKD patients, rules-based algorithm focused on erythropoietin delivery for renal condition and keto-analog was applied on LRx. We calculated the raw number of CKD patients and extrapolated it and described demographic characteristics from November 1st, 2019 to October 31th 2020.

Results: In LRx, we numbered 269,183 CKD patients corresponding to an extrapolated number of 678,102 patients with 40.8% of women and the mean age was of 77.0 years (±11.1) in the period of interest. This corresponded to a prevalence of 1%.

Conclusions: A combined approach using machine learning and rules-based algorithm may be useful in identifying CKD patients who require careful management of their renal condition.

Funding: Private Foundation Support

PO2297

CKD Among Patients with Dengue: A Comorbidity That Increases Hospitalization and Mortality

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Background: Dengue virus is one of the most important neglected tropical diseases in the world, with varying manifestations, including kidney involvement. The aim of this study was to investigate chronic kidney disease (CKD) and its association with outcomes among patients with dengue.

Methods: A cross-sectional study was conducted in Ceará State, northeast Brazil, in the period from January 2015 to December 2017, including all confirmed cases of dengue through clinical, epidemiology and laboratory tests (IgM specific antibodies or RT-PCR). We have made a comparison between patients with and without CKD, defined according to the KDIGO guidelines.

Results: A total of 161,880 patients were included. Patients with CKD were older (41±22 vs. 35±21 years, p<0.001), predominantly female (62 vs. 57%, p=0.004) and presented higher frequency of majority of symptoms and signs (fever: 89 vs. 86%, p=0.01; myalgia: 76 vs. 67%, p<0.001; rash: 35 vs. 22%, p<0.001; nausea: 42 vs. 23%, p<0.001). The most common comorbidities were hypertension and diabetes, which are also the most common causes of CKD (51 vs. 3.3% / 42 vs. 1.3%, p<0.001). Independent factors associated with CKD were: hematological disease (OR 8.08), auto-immune disease (OR 7.73), peptic ulcer disease (OR 7.19), hypertension (OR 5.06), diabetes (OR 2.57), leukopenia (OR 1.87), arthritis (OR 1.70), back pain (OR 1.43), petechia (OR 1.33) and nausea (OR 1.26). Need of hospitalization was significantly more frequent among the group with CKD (12.3% vs. 2.2%, p<0.001), and mortality was higher among CKD patients (2.2% vs. 0.1%, p<0.001), Figure 1.

Conclusions: CKD aggravates dengue severity, including the need of hospitalization and increased mortality. Patients with CKD and dengue should be carefully monitored, especially in epidemic periods.

Funding: Government Support - Non-U.S.

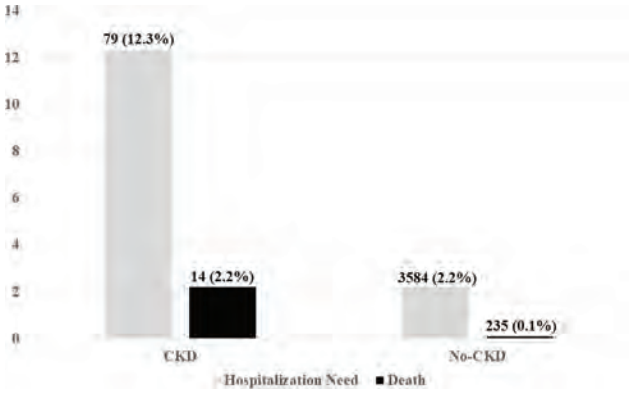

Figure 1. Hospitalization need and mortality rate according to the presence of chronic kidney disease (CKD) in patients with dengue in Fortaleza, Brazil, 2015-2017.

PO2298

Although Provider Awareness Is High, More Than Half of US Veterans with CKD Being Treated for Hypertension (HTN) Are Not Meeting Blood Pressure (BP) Targets

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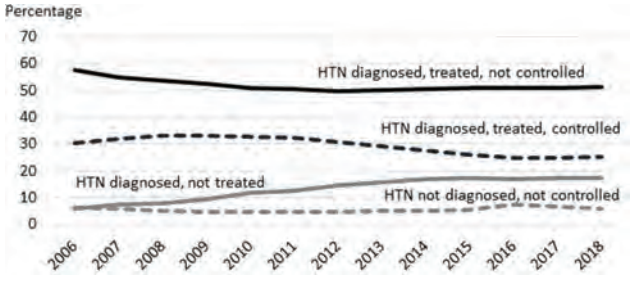
Background: HTN is a leading cause of kidney failure in the U.S. In people with CKD, BP control is critical to slow progression to kidney failure. We sought to assess HTN awareness among providers and BP control among Veterans with HTN and CKD.

Methods: We estimated both provider awareness (ICD code for HTN) and BP control (≤130/80 mmHg, ACC 2017) among ~12 million US Veterans between 2006 and 2018, aged 18+, with CKD and HTN, with 1+ outpatient visit each year. Veterans were determined to have CKD if they had either 1) an ICD diagnosis code, 2) eGFR < 60 ml/min/1.73m^2, and/or 3) urinary albumin-to-creatinine ratio 30+ mg/g; HTN if they had 1) a diagnosis, 2) were taking BP lowering medication, and/or 3) BP > 130/80. Treatment was defined as a prescription for BP lowering medication.

Results: From 2006 to 2018, ~94% of US veterans with CKD and HTN had a health provider-documented diagnosis code of HTN. The percentage of veterans with diagnosed HTN who were on BP-lowering medications, but did not have their BP under control (BP > 130/80 mmHg) declined from 57.6% to 51.3%. The percentage who had their BP under control increased from 30.2% in 2006 to 32.5% in 2010 but declined to 25.2% in 2018. The percentage with diagnosed HTN who were not receiving BP-lowering medications rose from 5.9% to 17.4%. The percentage of veterans with CKD and high BP who did not have a diagnosis of HTN remained between 5% and 6% throughout.

Conclusions: Provider awareness of HTN in the setting of an integrated health care system is high, as indicated by patients' recorded diagnosis of HTN. However, despite this high level of provider awareness, more than 50% of patients with diagnosed HTN in 2018 were not achieving the BP target of ≤130/80 mmHg, reflecting the difficulty in controlling BP in CKD patients. A better understanding of underlying factors, along with designing and implementing quality improvement programs may help improve this practice gap.

Funding: Other U.S. Government Support



PO2299

Arterial Stiffness Is Associated with the Progression of Abdominal Aortic Calcification in CKD: From the KNOW-CKD Study

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Background: Cardiovascular disease is an important cause of death in patients with chronic kidney disease. Vascular calcification is a hallmark of chronic kidney disease and an important risk factor for cardiovascular morbidity and mortality. Therefore, it is important to identify the factors that exacerbate vascular calcification for the prevention of cardiovascular complications in patients with chronic kidney disease. Although the relationship between arterial stiffness and vascular calcification is well-known, the association between the preexisting arterial stiffness and the progression of vascular calcification is not known. In this study, we analyzed the relationship between arterial stiffness measured by brachial-ankle pulse wave velocity (baPWV) and the progression of abdominal aortic calcification (AAC) evaluated by abdominal aortic calcium score (AACS).

Methods: We selected patients who underwent lumbar X-ray and AACS measurements at the start of the study and 4 years later from the KNOW-CKD cohort. After excluding 26 patients with previous peripheral vascular disease, we analyzed 906 patients. Participants were divided into 3 groups according to their baPWV. The progression of abdominal aortic calcification was defined as an increase in AACS after 4 years compared to the baseline.

Results: After 4 years, a total of 312 patients (34.4%) developed the progression of AAC. The progression of AAC was more frequent with higher baPWV. The incidence rates of AAC progression were 17.6%, 33.0% and 52.5% for T1 through T3 of baPWV (P<0.001). In multivariate logistic regression analysis adjusted for various cardiovascular risk factors, the odds ratio for the progression of AAC compared to T1 were 1.54 (95%CI 1.02-2.34) and 2.16 (95%CI 1.34-3.46) for T2 and T3 of baPWV.

Conclusions: Arterial stiffness is a risk factor for the progression of AAC in chronic kidney disease. This suggests that interventions that can improve arterial stiffness might be helpful in reducing cardiovascular complications in patients with chronic kidney disease.

Table. Multivariate-adjusted ORs (95% CI) for AAC progression according to baPWV

baPWV tertile	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
1	reference		reference		reference	
2	2.31 (1.57-3.37)	<0.001	1.54 (1.02-2.34)	0.041	1.54 (1.02-2.34)	0.042
3	5.17 (3.56-7.50)	<0.001	2.11 (1.32-3.37)	0.005	2.16 (1.34-3.46)	<0.001

Model 1: Unadjusted
Model 2: Adjusted for age, sex, systolic blood pressure, waist-hip ratio, diabetes, angiotensin-converting enzyme inhibitor or aldosterone receptor antagonist, statin, vitamin D analogue, calcium-base phosphate binder, eGFR, LDL cholesterol, HDL cholesterol, hsCRP, urine protein to creatinine ratio, calcium, phosphorus, vitamin D, and parathyroid hormone
Model 3: Adjusted for model 2 + current smoking status, alcohol intake, physical activity and baseline AAC-score
OR, odds ratio; AAC, abdominal aortic calcification; CI, confidence interval; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein

PO2300

Provider Practice Evaluation Survey: Assessment of Primary Care Provider Perspectives on Care Delivery for CKD Patients in Alberta

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Background: Chronic kidney disease (CKD) is highly prevalent in the adult population of Canada, with a steady rise in end-stage renal disease. The objective of this study was to assess current modes of practice regarding CKD patients, and assess barrier and facilitators in primary care for managing and referring CKD patients using electronic consultation (eReferral).

Methods: The Provider Practice Evaluation Survey was launched for primary care providers [PCPs (family physicians or general practitioners)] licensed to practice in Alberta. Associations between barriers and facilitators to electronic consultations and clinic practice parameters; and associations between screening for CKD in patients and clinic practice parameters were analyzed. Modified Poisson regression with robust error variance was used to estimate the relative risk (RR) and 95% confidence interval.

Results: A total of 48 PCPs responded to the survey. Awareness about the availability of the eReferral tool was more likely to be a barrier to use eReferral for PCPs of South Zone as compared to PCPs from Edmonton (RR: 2.00, 95% CI: 1.07-3.74). Compared to PCPs with >5% CKD patients in their clinical practice, PCPs with 16% to 26% CKD patients were more likely to perceive barriers to use eReferral; including the ease of use for the eReferral tool (RR: 1.62, 95% CI: 1.05-2.51), and limited staff and technical support as a barrier for eReferral (RR: 2.00, 95%CI: 1.18-3.40). There was a negative association between PCPs aged between 40 and 60 years and time constraints as a barrier compared with those younger than 40 years (RR: 0.66, 95% CI: 0.46-0.95). Regarding screening tools (criteria) to diagnose CKD, PCPs who had not used the eReferral tools were less likely to use hypertension (RR: 0.86, 95% CI: 0.75-0.98), diabetes (RR: 0.89, 95% CI: 0.79-0.999), and cardiovascular disease (RR: 0.72, 95% CI: 0.59-0.89) as CKD diagnostic tools compared to those using eReferral nephrology advice request tool.

Conclusions: The results will help implement innovative steps to rectify barriers to adoption of the eReferral system and standardized CKD diagnostic guidelines to improve patient care in Canada.

PO2301

Shrunken Pore Syndrome Is Associated with a Rise in Mortality in a Community-Based Population of Middle-Aged Individuals

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Background: Chronic kidney disease (CKD) is a risk factor for increased mortality mainly due to cardiovascular disease (CVD). Glomerular filtration rate (GFR) is the best way to estimate kidney function, but it cannot be measured. Creatinine and cystatin C are two molecules that are used in clinical practice to estimate GFR (eGFR). The lower eGFR, the higher is the mortality. CKD staging is therefore a good marker of mortality and development of CVD. However, there are patients who have the same CKD stage and risk factors for development of CVD but different outcome in mortality. Shrunken pore syndrome (SPS) has shown to be a marker of increased mortality in different patients groups regardless of their measured GFR. The theory behind SPS is supposed to be a difference in the renal filtration of small molecules like creatinine compared to middle sized molecules like cystatin C. Little is known about the prevalence of SPS and the effect on mortality in the general population. The aim of our study is to investigate this.

Methods: The study population consisted of 5061 individuals from the Malmö Diet and Cancer Cardiovascular cohort community-based study that was gathered during 1991 and 1996 in Malmö, Sweden. The individuals were 44-64 years old. Blood samples, anthropometric measurement and a questionnaire about life style etc was available. $CAPA_{CYC}$ formula was used for eGFR based on cystatin C and LMR_{CR} formula was used for eGFR based on creatinine. SPS was defined as $eGFR_{CYS} \leq 70\%$ of $eGFR_{CR}$. Generalized propensity score was used to match individuals with SPS and those without. Kaplan–Meier estimates were used to present survival probabilities in four $eGFR_{CYS}/eGFR_{CR}$ ratio intervals. To account for within quartet correlation, or frailty, Cox proportional hazard models with shared frailty was employed. Results are presented as hazard ratios (HR) with 95 % confidence intervals (CI).

Results: 405 individuals (8%) fulfilled the criterion for SPS. Median (2.5-97.5 percentiles) $eGFR_{cys}$ was 63 (38-97) and median $eGFR_{cr}$ was 70 (49-92) mL/min/1.73m^2. HR for mortality in individuals with SPS in the matched data was 2.43 (1.15 - 5.14).

Conclusions: Healthy middle age individuals with SPS have a doubled risk of all-cause mortality. Further studies are needed to explore the mechanisms behind the association between SPS and mortality.

PO2302

Associations Between Serum Biomarkers of Iron Stores and the Progression to Kidney Failure in Patients with Moderate-to-Severe CKD

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Background: We recently reported that lower levels of biomarkers of iron stores are associated with a higher risk of all-cause mortality and major adverse cardiovascular events in patients with moderate to severe chronic kidney disease (CKD). However, the impact of these parameters on the risk of kidney failure (KF), potentially a competing risk, has not been previously explored.

Methods: Patients from Brazil, France, Germany and the US in CKDopps (eGFR <60 mL/min at enrollment, under nephrology care) and with available TSAT and ferritin levels were included in the analyses. Cox models were used to estimate hazard ratios (HR) for the outcome of KF (defined as a composite endpoint including dialysis initiation, transplant, 40% decline of eGFR from baseline, or sustained eGFR <15 mL/min/1.73m^2).

Results: A total of 5,431 patients were evaluated (Brazil=337, France=2231, Germany=2112, US=751), mean eGFR 28±11mL/min/1.73m^2. Over median follow-up time of 2.0 [0.6-3.0] years, there were 1800 (33%) KF events (15.7/100 pt-years). TSAT had a U-shaped association with KF (with highest HR at TSAT<15%) in the crude analysis (Model 1 of Table 1). Neither TSAT nor ferritin had a directional association with KF after adjustment for confounders (Model 2).

Conclusions: Levels of biomarkers of iron stores, as captured by TSAT and/or ferritin, are not associated with development KF in patients with moderate to severe CKD under nephrology care. These findings further the understanding of our previous finding of a higher risk of mortality and cardiovascular events in this population with iron deficiency and high risk of CKD progression.

Funding: Commercial Support - Amgen Inc (since 1996, founding sponsor); Astellas Pharma Inc.; AstraZeneca Pharmaceuticals LP; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical CO., LTD; GlaxoSmithKline LLC; Horizon Therapeutics USA, Inc.; Italian Society of Nephrology (SIN); Japanese Society for Peritoneal Dialysis (JSPD); JMS Co., Ltd.; Kidney Research UK; Kidney Foundation Japan (KFJ); Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Terumo Corporation; Torii Pharmaceutical Co., Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd, Government Support - Non-U.S.

Table 1. Cox regression models demonstrating the absence of adjusted association of TSAT and ferritin with CKD progression

Exposure	N (%) patients	Model 1 HR (95% CI)	Model 1 P	Model 2 HR (95% CI)	Model 2 P
(A) TSAT (%)					
≤15	1033 (19%)	1.15 (0.99,1.34)	0.07	0.98 (0.83,1.17)	0.85
16-20	1149 (21%)	1.05 (0.90,1.21)	0.55	0.99 (0.84,1.18)	0.92
21-25	1244 (23%)	1.00 (0.85,1.17)	0.99	0.94 (0.80,1.11)	0.48
26-35	1420 (26%)	1 (ref)	–	1 (ref)	–
36-45	439 (8%)	1.04 (0.84,1.28)	0.72	1.01 (0.80,1.26)	0.96
46+	146 (3%)	1.12 (0.78,1.59)	0.54	0.94 (0.60,1.47)	0.77
(B) Ferritin (µg/L)					
<50	827 (15%)	0.75 (0.64,0.87)	<.01	0.99 (0.84,1.17)	0.88
50-99	1261 (23%)	0.98 (0.86,1.11)	0.72	1.07 (0.94,1.22)	0.31
100-299	2352 (43%)	1 (ref)	–	1 (ref)	–
300+	991 (18%)	1.01 (0.90,1.14)	0.84	0.90 (0.77,1.04)	0.14

Model 1 is stratified by country but otherwise unadjusted; a separate Model 1 was fit with either (A) TSAT or (B) ferritin as the exposure. Model 2 is additionally adjusted for patient age, sex, Black race, body mass index, eGFR, albuminuria, 11 summary comorbidities, erythropoiesis stimulating agents use, serum albumin, white blood cell, hemoglobin, and either ferritin or TSAT (depending on the exposure variable).

PO2303

Association Between the Triglyceride-Glucose (TyG) Index and Coronary Artery Calcification Progression in Non-Diabetic CKD

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Background: Patients with chronic kidney disease (CKD), the likelihood of complications of cardiovascular disease(CVD) may increase compared to general population. Quantity of coronary artery calcification (CAC) correlates with atherosclerotic plaque burden and increased quantity of CAC indicates a substantially increased cardiovascular events. In previous studies, the TyG index has been reported to associated with coronary artery calcification aggravation. We investigated whether the TyG index was related to coronary artery calcification aggravation in patients with mild renal insufficiency.

Methods: This retrospective longitudinal study included adult participants who voluntarily underwent at least two cardiac CT examination at the single center, between January 2006 and Octorbor 2018(n=1,516). The TyG index was determined using ln (fasting triglycerides [mg/dL] X fasting glucose [mg/dL]/2). Mean arterial pressure (MAP) was calculated as DBP + ((SBP – DBP)/3). Mild renal insufficiency CKD was defined as 60≤ eGFR ≤ 90ml/min/1.73m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation (mild-CKD group). CAC aggravation was defined as an increased coronary artery calcification score (CACS) in the in the follow-up period. To calculate the odds ratio for incident CKD, logistic regression analyses were performed.

Results: 1,516 patients were enrolled, of which 746 were in the mild-CKD group without diabetes. The CACS aggravation was significantly higher in participants with a tyG index of 8.9 or higher [OR 1.705 (1.351-2.152), P-value <0.001]. After adjusting for age, sex, MAP, Hemoglobin, Ca X P, potassium associated with increased risk of CAC in participants with mild renal insufficiency [OR 1.534 (1.058-2.224), P=0.027].

Conclusions: Among mild CKD without diabetes, TyG index of 8.9 or higher had a positive correlation with CAC progression.

Table 1. Risk of CACS aggravation according to TyG index in mild CKD group without Diabetes

	Model 1	Model 2	Model 3
TyG index*			
OR (95% CI)	1.705[1.351-2.152]	1.490[1.056-2.103]	1.534[1.058-2.224]
P	<0.001	0.023	0.027

Note: Model 1: Unadjusted model
Model 2: Adjusted for age, sex
Model 3: Adjusted for age, sex, MAP, Hemoglobin, Ca X P, potassium.
Abbreviations: OR, odds ratio; CI, confidence interval; MAP, mean arterial blood pressure
*TyG index ≥ 8.9

PO2304

Plasma Proenkephalin and Incident CKD in REGARDS

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Background: Plasma proenkephalin (PENK) is a precursor of active enkephalins. Higher blood concentrations have been previously associated with eGFR decline. Whether PENK concentrations vary by race and whether the association of PENK with incident CKD differs by race is uncertain.

Methods: In a nested cohort of 3,986 community-living participants within the REGARDS cohort, we measured PENK by ELISA. Primary outcomes were incident CKD (new eGFR < 60 mL/min/1.73m^2 plus 40% decline), significant eGFR decline (30% decline) and incident albuminuria (new UACR > 30mg/g) at a follow-up visit 9.4

years (mean) after baseline. We used logistic regression with inverse probability sampling weights for analysis, evaluating PENK per 2-fold higher level. We tested race interactions, and explored analyses stratified by race.

Results: Mean age was 63 years, 48% were black, and 51% were female. Baseline eGFR was 88 ml/min/1.73m^2. Higher PENK was associated with all 3 outcomes in unadjusted models. In the fully adjusted models, higher PENK remained associated with significant eGFR decline and incident albuminuria. Associations differed by race. P for interaction between PENK and race was <0.01. Higher PENK was more strongly associated with incident CKD and eGFR decline and incident albuminuria in Blacks.

Conclusions: In community-living individuals, higher PENK is associated with significant eGFR decline and incident albuminuria, independent of eGFR, albuminuria and CKD risk factors. These associations differed by race. Future studies should determine if PENK has utility to improve eGFR risk estimation without requiring race-specific adjustments in estimates.

Funding: Veterans Affairs Support

Table

Outcome	Overall (N=3,986) OR (95% CI)	Whites (N=2071) OR (95% CI)	Blacks (N=1915) OR (95% CI)
Incident CKD (N Events = 752)	1.06 (0.94, 1.19)	0.98 (0.83, 1.15)	1.15 (0.98, 1.36)
Sig. eGFR decline (N Events = 1,012)	1.24 (1.04, 1.48)	1.04 (0.80, 1.33)	1.46 (1.14, 1.86)
Incident albuminuria (N Events = 621)	1.25 (1.02, 1.54)	1.14 (0.86, 1.51)	1.43 (1.04, 1.98)

* Models adjusted for age, sex, race, BMI, SBP, DBP, diabetes, smoking, cholesterol, prevalent CVD, baseline eGFR and albuminuria. Last outcome not adjusted for albuminuria.

PO2305

Novel Approach to the Relation of Environmental Exposure and Kidney Dysfunction: Data Analysis from Korean National Environmental Health Survey (KoNEHS), 2015-2017

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Background: Forecasting patient outcomes with kidney disease using standard statistical techniques is complex to estimate effects of the environmental chemicals. Herein, we aim to assess risk prediction for kidney disease in the general population using novel methods.

Methods: Serum POPs, serum creatinine or urinary albumin were measured in subpopulation (n=1,266) among the general adult participants from the 3rd Korean National Environmental Health Survey (KoNEHS) (n=3,787). Classification algorithms were used for the prediction of chronic kidney disease (CKD), defined by estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR). In addition, weighted quantile sum (WQS), which provides weights to the components of the mixture, was used to assess multi-pollutant effects.

Results: Of 1,266 adult subjects and 44 variables, including baseline characteristics and laboratory findings, were analyzed for the modeling process. The risk prediction of CKD was presented by machine-learning algorithms using bagging, ridge, lasso, random forest and was compared to conventional algorithms using logistic regression. A decision-tree algorithm was presented that outperformed a conventional method such as logistic regression (AUC 0.653 vs. 0.621). Among various decision-tree models, the lipid-corrected polychlorinated biphenyl congener 153 (PCB 153) was selected as the best predictor of CKD. Because persistent organic pollutants (POPs) accumulate with age, stratification analysis was conducted based on age. In the WQS model, PCB 153 showed the highest weight in its contribution to lower eGFR after adjusting covariates in the middle-aged group (under 50 yrs) (p=0.0135). If subjects with young age (under 50 yrs) were hemoglobin level > 13.25 g/dl, the CKD was predicted as 71.4% in the high serum PCB153 group.

Conclusions: We propose a machine learning-based prediction model. POPs and age were interrelated as notable risk factors for CKD in healthy Korean volunteers.

PO2306

Prevalence and Associated Factors for CKD in Rural and Peri-Urban Bangladesh

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Background: Chronic Kidney Disease (CKD) is an increasing public health threat worldwide. Studies have documented CKD among adult population in urban Bangladesh, however, in rural and peri-urban settings still lagging behind. We aimed to generate data in understanding the prevalence and CKD-related factors.

Methods: We recruited participants randomly from the Demographic Surveillance System of Mirzapur, Bangladesh in two phases. In phase 1, we screened participants using a laboratory-based creatinine and albumin to creatinine ratio (ACR) and collected information on socio-demographic, lifestyles, and health histories. We evaluated the participants' CKD status following the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and their estimated glomerular filtration rate (eGFR). Those participants who had eGFR below 60 ml/min/1.73 m^2 and/or ACR ≥30 mg/g were considered for phage 2. After three months, in phase 2, we repeated the blood and urine test for GFR and ACR. A participant was diagnosed as a case of CKD if (s)he had eGFR below 60 ml/min/1.73 m^2 or had ACR ≥30 mg/g for more than three months as suggested by the Kidney Disease Outcomes Quality Initiative guidelines.

Results: We enrolled 928 participants; of them 872 completed the study procedure and included in the analysis. The mean ± standard deviation (SD) of age was 48.2 ± 16.4. In phase 1, probable CKD cases were 281 (32%), however, in phase 2, confirmed cases were 192 (22%) [stage-1, 4.0%; stage-2, 11.8%; stage-3, 5.5%; stage-4, 0.6%; stage-5, 0.11%]. In the multivariate logistic regression analysis, associated factors for prevalent CKD included aged ≥60 years (adjusted odds ratio [aOR], 5.02; 95% confidence interval [95% CI], 1.85 to 13.65), hypertension (aOR, 3.08; 95% CI, 2.07 to 4.59), diabetes (aOR, 2.52; 95% CI, 1.60 to 3.96), anemia (aOR, 2.50; 95% CI, 1.63 to 3.84) and presence of RBC in urine (aOR, 3.20; 95% CI, 1.71 to 5.98).

Conclusions: In rural and peri-urban Bangladesh, this is the first study of CKD prevalence, and repeated confirmatory testing revealed a prevalence of approximately 22%, which is higher than in urban setting. Findings suggested that CKD monitoring systems are required to assess the overall burden and effective steps should be taken to mitigate these major risk factors.

PO2307

Association of XOR Activity and NLRP3 Inflammasome Among CKD Patients

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Background: Previous studies have shown few result on the relationship between XOR activity and NLRP3 inflammatory in non-hemodialysis patients.

Methods: CKD patients in nephrology department with normal uric acid were recruited. General clinical data, blood biochemistry and other data were collected. XOR activity was detected by fluorescence colorimetry, XO activity was detected by double antibody sandwich ELISA, and NLRP3 Inflammasome were detected by competitive binding method. After correlation analysis, multiple (stepwise) regression analysis was performed to explore the correlation between XOR and NLRP3 inflammasome and the relationship with clinical data of patients.

Results: The correlation analysis of XOR activity, XO activity, XO/XOR ratio and NLRP3 Inflammasome with biochemical indicators showed that XOR activity was positively correlated with eGFR, DBP, FBG, and alanine transferase, and was negatively correlated with age, serum total protein, serum creatinine, and serum chloride concentration; Log(XO) was positively correlated with eGFR and FBG, and negatively correlated with serum chloride concentration;The ratio of XO/XOR was positively correlated with total protein, age and UA, and negatively correlated with eGFR, XOR and alanine transferase;NLRP3 inflammasome were positively correlated with XOR, Log(XO) and serum sodium concentration, and negatively correlated with sex;Multiple linear (stepwise) regression results showed that eGFR, FBG and DBP were independent influencing factors of XOR;eGFR, FBG, UA and total cholesterol were independent influencing factors of Log(XO); Serum creatinine, serum sodium concentration and XOR activity were independent influencing factors of NLRP3 Inflammasome, and there was no collinearity in statistical analysis. According to the value of eGFR, the patients were divided into two groups. The XOR activity, Log (XO), XO/XOR ratio, serum creatinine, urea nitrogen, UA, K, serum chloride concentration were compared between the two groups, and the differences were statistically significant.

Conclusions: In CKD patients, elevated fasting blood glucose and diastolic blood pressure are independent risk factors for XOR activity, while elevated XOR activity is an independent risk factor for NLRP3 Inflammasome. Therefore, controlling FBG and DBP in CKD patients has certain clinical reference significance for reducing XOR activity and further reducing NLRP3 Inflammasome.

PO2308

Trends in Volume, Appropriateness, and Outcomes of Referrals to Nephrology over the Last Two Decades: A Retrospective Analysis Using the Alberta Kidney Disease Network Database

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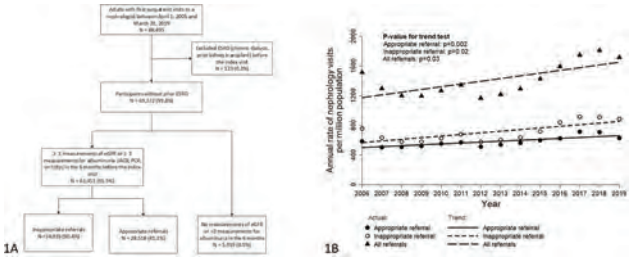
Background: It is well-established that guideline-concordant referrals to nephrology are associated with improved patient outcomes. However, some referrals are unnecessary (guideline-discordant) leading to high volumes and delays for referrals that are guideline concordant. We investigated the trends in the number of referrals to nephrology, and related outcomes in Alberta.

Methods: Retrospective cohort analysis of patients with at least one visit to a nephrologist from primary care between 2006 and 2019. A referral was considered appropriate based on the KDIGO defined criteria (estimated glomerular filtration rate

(eGFR) < 30 mL/min per 1.73m², albumin creatinine ratio (ACR) ≥ 30 mg/mmol or protein creatinine ratio ≥ 50 mg/mmol, or Urine dipstick ≥ 2+ protein on two consecutive measurements, and/or eGFR persistently declined ≥ 5 mL/min per 1.73m² from the first eGFR measurement).

Results: Of 69,372 patients (mean age 62.5; 50.7% female), only 28,518 (41.1%) referrals met criteria as guideline-concordant (Figure 1A). Patients referred in a guideline-concordant manner were significantly more likely to be older, men, and with comorbid conditions (diabetes, hypertension, and cardiovascular disease). There has been an increasing trend in the number of guideline concordant and discordant referrals from 2006 to 2019 (Figure 1B). Patients who met guideline-criteria for referrals were likely to be prescribed renoprotective medications but more likely to experience clinical outcomes of kidney failure, cardiovascular events, and all-cause mortality.

Conclusions: The number of referrals to nephrology from primary care continues to increase, and a large proportion of these referrals were guideline discordant. Interventions targeted to primary care at reducing the number of non-guideline concordant referrals are needed.



PO2309

Microscopic Hematuria and Leukocyturia Are Highly Prevalent in East Africa and Associated with CKD

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Background: Microscopic hematuria and leukocyturia may reflect parenchymal kidney disease; there have been few population-based studies of these urinary abnormalities in Africa.

Methods: We included a population-based sample of 3,686 East Africans. We defined hematuria and leukocyturia as heme and leukocyte esterase dipstick positive (≥1+), respectfully. We used sampling weights to estimate the community-based prevalence of hematuria and leukocyturia and used weighted multivariable log-link Poisson models to assess the association of potential risk factors with these abnormalities, and separately, the association of urine abnormalities with CKD (eGFR <60 mL/min/1.73m² or dipstick proteinuria ≥1+).

Results: Most participants with leukocyturia did not have hematuria or proteinuria; there was minimal overlap between hematuria and proteinuria **(Figure).** With sample weighting, the mean age was 38 years; 52% were female. The prevalence of hematuria was 3.7% in eastern Uganda, 2.8% in southwestern Uganda and 2.8% in Kenya. The prevalence of leukocyturia was 11.2% in eastern Uganda, 8.7% in southwestern Uganda and 1.6% in Kenya. Table 1 shows associations of potential risk factors with urine abnormalities. Both hematuria and leukocyturia were independently associated with prevalent CKD (aPR=2.7; 95% CI 1.4-4.9, and aPR=3.5; 95% CI 2.2-5.7, respectively).

Conclusions: Hematuria and leukocyturia are common in rural East Africa, with considerable regional difference. These urinary abnormalities may represent a unique pattern of kidney disease in this region.

Funding: NIDDK Support

Variables	Hematuria aPR (95% CI)	Leukocyturia aPR (95% CI)
Eastern Uganda (vs. Kenya)	0.96 (0.47-1.94)	9.79 (5.82-16.48)
Southwest Uganda (vs. Kenya)	0.90 (0.41-1.97)	8.44 (4.55-15.63)
Female	12.3 (4.57-33.22)	1.73 (1.09-2.76)
Age (Years)≥ 60 (vs. 18–29 years)	0.51 (0.19-1.36)	1.71 (1.06-2.78)
Primary school education (vs. Secondary school and beyond)	0.64 (0.31-1.33)	2.17 (1.03-4.60)
Any alcohol use	2.56 (1.23-5.33)	0.57 (0.30-1.11)
Any NSAIDs use	0.59 (0.36-0.98)	1.04 (0.72-1.52)

adjusted prevalence ratio (aPR); Adjusted for region, demographics (age, sex), wealth index, farming occupation, history of diabetes, hypertension, HIV, use of NSAIDs and traditional herbal medicines

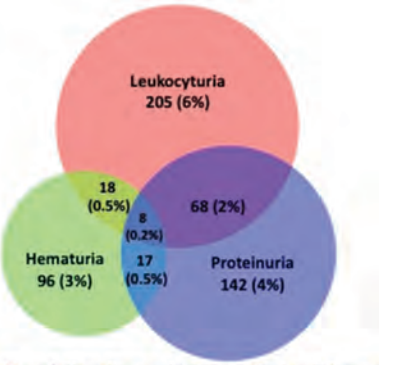

Figure 1: Venn diagram showing relationships between leukocyturia, hematuria and proteinuria among SEARCH-CKD participants. N(%) are unweighted estimates

PO2310

The Effect of Cardiometabolic Comorbidities on Risk of CKD Incidence: A Longitudinal Cohort Study

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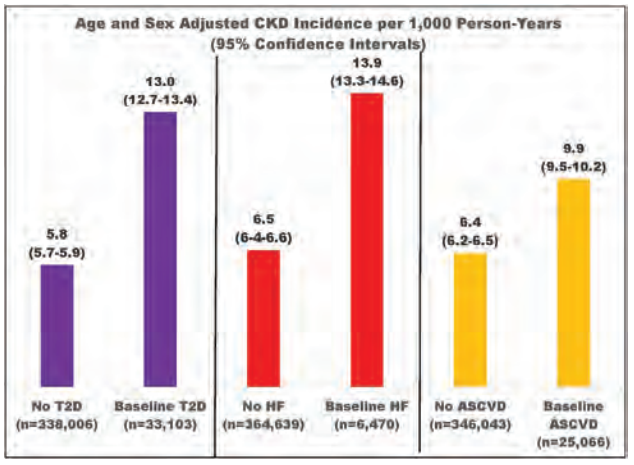
Background: Chronic kidney disease (CKD) and cardiometabolic conditions are closely inter-related. We studied the risk of incident CKD among patients who had or developed type 2 diabetes (T2D), atherosclerotic cardiovascular disease (ASCVD), or heart failure (HF).

Methods: We conducted a longitudinal cohort study using the electronic medical records of Kaiser Permanente Northwest to identify 371,109 adult patients without CKD at baseline (first known eGFR ≥60ml/min/1.73m² between 2005-2017) and followed them through 2019 for incident CKD (two eGFR measurements <60 3-12 months apart). We assessed T2D, ASCVD and HF at baseline and prior to CKD incidence. We used generalized estimating equation (GEE) models to calculate age/sex-adjusted CKD incidence per 1,000 person-years independently for baseline T2D, HF, and ASCVD. Time-dependent Cox regression models were used to determine the effect of baseline or development of T2D, ASCVD and HF on CKD incidence adjusting for age, sex, race/ethnicity, renin angiotensin aldosterone system (RAAS) inhibitor and statin use, smoking, and blood pressure ≥140/90 mmHg.

Results: Study subjects were 49.7±14.9 years old and 56% were women. CKD incidence among patients with T2D or HF was more than double vs. patients without T2D or HF, and 55% higher among patients with vs. without ASCVD (Figure). In the time-dependent model, risk of CKD incidence was increased by more than 2-fold by HF (hazard ratio 2.12, 95% CI 2.05-2.19), 71% by T2D (1.71, 1.66-1.75), and 26% by ASCVD (1.26, 1.23-1.30).

Conclusions: Cardiometabolic conditions, particularly HF and T2D are independent risk factors of incident CKD. Treating the cardiometabolic-renal syndrome as a single clinical entity may benefit these patients.

Funding: Commercial Support - Boehringer Ingelheim



PO2311

Determining the Association Between Continuity of Primary Care and Acute Care Use Among Adults with CKD in Alberta, Canada

Christy Chong, David Campbell, Meghan J. Elliott, Fariba Aghajafari, Paul E. Ronksley. *University of Calgary Cumming School of Medicine, Calgary, AB, Canada.*

Background: Acute care use is high among individuals with chronic kidney disease (CKD). It is unclear how relational continuity of primary care influences downstream acute care use. We aimed to determine if poor relational continuity of primary care is associated with higher rates of all-cause and potentially preventable acute care use among adults with CKD.

Methods: We conducted a population-based retrospective cohort study of adults with stages 3 and 4 CKD and at least three visits to a primary care provider between April 1, 2011 to March 31, 2014 in Alberta, Canada. Relational continuity was calculated using the Usual Provider Continuity index and descriptive statistics were used to summarize patient and acute care encounter characteristics. Adjusted rates (per 1,000 person-years) and incidence rate ratios for all-cause and CKD-related ambulatory care-sensitive condition (ACSC) hospitalizations and emergency department (ED) visits were estimated using negative binomial regression models.

Results: Among 86,475 individuals with CKD, 51.3%, 30.0%, and 18.7% of patients had high, moderate, and poor continuity of primary care, respectively. There were 77,988 all-cause hospitalizations, 204,615 all-cause ED visits, 6,489 (8.3% of all hospitalizations) CKD-related ACSC hospitalizations, and 8,461 (4.1% of all ED visits) CKD-related ACSC ED visits during a median follow-up of 2.3 years. Rates of all-cause hospitalization and ED use increased with poorer continuity of primary care in a stepwise fashion across CKD stages. Poor continuity of primary care was also associated with higher rates of CKD-related ACSC hospitalization and ED visits, particularly among individuals with stage 3 CKD.

Conclusions: Poor continuity of care is associated with increased acute care use and targeted strategies are needed to strengthen patient-provider relationships within primary care among those with CKD.

Funding: Other NIH Support - Canadian Institutes of Health Research (CIHR); Alberta Strategy for Patient Oriented Research SUPPORT Unit (AbSPORU)

PO2312

Submaximal Dose of Angiotensin Converting Enzyme Inhibitor and Angiotensin II Receptor Blockers Among Persons with Proteinuria

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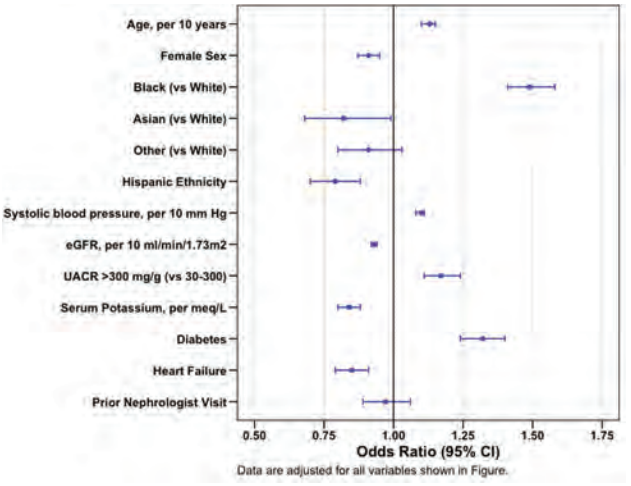
Background: Underutilization of angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) for treatment of albuminuria is a known quality of care gap. Among those treated with ACEi/ARB, submaximal doses represents another opportunity to improve CKD management.

Methods: Using the OptumLabs Data Warehouse®, a longitudinal, real-world dataset with deidentified claims and electronic health record data, we identified adults with proteinuria, defined as either urine albumin/creatinine ≥30 mg/g or protein/creatinine ≥150 mg/g, who were prescribed an ACEi/ARB between 1/1/2015 and 12/31/2016. Among patients without apparent contraindication to ACEi/ARB dose escalation (blood pressure <130/80 mmHg, eGFR <15 ml/min/1.73m^2, or prior diagnosis of acute kidney injury or hyperkalemia), we examined the proportion taking the maximal recommended dose of their ACEi/ARB, overall and by demographic and clinical factors. We used multivariable logistic regression to assess factors associated with submaximal dosing.

Results: Of 79,413 patients with proteinuria receiving ACEi/ARB therapy, 50% (n=39,733) had no apparent contraindication to dose escalation. 34% (n=13,566) of these patients were on maximal ACEi/ARB doses. In multivariable analyses, younger age, Asian race, Hispanic ethnicity, higher serum potassium, and non-diabetes status were associated with submaximal dosing (**Figure**).

Conclusions: Among persons with proteinuria and no apparent contraindication for ACEi/ARB dose escalation, over half were on submaximal doses. Concerns over hyperkalemia may drive underdosing. However, greater attention toward maximizing ACEi/ARB dose as tolerated, especially among patients without diabetes, could optimize cardiovascular and kidney health.

Funding: NIDDK Support



PO2313

Genetic Variant rs671 of ALDH2 Gene Is Associated with Reduced Renal Function in Chinese Population

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Background: ALDH2 is a mitochondrial aldehyde dehydrogenase and ALDH2 rs671 genetic polymorphism was associated with hypertension and diabetes. Genome-wide association analysis of East Asians revealed ALDH2 rs671 variant associated with kidney function traits, but comprehensive epidemiological studies are lacking. We conducted this study to explore the associations between ALDH2 rs671 and kidney function traits in Chinese population.

Methods: A total of 15,856 individuals completed medical check-up in a single center were enrolled. ALDH2 gene mutation detection kit was used to genotype the rs671 polymorphism. Clinical laboratory data were collected from the records of medical check-up. Urine albumin creatinine ratio (UACR) was tested in 5,168 individuals and the data was log-transformed for further analysis. Linear and logistic regression analysis were used to estimate the association between rs671 SNP and renal function traits.

Results: The average age was 48.8±9.7 years and the individuals were mainly males (67.0%). 17.7%, 13.0% and 30.6% individuals were obese, diabetic, and hypertensive, respectively. Frequencies of GG, GA, and AA genotypes were 68.0%, 29.4% and 2.6%. Male individuals with A allele were associated with a significant increased level creatinine (β = 1.664, 95% CI: 1.141, 2.186) and blood urea nitrogen (β = 0.156, 95% CI: 0.107, 0.205), and reduced estimated glomerular filtration rate (eGFR, β = -1.057, 95% CI: -1.347, -0.767), uric acid (β = -8.893, 95% CI: -11.908, -5.877), logUACR (β = -0.066, 95% CI: -0.122, -0.011). Similar associations were not observed in female individuals. Besides, we did not observe association between ALDH2 genotype and chronic kidney disease (CKD), albuminuria, or proximal tubular injury.

Conclusions: ALDH2 rs671 polymorphisms were associated with decreased renal function in male individuals other than the females. Further analyses were needed for further explore the direct and indirect effects of ALDH2 SNP on CKD, albuminuria, and proximal tubular injury.

Funding: Government Support - Non-U.S.

PO2314

Impact of Dietary Fatty Acid on All-Cause Mortality According to Kidney Function Based on a Nationwide Population Study

Yaerim Kim,[1] Kyungho Ha,[6] Jeonghwan Lee,[2] Jae Yoon Park,[3] Kyung Don Yoo,[4] Yong Chul Kim,[5] Jin hyuk Paek,[1] Woo Yeong Park,[1] Kyubok Jin,[1] Seungyeup Han,[1] Dong Ki Kim,[5] Kwon Wook Joo,[5] Chun Soo Lim,[2] Jung Pyo Lee.[2] *[1]Keimyung University School of Medicine, Daegu, Daegu, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [3]Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; [4]Ulsan University Hospital, Ulsan, Republic of Korea; [5]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [6]Jeju National University, Jeju, Jeju, Republic of Korea.*

Background: Although the relationship between fatty acids and the risk of mortality has been long-lasting discussed, there is little evidence to support that the effect of saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA). This study aims to investigate the association between dietary fatty acids and all-cause mortality among the general population.

Methods: We used data from the 92,062 participants of US National Health and Nutrition Examination Survey 1999-2015. The intake of fatty acids was adjusted with the total energy intake and divided by the quartile, the first quartile group was regarded as the reference. We used a multivariate Cox-proportional hazard model to identify the impact of fatty acids on all-cause mortality.

Results: A total of 36,747 subjects were finally included in the study. During 97.9 ± 53.9 months, there were 922 (4.4%) and 3,544 (22.4%) death cases in eGFR ≥90 and <90 mL/min/1.73m^2 groups, respectively. Among 8 different SFA, hexadecanoic acid (adjusted hazard ratio [aHR] 1.13, 95% confidence interval [CI] 1.15-1.26 in 4th quartile [Q4]) and octadecanoic acid (aHR 1.13, 95% CI 1.15-1.25 in Q4) showed that greater intake was associated with the increased risk for all-cause mortality. In addition, most PUFA except eicosatetraenoic acid showed a beneficial effect on all-cause mortality. Among subjects with eGFR ≥90, the harmful effect of SFA was attenuated and the beneficial effect of PUFA remained in only octadecatrienoic acid. On the contrary, for the subjects with eGFR <90, the harmful effect of hexadecanoic acid (aHR 1.17, 95% CI 1.05-1.32 in Q4) and octadecanoic acid (aHR 1.16, 95% CI 1.04-1.30 in Q4) was exacerbated. The beneficial effect of PUFA was also prominent in this group; octadecatrienoic acid (aHR 0.86, 95% CI 0.77-0.97 in Q4), eicosapentaenoic acid (aHR 0.86, 95% CI 0.79-0.98 in Q4), docosapentaenoic acid (aHR 0.88, 95% CI 0.79-0.99 in Q4), and docosahexaenoic acid (aHR 0.88, 95% CI 0.79-0.99 in Q4).

Conclusions: The impact of dietary fatty acid on all-cause mortality was different in according to the kidney function. More specified and targeted counseling for restricting SFA and encouraging PUFA needs to be considered especially for subjects with lower eGFR.

PO2315

Impact of Dietary Beta-Carotene on All-Cause Mortality According to Different Clinical Conditions, Including Decreased Kidney Function

Yaerim Kim,[1] Kyungho Ha,[6] Jeonghwan Lee,[2] Jae Yoon Park,[3] Kyung Don Yoo,[4] Yong Chul Kim,[5] Jin hyuk Paek,[1] Woo Yeong Park,[1] Kyubok Jin,[1] Seungyeup Han,[1] Dong Ki Kim,[5] Kwon Wook Joo,[5] Chun Soo Lim,[2] Jung Pyo Lee.[2] *[1]Keimyung University School of Medicine, Daegu, Daegu, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [3]Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; [4]Ulsan University Hospital, Ulsan, Republic of Korea; [5]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [6]Jeju National University, Jeju, Jeju, Republic of Korea.*

Background: Beta-carotene has been announced that was inversely associated with the risk of all-cause mortality, but the association in the subgroup was not clear yet. Herein, we aimed to evaluate the impact of beta-carotene on all-cause mortality according to the different clinical settings among the general population.

Methods: We used employing data from the 92,062 subjects of US National Health and Nutrition Examination Survey 1999-2015. The intake of beta-carotene was divided into the quartile; the first quartile group was regarded as the reference. The subgroup was made by 1) the presence of hypertension, 2) diabetes, 3) the status of alcohol consumption, 4) smoking status, and 5) estimated glomerular filtration rate (eGFR) 90 mL/min/1.73m^2, respectively. We used a multivariate Cox-proportional hazard model to identify the impact of beta-carotene on all-cause mortality.

Results: A total of 36,747 subjects were finally included in the study. There were 14,469 (39.4%), 4,704 (12.8%), and 15,804 (43.0%) subjects with hypertension, diabetes, and eGFR <90 mL/min/1.73m^2, respectively. There were 8,774 (23.9%) of ex-smokers and 13,694 (37.3%) of non-alcoholics, respectively. During 97.9±53.9 months, there were 4,465 (12.2%) death were detected. After adjusted with multivariable, greater intake of beta-carotene significantly reduced the risk for all-cause mortality in subjects without hypertension (adjusted hazard ratio [aHR] 0.81, 95% confidence interval [CI] 0.66-0.99 in 4th quartile group [Q4]), without diabetes (aHR 0.85, 95% CI 0.75-0.96 in Q4), non-alcoholics (aHR 0.86, 95% CI 0.74-0.99 in Q4), and ex-smokers (aHR 0.79, 95% CI 0.66-0.93 in Q4), respectively. On the contrary, according to the eGFR, participants with eGFR <90 mL/min/1.73 m^2 had a beneficial effect of dietary beta-carotene (aHR 0.82, 95% CI, 0.73-0.93 in Q4) compared to the participants with eGFR ≥90 mL/1.73 m^2 (aHR 1.00, 95% CI, 0.78-1.27).

Conclusions: Among the various medical conditions, decreased kidney function status was the only condition to predict the beneficial effect of dietary beta-carotene. More specified and targeted counseling for encouraging intake of beta-carotene needs to be considered especially for subjects with lower eGFR.

PO2316

Reduced Differences in Clinical Outcomes Between Black and White Veterans with Incident CKD After Removal of Race from Estimated Glomerular Filtration Rate (eGFR)

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Background: Assessing outcomes for racial subgroups can guide strategies to mitigate health and healthcare inequalities. We assessed differences in clinical outcomes by Black and White race following incidence of CKD defined when eGFR was computed with and without a race coefficient.

Methods: The study population was veterans, either non-Hispanic White or non-Hispanic Black, in the US Veterans Health Administration who had incident CKD stage G3 or higher (i.e., first eGFR<60 mL/min/1.73 m^2 for >3 months) between 2007 and 2016. eGFR values were calculated first using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) with its race term included and again using the same equation without the race coefficient (CKD-EPI-RACEout). We examined risks of initiating kidney replacement therapy (KRT) and death in Blacks and Whites, with follow-up from incident CKD until May 31, 2018 or up to 10 years.

Results: 115,374 Black veterans had incident CKD defined by CKD-EPI-RACEout vs. 84,090 by CKD-EPI; and 507,303 White veterans by CKD-EPI, with mean ages at CKD incidence of 64, 67 and 73 years, respectively. Blacks with CKD defined by CKD-EPI-RACEout had lower rates of both KRT and death (8.2 and 44.8 per 1000 patient-years, respectively) compared with Blacks by CKD-EPI (Table). After adjustment for age, sex, eGFR at CKD incidence, and CKD incidence year, Blacks by CKD-EPI-RACEout had a 41% greater risk of KRT than Whites, a markedly decrease from the 172% greater risk with CKD-EPI. Also, Blacks by CKD-EPI-RACEout had a 7% lower risk of death than Whites, in contrast to a 10% greater risk of death with CKD-EPI.

Conclusions: Compared to Whites, Blacks with incident CKD defined by CKD-EPI eGFR without the race coefficient remained more likely to develop KRT, though the relative risk was greatly attenuated; conversely, they had slightly longer survival after case-mix adjustment. Different methods of accounting for race in GFR estimation would affect measures of health outcome disparities in CKD.

Funding: NIDDK Support

Hazard ratios of outcomes for Black versus White veterans with incident CKD

	Kidney replacement therapy (KRT)			Death		
	Event rate (per 1000 patient-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) (age, sex, eGFR and incident-year)	Event rate (per 1000 patient-years)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI) (age, sex, eGFR and incident-year)
Black, identified by CKD-EPI without race coefficient	8.2	2.42 (2.33-2.51)	1.41 (1.36-1.46)	44.8	0.60 (0.59-0.61)	0.93 (0.92-0.94)
Black, identified by CKD-EPI	15.2	4.56 (4.40-4.71)	2.72 (2.62-2.82)	62.9	0.85 (0.84-0.86)	1.10 (1.09-1.12)
White	3.4	1	1	74.3	1	1

PO2317

Impact of Removing the Race Coefficient from Estimation of Glomerular Filtration Rate (eGFR) at the University of Washington

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Background: The inclusion of the race coefficient in eGFR estimates for patients identified as Black has been widely debated. In response, our institution eliminated the race coefficient when reporting eGFR on June 1, 2020. We evaluated changes in prescription of metformin, dialysis initiation and referral to subspecialists among Black and non-Black patients before vs. after the change in eGFR reporting.

Methods: We manually reviewed data of self-identified Black patients with CKD within the UW system between June through November of 2019 (before change in eGFR reporting) and 2020 (after change in eGFR reporting). In addition, data from the electronic medical record (EMR) was extracted for subspecialty referral rates for Black and non-Black patients during this same time frame. We compared 6-month data pre/post change of eGFR and determined differences in: initiation and discontinuation of metformin, indication for and mean eGFR at dialysis initiation, and new referrals to nephrology, transplant and vascular surgery.

Results: After the change in eGFR reporting, rates of metformin initiation increased (4/223 in 2020 vs. 0/219 in 2019), while discontinuation rates were stable (18% in 2019 vs. 15% in 2020) among Black patients with CKD. Rates of dialysis initiation were comparable (2.7% in 2020 vs. 1.4% in 2019, mean eGFR 8 vs. 13 ml/min/1.73m^2) in Black patients with CKD, with the primary indication of uremic symptoms remaining unchanged. Comparing Black vs. non-Black patients, subspecialty referral rates for nephrology and transplant nephrology were higher for Blacks after the change in eGFR reporting (Figure 1).

Conclusions: After removing the race coefficient from eGFR reporting, patterns of medication prescription rates and dialysis initiation did not substantially change, however subspecialty referral rates increased for Black patients with CKD. We acknowledge that the COVID-19 pandemic may have impacted these trends, but the trends overall are encouraging for improving health outcomes and nephrology access to care for Black patients with CKD.

Figure 1. Differences in subspecialty referral rates at the University of Washington with the inclusion of the race coefficient in eGFR reporting (2019) and after exclusion of the race coefficient in eGFR reporting (2020)

	June 1-November 30, 2019 (with race coefficient in eGFR)		June 1-November 30, 2020 (without race coefficient in eGFR)		Change from 2019 to 2020*	
	Black patients	Non-Black patients	Black patients	Non-Black patients	% change for Black patients	% change for non-Black patients
New Nephrology referrals	133	783	157	874	+18%	+11.6%
Transplant Nephrology referrals	22	150	26	146	+18.2%	-2.7%
Vascular surgery referrals	82	817	82	800	0%	-2.1%

*calculated as 2020 count-2019 count divided by 2019 count

PO2318

Elimination of the Race Coefficient from eGFR Calculation on Clinical Care and CKD Research Among a National US Veteran Cohort

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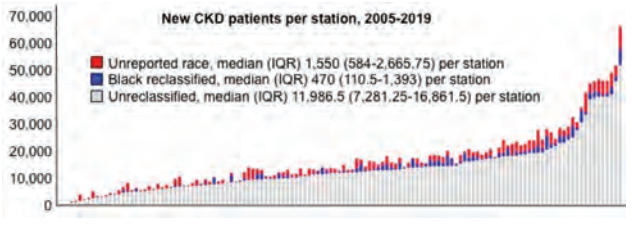
Background: Elimination of the race coefficient from the CKD-EPI equation has been proposed as an important step to improve healthcare disparities faced by Black persons with chronic kidney disease (CKD).

Methods: We identified U.S. Veterans with incident non-dialysis CKD stages 3-4 based on laboratory data from 2005-2019 from the Veterans Affairs (VA) Corporate Data Warehouse. Demographic characteristics and laboratory values were used to calculate estimated glomerular filtration rate (eGFR) by the CKD-EPI equation with and without the race coefficient. We identified Black persons who were reclassified from non-CKD to CKD status or to a different CKD stage, as well as individuals whose race was not reported and eGFR could not be calculated using a race-based equation. The number of additional persons with CKD identified without the race coefficient was evaluated by VA station.

Results: There were 1,765,410 individuals with CKD stages 3-4 by race-based eGFR. Eliminating the race coefficient resulted in reclassification of 119,142 (35.2%) Black individuals as having CKD stages 3a, 3b, or 4, accounting for a 6.7% increase in incident CKD among all races and a 54.3% increase among Black persons. Of reclassified Black individuals, 77% had hypertension, 14% had cardiovascular disease, 51% were prescribed either an ACE inhibitor or an ARB, and 48% were prescribed statins. There were also 245,340 individuals with unreported race who were newly classifiable as having CKD when eliminating the race coefficient. Median (IQR) number of reclassified individuals per VA station was 470 (110.5-1,393) reclassified Black persons and 1,550 (584-2,665.75) individuals of unidentified race (Figure).

Conclusions: Eliminating the eGFR race coefficient will lead to substantial but variable impact on clinical care and CKD research across VA locations nationally. Ideally this shift will achieve more equitable clinical outcomes for Black persons and expand inclusion in CKD clinical trials and observational research to advance CKD care.

Funding: Veterans Affairs Support



Reclassified Black and unreported race patients with CKD per VA station

PO2319

Comparing Estimated Glomerular Filtration Rates (eGFR) for US Black Veterans with and Without the Black-Race Coefficient and Normalization to a Fixed Body Surface Area (BSA)

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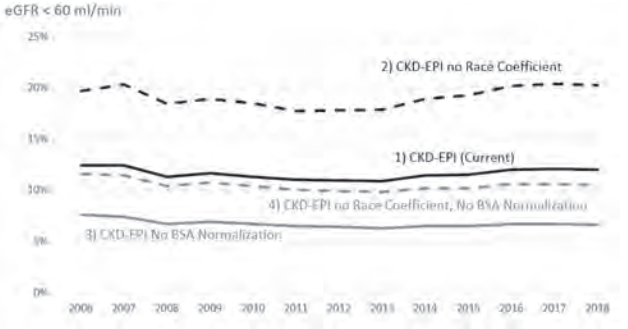
Background: The CKD-EPI estimation of GFR includes two corrections: 1) increasing eGFR for Blacks by 15.9% to more accurately reflect measured GFR; 2) normalizing eGFR in all races to a fixed value (1.73 m^2) of BSA to compare across populations. We aimed to assess the impact of removing both corrections—separately and together—on the prevalence of CKD in Black US Veterans.

Methods: Among 7 million Black US Veterans, aged 18+ with at least one serum creatinine lab measurement (2006-2018), we estimated the prevalence of eGFR < 60, using four GFR-correction methods: 1) eGFR using the CKD-EPI equation with the Black-race coefficient and normalized to a BSA of 1.73 m^2; 2) #1, without the Black-race coefficient; 3) #1, without normalization for BSA; and 4) #1, without the Black-race coefficient or normalization for BSA.

Results: Among Black Veterans, the average age was 57 years, 87% males, and average BSA was 2.11 m^2. The prevalence of CKD varied appreciably by the method of GFR estimation. CKD prevalence was highest (15-20%) throughout the 13-year study period without use of the Black-race coefficient (#2) and lowest (6-8%) without normalization for BSA (#3). The method with neither the Black-race multiplier nor BSA normalization (#4) yielded similar estimates of CKD prevalence as the CKD-EPI method of eGFR estimation (#1), differing by <2% throughout the study period. Patient-level agreement between the latter two methods was nearly 80%.

Conclusions: Our results show good agreement between Black Veterans classified as having CKD using the CKD-EPI equation with both corrections and those same veterans classified with CKD without either correction. Pending recommendations from the NKF-ASN Task Force, the latter method (#4) offers a simplified procedure to provide individualized GFR estimates on the original scale (mL/min) for all individuals.

Funding: Other U.S. Government Support



* eGFR without BSA normalization=eGFR (CKD-Epi)*(BSA/1.73), where BSA=(Wt$^{0.5}$*Ht$^{0.5}$)/60, according to Mosteller (1987)

PO2320

Social Determinants of Health (SDOH), Environmental Inequities and ESRD Among US Veterans: An Integration of Ecological and Spatial Approaches

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Background: Disparities in kidney health are often due to underlying environmental and social determinants of health (SDOH). We assessed geographic variation and the association between air pollution, SDOH, and ESRD in US veterans at county-level.

Methods: We used data from about 3 million Veterans with CKD between the years of 2006-2016 (prevalent and incident CKD cases). Environmental and SDOH were obtained from various data sets, including the American Community Survey (2009), the National Neighborhood Data Archive (2006) and others. County prevalence of ESRD was calculated as # ESRD cases/1000 person-years. County-level environmental factors and SDOH included average daily PM2.5, neighborhood disadvantage index, etc. A geographically weighted regression model (GWR) was applied to explore the relationship between SDOH, air pollution and prevalence of ESRD.

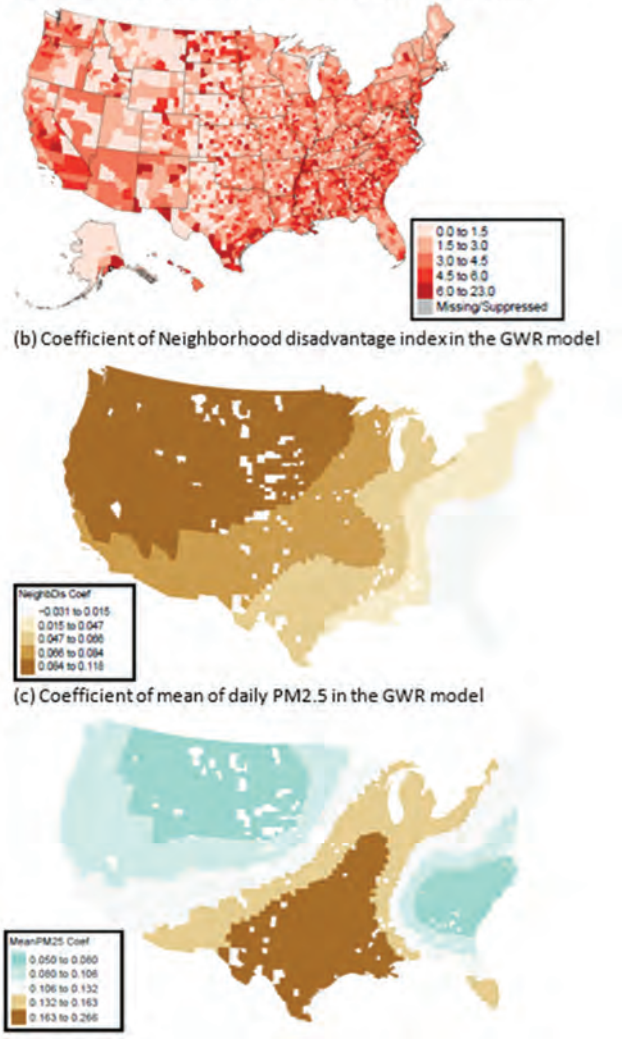
Results: Average of county-level prevalence of ESRD was 3.1/1000 person-years (SD=0.21, n=3,231). The prevalence of ESRD was higher in the rust-belt area of the Midwest and the Southeast region (Fig1a). Neighborhood disadvantage index was

associated with higher ESRD prevalence in the West and parts of the Midwest (Fig1b). PM2.5 was associated with higher prevalence in the East North Central and South West Central regions (Fig1c).

Conclusions: Variation exists in the association between environmental factors, SDOH and the presence of ESRD geographically. It highlights the importance of attention to the environment and community-based SDOH, toward preventing and managing ESRD based on residence and individualized patient care.

Funding: Veterans Affairs Support

Figure 1 Distribution of prevalence of ESRD and the association between social and environmental characteristics and prevalence of ESRD at county level



PO2321

Facility-Level Variation and Racial Disparities in Albuminuria and Serum Creatinine Dual Testing in the US Veterans Health Administration (VHA) Health Care System

Yun Han,[1] Nicole Bhave,[1] Diane Steffick,[1] Kara Zivin,[4,1] Alain Koyama,[2] Meda E. Pavkov,[2] Neil R. Powe,[3] Delphine S. Tuot,[3] Rajiv Saran.[1] *[1]University of Michigan, Ann Arbor, MI; [2]Centers for Disease Control and Prevention, Atlanta, GA; [3]University of California San Francisco, San Francisco, CA; [4]VA Ann Arbor Healthcare System, Ann Arbor, MI.*

Background: Simultaneous urine testing for albumin (UAlb) and serum creatinine (SCr), i.e., 'dual testing', is now an accepted quality measure in the management of diabetes. As kidney disease is defined by both UAlb and SCr testing, this approach could be more widely adopted in kidney care. We therefore sought to assess facility-level variation and racial differences in performance of dual testing in the integrated VHA health care system.

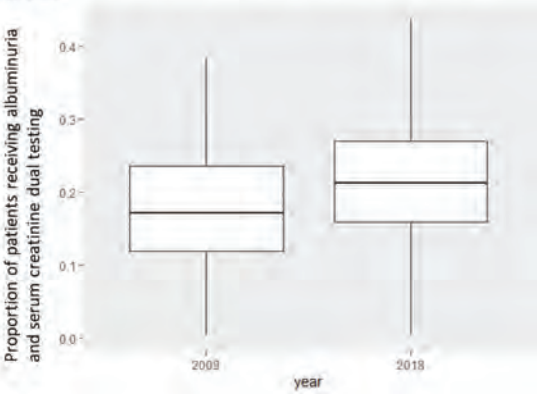
Methods: We included patients with any inpatient or outpatient visit to the VHA during the period 2009-2018. Dual testing was defined as UAlb and SCr testing in the outpatient setting within a fiscal year. A generalized linear mixed-effects model was applied to explore individual level (demographics and comorbidities) and facility level predictors of receiving dual testing.

Results: We analyzed data from approximately 6 million veterans per year (total n=69,102,389; 91.1% male). Dual testing increased on average from 17% to 21%, but varied substantially among VHA centers (0.3% to 43.7% in 2018) (Figure). Dual testing was strongly associated with diabetes (odds ratio [OR]: 10.4, 95% CI 10.3-10.5, p<0.0001) and not associated with VHA center complexity level. Despite a higher proportion of Black veterans receiving dual testing compared to White veterans (24.0% vs 21.7% in 2018), they were less likely to be tested after adjusting for other individual and facility characteristics (OR: 0.93, 95% CI 0.92-0.93, p<0.0001).

Conclusions: Performance of dual testing varied among VHA centers and is low in both White and Black veterans. Simultaneously incorporating UAlb and SCr for kidney care may help improve both risk stratification and management of individuals with or at risk of kidney disease.

Funding: Other U.S. Government Support

Figure. Facility variation in albuminuria and serum creatinine dual testing in the Veterans Health Administration



PO2322

Three New Race-Free, Community-Based Equations to Estimate GFR: The Machine Learning Estimation of Renal Function (MLERF) Equations

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Background: As inclusion of race in glomerular filtration rate (GFR) estimation has become an increasingly controversial issue, it is of vital importance to propose race-free equations and evaluate their performance.

Methods: Using Multivariable Fractional Polynomials (MFP), Generalized Additive Models (GAM), and Random Forests (RF), we developed three new GFR estimating equations from the community-based Genetic Epidemiology Network of Arteriopathy Study (GENOA) study (N=1010). We then compared performance of the new equations to the CKD-EPI creatinine equation using the Epidemiology of Coronary Artery Calcification (ECAC) cohort study and the Assessing Long Term Outcomes in Living Kidney Donors (ALTOLD) (N=792). Due to lack of black participants in external data, we also evaluate performance of equations in Black participants internally using development data. A rigorous bootstrapping method, allowing equation coefficients to change for each bootstrap sample, was used to evaluate performance of our new equations to address the issue of overfitting.

Results: Our final equations were based on creatinine, age and sex. The addition of race yielded only minor nonsignificant improvements in RMSE and thus race was not included in the final equations. In external data (Figure), our new equations showed similar P30, RMSE, bias and precision compared to the CKD-EPI creatinine equation which included race as a predictor. Our equations also showed marked improvements in terms of bias and accuracy for Black participants over the CKD-EPI creatinine equation in the development data.

Conclusions: Performance of our new race-free equations using community-based cohorts were comparable to CKD-EPI creatine equation in external validation and superior in Black participants in internal validation. Our study indicated that race can be removed from equations to estimate GFR in Black and White participants without significantly sacrificing equation performance.

Data set	Equation	group	Bias Median of eGFR – mGFR (95% CI), ml/min/1.73 m²	Precision IQR of eGFR – mGFR (95% CI), ml/min/1.73 m²	Accuracy Root Mean Square Error, (95% CI), ml/min/1.73 m²	Accuracy P30 (eGFR within 30% of mGFR) (95% CI), %
External validation data (ECAC & ALTOLD)	MFP equation	Overall	2.5(1.4, 3.9)	17.4(16.1, 19.1)	0.2(0.18, 0.23)	90.2(88.1, 92.2)
	GAM equation	Overall	-0.2(-1.3, 0.8)	17.6(16, 19.1)	0.21(0.18, 0.24)	90,5(88.5, 92.6)
	RF equation	Overall	0.7(-0.4, 2.2)	17.4(16.2, 18.9)	0.21(0.18, 0.24)	90.8(88.8, 92.8)
	CKD-EPI Creatinine equation	Overall	3.1(1.9, 4.7)	17.4(16.1, 18.7)	0.21(0.19, 0.24)	88.6(86.4, 90.8)
Internal validation data (GENOA)	MFP Equation	Black	-3.8(-4.8, -2.7)	21.5(20.6, 22.3)	0.25(0.25, 0.25)	82.2(81, 83.2)
	GAM equation	Black	-3.7(-4.9, -2.6)	21.2(20.2, 22.2)	0.25(0.24, 0.25)	82.8(81.2, 84)
	RF equation	Black	-1.7(-2.4, -0.9)	14.3(13.1, 15.6)	0.19(0.18, 0.21)	89.4(87.3, 91.4)
	CKD-EPI Creatinine equation	Black	7(5.4, 8.9)	21.5(19.2, 24.8)	0.28(0.26, 0.31)	74.5(70.6, 78.5)

eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate; MFP:Multivariable Fractional Polynomials; GAM:Generalized Additive Models; RF:Random Forests ; ECAC:The Epidemiology of Coronary Artery Calcification ; ALTOLD: The Assessing Long Term Outcomes in Living Kidney Donors; GENOA: The Genetic Epidemiology Network of Arteriopathy Study.

Performance of Equations

PO2323

Non-GFR Determinants of Serum Creatinine and Race in GFR Estimating Equations: Findings from the CRIC Study

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Background: Understanding and controlling for the non-GFR determinants of serum creatinine (SCr) that correlate with race may facilitate development of GFR estimating equations without a race term.

Methods: This is a cross-sectional study of 1248 Chronic Renal Insufficiency Cohort (CRIC) participants who underwent urinary ^{125}I-iothalamate clearance GFR (iGFR) and 24-hour urine creatinine clearance measurement at study entry. We first evaluated if Black (vs. non-Black) race was independently associated with different components of creatinine production, secretion and excretion that may contribute to variations in SCr independent of measured GFR (i.e. non-GFR determinants of SCr). We then assessed whether any of these potential explanatory variables could independently or jointly replace the term for Black race in GFR estimating equations using SCr.

Results: Mean±SD age of the study population was 55.9±12.1 yrs; iGFR 48±20 ml/min/1.73m^2; median [IQR] SCr 1.5 [1.3-2.0] mg/dL; 43% were female and 37% self-identified as Black. Black race was associated with greater height, weight, BMI, BSA, bioelectrical impedance analysis (BIA)-phase angle and fat-free mass, and 24-hour urine creatinine excretion. Black race was not associated with higher dietary protein intake (assessed by either self-report or 24-hour urine urea nitrogen) or less tubular secretion of creatinine (quantified as difference between creatinine clearance and iGFR). In a model regressing iGFR on SCr, age, sex, and race (Black vs. non-Black), there were modest attenuations for the race terms when factors were considered individually (**Table**). A multivariable model maximized attenuation, but there remained a 8.7% higher iGFR in Black participants (vs. 12.8% in base model)(**Table**).

Conclusions: Modeling non-GFR determinants of SCr, which varied by race, did not eliminate the incremental value of including race in SCr-based GFR estimating equations.

Funding: NIDDK Support

Association between Black race and iGFR after controlled for non-GFR determinants of serum creatinine which vary by self-report Black race

		Self reported Black race (vs. non-Black race)
		% Higher iGFR (95% CI)
Base Model: ln(iGFR) = [Race or African ancestry] + ln(SCr) + Age + Sex		12.8 (9.7 -15.9) %
Base model with potential explanatory variables considered individually: ln(iGFR) = [Race or African ancestry] + ln(SCr) + Age + Sex +	Body mass index	13.8 (10.7-17.0) %
	Body surface area	13.1 (9.9-16.3) %
	Height	12.0 (9.0-15.1) %
	Weight	13.4 (10.3-6.6) %
	ln(BIA phase angle)	10.5 (7.5-13.6) %
	BIA estimated fat-free mass	12.4 (9.2-15.6) %
	24-hr urine creatinine	10.7 (7.7-13.7) %
Base model with several potential explanatory variables considered simultaneously: ln(iGFR) = [Race or African ancestry] + ln(SCr) + Age + Sex + Height + Fat-free mass + ln(BIA phase angle) + 24-hr urine creatinine		8.7 (5.8-11.7) %

PO2324

Effect of Removing Race Coefficient (RC) from Estimated Glomerular Filtration Rate (eGFR) Among Black Adults in the US Military Health System (MHS)

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Background: The use of race in calculating eGFR is under scrutiny as a possible contributor to healthcare disparities in the US. Using the MHS electronic medical record, we evaluated the effect in Black adults of removing eGFR race adjustment on the overall prevalence of chronic kidney disease (CKD) and on the prevalence at specific levels of eGFR important in clinical decision-making.

Methods: Fiscal Year (FY) 2015 data were extracted from the MHS Data Repository for individuals of Black race aged ≥18 without end-stage kidney disease. eGFR was calculated from serum creatinine using the CKD-EPI equation both with and without adjustment for Black race. CKD was defined as having the most recent eGFRs in the FY persistently <60 mL/min/1.73m2 for more than 3 months (KDIGO criteria). Statistical significance was determined by chi-square.

Results: 136,934 Black individuals (age=43±14 years, 38% female, 40% active duty) had serum creatinine measured a total of 259,930 times. With RC, mean eGFR was 98.1±25.7, 4.5% had at least one eGFR <60, and 1.3% met CKD by KDIGO criteria (Table). Removal of RC decreased mean eGFR to 84.7±22.2 (Δ=−13.5±3.6) and increased CKD prevalence to 2.1% (Δ=+68%). Without RC, 0.9% of those with GFR≥60 were reclassified as having CKD stage 3 and 5.6% of those with CKD stage 3 reclassified into CKD stages 4-5. Without RC the prevalence of CKD stages 3b-5 increased by 75%, of CKD stages 4-5 by 65%, and of eGFR<20 (eligible for transplant listing) by 71%. Among active duty, removal of RC increased prevalence of CKD by 102% and of CKD stages 3b-5 by 68%.

Conclusions: Removal of the RC resulted in significant reclassification from non-CKD to CKD and from lower to higher stages of CKD. Consequences for patient education, treatment decisions, resource utilization, and clinical outcomes may benefit from further study. *The views expressed in this abstract are those of the authors and do not reflect official policy of the Departments of Army/Navy/Air Force, Department of Defense, Department of Health and Human Services, or the US Government.*

Funding: Other U.S. Government Support

Denominator= 136,934	n (prevalence)		Change	*p*
	With RC	Without RC		
eGFR < 60 (CKD3–5)	1716 (1.3%)	2890 (2.1%)	+68%	<0.001
eGFR = 30-59 (CKD3)	1580 (1.2%)	2666 (1.9%)	+69%	<0.001
eGFR < 45 (CKD3b-5)	556 (0.4%)	973 (0.7%)	+75%	<0.001
eGFR < 30 (CKD4-5)	136 (0.1%)	224 (0.2%)	+65%	<0.001
eGFR < 20 (transplant listing)	34	58	+71%	0.0016

PO2325

Social Determinants of Health and Estimated GFR in the MDRD Study

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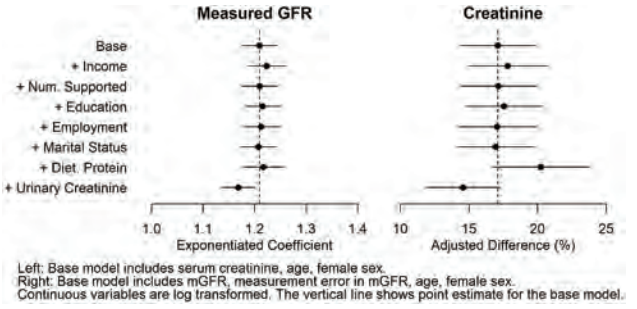
Background: Use of race in medical algorithms is facing increasing scrutiny. One concern is that race differences do not reflect biological differences, but rather differences in social determinants of health (SDH). The MDRD Study equation was the first eGFR equation to include race [self-identified and categorized as Black vs non-Black] in addition to age, sex and serum creatinine (Scr), due to observed differences between Black and non-Black individuals in mean measured GFR (mGFR) (1.21 times higher with the same age, sex and Scr) and mean Scr (17.1% higher for the same age, sex and mGFR, accounting for mGFR measurement error). Subsequent analysis suggested higher mean creatinine excretion and lower mean creatinine secretion in Black individuals. Here we explore the impact of SDH on the Black race coefficient in the MDRD Study equation and on the racial difference in observed Scr in the MDRD Study.

Methods: SDH and related variables included income, household size, education, employment, marital status, dietary protein and creatinine excretion. We examined the magnitude of the Black race coefficient and the observed race difference in Scr without and with adjustment for SDH variables.

Results: Among the 1628 participants at baseline visit 3, mean mGFR was 40 (range 5-168) and 12% were Black individuals. There were significant differences between Black and non-Black individuals for all SDH except dietary protein. Addition of SDH (Figure) did not substantially alter the Black race coefficient in eGFR (left) or the race difference in mean Scr (right).

Conclusions: We were not able to show that these SDH account for the observed race differences in the relationship between mGFR and Scr in the MDRD Study. Key limitations include availability of SDH variables, residual confounding between race and SDH, and a single study of patients with CKD from 30+ years ago which may not reflect a more contemporary diverse population. These results do not detract from concerns for use of race in GFR estimation.



Left: Base model includes serum creatinine, age, female sex.
Right: Base model includes mGFR, measurement error in mGFR, age, female sex.
Continuous variables are log transformed. The vertical line shows point estimate for the base model.

PO2326

Impact of Race/Ethnicity on the Current Screening Approach for CKD

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Background: KDIGO recommends screening for chronic kidney disease (CKD) with both estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (ACR). Screening is advised for people with diabetes mellitus, hypertension and/or cardiovascular disease (CVD). People of African descent are at increased risk for CKD, while several reports indicate that the screening approach insufficiently capture CKD in this group. eGFR correction for African race/ethnicity may contribute to this discrepancy, but age and socioeconomic status (SES) may be involved. We assessed whether CKD detection is influenced by race/ethnicity correction and we defined how age >50 yr or lower SES influence CKD detection.

Methods: Baseline data of 21,617 participants (mean age 44 yr, 43% male) of Dutch (4,564), South-Asian Surinamese (3,043), African Surinamese (4,151), Ghanaian (2,339), Moroccan (3,614) and Turkish (3,096) ethnicity included in the multi-ethnic HELIUS cohort study (Amsterdam, The Netherlands) were analysed. We defined CKD as eGFR (CKD-EPI formula, <60mL/min/1.73m^2) and/or ACR (≥3mg/mmol). Detection rate was characterised by the c-statistic for three screening approaches in each ethnic group; I) the traditional approach (i.e. screening when having diabetes mellitus, hypertension or CVD); II) the traditional approach plus age >50yr; and III) the traditional approach plus low SES (i.e. none or elementary schooling). C-statistic with and without correction for race/ethnicity were compared.

Results: Of participants, 2335 (11%) had CKD. Estimated CKD was slightly more prevalent in participants of African Surinamese (11 vs 13%) and Ghanaian (12 vs 14%) descent, when the correction for race/ethnicity was discontinued. Compared to approach I, approach II and approach III did not have a higher c-statistic, overall and within African origin subgroups. Results with and without ethnicity/race were similar.

Conclusions: Our study shows that discontinuation of the race/ethnicity correction, or addition of age > 50 yr and low SES as criteria for CKD screening have little impact on the detection rate of the currently advised screening approach.

C-statistic (95%-CI)	Approach I		Approach II		Approach III	
	Corrected	Uncorrected	Corrected	Uncorrected	Corrected	Uncorrected
Overall	0.63 (0.62-0.64)	0.63 (0.62-0.64)	0.64 (0.63-0.65)	0.64 (0.63-0.65)	0.63 (0.62-0.65)	0.64 (0.63-0.65)
African Surinamese	0.63 (0.60-0.66)	0.63 (0.61-0.66)	0.63 (0.61-0.66)	0.64 (0.61-0.66)	0.63 (0.60-0.66)	0.64 (0.61-0.66)
Ghanaian	0.58 (0.55-0.62)	0.59 (0.56-0.63)	0.60 (0.56-0.64)	0.59 (0.55-0.62)	0.59 (0.56-0.63)	0.59 (0.56-0.63)

PO2327

Impact of Race/Ethnicity and Age on Survival in Advanced CKD Patients Treated with Conservative Management vs. Dialysis

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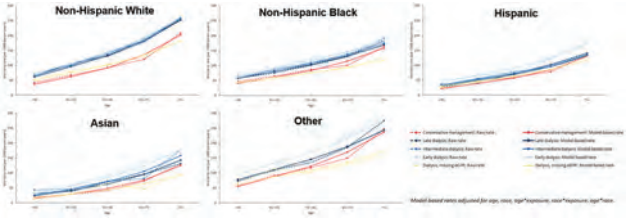
Background: Given evidence that dialysis may not offer survival benefit nor improved quality of life in certain groups (elderly, multi-morbid), there is growing interest in conservative management (CM) as an alternative treatment strategy for advanced CKD. Yet little is known about the impact of CM vs. dialysis on CKD outcomes, including mortality, across different racial/ethnic and age groups.

Methods: In a national cohort of 309,188 advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days), we compared mortality rates in patients treated with CM vs. dialysis from 1/1/07-6/30/20 from the OptumLabs® Data Warehouse (OLDW), which contains de-identified administrative claims, including medical and pharmacy claims and enrollment records for commercial and Medicare Advantage enrollees as well as electronic health record data. Patients were categorized according to receipt of dialysis vs. CM, defined as those who did vs. did not receive dialysis within 2-yrs of the index eGFR (1st eGFR <25), with the former group parsed according to timing of dialysis initiation, defined as late, intermediate, vs. early dialysis (eGFRs <5, 5-<10, vs. ≥10 at dialysis transition). We used Poisson regression to compare mortality rates in CM vs. dialysis patients across race/ethnicity and age.

Results: Whereas late, intermediate, and early dialysis had higher mortality rates than CM in Non-Hispanic Whites across all age groups, in Hispanic patients CM and dialysis had similar mortality rates across all ages. In Non-Hispanic Blacks, Asians, and Other races/ethnicities, CM vs. late dialysis had similar mortality rates among those ≥75 yrs old, whereas CM demonstrated survival benefit vs. all dialysis groups in younger ages.

Conclusions: In a diverse, nationally representative cohort of CKD patients, we observed differential relationships between CM vs. dialysis on mortality rates across race/ethnicity and age. Further research is needed to determine which patient characteristics and health services optimize candidacy and choice of CM vs. dialysis to enable a personalized approach.

Funding: NIDDK Support



PO2328

Evaluation of the Cambridge GFR Estimating Equation in a Diverse Population

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Background: Evaluation of GFR is not standardized in oncology; serum creatinine (Scr), estimated creatinine clearance (eClcr) using the Cockcroft Gault equation, and estimated GFR (eGFR) using Scr (eGFRcr) using the MDRD Study or CKD-EPI equation are often used interchangeably. KDIGO guidelines recommend eGFRcr, using standardized Scr and the CKD-EPI equation as the initial test in adults, and confirmatory tests using serum cystatin C (eGFRcys or eGFRcr-cys), measured creatinine clearance (mClcr) or measured GFR (mGFR) using exogenous filtration markers.

Methods: Janowitz and colleagues recently reported a new equation developed in patients with cancer that can be used with or without IDMS-traceable assays, CamGFRv2 (Williams et al. Clin Cancer Res 2021), which performed better than CKD-EPI eGFR in the development population, but which has not been evaluated in an external validation population. To determine if CamGFRv2 could be used in other settings, we evaluated CamGFRv2 and other commonly used equations in two large, diverse study populations.

Results: Study populations included the CKD-EPI 2009 external validation population [n=3771, mean (SD) age 49.2 (14.6), mGFR 69.2 (35.5) ml/min/1.73 m^2), men 54.1%, African American 10%, diabetes 28.2%, and CKD-EPI 2012 external validation population [n=1119, mean (SD) age, 49.9 (16.6) years, mGFR 69.8 (41.0) ml/min/1.73 m^2, men 59.3%, African American 3%, diabetes 53.1%]. (Note: study participants were not included in the development of the CKD-EPI equations.) No eGFRcr equation, including CamGFRv2, performed better than the CKD-EPI equation. As previously reported, CKD-EPI eGFRcr-cys performed better than CKD-EPI eGFRcr or eGFRcys (Inker et al. NEJM 2012).

Conclusions: In conclusion, eGFRcr using CamGFRv2 is not more accurate than using CKD-EPI in a diverse population. Studies comparing CamGFRv2 vs. CKD-EPI equations in patients with cancer are needed

eGFR marker	Equation	Demographic Variables	Bias	Precision IQR	Accuracy 1-P$_{30}$(%)	Accuracy RMSE
2009 External Validation (N=3771)						
eGFRcr	CKD-EPI	ASR	2.6 (2.2, 3.0)	17.1 (16.4, 17.9)	16.0 (14.8, 17.1)	0.251 (0.242, 0.261)
eGFRcr	MDRD	ASR	5.7 (5.3, 6.3)	18.9 (17.9, 19.9)	19.5 (18.3, 20.9)	0.276 (0.267, 0.285)
eGFRcr	CG	AS	-8.0 (-8.7, -7.2)	24.9 (24.0, 25.9)	37.5 (35.9, 39.0)	0.366 (0.354, 0.377)
eGFRcr	CamGFRv2*	AS	6.7 (6.1, 7.4)	21.0 (20.1, 22.0)	23.2 (21.9, 24.6)	0.301 (0.291, 0.312)
2012 External Validation (N=1119)						
eGFRcr	CKD-EPI	ASR	3.9 (3.1, 4.7)	15.4 (14.3, 16.5)	12.7 (10.8, 14.7)	0.224 (0.213, 0.235)
eGFRcr	MDRD	ASR	6.3 (5.5, 7.7)	19.4 (17.4, 21.0)	17.4 (15.2, 19.6)	0.256 (0.246, 0.267)
eGFRcr	CG	AS	-3.6 (-4.4, -2.8)	19.1 (17.7, 21.0)	27.3 (24.7, 29.9)	0.293 (0.275, 0.310)
eGFRcr	CamGFRv2	AS	8.2 (7.4, 9.2)	22.8 (20.8, 24.7)	25.2 (22.6, 27.8)	0.293 (0.278, 0.311)
eGFRcys	CKD-EPI	AS	3.3 (2.3, 4.4)	16.4 (14.8, 17.7)	14.2 (12.2, 16.3)	0.234 (0.219, 0.250)
eGFRcr-cys	CKD-EPI	ASR	3.8 (3.1, 4.5)	13.4 (12.3, 14.4)	8.5 (7.0, 10.2)	0.189 (0.178, 0.201)

Bias is computed as the median of the difference between mGFR and eGFR. IQR, interquartile range; of the differences between mGFR and eGFR, is 25th and 75th percentiles of the differences. Units for bias and IQR are ml/min/1.73 m^2. 1- P$_{30}$ and RMSE are measures of accuracy. P$_{30}$ is computed as percent (%) of eGFR less than ±30% different from mGFR; 1-P$_{30}$ indicates large errors; RMSE, root mean square error, is a computed on the log scale.
*N=3750 (21 participants were missing height or weight)
Comparisons: CKD-EPI eGFRcr is the reference. Green shading indicates that the point estimate is closer to zero than the reference and CI does not overlap the reference, and as Orange shading indicates that the point estimate is further from zero than the reference and CI does not overlap the reference.
Abbreviations: mGFR, measured GFR; eGFR, estimated GFR; eGFRcr, eGFR using serum creatinine; eGFRcys, eGFR using using serum cystatin C; eGFRcr-cys, eGFR using serum creatinine and cystatin C; A, age; S, sex; R, race; IQR, interquartile range; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; CG, Cockcroft-Gault; CamGFRv2, Cambridge GFR equation version 2.

Performance of eGFR Equations in Diverse Study Populations

PO2329

Racial and Ethnic Predictors of Hyperkalemia Recurrence

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Background: Understanding predictors of recurrent HK may help healthcare providers provide a more individualized approach to HK management. This study aims to explore if race and ethnicity are independently associated with recurrent HK.

Methods: The cohort consisted of 2,457,498 US veterans who had a HK event (sK >5.0 mEq/L) between 2004 and 2018. We evaluated possible demographic predictors of 1-year HK recurrence using Fine and Gray competing risk regression model, which the competing event was all-cause mortality within 1 year after index HK event. We defined HK recurrence as the third or later potassium measurement after the index HK measurement, and patients need to have at least one or more normal potassium measurements (≤5 mEq/L) between the HK events.

Results: Cohort mean age was 63±13yrs, mean index potassium level was 5.31±0.29 mEq/L, and median (IQR) index eGFR was 68 (49,86) mL/min/1.73m^2; 96% were male, 13% were Blacks, and 6% were Hispanic. Overall, 17% of patients had a HK recurrence within 1 year after index HK occurrence. Black patients had a 19% higher risk of 1-year HK recurrence (hazard ratio [HR] [95% CI]: 1.19 [1.18, 1.20]) compared to White patients. Hispanic patients had a 34% higher risk of 1-year HK recurrence (hazard ratio [HR] [95% CI]: 1.34 [1.32, 1.36]) compared to non-Hispanic patients. Other predictors for high risk of 1-year HK recurrence include older age (15% higher for each 15 year increment of age) and male (22% higher compared to female) (Table).

Conclusions: Being Hispanic, Black, male, or older age, was associated with a higher risk of HK recurrence within 1 year after index HK event. Further studies are needed to understand the reasons for these disparities and their potential associations with clinical management of HK.

Funding: Commercial Support - AstraZeneca

Risk of 1-year Hyperkalemia Recurrence

Variables	HR (95% CI)	p-value
Age (for each 15 year increment)	1.15 (1.14,1.15)	<.0001
Male vs. Female	1.22 (1.19,1.25)	<.0001
Race (ref: Caucasian)		
American Indian or Alaska Native	0.94 (0.90,0.98)	0.0026
Asian	0.92 (0.88,0.96)	0.0005
Black or African American	1.19 (1.18,1.20)	<.0001
Native Hawaiian or Other Pacific Islander	1.03 (0.99,1.06)	0.1085
Unknown	0.97 (0.96,0.99)	0.0094
Ethnicity (ref: non-Hispanic)		
Hispanic or Latino	1.34 (1.32,1.36)	<.0001
Unknown by Patients	1.07 (1.05,1.10)	<.0001
Comorbidities		
CHF	1.23 (1.22,1.24)	<.0001
PVD	1.08 (1.07,1.10)	<.0001
CVD	1.01 (0.99,1.02)	0.4713
DEMENTIA	0.80 (0.79,0.82)	<.0001
CPD	1.08 (1.07,1.09)	<.0001
RHEUM	1.10 (1.07,1.13)	<.0001
ULCER	1.10 (1.07,1.13)	<.0001
PARALYSIS	1.17 (1.13,1.20)	<.0001
RENAL	1.48 (1.46,1.50)	<.0001
AIDS	1.15 (1.10,1.21)	<.0001
Diabetes	1.52 (1.51,1.54)	<.0001
Liver Disease	1.41 (1.38,1.43)	<.0001

PO2330

Ethnic Differences for Incident CKD in Asians

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Background: Chronic kidney disease (CKD) is a growing health burden in Asia but there is sparse data on incident CKD among different ethnic groups. We aimed to describe the incidence and risk factors associated with incident CKD in the major ethnic groups in Asia.

Methods: Prospective cohort study of 5580 general population participants age 40-80 years (2234 Chinese, 1474 Malays and 1872 Indians) in Singapore who completed both baseline and 6-year follow up visits. Incident CKD was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 in those free of CKD at baseline.

Results: The 6-year incidence of CKD was highest among Malays (10.0%), followed by Chinese (6.1%) and Indians (5.8%). Logistic regression showed that older age, diabetes, higher systolic blood pressure and lower eGFR were independently associated with incident CKD in all 3 ethnic groups, while hypertension and cardiovascular disease were independently associated with incident CKD only in Malays. The same factors were identified by machine learning approaches gradient boosted machine (GBM) and random forest (RF) to be the most important for incident CKD (Figure 1). Adjustment for clinical and socioeconomic factors reduced the excess risk in Malays by 60% compared to Chinese but only 13% compared to Indians.

Conclusions: Incidence of CKD is high among the main Asian ethnic groups in Singapore, ranging between 6-10% over 6 years. Differences between ethnic groups were partially explained by clinical and socioeconomic factors. These findings may inform policy development and resource allocation to target risks factors to reduce incident CKD.

Funding: Government Support - Non-U.S.

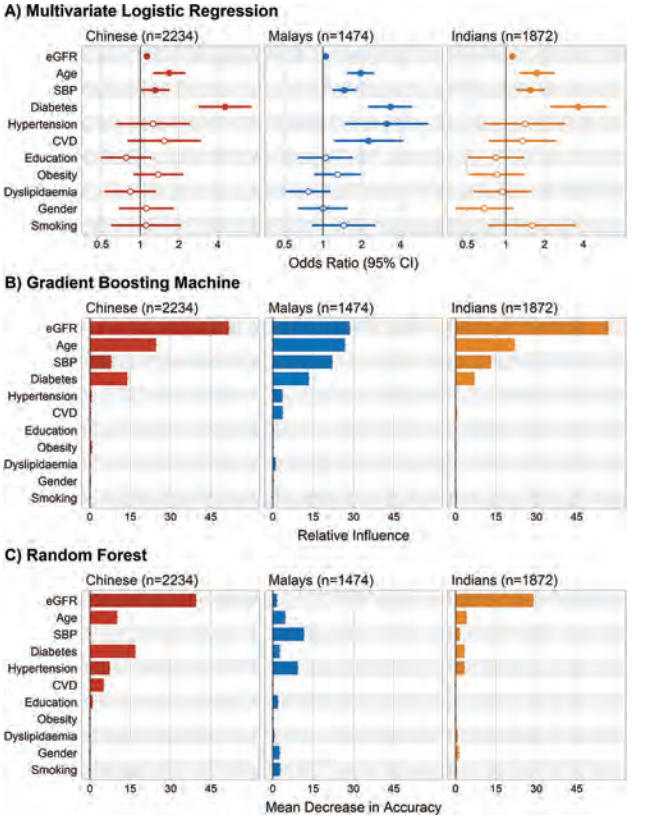

Figure 1. Variables associated with incident CKD in each ethnic group, analysed by (A) Logistic Regression (LR), (B) Gradient Boosted Machine (GBM) and (C) Random Forest (RF).

PO2331

Muscle Mass and Estimates of Renal Function: A Longitudinal Cohort Study

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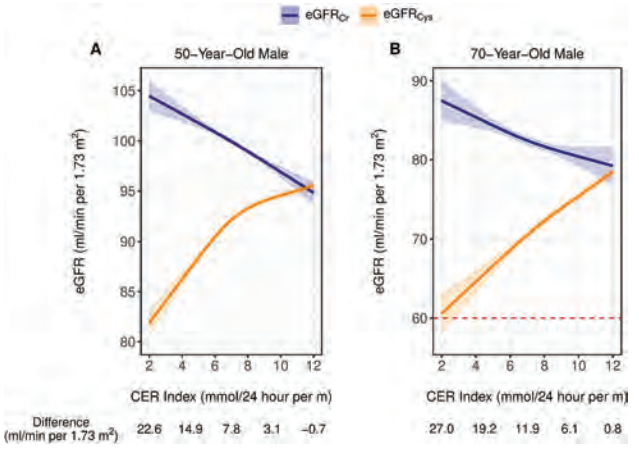
Background: Current guidelines suggest using creatinine-based estimated glomerular filtration rate ($eGFR_{Cr}$) as measurement of renal function, but muscle mass as key determinant of creatinine after renal function may lead to imprecise estimates. We explored effects of 24-hour height-indexed creatinine excretion rate (CER index) – as accurate marker of muscle mass – on $eGFR_{Cr}$ and muscle mass-independent cystatin C-based eGFR ($eGFR_{Cys}$) and predicted probabilities of misclassification given age, sex, and CER index.

Methods: We included 8,076 community-dwelling individuals enrolled in the PREVEND study. Misclassification was defined as $eGFR_{Cr}$ ≥60 ml/min/1.73 m^2 when $eGFR_{Cys}$ was <60 ml/min/1.73 m^2. Cross-sectional associations were quantified with quantile regression and logistic regression and longitudinal associations with linear mixed-effects models.

Results: In a simulated 70-year-old male with low muscle mass (CER index of 4 mmol/24 hour/m), predicted baseline $eGFR_{Cr}$ and $eGFR_{Cys}$ were 87.5 and 60.5 (difference: 27.0) ml/min/1.73 m^2, respectively (**Figure**). Percentages (95% CI) of misclassification in males and females older than 60 years with low muscle mass were 18.5% (14.8% to 22.1%) and 15.2% (11.6% to 18.8%), respectively. Over time, for that same 70-year-old male, $eGFR_{Cr}$ and $eGFR_{Cys}$ disagreed with 2.3, 4.9, 7.7, and 10.7 ml/min/1.73 m^2 at baseline, 5 years, 10 years, and 15 years of follow-up, respectively.

Conclusions: Low muscle mass may cause considerable overestimation of single measurements of $eGFR_{Cr}$. Muscle wasting may cause spurious overestimation of repeatedly measured $eGFR_{Cr}$. Implementing muscle mass-independent markers for estimating renal function, like cystatin C as superior alternative to creatinine, is crucial to accurately assess renal function in settings of low muscle mass or muscle wasting.



PO2332

Muscle Is a Non-GFR Determinant of Serum Filtration Marker Levels and Is Associated with Differential Accuracy of GFR Estimating Equations in Older Adults

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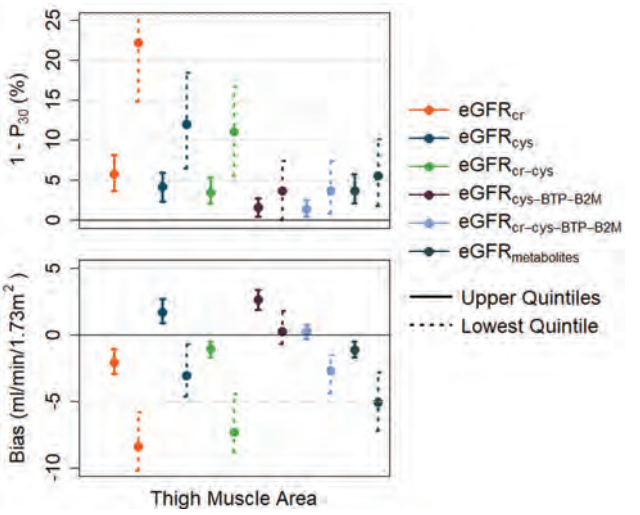
Background: Current GFR estimating equations using creatinine are limited by association with muscle. It is not known whether this is true for recently developed equations using novel filtration markers. These associations are relevant for older adults in whom reduced muscle mass is common.

Methods: In a cross-sectional analysis of 540 community dwelling older adults in Reykjavik, Iceland, serum levels of creatinine (Cr), cystatin-C (Cys), and novel filtration markers (beta-trace protein [BTP], beta-2-microglobulin [B2M], N-acetylthreonine, pseudouridine, phenylacetylglutamine, and tryptophan) were measured, and GFR was measured using clearance of iohexol (mGFR). GFR was estimated from Cr, Cys, or panels of novel filtration markers using CKD-EPI equations. Thigh muscle area (TMA) was assessed using computed tomography. The association of each filtration marker with TMA was determined using linear regression with adjustment for mGFR, GFR measurement error, age, and sex. The performance of the estimating equations was assessed using bias and percent of large (≥30%) errors (1-P_{30}) among those in the lowest sex-specific quintile of TMA compared to the upper four quintiles.

Results: Mean age was 80 (SD 3.8) years, with a mean mGFR of 63 (SD 16) ml/min/1.73m^2. After adjusting for mGFR, all filtration markers had a residual association with TMA, but Cr had a substantially greater association even after adjustment for age and sex. Both bias and 1-P_{30} were greater in the subgroup with low TMA for eGFR from Cr and/or Cys but not for panel eGFR equations (see figure).

Conclusions: Panel eGFR may be preferable in older adults with low muscle mass. Practical tests are needed to identify individuals with low muscle mass for whom eGFR from Cr and Cys may be less accurate.

Funding: Other NIH Support - The measurements and analyses were supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases grant R01DK097020 “Estimating GFR from a Panel of Endogenous Filtration Markers” to Tufts Medical Center. The AGES-Kidney study is supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (R01-DK082447 and supplement 01A1S1 to A.S.L.). E.F. received funding from the NIDDK grant T32DK007777 “Epidemiology, Clinical Trials and Outcomes Research in Nephrology” to Tufts Medical Center



PO2333

Gender-Specific Glomerular Filtration Rate Reference Values for Healthy Individuals Aged 18 to 90 Years

Anne-Laure Faucon,[1,2] Marie Metzger,[1,2] Cedric Gauci,[3] Pascal Houillier,[3,4] Anne Blanchard,[3,4] Jean-Philippe Haymann,[3,4] Martin Flamant,[3,4] Benedicte Stengel,[1,2] Marc Froissart.[5] *[1]Centre de recherche en Epidémiologie et Santé des Populations Inserm U1018, Villejuif, France; [2]Universite Paris-Saclay, Paris, France; [3]Assistance Publique - Hopitaux de Paris, Paris, France; [4]INSERM, Paris, France; [5]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.*

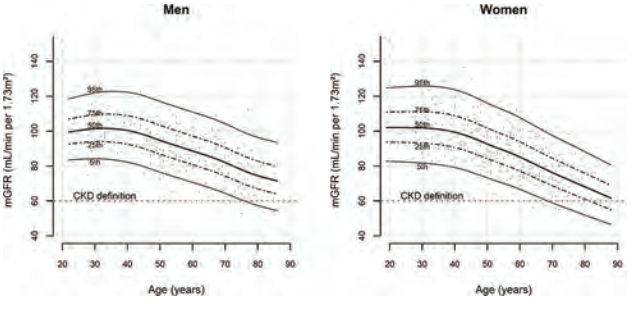
Background: Normal glomerular filtration rate (GFR) values based on a reference method are lacking in the elderly. We measured GFR (mGFR) in healthy individuals 18 to 90 years of age to describe normal mGFR decline with age, by gender, and evaluated the performances of GFR-estimating equations in this population.

Methods: We measured GFR with renal clearance of ^{51}Cr-EDTA in 630 healthy men and women, aged 18-90 years. GAMLSS were used to provide reference values of GFR, and a piecewise linear regression model, to assess the relationship between GFR, age and gender. Bias, precision and accuracy of the CKD-EPI and FAS equations were evaluated.

Results: Participants (43% men) had a mean mGFR of 90.5±15.9 mL/min/1.73m^2. The 5th percentile stayed above 60 mL/min/1.73m^2 up to 80 years in men, but reached this threshold at age 63 in women, 25% of them getting below at age 76. In both genders, mGFR distribution physiologically declined as from 40 years (Figure), significantly faster in women than in men, 0.83±0.09 *vs* 0.67±0.07 mL/min/1.73 m^2 per year, p<0.001. Overall, median bias was significantly lower for the FAS than the CKD-EPI equation (-1.6 [95%CI: -2.9 ; -0.1] vs 3.4 [1.8 ; 4.9] mL/min/1.73 m^2, p < 0.001), whereas precision and P30 accuracy, 6.6 [4.9 ; 8.8] for FAS vs 8.5 [6.6 ; 10.9] for CKD-EPI, did not significantly differ between them. Performance metrics were similar in men and women, but differed across age classes. Above 65 years, CKD-EPI appeared to overestimate and FAS to substantially underestimate mGFR.

Conclusions: Ageing appears to be associated with faster GFR decline in women than in men, which may explain the paradoxical association of high CKD prevalence and low kidney failure incidence in women. Age- and gender-specific reference values should be considered for CKD diagnosis and drug dosing guidelines, particularly in the elderly.

Funding: Government Support - Non-U.S.



PO2334

Epidemiology of CKD Based on Age-Adapted GFR Thresholds

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Background: Age-adapted GFR criteria for definition of chronic kidney disease (CKD) have been proposed to account for normal age-related decline in kidney function. The aim of this study was to determine the prevalence and incidence of CKD stages 1-5 based on age-adapted GFR thresholds compared with current KDIGO GFR criteria.

Methods: In this retrospective study, we obtained all serum creatinine (SCr) values and urine protein measurements from every clinical laboratory in Iceland in 2008-2016. Clinical data, including ICD-10 diagnosis codes, were retrieved from nationwide electronic medical records. Estimated GFR was calculated from SCr using the CKD-EPI equation. CKD was defined as presence of kidney damage, either proteinuria or ICD-10 diagnosis codes indicative of kidney disease, or reduced eGFR for ≥3 months. Reduced eGFR was defined as <60 mL/min/1.73 m^2 according to the standard KDIGO criteria or based on the following age-adapted thresholds: <75 mL/min/1.73 m^2 for age <40 years, <60 mL/min/1.73 m^2 for 40-65 years and <45 mL/min/1.73 m^2 for age ≥65 years. Incidence of CKD was calculated in individuals without evidence of CKD at study entry. Prevalence and incidence were standardized to the EU-27 population.

Results: We obtained 2,120,147 SCr values for 218,437 individuals. The median age was 46 (range, 18-107) years; 47% were men. A total of 25,996 individuals met the KDIGO criteria for CKD compared with 17,593 when the age-adapted criteria were applied. The mean annual age-standardized prevalence per 100,000 overall and for men and women was 5940, 5130 and 6750, respectively, using the KDIGO criteria, and 3640, 3270 and 4010, respectively, applying the age-adapted GFR thresholds. The mean annual age-standardized incidence of CKD per 100,000 overall and for men and women was 671, 649 and 694, respectively, using the KDIGO criteria and 501, 480 and 522, respectively, applying the age-adapted thresholds.

Conclusions: This nationwide Icelandic study comprising SCr values and other markers of kidney damage for the majority of the Icelandic population demonstrates a markedly lower CKD prevalence and incidence with use of age-adapted GFR thresholds as compared with the standard KDIGO criteria.

Funding: Government Support - Non-U.S.

PO2335

Estimated Glomerular Filtration Rate Equations Based on Cystatin C Are Determined by Bioimpedance-Retrieved Fat Mass Index in Swedish Adults

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Background: The growing burden of obesity and its associations with chronic kidney disease (CKD) is becoming a hot topic for nephrologist. CystatinC, a marker of kidney function, tends to be increased in obesity. We hypothesize that bioimpedance acquired fat mass index acquired is associated with estimated glomerular filtration rate (eGFR) based on cystatinC.

Methods: 5061 subjects, born 1926-45, were selected from the population based Malmö Diet and Cancer cohort (MDC CC). They underwent body composition analysis (BIA-103 RJL system) and biochemistry during the year 1991-95. Men and women were divided into 3 groups according calculated fat mass index z-score (FMIz): low(<-1), middle(>-1,<1), high(>1). eGFR calculated using 4 equations: Chronic Kidney Disease Epidemiology Collaboration 2012 (CKD-EPI creatinine, CKD-EPI cystatinC), cystatinC eGFR based on Caucasian, Asian, pediatric, and adult cohorts (CAPA), the Lund-Malmö revised creatinine equation (LMrev).

Results: CystatinC correlated with fat weight (kg), FMI and FMIz in both sexes, meanwhile creatinine was not associated with muscle mass. Significant sex difference observed in high FMIz group revealing lower CAPA and lower CKD-EPI cystatin C values in women and no differences in creatinine based eGFR both in men and women (Fig.1). Women with high FMIz tended to have higher body mass index compared to men (p<0.001) and no age difference. Muscle mass remained almost unchanged in FMIz groups in both sexes.

Conclusions: The correlation between cystatinC and fat weight may be due to several reasons. Obesity induced CKD is one. Further studies are warranted to exclude that cystatinC originates from adipose tissue. The use of cystatinC eGFR equations should be used with caution in obese individuals, especially in women.

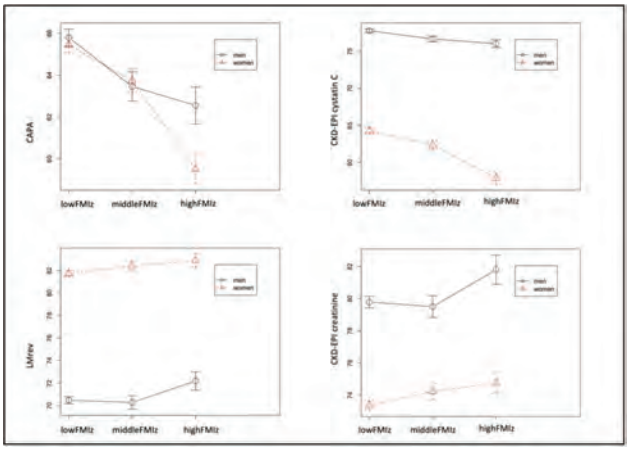

Fig.1 Kidney function calculated by different estimated glomerular filtration rate equations with regadrs to sex and fat mass index z-score group

PO2336

Estimated GFR Slope and Risk of Subsequent ESKD in Japanese Patients with CKD: The CKD-JAC Study

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Background: Slope of estimated glomerular filtration rate (eGFR), or rate of eGFR change, is a well-accepted measure of kidney disease progression. Previous studies have shown strong associations between eGFR slope and subsequent ESKD, but there is a dearth of evidence in Asian populations. We aimed to investigate the association between eGFR slope and subsequent ESKD in Japanese patients with CKD using data from the Chronic Kidney Disease Japan Cohort (CKD-JAC) Study.

Methods: We investigated the association of 2-year change in eGFR (slope) with ESKD over the long term. Slopes were estimated with the linear mixed models with an unstructured variance-covariance matrix, random intercept, and random slope for each individual to estimate slope (mixed model slope) or the least-squares linear regression (least-squares slope). We also conducted sensitivity analyses to investigate the association of 1- and 3-year changes in eGFR with ESKD.

Results: Of the total 2966 participants, we included 2381 individuals after excluding those who were censored within the 2-year baseline period (n = 509) and those with eGFR measured less than twice each year (n = 76). The mean slope was -1.70 ± 2.63 ml/min per 1.73 m^2 per year when estimated by the mixed-effects model and -1.69 ± 3.18 ml/min per 1.73 m^2 per year when estimated by least squares. The restricted cubic splines showed that the association between eGFR slope and ESKD was linear. The adjusted hazard ratio for ESKD associated with a lesser eGFR decline by 1 ml/min/1.73m^2 per year was 0.69 (95% CI: 0.66 to 0.73) for the mixed model slopes and 0.74 (95% CI: 0.71 to 0.77) for the least-squares slope. Sensitivity analysis showed that the association between eGFR slope and ESKD was pronounced when the slope was estimated over a longer baseline period.

Conclusions: Our study confirmed a robust and strong association between eGFR slope and subsequent ESKD in Japanese patients with CKD.

Funding: Commercial Support - Kyowa kirin Co.,Ltd.

PO2337

REVEAL-CKD: Prevalence of Undiagnosed Early CKD in France and Japan

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Background: Screening and monitoring of at-risk populations, such as those with type 2 diabetes (T2D), is necessary for early detection and management of chronic kidney disease (CKD). Global prevalence of undiagnosed early CKD and associated factors have not been recently studied. The objective of the REVEAL-CKD study is to assess the prevalence of undiagnosed stage 3 (S3) CKD.

Methods: REVEAL-CKD is a multi-national, multi-region secondary data study. Data for the French study cohort was extracted from THIN Cegedim (Cegedim Health Data, Boulogne-Billancourt, France) an electronic medical record (EMR) database from outpatient primary care practices. RWD database (Real World Data Co., Ltd., Kyoto, Japan) linking hospital systems' EMR with reimbursement claims, was used for the

Japanese cohort. The study population included patients aged ≥18 years between 2015-2020 with two consecutive estimated glomerular filtration rate (eGFR) readings ≥30 and <60 mL/min/1.73 m² recorded >90 and ≤730 days apart. Undiagnosed CKD was defined as the absence of an associated CKD diagnosis code any time before 12 months prior to the first eGFR measurement and up to 6 months after the second eGFR. Presence of recorded urine albumin-to-creatinine ratio (UACR) was also assessed.

Results: After applying the eligibility criteria the study cohorts included 23,160 patients in France and 90,902 in Japan, and the proportions of patients with undiagnosed S3 CKD were 95.4% (95% confidence interval [CI] 95.1, 95.7) and 92.1% (91.9, 92.3), respectively. Prevalence in both cohorts was consistent across subgroups stratified by age (45-65, and >65 y), sex, and presence of comorbidities (T2D, HTN, and heart failure) with the exception of T2D in Japan, where undiagnosed prevalence was 82% (95% CI 81.9, 83.0). Only 2.4% of patients in the cohort in France and 5.5% in Japan had a record of a UACR value.

Conclusions: The results presented here indicate that a high proportion of early CKD patients in France and Japan are undiagnosed, with a very low frequency of UACR testing. With the advent of promising novel therapies to mitigate disease progression in patients at risk and the potential to improve patient outcomes, a clear imperative exists to highlight the importance of early CKD detection, diagnosis, and intervention.

Funding: Commercial Support - AstraZeneca

PO2338

Trends in CKD Awareness and Related Clinical and Demographic Characteristics in Korea from 1998 to 2018

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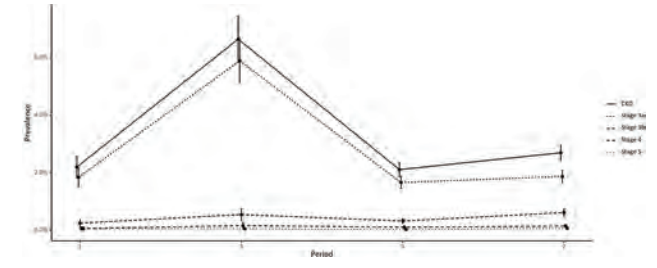
Background: Chronic kidney disease (CKD) is a common and growing problem in Korea. Although CKD awareness is the first step of CKD management, evidence indicates that the rate of CKD awareness is unsatisfactory worldwide. Thus, we investigated the trend of CKD awareness for CKD patients in Korea.

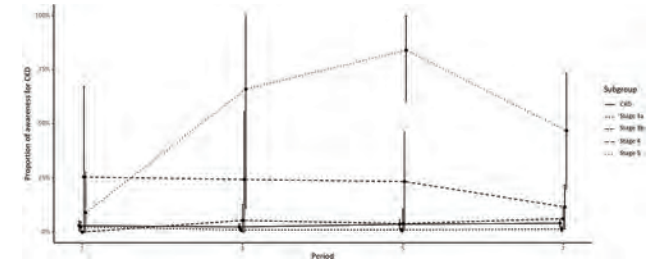
Methods: Through analyzing data of Korea National Health and Nutrition Examination Survey (KNHAES) in 1998 (phase I), 2005 (phase III), 2010-2012 (phase V), and 2016-2018 (phase VII), we evaluated the rate of CKD awareness according to CKD stage in each phase of KNHANES. CKD was defined when estimated glomerular filtration was below 59 ml/min/1.73m². Clinical and sociodemographic characteristics were compared between CKD awareness and unawareness groups. Multivariate regression analysis was used to calculate adjusted odds ratio (OR) and 95% confidence interval (CI) for CKD awareness (adjusted OR [95% CI]) in given socioeconomic and clinical factors.

Results: The overall rate of CKD awareness remained at low levels less than 4.1% across all phases of KNHANES. In particular, the rate of CKD awareness was remarkably low in stage 3 CKD. Compared to CKD unawareness group, CKD awareness group was of young age, higher income, higher education, more medical aid, higher prevalence of comorbidities, and more advanced CKD. In multivariate analysis, CKD awareness was significantly associated with younger age (0.95 [0.93-0.98]), medical aid (4.35 [1.95-9.73]) and renal function (0.90 [0.88-0.92]).

Conclusions: The rate of CKD awareness has been consistently low in Korea. This trend warrants the special endeavor to promote CKD awareness in Korea.



CKD prevalence in Korea from 1998 to 2018



CKD awareness in Korea from 1998 to 2018

PO2339

Usefulness of Machine-Learning-Predicted Probability as a New Risk Index for Prediction of Renal and Life Prognoses of CKD

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Background: Personalized and accurate prediction is useful for chronic kidney disease (CKD) therapy. Predialysis death is a competitive risk of dialysis in CKD patients and lowers the accuracies of the prediction of their renal and life prognoses. Thus, we determined whether machine-learning-predicted probability works as an index for the risks of predialysis death and dialysis in CKD patients and attempted its application.

Methods: We constructed a database of electronic-medical-record data of CKD patients in Japan, and developed risk prediction machine-learning models using random forest (RF), Gradient Boosting Decision Tree, and eXtreme Gradient Boosting for the prediction of dialysis and death over 1 year. The performances of the probabilities estimated using the models were compared by the bootstrap method with those of clinical indices in a prospective cohort study of CKD patients (n=67,957).

Results: Sixteen models were developed and showed statistically significantly higher C-statistics than clinical indices. Two RF models including 22 or 8 variables showed high C-statistics: 0.932 (95% CI 0.916, 0.948) and 0.93 (0.915, 0.945), respectively, which were higher than estimated glomerular filtration rate and urinary protein levels (p<0.0001). Cox proportional hazards models with the spline term showed the relationship between the high probabilities and the high outcome risks (p<0.0001). We also developed a Web-based risk prediction system using those two models.

Conclusions: This study showed that the machine-learning-based probability is useful as a new risk index for dialysis and death and applicable to clinical practice.

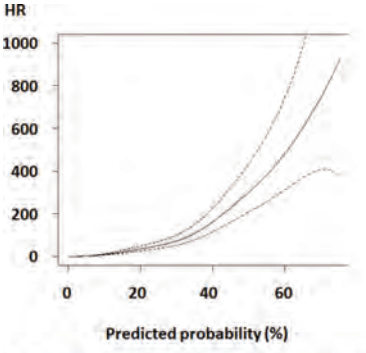

Fig. Relationships between the probabilities expected by the model of primary outcome and the outcome risks. p<0.0001.

PO2340

A Machine Learning Algorithm to Identify Patients with Possible Non-Dialysis-Dependent CKD

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Background: The DAKOTAH study is a retrospective study of patients with non-dialysis-dependent chronic kidney disease (NDD CKD) in France based on data from the Echantillon Généraliste des Bénéficiaires database. A stepwise machine learning approach was used to identify patients with possible NDD CKD who could not be captured using the NDD CKD case definition (**Figure**).

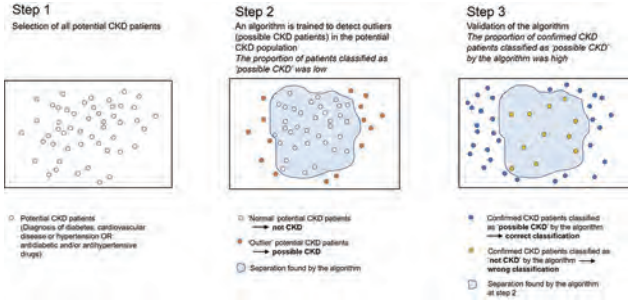
Methods: First, the 'potential CKD' population was designated as patients with a diagnosis of diabetes, cardiovascular disease or hypertension, or with ≥3 prescriptions for antidiabetic and/or antihypertensive drugs, during 2012–2017. Second, an unsupervised algorithm was trained to identify patients very likely to have CKD ('possible CKD') in the potential CKD population. Similarity between patients was based on CKD-related variables: sex; number and duration of hospitalizations for renal failure; number of GP

visits; medications; and biological exams. A distance metric between patients was defined based on these variables, and patients having similar characteristics were positioned close to one another. The algorithm learned to construct a spherical boundary around the non-CKD population, to create a decision rule for possible CKD versus non-CKD, with outliers considered possible CKD.

Results: The algorithm was validated by application to both the potential CKD population and a confirmed CKD patient pool. From the potential and confirmed CKD populations, 21% and 65% of patients were classified as possible CKD, respectively. Similarities were observed between the two groups regarding hospitalizations and selected biological exams.

Conclusions: This machine learning-derived decision rule could be a tool to identify undiagnosed patients with NDD CKD.

Funding: Commercial Support - Astellas Pharma Inc.



PO2341

Developing an Electronic Health Record (EHR)-Based Model for Delineating Advanced CKD Cohort in Veterans Affairs (VA) System

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Background: Late diagnosis of chronic kidney disease(CKD) and non-referral to nephrology are important limiting concerns for pre-end stage kidney disease(ESKD) nephrology care, including dialysis modality education. Querying existing electronic database with longitudinal patient-level data can improve recognition of advanced, stage 4/5 CKD and facilitate evidence-based pre-ESKD care. Using a mixed approach of electronic query followed by manual chart review, we report the development of an Electronic Health Records (EHR)-based model that allows identification and quantification of advanced CKD burden in a regional Veterans Healthcare System(VHS).

Methods: We identified all Veteran enrollees at a large regional VHS using VA Informatics & Computing Infrastructure data set. Among these, we identified all Veterans with an eGFR below 30ml/min or an existing ICD-10 diagnostic code for stage 4/5 CKD within last 12 months. We applied diagnostic and procedure codes for dialysis, ESKD, and acute kidney injury(AKI) in an iterative approach to improve the accuracy of identifying non-dialysis advanced CKD cohort.

Results: Of 148,164 active enrollees within VHS, our initial model of using a single eGFR <30 ml/min identified 3,813(2.57%) Veteran enrollees with advanced CKD. Manual review of a select cohort(n=787) showed 63.3% error rate, with high rates of ESKD and AKI being major confounders. Successive iterations involved exclusions of ESKD and AKI codes and incorporation of a second latest eGFR >90 days before latest eGFR. The final EHR-based advanced CKD model included 1,329(0.89%) Veteran with the residual error of 14.4% on manual chart review without the possibility of further automated exclusions. Of these, 872 were found to have definite advanced CKD and 457 were classified as probable advanced CKD based on whether both or only one of the latest two eGFRs more than 90 days apart were below 30 ml/min with CKD.

Conclusions: An EHR-based model to identify advanced CKD can be successfully developed for a regional VHS with over 85% accuracy. Further testing is needed to determine its wider applicability across additional VHA sites, and if validated, this model can be applied across the VHA electronic data to identify the burden of advanced CKD for needs assessment and clinical care among Veterans.

Funding: Veterans Affairs Support

PO2342

Developing a Prediction Model for Incidence of Newly Detected CKD Among US Veterans, 2009-2018

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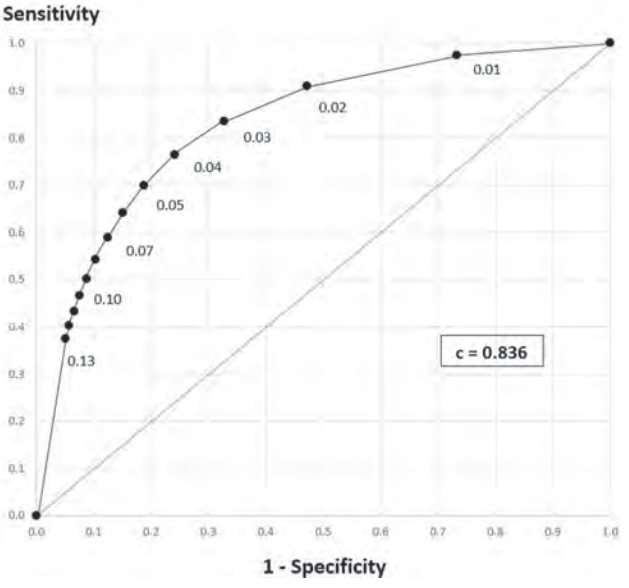
Background: Both screening and awareness of CKD remain low in the US. We sought to develop a tool to aid physicians and health systems in identifying patients most likely to develop CKD, using a large national sample of patients in the Veterans Health Administration (VHA).

Methods: Using 29,524,195 observations from Veterans, aged 18+ with outpatient s. creatinine data (2006-2018), we modeled the probability of newly detected CKD using discreet survival methods. Veterans were screened for 2-3 years to ensure no pre-existing CKD. Newly detected CKD was defined as a diagnosis or by laboratory measurement (eGFR <60 ml/min/1.73m^2 or UACR 30+ mg/g). Predictors included demographics, comorbidities, nephrotoxic medications, and laboratory values updated each year. Model fit assessed by the c-statistic.

Results: The cohort had a mean age of 59 years with 89% males and 15% Black race. The average eGFR was 87 ml/min/1.73m^2 and median UACR was 8 mg/g, with an average of 3.9 years follow-up. The largest predictors of incident CKD were diabetes, kidney stones, urinary tract infections, sickle cell anemia, and an eGFR between 60-69 ml/min/1.73m^2. Concordance was high (c-statistic=0.84, Fig: ROC curve). Using a threshold of 3% risk for screening would require testing ~1/3 of Veterans (~1 million per year), yielding an 83% true positive and a 17% false negative rate.

Conclusions: We are able to accurately predict the probability of incident CKD in the VHA. This predictive model has the potential for improving targeted screening efforts for CKD, facilitating its earlier detection, raising awareness, and reducing disparities. If externally validated, the impact of these findings would be generalizable to populations/ health systems beyond the VHA.

Funding: Veterans Affairs Support



PO2343

A Population Health Survey-Based Prediction Equation for Incident CKD: The CKD Population Risk Tool CKDPort/PREDICT-CKD LIFESTYLE

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Background: Chronic kidney disease awareness among the general public is less than 10%. Patients' health behaviours are known to be associated with CKD development and disease progression. Prediction tools that engage the general public with their self-reported health information could increase awareness, identify modifiable lifestyle risk factors, empower patients, and prevent disease. The study objective was to develop and validate a population health survey-based prediction equation to determine the risk of incident CKD in the general public.

Methods: Participants who completed the Canadian Community Health Survey (CCHS) were linked to laboratory and hospital admission data between 2000 and 2015 in Ontario, Canada. The primary outcome was incident CKD (eGFR < 60 ml/min/1.73m^2) with up to 8 years of follow-up. Models accounted for the competing risk of all-cause mortality. The CCHS is a random, comprehensive, prospective, general population survey that captures information on demographics, co-morbid illnesses, lifestyle and behaviours, diet, body mass index and mood. External validation was performed using data from the UK Biobank.

Results: From 22,200 eligible adults, 1,981 (8.9%) developed incident CKD during a mean follow-up time of 8 years. Domains included in the final reduced model were baseline eGFR, smoking, alcohol, physical activity, education, mood, fruit and vegetable intake, diabetes, hypertension, heart and lung disease, urinary incontinence, cancer, and BMI. The model demonstrated excellent discrimination in individuals with and without a baseline eGFR measure (5-year c-statistic with baseline eGFR: 0.84 95%CI 0.82-0.85, without 0.81 95%CI 0.80-0.82), was well calibrated (Brier score at 5-years with baseline eGFR: 0.07 95%CI 0.007-0.08, without 0.08 95%CI 0.07-0.08), and was consistent in a sensitivity analysis using 2 measures of eGFR > 90 days apart to define the outcome. The model was consistent with external validation.

Conclusions: Lifestyle and health behaviour information from population-based health surveys can predict incident CKD in the population with excellent discrimination and can be used to improve public engagement in CKD awareness.

PO2344

Predicting ESKD Risk and Time to RRT Initiation Based on Past Slope and Current Value of eGFR: The CKD-JAC Study

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Background: Past slope and current estimated glomerular filtration rate (eGFR) are used to predict future risk of end-stage kidney disease (ESKD) and time to renal replacement therapy (RRT) initiation in clinical practice, but there is limited quantitative evidence supporting this practice. To address this, we analyzed data from the Chronic Kidney Disease Japan Cohort (CKD-JAC) Study.

Methods: We investigated the association of 2-year eGFR slope, estimated using linear mixed models, with subsequent risk of ESKD using Cox regression models, adjusting for eGFR and other potential confounders collected 2 years after cohort entry. We calculated the net reclassification improvement (NRI) to assess whether adding past slope to age, sex, eGFR, and urine albumin-to-creatinine ratio (UACR) improves ESKD risk prediction. We predicted time to RRT initiation based on the past slope and current eGFR, assuming eGFR of 6 mL/min/1.73m^2 to be the timing of RRT initiation, and compared it with actual time to RRT initiation.

Results: We included 2381 participants who had survived free of ESKD for 2 years and with eGFR measurements at least twice each year. The mean 2-year eGFR slope was -1.70 ± 2.63 mL/min per 1.73 m^2 per year. During a median follow-up of 4.7 years after the 2-year slope evaluation period, 175 participants died and 810 reached ESKD requiring RRT. In adjusted analysis, lesser slope of eGFR decline was associated with lower risk of ESKD (hazard ratio per 1 mL/min per 1.73 m^2 per year, 0.89; 95% CI, 0.87 to 0.92). Adding past eGFR slope to age, sex, eGFR, and UACR substantially improved classification accuracy in 2-year risk prediction of ESKD, with an NRI of 0.343 (95% CI, 0.036 to 0.662). Among 560 individuals who were predicted to initiate RRT during the study period and actually reached ESKD, the median predicted time to RRT was 30.6 months (IQR, 13.0 to 55.7), the median actual time to RRT was 25.5 months (IQR, 12.3 to 47.0), and the median of these differences was -1.5 months (IQR, -14.3 to 7.3). The prediction became more accurate as RRT initiation was predicted to occur in the closer future.

Conclusions: Our results indicate that past eGFR slope adds information to ESKD risk assessment beyond current eGFR and that combination of these informs prediction of time to RRT initiation.

Funding: Commercial Support - Kyowa Kirin Co.,Ltd.

PO2345

Need and Preference Assessments for Renal Care and Comprehensive Pre-ESKD Education Services for Advanced CKD Veterans

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Background: Current guidelines suggest Specialty Renal Care (SRC) and comprehensive pre-end-stage kidney disease (ESKD) education (CPE) Services for all patients with advanced, stage 4/5 chronic kidney disease (CKD). Despite this, half of incident ESKD patients receive none or <6months pre-ESKD renal care. Estimating outstanding needs and understanding Veterans preferences for receiving such care can improve resource allocations and quality of care for Veterans Health Administration(VHA). We conducted a community-based evaluation of advanced CKD Veterans to assess their current state of and outstanding needs and preferences for SRC and CPE at North Florida/South Georgia(NF/SG) VHA system(VHS).

Methods: Through an iterative approach of electronic health records(EHR) query followed by manual review of randomly selected EHRs, we created a model for isolating advanced CKD cohort at NF/SG VHS. We then sorted the cohort in a random order, and mail-invited Veterans with up to three attempted calls for those who do not call back to actively opt-out of participation. Surveys were conducted for those agreeable for participation.

Results: Of the 148,164 active enrollees, we identified 1329 (0.9%) Veterans with advanced CKD. Of the 226 Veterans randomly selected mail-invites, 166 made final contact; 94 completed, 50 asked for more time, and 22 refused to participate in the surveys. Awareness of CKD (91%) and prevalence of renal care (86%) were high among respondents albeit, 40(50%) received renal care from non-VA providers. Aggregate outstanding need for VA-preferred SRC and CPE were 14(15%) and 69(73%) respectively. Among these, the preferences for receiving SRC were 6(43%) & 8(57%) and receiving CPE were 21(30%) & 34(50%) through in-person and telemedicine-based care respectively. There were significant differences in needs and preferences across the socio-demographics and rural-urban spectrum.

Conclusions: Despite high awareness of CKD diagnosis and prevalence of SRC, there is significant outstanding need for targeted CPE services in advanced CKD Veterans. Further validation of this model at additional VHSs and its application across the system can allow projection of outstanding needs for SRC and CPE across the VHA and guide appropriate allocation of resources to improve Veteran outcomes.

Funding: Veterans Affairs Support

PO2346

Artificial Intelligence-Based Prediction Model for Screening Veteran Patients at Risk of Developing CKD

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Background: Developing effective screening tool for Chronic kidney disease (CKD) helps in reducing morbidity, mortality as well as cost and burden to the health system. Here we present preliminary result on feasibility and performance of employing Convolutional Neural Network (CNN) prediction model in detecting patients who are at-risk of CKD based on longitudinal data from Electronic Health Records (EHR).

Methods: A synthetic dataset containing a total of 100,000 synthetic patient records, derived from cross-sectional cohort of Veteran from the general population, was used to train and validate the prediction model. The dataset was generated by using Synthea™, a patient generator tool, and contains standard data elements that are commonly used in major Electronic Health Record systems. A total of 12,503 patients with CKD and 48,212 patients without CKD matched by propensity score along with 290 other features including anthropometrics, medication, comorbidities, and laboratory data were used to train and validate the prediction model.

Results: The CNN algorithm has been designed, implemented and tested using the synthetic dataset, achieving precision of 0.918, recall of 0.739, specificity of 0.983, accuracy of 0.932, and AUROC of 0.937 as depicted in Figure 1. Additionally, based on the dataset, age, diabetes, elevated BMI and medication taken, specifically 24 HR Metformin Hydrochloride, represent the topmost important features to predict the onset of CKD.

Conclusions: Using CNN and synthetic veteran patient dataset, we have demonstrated a viable prediction model for CKD detection in healthy patients at-risk of CKD using longitudinal data from EHR system. The prediction model can be easily deployed in a CKD screening program in healthcare institutions with existing EHR systems.

Funding: Veterans Affairs Support

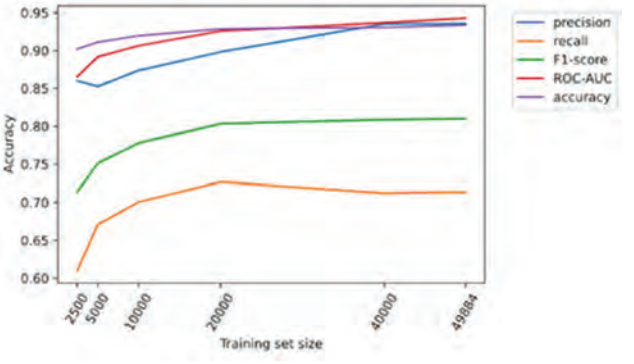

Figure 1: Onset of CKD Prediction Metrics

PO2347

Identifying Hotspots of CKD in the United States with Data from a Large National Clinical Laboratory Network

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Background: CKD is typically detected through routine laboratory testing. We sought to assess the feasibility of analyzing data from one of the largest clinical laboratory networks in the US to map CKD hotspots across the nation.

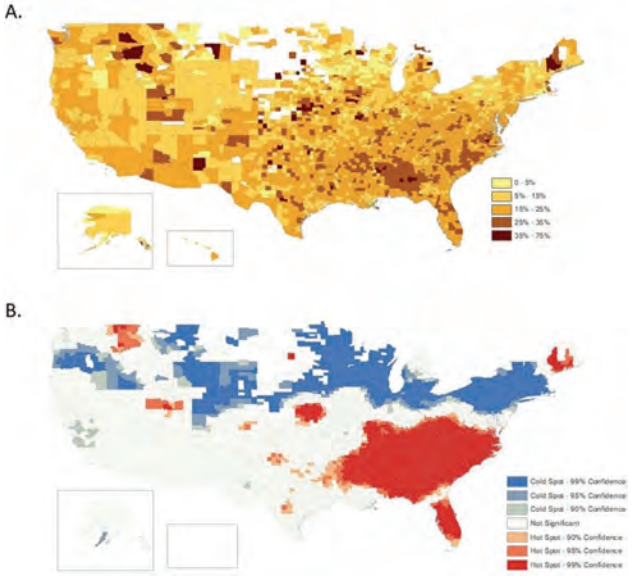
Methods: Laboratory results for serum creatinine were analyzed from a nationally standardized laboratory platform with the Laboratory Corporation of America (Labcorp) across a 6-month period (July to December 2019, n=21,884,579). We assessed the percent of results with eGFR <60 ml/min/1.73m^2 (CKD stages 3-5) at US county-level (n=2,972 counties, <11 results supressed). Due to lack of race information, the CKD-Epi equation without the race coefficient was employed for the entire population. Hotspot analyses were conducted using the Getis-Ord Gi* statistic.

Results: The total population was 44% male with mean age of 56 years. eGFR results < 60 ml/min/1.73m^2 totalled 4,165,540 (19%) and county-level distribution ranged from 0% to 75% (Fig. A) with an overall mean age of 72 and 44% male. Results of the hotspot analysis (Fig. B) shows the percent of decreased kidney function varies markedly across

the US, with clear hot spots in the south and southeast, far northeast, Pacific Northwest, Missouri, Colorado, and Utah. The upper midwest and most of the northeast appeared as cold spots, with the southwest being neither a hot nor cold spot.

Conclusions: We demonstrate the feasibility of leveraging a large national laboratory network database for mapping the distribution of county prevalence of CKD and identification of CKD hotspots. Ongoing work is focusing on understanding factors underlying these hotspots and will help guide population health improvement, raise awareness, guide health policy and direct public health action and quality improvement efforts related to kidney disease.

Funding: Commercial Support - Laboratory Corporation of America Holdings



PO2348

Healthy People 2020 Final Review of National CKD Objectives

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Background: Chronic Kidney Disease **(**CKD) is a significant public health problem in the United States (US) and a major source of disability and poor quality of life for those afflicted. An estimated 14.9% of adults ages 20 or older had physiological evidence of CKD determined from data collected through the 2015-18 National Health and Nutrition Examination Survey (NHANES). In 2018, more than 130,000 people in the US began treatment for end-stage kidney disease (ESKD), the final stage of CKD. Kidney diseases are one of the leading causes of death in the US, and CKD exacts a high economic burden. Overall Medicare costs for people with CKD were over $81.8 billion in 2018, or $23,700 per person. Total Medicare spending (excluding prescription drugs) for patients with ESKD reached $36.6 billion in 2018, or $80,000 per person, accounting for about 7% of the Medicare paid claims costs.

Methods: Reflecting the importance of CKD, 24 CKD objectives were included in Healthy People 2020 (HP2020) as national health goals. These objectives focused on improving cardiovascular care in patients with CKD; increasing the proportion of patients with CKD and diabetes who received recommended evaluation and treatment; improving follow-up care in people with acute kidney injury, reducing the death rate and percentage of the US population with CKD, and increasing CKD awareness in persons with impaired kidney function. All CKD objectives in HP2020 were measurable, having at least one data point from national data systems including the NHANES, National Death Index, and the US Renal Data System.

Results: As of the HP2020 Final Review, 15 objectives had met their target (n=11) or showed improvement (n=4). Four objectives, including CKD prevalence and awareness, showed little or no detectable change, and three objectives on receiving kidney transplant and on the number of deaths for persons with a functioning kidney transplant moved away from the target. The remaining two objectives were informational (i.e., no targets set) and were not evaluated. Disparities persisted by sex, race/ethnicity, and socioeconomic status.

Conclusions: Several of these measures will continue to be tracked over the next decade as CKD objectives in HP2030. The HP website includes HP2020 and HP2030 data.

PO2349

A Systematic Literature Review of Treatment Patterns, Safety Profiles, and Long-Term Disease Progression in Patients with CKD and Type 2 Diabetes Mellitus

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Background: CKD affects ~40% of patients with diabetes. Current guidelines recommend optimization of blood pressure and glycemic control in patients with T2D to reduce the risk of CKD progression. Despite this, patients with T2D are still advancing to ESRD. Real-world treatment patterns, safety profiles of current treatments, and residual risk for long-term disease progression in patients with CKD and T2D were explored.

Methods: A systematic literature review was conducted of real-world observational studies in the US in patients with CKD and T2D. Articles published in the past 10 years were identified from Embase and MEDLINE and were evaluated by 2 independent reviewers.

Results: A total of 17 studies were included in the review. In the 16 studies that examined treatment patterns among patients with CKD and T2D, all drug classes of interest (steroidal mineralocorticoid receptor antagonist [MRA], ACEI, ARB, GLP-1RA, and SGLT-2i) were reported. The proportions of patients treated with ACEIs (34%–70%) or ARBs (12%–66%) varied widely, with approximately 45% to 95% of patients prescribed either an ACEI or an ARB. Small proportions of patients (<10%) were treated with MRAs, GLP-1RAs, and SGLT-2is; though steroidal MRA does not have an indication in CKD in T2D. In the 4 studies that examined renal function decline while on a treatment of interest, 1-year progression rates ranged from 3.3% to 29.9%. Three studies reported rates of on-treatment ESRD progression, which ranged from 9.1% to 10%. In the 4 studies reporting AEs in patients treated with MRAs, ACEIs, and/or ARBs, notable clinical events included stroke (12.6% among MRA non-users to 31.3% among spironolactone users) and hyperkalemia (9.1% among MRA non-users to 29.9% among spironolactone users).

Conclusions: The identified studies suggest that patients with CKD and T2D may not be optimized on current treatment options to slow renal function decline and reduce the risk of CV events in these patients. Despite current treatment options, a residual risk of CKD progression and CV morbidity remains. New therapies are needed to slow long-term disease progression.

Funding: Commercial Support - Bayer US LLC

PO2350

International Variation in the Incidence of Kidney Failure in the CKD Outcomes and Practice Patterns Study (CKDopps)

Natalia Alencar de Pinho,[1] Roberto Pecoits-Filho,[2,3] Brian Bieber,[2] Daniel G. Muenz,[2] Antonio A. Lopes,[4] Helmut Reichel,[5] Christian Combe,[6] Bruce M. Robinson,[2] Benedicte Stengel.[1] *[1]Paris-Saclay University, UVSQ, Inserm, Center for Research in Epidemiology and Population Health, Villejuif, France; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [4]Universidade Federal da Bahia, Salvador, Brazil; [5]Nephrological center, Villingen-Schwenningen, Germany; [6]Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France.*

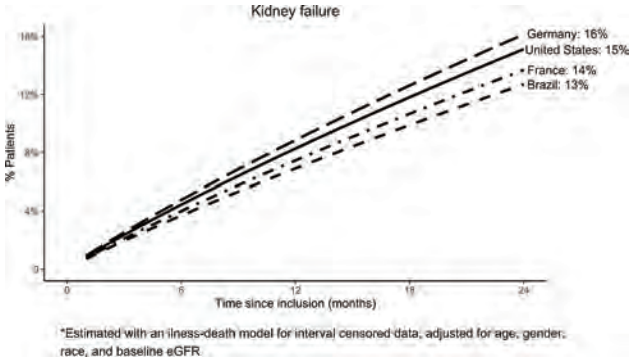
Background: Data from kidney replacement therapy (KRT) registries suggest large international variation in the incidence of kidney failure (KF). However, these data strongly depend on treatment availability and practices of KRT initiation. Measuring the incidence of sustained low eGFR, i.e. <15 mL/min/1.73 m^2, would enable to explore differences in progression to KF across countries after adjusting for individual characteristics.

Methods: We analyzed data from patients with CKD stages G3-G4, under nephrology care in representative samples of clinics in Brazil (n= 747), France (n= 2786), Germany (n= 2539), and the United States (n=1309), participating in the CKDopps. We used Weibull PH models to compare the risk of KRT initiation across countries, and Illness-death models for interval censored data, to compare the risk of sustained low eGFR and to estimate probabilities of KF (composite of KRT initiation and sustained low eGFR).

Results: Median age (years) ranged from 67 in Brazil to 75 in Germany, mean baseline eGFR (ml/min/1.73m^2) from 27 in Germany to 33 in France; male sex from 52% in the United States to 66% in France. After a median follow-up of 4.0 (2.6-5.0) years, 1648 patients met a sustained low eGFR, and 1343 initiated KRT. Compared with the United States, the adjusted hazard ratios indicated 44%- lower risk of KRT initiation in Brazil (95%CI 0.39 to 0.79), similar risk in France (1.05, 95%CI 0.83 to 1.33), and 41%- higher risk in Germany (95% CI 1.12 to 1.77). The same pattern was observed for sustained low eGFR, but differences were narrowed. Two-year cumulative probability of KF ranged from 13% in Brazil to 16% in Germany (Figure).

Conclusions: The incidence of KF varies across CKDopps countries, but to a much lesser extent than the incidence of KRT initiation. This finding highlights the relevance of such approach to disentangle the effects on CKD progression from those on access to care.

Funding: Commercial Support - Akebia Therapeutics, Inc.; Amgen Inc (since 1996, founding sponsor); AstraZeneca Pharmaceuticals LP; Bard Peripheral Vascular, Inc.; Baxter Healthcare Corp; Bayer Yakuhin, Ltd; Chugai Pharmaceutical Co., LTD; Dialyze Direct, LLC; Fresenius Medical Care Asia-Pacific Ltd; GlaxoSmithKline LLC; Japanese Society for Peritoneal Dialysis; JMS Co., Ltd.; Kidney Research UK Kidney Foundation Japan; Kissei Pharmaceutical Co., Ltd; Kyowa Kirin Co., Ltd. (since 1999 for Japan DOPPS); Merck Sharp & Dohme Corp; Nikkiso Co., Ltd.; ONO Pharmaceutical Co., Ltd; Sanofi-Aventis Deutschland GmbH; Terumo Corporation ;Torii Pharmaceutical Co., Ltd; Vifor-Fresenius Medical Care Renal Pharma Ltd, Government Support - Non-U.S.



PO2351

Development and Validation of an Algorithm to Predict Risk of 90-Day Hospitalization for Patients with CKD

Steph Karpinski,[1] Scott Sibbel,[1] Kathryn S. Gray,[1] Adam G. Walker,[1] Jiacong Luo,[1] Carey Colson,[1] Justin M. Kindy,[2,3] Tiffany L. Bray,[2,3] Steven M. Brunelli.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO; [3]DaVita Integrated Kidney Care, Denver, CA.*

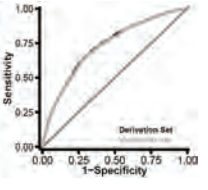
Background: Patients with chronic kidney disease (CKD) are at higher risk of being admitted to the hospital than the general population. Hospitalizations in CKD patients are often associated with higher medical costs, increased morbidity, and increased risk of transition to end-stage kidney disease (ESKD). Nationally, there seems to be an increasing focus on the management of CKD upstream of ESKD. Identification of CKD patients at greatest risk of hospitalization may hold promise to improve clinical outcomes and judicious allocation of health care resources.

Methods: This model was developed using Medicare Part A and Part B claims from calendar years 2017-2019. Data from 50,000 unique patients diagnosed with CKD stages 3-5, no evidence of ESKD, or claims for dialysis were split into derivation (n = 40,000) and validation (n = 10,000) sets. The predicted outcome was all-cause hospital admissions, which occurred in 10.4% of patients 90 days after scoring. Overall performance of candidate models was assessed using area under the curve (AUC) of the receiver operating curve in addition to positive predictive value (PPV) and sensitivity across a variety of thresholds.

Results: The best model that we tested was a gradient boosting machine algorithm based on 399 input terms, which represented 147 unique clinical constructs. The model demonstrated good ability to discriminate (AUC = 0.73), which was stable when tested in a validation set (AUC = 0.73). The PPV in the validation set was 30.6%, 24.0%, and 21.6% at the 10%, 20%, and 30% thresholds, respectively. The sensitivity in the validation set was 28.8%, 45.3%, and 60.9% at the 10%, 20%, and 30% thresholds, respectively.

Conclusions: We developed an algorithm that uses only information derived from medical claims to identify CKD 3-5 patients at highest risk of being hospitalized in the near-term. This algorithm could be used as a decision support tool for clinical programs focusing on the management of CKD patient populations.

	Derivation Set	Validation Set
Patients	40,000	10,000
Hospitalized	10.4%	10.6%
AUC	0.73	0.73
10% Threshold (PPV/Sensitivity)	29.6%/28.5%	30.6%/28.8%
20% Threshold (PPV/Sensitivity)	24.0%/46.6%	24.0%/45.3%
30% Threshold (PPV/Sensitivity)	21.2%/61.3%	21.6%/60.9%



PO2352

CKD and Risk of Incident Hospitalization with Clostridioides difficile Infection: Findings from the Atherosclerosis Risk in Communities Study

Junichi Ishigami,[1] Keiichi Sumida,[2] Morgan Grams,[3] Alex R. Chang,[4] Pamela L. Lutsey,[5] Andrew S. Levey,[6] Josef Coresh,[1] David W. Dowdy,[1] Kunihiro Matsushita.[1] *[1]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [2]The University of Tennessee Health Science Center College of Medicine, Memphis, TN; [3]Johns Hopkins Medicine, Baltimore, MD; [4]Geisinger Health, Danville, PA; [5]University of Minnesota Twin Cities, Minneapolis, MN; [6]Tufts Medical Center, Boston, MA.*

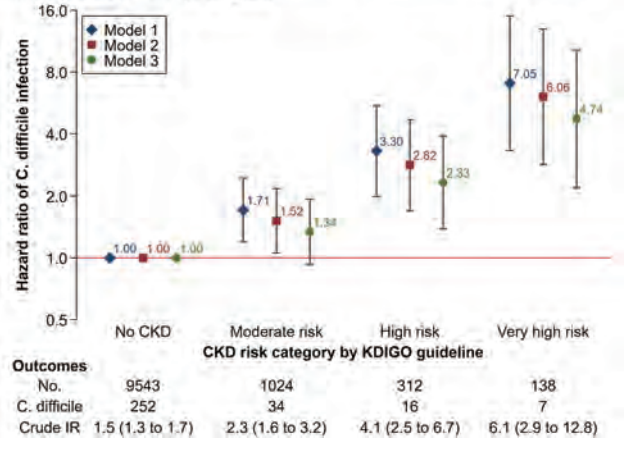
Background: *Clostridioides difficile* (*C. difficile*) infection is a major public health priority in the US. Individuals with CKD are at high risk of infection and hospitalization in general; however, the association of CKD with the risk of *C. difficile* disease has not been systematically evaluated.

Methods: We evaluated data from 11,017 participants of the ARIC Study (mean age, 63 years; 56% female; 22% Black) to explore the association of CKD with the risk of incident hospitalization with *C. difficile* infection. We categorized the study population into four risk categories defined by eGFR and ACR: CKD was defined as eGFR <60 ml/min/1.73m^2 or ACR ≥30 mg/g, and no CKD was defined as low risk. CKD was subdivided into moderate, high, and very high risk. Adjusted HRs were estimated using Cox regression models.

Results: During a median follow-up of 20.1 years, 309 participants had incident hospitalization with *C. difficile* infection. In multivariable Cox regression analysis, there was a graded association of CKD risk category with the risk of hospitalization with *C. difficile* infection, with adjusted HRs of 4.74 [2.29 to 10.23] for CKD with very high risk, 2.33 [1.39 to 3.90] for CKD with high risk, and 1.34 [0.93 to 1.93] for CKD with moderate risk compared to no CKD (P-for-linear-trend, <0.001) (Figure 1). These findings were consistent in subgroup analyses and sensitivity analyses, including analyses that accounted for frequency of prior hospitalization and for the risk of hospitalization itself.

Conclusions: In this community-based cohort, CKD was associated with the risk of hospitalization with *C. difficile* infection. Individuals with CKD should be a key target population for public health initiatives and clinical approaches to prevent *C. difficile* infection.

Figure 1: Hazard ratios of hospitalization with *C. difficile* infection according to the severity of CKD by KDIGO guideline. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and race. Model 3 was further adjusted for body mass index, education level, ever smoking, lifetime alcohol use, hypertension, diabetes, total cholesterol, high-density lipoprotein cholesterol and prevalent cardiovascular disease. Crude incidence rates (IRs) and their 95% confidence intervals (CIs) are per 1,000 person-years.



Outcomes				
No.	9543	1024	312	138
C. difficile	252	34	16	7
Crude IR	1.5 (1.3 to 1.7)	2.3 (1.6 to 3.2)	4.1 (2.5 to 6.7)	6.1 (2.9 to 12.8)

PO2353

Lower Serum Bicarbonate Is a Risk Factor for Hospitalization for Infection Among Patients with CKD

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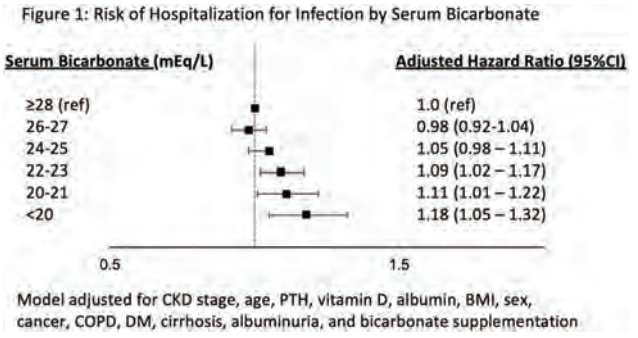
Background: Hospitalization due to infection is common in patients with CKD; both lower eGFR and albuminuria are risk factors. Metabolic acidosis impairs neutrophil function in ESRD patients via delayed apoptosis, enhanced phagocytosis, and increased oxidative burst reactions, however serum bicarbonate has not been investigated as a risk factor for infection in patients with non-dialysis CKD.

Methods: We utilized a central data warehouse from Mass General Brigham for patients with ≥1 diagnostic code for CKD between 2010-2020. CKD was defined as 2 outpatient eGFR values <60 mL/min/1.73m^2 at least 3 months apart. Patients were excluded if they had a kidney transplant, a humoral immunodeficiency, or ESRD on dialysis prior to index date. The primary outcome was hospitalization for infection (defined by primary diagnosis of urinary tract infection/ pyelonephritis, pneumonia, cellulitis, or bacteremia). We examined outpatient baseline serum bicarbonate and risk of initial hospitalization for infection using Cox proportional hazards models adjusting for potential confounders. Patients were censored at time of first infection, last lab value, or death.

Results: We included 36,647 patients with CKD, and 8,521 were hospitalized for infection. When adjusting for covariates, the risk for infection increased as serum bicarbonate decreased (Figure 1). A serum bicarbonate of <20 mEq/L compared to ≥28 mEq/L was independently associated with an 18% (95% CI 1.05-1.32) higher risk of hospitalization. In the adjusted model, CKD stage 5 was associated with a 69% (95% CI 1.47-1.94) increased risk of infection compared to CKD stage 3a. Albuminuria ≥300 mg/g was associated with a 28% (95% CI 1.14-1.44) increased risk of composite infection compared to <10 mg/g.

Conclusions: Our findings suggest that clinicians should consider lower serum bicarbonate a risk factor for infection in patients with CKD. Future studies should explore whether bicarbonate supplementation can reduce risk of infection.

Funding: NIDDK Support



PO2354

Albuminuria Testing in Hypertension and Diabetes

Jung-Im Shin, Alex R. Chang, Yingying Sang, Ron T. Gansevoort. Chronic Kidney Disease Prognosis Consortium *CKD Prognosis Consortium, Baltimore, MD.*

Background: Albuminuria is an under-recognized component of chronic kidney disease (CKD) definition, staging, and prognosis. Despite significant advances in therapies for patients with albuminuria, guidelines, particularly for hypertension, conflict on recommendations for urine albumin-to-creatinine ratio (ACR) measurement.

Methods: We separately analyzed 1,305,841 adults with diabetes in 25 cohorts and 2,111,587 non-diabetic adults with hypertension in 21 cohorts from the CKD Prognosis Consortium. We estimated ACR testing rates during a 2-year window, and developed and utilized risk prediction models for prevalent albuminuria (ACR ≥30 mg/g) to determine if high-risk patients for albuminuria are more likely to be tested and to estimate the burden of undetected albuminuria.

Results: Overall, the ACR testing rate was 35.3% in diabetes and 4.1% in hypertension. Among patients with diabetes, testing rates varied greatly across the different health systems and were largely unrelated to the predicted risk of prevalent albuminuria (**Figure A**). Among patients with hypertension, testing rates were low and also unrelated to the predicted risk of prevalent albuminuria (**Figure B**). The estimated ratio (cohort range) of undetected (due to lack of testing) to detected prevalent albuminuria was 1.8 (0.2-7.6) in diabetes and 19.5 (0.8-78.3) in hypertension.

Conclusions: Real-world ACR testing is low, particularly among non-diabetic patients with hypertension, and testing is unrelated to predicted risk. There are large swaths of the population with diabetes or hypertension with undiagnosed CKD, suggesting that regular albuminuria screening should be emphasized for early detection of CKD and appropriate initiation of treatment with cardiovascular and kidney benefits.

Funding: NIDDK Support, Private Foundation Support

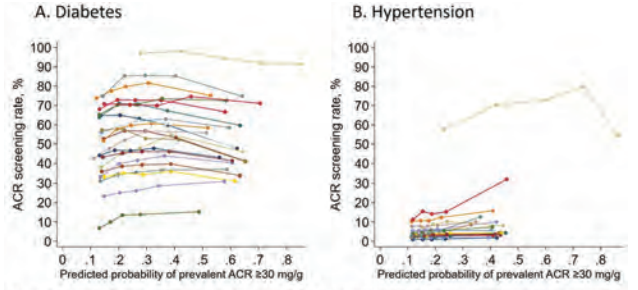


Figure. ACR screening rate (≥1 during 2-year period) in (A) diabetes (N=605,742 in 23 cohorts*) and (B) hypertension (N=1,057,825 in 19 cohorts*) by the quintiles of cohort-specific predicted probability of prevalent ACR ≥30 mg/g.
*Cohorts with in-house data only from three countries.

PO2355

Increasing Proteinuria Screening to Reduce CKD Progression in High-Risk Patients

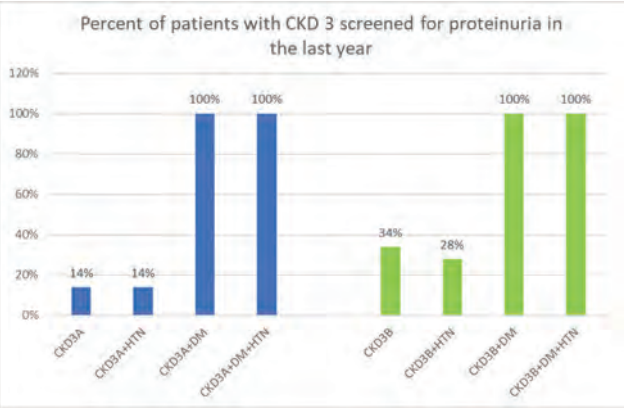
Jaclyn Khil, Nika Carrillo, Nirmala D. Ramalingam, H. Nicole Tran, Sijie Zheng. *Kaiser Permanente, Oakland, CA.*

Background: Chronic Kidney Disease (CKD) affects 15% of the US population and is underrecognized by patients and clinicians. Screening for proteinuria is essential in prompting primary care doctors (PCPs) to initiate treatments proven to decrease progression to end stage renal disease, cardiovascular events and mortality in these patients. However, screening rates remain low -- one study showed only 13% of adults with CKD had proteinuria/albuminuria testing. Our objective was to identify the high-risk patients with CKD who did not recieve annual proteinuria testing, with the long-term goal of addressing barriers to quality care.

Methods: We identified 4214 patients between October and December 2020 within our healthcare system who had a diagnosis of CKD 3 or 4 and categorized them as having diabetes/not having diabetes and having hypertension/not having hypertension. We then assessed how many patients had proteinuria testing in the last year, which included a urinalysis, urine protein to creatinine ratio or urine microalbumin.

Results: Results showed that 100% of patients with diabetes had screening in the last year regardless of CKD stage or hypertension (HTN). For those with CKD3A/HTN only 14% (171/1226) had screening in the last year and for those with CKD3B/HTN only 28% (98/347) had screening in the last year. For patients with CKD3A and CKD3B (without HTN/diabetes), 14% (125/892) and 34% (48/142) respectively had appropriate screening.

Conclusions: Within our large, integrated healthcare system, rates of proteinuria screening in diabetic patients were strikingly high. In contrast, most patients with CKD3 and HTN did not receive testing in the last year. One explanation for this is the workflow in place to help PCPs manage their patients with diabetes, which includes automated reminders and a dedicated multidisciplinary team. Applying a similar systematic, protocol-based workflow to all patients with CKD may help to increase screening rates and improve overall quality of care.



PO2356

The Association of CKD Severity with Stroke Subtype Using the TOAST Classification

Salmi T. Noor,[1] Sarah E. Bota,[2] Anna E. Clarke,[2] Dearbhla Kelly,[3,4] Greg A. Knoll,[1,5] Manish M. Sood.[1,5] *[1]University of Ottawa Faculty of Medicine, Ottawa, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Ottawa, ON, Canada; [3]University of Oxford Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom; [4]John Radcliffe Hospital, Oxford, United Kingdom; [5]Ottawa Hospital Research Institute, Ottawa, ON, Canada.*

Background: Ischemic stroke affects approximately 67.5 million people worldwide. The risk of acute ischemic stroke largely increases with advanced chronic kidney disease (CKD). However, whether the risk of specific ischemic stroke subtype varies with declining kidney function remains unclear. The purpose of this study was to assess the association between ischemic stroke subtypes (cardioembolic [CE], arterial, lacunar, other) classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and CKD stage.

Methods: This is a cross-sectional, retrospective cohort study of adults (≥18 years) with an ischemic stroke who presented to the emergency department in Ontario, Canada between April 1, 2002- March 31, 2013 and who had an inpatient serum creatinine measurement or were on chronic dialysis. All patients captured in the stroke registry with an estimated glomerular filtration rate (eGFR) were included and CKD severity was categorised as ≥60, 30-59, <30 mL/min/1.73m^2 or chronic dialysis.

Results: A total of 17,434 individuals with an ischemic stroke were included (58.9% eGFR ≥60, 34.7% eGFR 30-59, 6.0% eGFR<30, 0.5% on chronic dialysis; mean age of 73 years; 48% female). Among patients with an eGFR 30-59 (50.4%) and < 30 (50.6%), CE stroke was more common compared to those with an eGFR >60 (36.8%) or on chronic dialysis patients (37.3%). The odds of CE stroke vs. non-CE stroke were **eGFR 30-59** odds ratio (OR) 1.20 95% confidence interval (CI) 1.10-1.31, **eGFR<30** OR 1.21 95% CI 1.02-1.44, **dialysis** OR 0.86 95% CI 0.48-1.57, **eGFR>60** referent). We found lower adjusted odds of lacunar stroke in those with advanced CKD (lacunar vs. non-lacunar: **eGFR 30-59** OR 0.85 95% CI 0.77-0.93, **eGFR<30** OR 0.73 95% CI 0.61-0.88, **dialysis** OR 1.25 95% CI 0.68-2.28, **eGFR>60** referent). In subgroup analyses **(eGFR>=30 and <30)**, CE strokes were also more common in those >65 years, with atrial fibrillation, no anticoagulation or an INR <2.

Conclusions: Chronic kidney disease (eGFR<60, pre-dialysis CKD) is associated with a higher odds of CE stroke compared to patients with normal to high kidney function or those on chronic dialysis. Normal/mildly decreased eGFR were associated with the development of lacunar strokes. Detailed stroke subtyping in CKD may therefore provide mechanistic insights and refocus treatment strategies in this vulnerable group.

PO2357

Major Cardiovascular Events and Subsequent Risk of Kidney Failure: A CKD Prognosis Consortium Study

Patrick B. Mark, Juan J. Carrero, Frank L. Visseren, Benedicte Stengel. Chronic Kidney Disease Prognosis Consortium *CKD Prognosis Consortium, Baltimore, MD.*

Background: Chronic kidney disease (CKD) increases risk of cardiovascular disease (CVD). However, less is known about how CVD is associated with future risk of kidney failure. We quantified the association of incident major CVD events with subsequent risk of kidney failure requiring replacement therapy (KFRT).

Methods: We analyzed data on 18,671,338 individuals from 80 cohorts in the CKD Prognosis Consortium with baseline eGFR and CVD data. We assessed impact of incident coronary heart disease (CHD), heart failure (HF), atrial fibrillation (Afib) and stroke events as a time-varying exposure on the outcome of KFRT in Cox proportional hazard models.

Results: Mean age was 53 years and mean eGFR was 88 ml/min/1.73m^2, 57% were women, 9% were black, 12% had diabetes and 30% had ACR available (median 13 mg/g); 9% had prevalent CHD, 3% HF, 2% Afib, and 4% prior stroke. During follow up there were 175,886 CHD, 480,963 HF, 428,419 Afib and 211,423 stroke incident events and 85,513 (0.5%) patients required KFRT. Each CVD event increased the adjusted hazard ratio (HR) for subsequent KFRT (**Table**). The increased hazard was highest in the first year after CVD incidence and attenuated thereafter. HRs were modestly weaker at lower eGFR. HF showed the strongest association before and after adjustment for other CVD subtype incidence. Absolute risk of KFRT associated with incident CVD after accounting for competing risk of mortality was higher for lower baseline eGFR and higher ACR, with 2-year KFRT risk of 25%, 28%, 20% and 20% for CHD, HF, Afib and stroke in subjects with eGFR 15-29 ml/min/1.73m^2 and ACR >300 mg/g.

Conclusions: Incident CVD events are strongly and independently associated with risk for KFRT, with greatest risk in the first year following HF, then CHD and stroke. These data highlight need for greater awareness of KFRT risk following CVD events. Specific strategies to elucidate mechanisms and test interventions to reduce the KFRT risk post CVD events warrant investigation.

Funding: NIDDK Support, Private Foundation Support

Table. Adjusted hazard ratios for associations between incident cardiovascular diseases (CVD) with risk of kidney failure replacement therapy (KFRT)

	Myocardial Infarction	Stroke	Heart Failure	Atrial fibrillation
	KFRT Adjusted HR (95% CI)			
Incident overall	3.1 (2.9, 3.3)	2.0 (1.9, 2.1)	4.4 (4.1, 4.6)	2.8 (2.7, 3.0)
Incident < 1y	20.4 (17.8, 23.3)	10.2 (9.3, 11.2)	25.4 (22.1, 29.1)	15.2 (13.1, 17.8)
Incident 1-2y	3.6 (3.2, 4.1)	3.0 (2.6, 3.4)	5.2 (4.7, 5.9)	2.6 (2.3, 3.0)
Incident 2y+	1.0 (0.91, 1.1)	0.90 (0.83, 0.99)	1.3 (1.2, 1.5)	0.70 (0.62, 0.78)
	Model adjusting first incident CVD event subtypes for each other			
Incident overall	1.4 (1.4, 1.5)	1.3 (1.2, 1.4)	3.6 (3.3, 3.8)	1.5 (1.3, 1.6)
Incident < 1y	2.2 (1.9, 2.6)	2.5 (2.2, 2.8)	15.3 (13.7, 17.1)	2.7 (2.3, 3.2)
Incident 1-2y	1.5 (1.3, 1.7)	1.7 (1.5, 2.0)	4.6 (4.1, 5.2)	1.1 (0.93, 1.2)
Incident 2y+	0.88 (0.77, 1.0)	0.85 (0.76, 0.94)	1.4 (1.3, 1.6)	0.67 (0.58, 0.77)

*Adjusted for age, sex, race, smoking, diabetes, blood pressure, use of antihypertensive meds, total cholesterol, HDL cholesterol, lipid lowering meds, BMI, eGFR, ACR (or missing indicator & its interaction with diabetes and eGFR)

PO2358

Bidirectional Association Between Kidney Function and Atrial Fibrillation in the General Population

Anna C. van der Burgh, Sven Geurts, M.Arfan Ikram, Ewout J. Hoorn, Maryam Kavousi, Layal Chaker. *Erasmus MC, Rotterdam, Netherlands.*

Background: A potential bidirectional relationship between kidney dysfunction and atrial fibrillation (AF) has been suggested, but has not been studied in the general population. Therefore, we aimed to study the association of different assessments of kidney function with prevalent and incident AF in the general population.

Methods: Participants aged ≥ 45 years from the Rotterdam Study, a population-based cohort study, with information on kidney function and AF were included. Assessments of kidney function included single assessments of estimated glomerular filtration rate (eGFR) based on serum creatinine (eGFRcreat), serum cystatine C (eGFRcys), or both (eGFRcreat-cys), and the urine albumin-to-creatinine ratio (ACR), and repeated assessments of eGFRcreat. Incident chronic kidney disease (CKD) was defined as the first time eGFRcreat dropped <60 ml/min per 1.73 m^2. Cox-proportional hazards, logistic regression, linear mixed, and joint models were used to investigate the associations of eGFR with incident and prevalent AF. Absolute 10-year risk of AF was computed using a competing risk analysis. All models were adjusted for potential confounders including cardiovascular risk factors.

Results: During a median follow-up time of 8.0 years, 780 incident AF cases occurred in 9,288 participants (mean age 64.9 years, 57.2% female). Lower eGFRcys and eGFRcreat-cys were significantly associated with an increased risk of incident AF (hazard ratio (HR) 1.08, 95% confidence interval (CI) 1.03-1.14 and HR 1.07, 95% CI 1.01-1.14, respectively, per 10 ml/min per 1.73 m^2 decrease in eGFR), while eGFRcreat was not. No association between urine ACR and incident AF was found. Absolute 10-year risk of developing AF increased from 4.9% to 7.1%, when comparing eGFRcys levels of 90 to 60 ml/min per 1.73 m^2. Prevalent AF (409 cases) was associated with on average 2.85 ml/min per 1.73 m^2 lower eGFRcreat levels over time and furthermore, a faster decline of eGFRcreat with aging was revealed when compared to participants without prevalent AF. Prevalent AF was also associated with a 1.3 fold increased risk of incident CKD.

Conclusions: Kidney function and AF are bidirectionally associated. This insight may be used to improve prediction and prevention of both conditions, for example through targeted screening programs in the general population.

PO2359

Longitudinal Ankle Brachial Index and Risk of CKD Progression

Kirsten S. Dorans,[1] Jing Chen,[2,1] Xingyan Li,[1] Hua He,[1] Jordana B. Cohen,[3] Alan S. Go,[4] L. Lee Hamm,[2,1] Edward J. Horwitz,[9] Bernard G. Jaar,[5] James P. Lash,[6] Rupal Mehta,[7] Sylvia E. Rosas,[8] Anand Srivastava,[7] Jonathan J. Taliercio,[10] Jiang He.[1,2] CRIC Study Investigators *[1]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [2]Tulane University School of Medicine, New Orleans, LA; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [4]Kaiser Permanente Northern California, Oakland, CA; [5]Johns Hopkins Medicine, Baltimore, MD; [6]University of Illinois at Chicago, Chicago, IL; [7]Northwestern University Department of Medicine, Chicago, IL; [8]Joslin Diabetes Center, Boston, MA; [9]MetroHealth Medical Center, Cleveland, OH; [10]Cleveland Clinic, Cleveland, OH.*

Background: Individuals with chronic kidney disease (CKD) are more likely than the general population to have low or high ankle brachial index (ABI). Low ABI is a predictor of adverse outcomes in CKD, but the relationship of ABI with renal outcomes in CKD is not well studied. As ABI is a simple noninvasive measure, it is important to better understand how ABI relates to CKD progression.

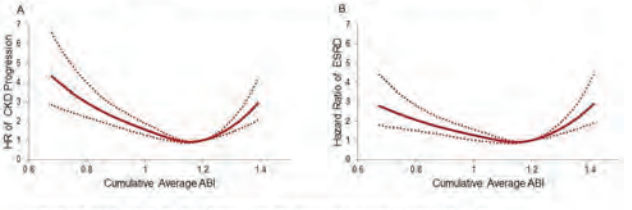
Methods: We carried out a prospective study of 3216 participants with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study without clinical peripheral arterial disease. We used Cox proportional hazards regression to test the associations of baseline ABI and of cumulative average ABI with risk of CKD progression [50% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease (ESRD)] and with risk of ESRD, adjusting for important confounding factors. ABI was measured at annual visits. The shapes of the relationships of exposures with outcomes were assessed with restricted cubic splines.

Results: At baseline, average age was 57.8 years and average eGFR was 44.8 ml/min/1.73m^2. During follow-up, 1297 individuals had CKD progression (median follow-up 6.9 years, 7 ABI measurements) and 1049 developed ESRD (median follow-up 10.8 years, 6 ABI measurements). In multivariable-adjusted models, there were U-shaped associations of baseline ABI with CKD progression and with ESRD (p for curves <0.001). In models adjusted for baseline ABI, similar U-shape relationships were observed for the associations of cumulative average ABI with CKD progression and with ESRD (p for curves <0.001; **Figure**).

Conclusions: This study indicates that both high and low ABI are associated with increased risk of CKD progression and ESRD and that even after adjustment for baseline ABI, repeated measures of ABI averaged over time are associated with CKD progression and ESRD. These findings suggest that ABI can be used to facilitate risk stratification for CKD progression.

Funding: NIDDK Support, Other NIH Support - National Institute of General Medical Sciences

Figure. Spline plot of multivariable-adjusted hazard ratios at 95% confidence intervals of (A) CKD progression and (B) ESRD associated with cumulative average ankle brachial index



Adjusted for age, sex, race, clinic site, baseline ABI, and demographic, clinical and lifestyle factors.

PO2360

Urinary Peptidome Analysis to Predict the Risk of CKD Progression to Kidney Failure

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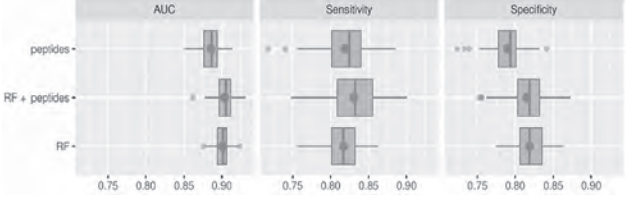
Background: Urinary peptidomics (UP) has emerged as one of the most attractive areas in the identification of biomarkers for characterizing CKD but its potential to predict the risk of CKD progression has not been fully investigated. The aims of the present study were to explore if a UP signature can improve the prediction of kidney failure (KF), compared to the risk factors (RF) included in the KF risk equation.

Methods: Within the Chronic Kidney Disease-Renal Epidemiology and Information Network prospective cohort of patients with CKD stage G3-G5 (N=3033), we conducted a case-cohort study of 892 patients, including 262 who progressed to KF as defined by the initiation of dialysis or preemptive kidney transplantation over 3-year follow-up. UP analysis was performed on samples collected at baseline using capillary electrophoresis coupled to mass spectrometry. Three logistic regression models with elastic-net penalty were developed with different sets of predictors: (1) peptides alone, (2) RF including age, sex, eGFR and urinary albumin to creatinine ratio, and (3) peptides and RF. We performed 50-repeated 2-fold cross-validation to choose the 3 optimal models and measure their performances (AUC, sensitivity and specificity). External independent validation was performed in a Belgian cohort of 270 patients with CKD Stages G3-G5 including 28 progressing to KF over 3-year follow-up.

Results: A signature of 174 peptides predicted KF risk in the first model (Figure). The independent validation of the UP signature in the Belgian cohort confirmed the prognostic potential of the peptide signature displaying a AUC of 0.928 [0.887-0.969] (sensitivity, 86% [71%-96%] and specificity, 81% [65%-94%]). RF alone also predicted KF risk with high precision, and the addition of peptides did not significantly improve this prediction (Figure).

Conclusions: We have identified a UP signature that predicts KF risk with high precision, but did not significantly ameliorate the prediction obtained by a combination of age, sex, eGFR and albuminuria.

Funding: Government Support - Non-U.S.



PO2361

Plasma Biomarkers and Incident CKD in Individuals Without Diabetes

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Background: Earlier prediction of CKD may facilitate risk factor mitigation prior to advanced disease. Albuminuria and reduced GFR are relatively insensitive markers of early CKD. We examined the association of several novel plasma biomarkers with incident CKD.

Methods: We used a case cohort design in participants without diabetes in the Multiethnic Study of Atherosclerosis (MESA) and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohorts with a baseline eGFR ≥60 ml/min/1.73 m^2. Incident CKD was defined as the development of an eGFR <60 ml/min/1.73 m^2 and ≥40% decline in eGFR from baseline. We measured plasma markers of inflammation/fibrosis—soluble tumor necrosis factor receptors 1 and 2 (TNF-R1 and TNF-R2), monocyte chemotactic protein-1 (MCP-1) and soluble urokinase-type plasminogen activator receptor (suPAR)—and tubular injury (kidney injury marker 1, KIM-1) and repair [chitinase 3-like protein 1 (YKL-40)]. Cox regression models weighted for the case cohort design were used to estimate hazard ratios.

Results: In MESA (median follow-up 9.2 years), there were 497 individuals in the subcohort and 163 cases of incident CKD. In REGARDS (median follow-up 9.4 years), there were 497 individuals in the subcohort and 497 cases of incident CKD. Plasma KIM 1, suPAR, TNF-R1, TNF-R2 and YKL-40 concentrations were all independently associated with incident CKD in MESA. In REGARDS, TNF-R1 and TNF-R2 were independently associated with incident CKD (Table).

Conclusions: Plasma concentrations of soluble TNF-R1 and TNF-R2 are consistently associated with incident CKD in non-diabetic community-living individuals, independent of eGFR, UACR, and other CKD risk factors.

Funding: NIDDK Support

Association of individual plasma biomarkers (HR (95% CI) per two fold higher) with incident CKD

	MESA		REGARDS	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
KIM-1	1.79 (1.46, 2.20)	1.38 (1.05, 1.81)	1.14 (0.97, 1.33)	1.11 (0.94, 1.31)
MCP-1	1.59 (1.14, 2.22)	1.17 (0.76, 1.79)	1.32 (1.05, 1.66)	1.25 (0.98, 1.59)
suPAR	3.04 (2.08, 4.45)	1.96 (1.10, 3.49)	1.33 (1.02, 1.74)	1.28 (0.95, 1.72)
TNF-R1	2.53 (1.80, 3.55)	1.65 (1.04, 2.62)	1.57 (1.19, 2.06)	1.99 (1.43, 2.76)
TNF-R2	3.39 (2.25, 5.12)	2.02 (1.21, 3.38)	1.52 (1.11, 2.07)	1.76 (1.22, 2.54)
YKL-40	1.90 (1.57, 2.30)	1.38 (1.09, 1.75)	1.08 (0.95, 1.24)	1.07 (0.92, 1.24)

*adjusted for age, sex, race/ethnicity, education, BMI, SBP, HTN meds, smoking, UACR, and eGFR

PO2362

Tubular Secretion Markers and Declining Kidney Function in the SPRINT Trial

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Background: Tubular secretion is an important aspect of kidney function that is not routinely assessed. Emerging evidence suggests that impaired secretion may be associated with increased risk of kidney function decline.

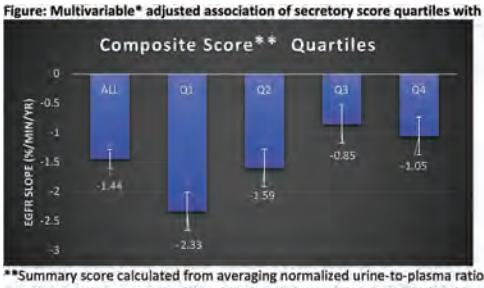
Methods: In a cohort of 2089 SPRINT trial participants with baseline eGFR < 60ml/min/1.73m^2, we measured a panel of 10 solutes in serum and urine, that were previously identified as markers of tubular secretion. We created a standardized composite secretory score using the urine to plasma ratios of all 10 biomarkers. We evaluated associations of this composite score with annual % eGFR decline and progression of CKD (>30% loss of eGFR) using multivariable linear regression and Cox regression models, respectively.

Results: Mean participant age at baseline was 73 years, 41% were female, and 24% identified as Black. The mean eGFR varied by secretion score quartile: from 39 ml/min/1.73m^2 in the lowest quartile to 51 ml/min/1.73m^2 in the highest quartile. In multivariable adjusted analyses, eGFR declined faster for participants in the lower two quartiles of secretory score compared with participants in the higher two quartiles (**Figure**). There was no significant interaction between secretion score and randomized treatment assignment for the outcome of eGFR decline. In unadjusted models, each 1-SD higher secretion score was associated with a lower risk of CKD progression (HR 0.49; 95% CI, 0.35, 0.70), but this association was attenuated by multivariable adjustment (HR 0.75, 95% CI 0.53, 1.07).

Conclusions: Impaired secretory function as measured by a panel of endogenous markers is associated with faster decline in eGFR among persons with CKD.

Funding: NIDDK Support

Figure: Multivariable* adjusted association of secretory score quartiles with annual % eGFR decline



**Summary score calculated from averaging normalized urine-to-plasma ratios of adipic acid, cinnamoylglycine, p-cresol sulfate, 1,7-dimethyluric acid, 2-furoylglycine, hippuric acid, m-hydroxy Hippurate, indoxyl sulfate, phenylacetylglutamine, tiglylglycine, and 1,3,7-trimethyluric acid.
*Adjusted for baseline age, sex, race, intervention arm, smoking, body mass index, systolic blood pressure, number of antihypertensive medications, prevalent cardiovascular disease, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, statin use, baseline eGFR and urine albumin.

PO2363

The Use of Plasma Biomarker-Derived Clusters for Clinicopathologic Phenotyping: Results from the Boston Kidney Biopsy Cohort

Insa M. Schmidt,[1] Prasad Patil,[5] Steele Myrick,[5] Ingrid F. Onul,[1] Anand Srivastava,[3] Ragnar Palsson,[6] Isaac E. Stillman,[4] Helmut G. Rennke,[2] Sushrut S. Waikar.[1] *[1]Boston Medical Center, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Boston University School of Public Health, Boston, MA; [6]Landspitali, Reykjavik, Iceland.*

Background: Protein biomarkers may provide non-invasive insight into kidney disease pathology. Prior studies have not evaluated whether unsupervised clustering analyses of multiple plasma protein biomarkers may identify phenotypically distinct kidney diseases.

Methods: We performed unsupervised hierarchical clustering on 225 plasma biomarkers measured in 541 individuals enrolled into the Boston Kidney Biopsy Cohort, a prospective cohort study of individuals undergoing clinically indicated native kidney biopsy with adjudicated clinicopathologic diagnoses and semiquantitative scores of histopathology. Chi-square tests compared differences in proportions of clinicopathologic diagnoses by cluster membership. We examined contributions of biomarkers to each cluster and explored cluster-specific pathways using principal component analysis and pathway enrichment analysis, respectively.

Results: The biomarker-derived clusters partitioned subjects into 3 groups. The mean eGFR was 71.4±29.2, 72.5±34.3, and 39.3±31.3 ml/min/1.73m² in Cluster 1, 2, and 3, respectively. Compared to Cluster 1, individuals in Cluster 3 were more likely to have tubulointerstitial disease (p<0.001) and diabetic nephropathy (p<0.001), (Figure 1). The top-contributing biomarker in Cluster 1 was AXIN, a negative regulator of the Wnt signaling pathway. The top-contributing biomarker in Cluster 2 and 3 was Placental Growth Factor, a member of the VEGF family. The top ranked pathways were tumor-necrosis factor receptor-related signaling and interleukin and cytokine signaling in Cluster 1, 2, and 3, respectively.

Conclusions: Clusters of plasma biomarkers may identify individuals with distinct forms of CKD, which may uncover relevant pathways and biomarker candidates for clinicopathologic phenotyping of kidney diseases.

Funding: NIDDK Support

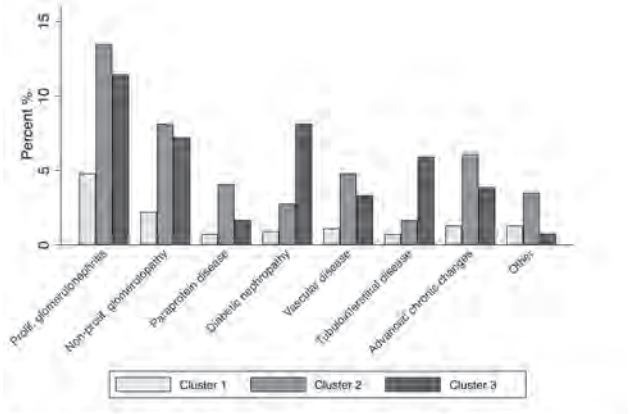


Figure 1. Distribution of clinicopathologic diagnoses by cluster membership.
P-values from Chi square Tests: Proliferative Glomerulonephritis, p=0.298; Non-proliferative glomerulopathy, p=0.929; Paraprotein disease, p=0.069; Diabetic nephropathy, p<0.001; Vascular disease, p=0.532; Tubulointerstitial disease, p<0.001; Advanced chronic changes, p=0.277; Other (minor abnormalities or relatively preserved parenchyma), p=0.003.

Figure 1

PO2364

DAPA-CKD: A Regional Analysis of Kidney and Cardiovascular Outcomes

Ricardo Correa-Rotter,[1] Priya Vart,[2] Niels Jongs,[2] Fan Fan Hou,[3] Glenn M. Chertow,[4] Anna Maria Langkilde,[5] John McMurray,[6] Peter Rossing,[7,8] David Sjostrom,[5] Bergur V. Stefansson,[5] Robert D. Toto,[9] Walter Douthat,[10] Elizabeth T. Escudero,[11] Rey A. Isidto,[12] Dinesh Khullar,[13] Harpreet S. Bajaj,[14] David C. Wheeler,[15] Hiddo J. L Heerspink.[2,16] *[1]The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; [2]University Medical Center Groningen, Groningen, Netherlands; [3]Southern Medical University, National Clinical Research Center for Kidney Disease, Guangzhou, China; [4]Stanford University School of Medicine, Stanford, CA; [5]AstraZeneca, Gothenburg, Sweden; [6]University of Glasgow, Glasgow, United Kingdom; [7]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [8]University of Copenhagen, Copenhagen, Denmark; [9]UT Southwestern Medical Center, Dallas, TX; [10]Hospital Privado Universitario de Cordoba, Cordoba, Argentina; [11]Hospital Arzobispo Loayza, Cayetano Heredia University, Lima, Peru; [12]Healthlink Medical, Dental, Surgical Clinics and Diagnostics Center, Iloilo City, Philippines; [13]Max Super Speciality Hospital Saket, New Delhi, India; [14]LMC Diabetes and Endocrinology, Brampton, ON, Canada; [15]University College London, London, United Kingdom; [16]The George Institute for Global Health, Newtown, NSW, Australia.*

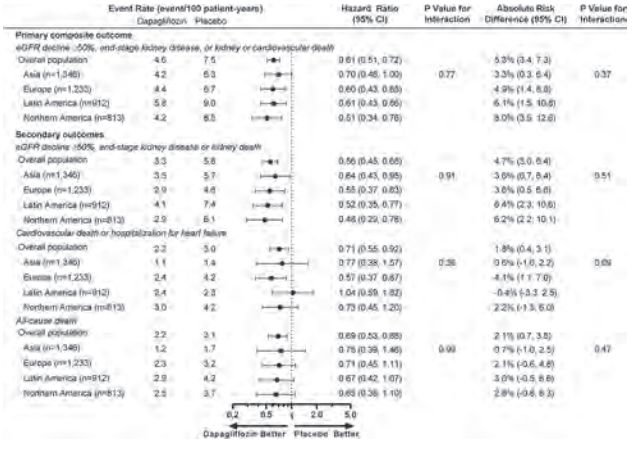
Background: The DAPA-CKD trial (NCT03036150) demonstrated that dapagliflozin reduced the risk of kidney and cardiovascular (CV) events in patients with chronic kidney disease (CKD) and albuminuria, with and without type 2 diabetes. We aimed to determine whether the effects of dapagliflozin varied by pre-specified geographic region.

Methods: We randomized 4304 adults with baseline estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urinary albumin-to-creatinine ratio 200–5000 mg/g to dapagliflozin 10mg or placebo once daily; median follow-up was 2.4 years. We compared baseline data, primary and secondary outcomes, and safety of the 4 regions (Asia, Northern America, Latin America, Europe).

Results: Compared to other regions, participants from Asia had lower body mass index, less frequent use of diuretics and better blood pressure control. The figure displays the primary and secondary outcomes by region and treatment assignment. Dapagliflozin consistently reduced the risk of the primary composite endpoint (eGFR decline ≥50%, end-stage kidney disease, or kidney or CV death) across the 4 regions by 30 to 49%, with no significant heterogeneity (p=0.77). Similarly, there was no evidence of differences in secondary outcomes between regions. Serious adverse events in the dapagliflozin and placebo groups were similar across the 4 regions.

Conclusions: Despite differences in patient characteristics, the beneficial effects of dapagliflozin on kidney and CV endpoints in patients with CKD and albuminuria were similar across pre-specified geographic regions.

Funding: Commercial Support - AstraZeneca



PO2365

Effects of Dapagliflozin in Patients with CKD and Albuminuria, with and Without Diabetes, by Use and Non-Use of Cardiovascular Medications: DAPA-CKD Trial

Ricardo Correa-Rotter,[1] Glenn M. Chertow,[2] Patrick B. Mark,[3] Michal P. Nowicki,[4] Priya Vart,[5] Niels Jongs,[5] Anna Maria Langkilde,[6] John McMurray,[3] Peter Rossing,[7,8] David Sjostrom,[6] Bergur V. Stefansson,[6] Robert D. Toto,[9] David C. Wheeler,[10] Hiddo J. L Heerspink.[5,11] *[1]The National Medical Science and Nutrition Institute Salvador Zubiran, Mexico City, Mexico; [2]Stanford University School of Medicine, Stanford, CA; [3]University of Glasgow, Glasgow, United Kingdom; [4]Medical University of Lódz, Lódz, Poland; [5]University Medical Center Groningen, Groningen, Netherlands; [6]AstraZeneca, Gothenburg, Sweden; [7]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [8]University of Copenhagen, Copenhagen, Denmark; [9]UT Southwestern Medical Center, Dallas, TX; [10]University College London, London, United Kingdom; [11]The George Institute for Global Health, Newtown, NSW, Australia*.

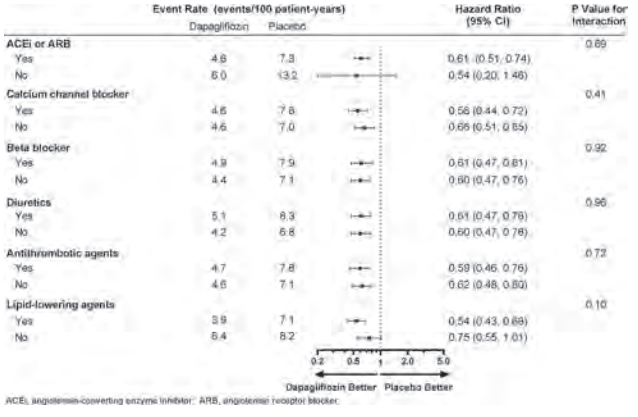
Background: The DAPA-CKD trial (NCT03036150) demonstrated that dapagliflozin reduced the risk of kidney and cardiovascular (CV) events in patients with chronic kidney disease (CKD) and albuminuria with and without type 2 diabetes. We aimed to determine whether baseline CV medications modified dapagliflozin treatment effect.

Methods: We randomized 4304 adults with baseline eGFR 25–75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio 200–5000 mg/g to either dapagliflozin 10 mg or placebo once daily. The primary endpoint was a composite of ≥50% estimated glomerular filtration rate (eGFR) decline, end-stage kidney disease, and kidney or CV death. Here we categorized patients according to baseline CV medication use.

Results: Patients were required by protocol to receive a stable dose of a renin-angiotensin system inhibitor. The figure shows the effect of dapagliflozin compared with placebo, according to use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (97.0%), calcium channel blockers (50.7%), beta-blockers (39.0%), diuretics (43.7%), antithrombotic (47.4%) and lipid-lowering (69.4%) agents. The benefit of dapagliflozin was consistent across all background treatment subgroups, and findings were similar for pre-specified secondary outcomes (composite kidney endpoint, composite CV endpoint, and all-cause mortality).

Conclusions: The beneficial effects of dapagliflozin on kidney and CV endpoints in patients with CKD and albuminuria were evident among patients treated and not treated with a variety of CV medications.

Funding: Commercial Support - AstraZeneca



PO2366

Quételet (Body Mass) Index and Effects of Dapagliflozin in CKD

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Background: The DAPA-CKD trial (NCT03036150) demonstrated a reduction of the risk of kidney and cardiovascular (CV) events with dapagliflozin in patients with chronic kidney disease (CKD) and albuminuria with and without type 2 diabetes. We aimed to assess the effects of the SGLT2 inhibitor dapagliflozin in patients stratified by Quételet (body mass) index (BMI).

Methods: We randomized 4304 adult patients with estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m^2 and urinary albumin-to-creatinine ratio 200–5000 mg/g to dapagliflozin 10 mg or placebo once daily. The primary outcome was a composite of sustained decline in eGFR of ≥50%, kidney failure, or death from kidney or CV causes. Secondary outcomes were a kidney composite endpoint, a CV composite endpoint, and all-cause mortality. We categorized patients according to World Health Organization criteria: lean or ideal (BMI <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), grade 1 obesity (BMI 30 to <35 kg/m^2), and grade 2/3 obesity (BMI ≥35 kg/m^2).

Results: Among 4296 (99.8%) randomized patients with available height and weight data, 888 (20.7%), 1491 (34.7%), 1136 (26.4%), and 781 (18.2%) were categorized as lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity, respectively. Hazard ratios (HRs) (dapagliflozin versus placebo) and 95% confidence intervals (CIs) for the primary composite endpoint were 0.60 (0.43–0.85), 0.55 (0.40–0.75), 0.71 (0.49–1.04), and 0.57 (0.37–0.87), among patients in the lean or ideal, overweight, grade 1 obesity, and grade 2/3 obesity groups (interaction p=0.72), respectively, indicating no significant heterogeneity in the dapagliflozin treatment effect. Corresponding HRs (95%CI) for the kidney composite endpoint: 0.55 (0.38–0.80), 0.54 (0.37–0.78), 0.51 (0.32–0.83), and 0.60 (0.36–0.98) (interaction p=0.98); CV composite endpoint: 0.88 (0.44–1.74), 0.72 (0.44–1.19), 0.94 (0.60–1.48), and 0.46 (0.27–0.77) (interaction p=0.21); and all-cause mortality: 0.78 (0.44–1.40), 0.51 (0.33–0.79), 0.98 (0.60–1.62), and 0.65 (0.36–1.18) (interaction p=0.27).

Conclusions: Among patients with CKD and albuminuria, with or without type 2 diabetes, kidney and CV benefits of dapagliflozin were evident across the spectrum of body size.

Funding: Commercial Support - AstraZeneca

PO2367

Efficacy and Safety of Roxadustat for the Treatment of CKD Anemia in Patients Enrolled in the United States as Compared with the Global Cohort

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Background: Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor increases hemoglobin (Hb) in non-dialysis (NDD) and dialysis dependent (DD) chronic kidney disease (CKD). Because of different clinical practices and demographic factors, it is important to evaluate efficacy and safety by region.

Methods: In a secondary analysis of data from 3 phase 3 studies of Roxadustat vs. placebo in NDD-, and 3 phase 3 studies of Roxadustat vs. epoetin alfa in DD-CKD, US patients were compared to the global cohort. Mean change from baseline in Hb averaged over weeks 28–52 regardless of rescue therapy and treatment emergent adverse events with occurrence in ≥5% of patients were assessed.

Results: Of the patients enrolled in the NDD and DD trials, 23.2% and 45.4% were enrolled in the US, respectively. Compared with global patients, US patients were older, had a higher BMI, and more frequently had type I or II diabetes mellitus and cardiovascular/thromboembolic diseases (Table). US DD patients had a higher mean baseline Hb (SD) (10.16 g/dL [0.92]) compared with the global cohort (9.65[1.30]). Efficacy was similar between US and global patients; least square mean (LSM) differences in NDD patients were 1.61 g/dL (95% CI: 1.48, 1.74) vs. 1.72 (95% CI:1.65, 1.79) (both p<0.0001) comparing roxadustat to placebo; LSM differences in DD patients were 0.33 (95% CI: 0.24, 0.42) vs. 0.26 (95% CI: 0.20, 0.33) (both p<0.0001) comparing roxadustat to epoeitin alfa. Safety was comparable between treatment arms in US and global patients.

Conclusions: Patients enrolled in the US were older and were more likely to have comorbidities in both the NDD and DD trials, Roxadustat efficacy and safety in the US were similar to global patients.

Funding: Commercial Support - FibroGen, Inc., Astellas, AstraZeneca

Table 1. Differences between US and global cohorts in demographic and disease characteristics

Parameters	NDD subgroup		DD subgroup	
	US (N=992)	Global (N=4270)	US (N=1762)	Global (N=3880)
Age (yrs) [1]				
18 – 64 (%)	396 (39.9)	2274 (53.3)	1196 (67.9)	2846 (73.4)
65 – 74 (%)	273 (27.5)	1103 (25.8)	381 (21.6)	701 (18.1)
>=75 (%)	323 (32.6)	893 (20.9)	185 (10.5)	333 (8.6)
Race, n (%)				
American Indian or Alaska Native	4 (0.4)	60 (1.4)	28 (1.6)	134 (3.5)
Asian	43 (4.3)	1546 (36.2)	78 (4.4)	533 (13.7)
Black or African American	305 (30.7)	343 (8.0)	701 (39.8)	714 (18.4)
Native Hawaiian or Other Pacific Islander	3 (0.3)	8 (0.2)	11 (0.6)	12 (0.3)
White	625 (63.0)	2026 (47.4)	897 (50.9)	2353 (60.6)
Other	12 (1.2)	287 (6.7)	28 (1.6)	134 (3.5)
BMI (kg/m^2)				
n	990	4261	1758	3875
Mean (SD)	30.61 (7.19)	26.97 (6.03)	30.09 (7.24)	27.59 (6.72)
Baseline Disease characteristics				
Diabetes Mellitus (Type I or II), n (%)	722 (72.8)	2428 (56.9)	1218 (69.1)	1826 (47.1)
Cardiac, Cerebrovascular, or Thromboembolic Disease, n (%)	472 (47.6)	1578 (37.0)	1106 (62.8)	1871 (48.2)

[1] Age at informed consent (001, 002, 060, 063, 064) or first dose date (608).

[2] Subjects may have more than one CKD etiology.

BMI = body mass index, CKD = chronic kidney disease, DD = dialysis dependent, NDD = non-dialysis dependent SD = standard deviation

PO2368

Correlates and Consequences of an Acute Decline in Estimated Glomerular Filtration Rate in Response to the SGLT-2 Inhibitor Dapagliflozin

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Background: In the DAPA-CKD trial (NCT03036150), dapagliflozin slowed the rate of progression of chronic kidney disease (CKD) in CKD patients with and without type 2 diabetes. However, dapagliflozin can cause a reversible acute decline in estimated glomerular filtration rate (eGFR), which is considered to be a hemodynamic effect. Predictors of the initial eGFR decline and its association with safety outcomes are unknown.

Methods: In DAPA-CKD, 4304 participants with urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g and eGFR 25–75 mL/min/1.73m^2 were randomized to dapagliflozin 10 mg or placebo once daily, added to standard care, and followed for median 2.4 years. We categorized decline in eGFR from baseline to Week 2 in percentages (>10% decline; between 0 and 10% decline; and no decline) and absolute changes (>3 mL/min/1.73m^2; between 0 and 3 mL/min/1.73m^2; and no decline).

Results: A total of 4157 patients (96.6% of full cohort) had eGFR data available at baseline and Week 2. In the dapagliflozin and placebo groups, 1026 (49.4%) and 494 (23.7%) experienced an acute decline in eGFR of >10%, respectively. The odds ratio for a decline in eGFR of >10% with dapagliflozin compared with placebo was 3.2 (95%CI 2.8–3.6; p<0.001). The odds ratio for an acute eGFR decline of >10% was consistent across patient subgroups defined by baseline sex, eGFR, UACR, diabetes status, blood pressure, body mass index, or cardiovascular disease history. The only exception was that white participants and participants ≥65 years were more likely to experience an acute eGFR decline of >10% following dapagliflozin initiation relative to placebo (interaction p<0.025 for both). Rates of serious adverse events and adverse events of special interest in those treated with dapagliflozin were unrelated to the degree of acute eGFR decline.

Conclusions: Although acute declines in eGFR occurred more frequently with dapagliflozin, it is not associated with an increased risk of adverse events, supporting the safe use of dapagliflozin in patients with CKD stage 2 to 4.

Funding: Commercial Support - AstraZeneca

PO2369

A Comparison of the Efficacy of Patiromer Plus RAAS Inhibitor Therapy in Patients with CKD and Diabetes to a Cohort of Patients Not Using Patiromer: A Real-World Analysis Using Propensity Score Matching

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Background: The AMETHYST-DN trial evaluated the use of patiromer (PAT) to treat hyperkalemia in patients (pts) with diabetes and CKD treated with RAASi. This analysis compared the progression of proteinuria and eGFR in AMETHYST-DN pts with a matched, real-world group of CKD pts with diabetes not receiving PAT.

Methods: Pts from AMETHYST-DN were closely matched with Salford Kidney Study (SKS) pts (a large CKD cohort in the United Kingdom). Matching was performed for age, gender, baseline systolic and diastolic blood pressure (BP), heart failure (HF) status, serum K^+ and eGFR by propensity scores generated from a logistic regression analysis (1:1, nearest neighbour method). All pts were followed up for a median duration of 12 months. The median change in proteinuria and eGFR between baseline and 12-month follow-up were compared between groups.

Results: Out of 3564 pts recruited into the SKS from Oct 2002 to Dec 2019, 526 diabetic pts were eligible for matching with the 304 AMETHYST-DN pts. Propensity score matching yielded a well-matched cohort of 142:142 pts for the trend analysis. Median age was 68 yrs, 68% were male, median BP was 152/80 mmHg, and 27% had HF. Median eGFR was 32.5 mL/min/1.73m^2 and uACR was 283 mg/g. RAASi use was 100% at baseline and 99% at follow-up in AMETHYST-DN pts. In contrast, RAASi use was 60% at baseline declining to 43% at 12-month follow-up in the SKS cohort. Trend analysis showed a significant difference in the rate of change in proteinuria at 12 months in AMETHYST-DN vs SKS pts (−31 mg/g vs +9 mg/g, p=0.023). No significant difference was observed for eGFR change (Table).

Conclusions: PAT enabled sustained RAASi use in 99% of pts in AMETHYST-DN, compared to 43% pts in a matched SKS cohort over 12 months. AMETHYST-DN pts had significantly reduced proteinuria at follow-up compared to SKS CKD pts, possibly due to continuation of RAASi enabled by PAT. No significant changes in eGFR were observed in either group.

Funding: Commercial Support - Vifor Pharma

Table. Outcomes in the matched sample of patients from AMETHYST-DN and Salford Kidney Study

Variable	AMETHYST-DN (n=142)	SKS cohort (n=142)	*p*-value
Serum potassium, mEq/L			
Baseline	5.2 (5.2 to 5.5)	5.3 (5.2 to 5.5)	0.671
Last follow-up	4.7 (4.3 to 4.9)	5 (4.6 to 5.4)	<0.001
Median change from baseline	−0.46 (−0.89 to −0.005)	−0.30 (−0.70 to 0.10)	0.071
eGFR, mL/min/1.73m^2			
Baseline	32 (23 to 41)	33 (26 to 41)	0.536
Last follow-up	32.5 (23 to 46)	31 (21.5 to 45)	0.303
Median change from baseline	−2 (−9 to 6)	−1 (−5 to 2.5)	0.72
uACR, mg/g			
Baseline	422.3 (72.1 to 1516)	294 (82.3 to 902)	0.616
Last follow-up	321.7 (49.3 to 1384)	343 (103 to 923)	0.282
Median change from baseline	−31.3 (−420.5 to 64.5)	8.8 (−176.4 to 173.5)	0.023
RAASi use, n (%)			
Baseline	142 (100%)	85 (59.8%)	<0.001
Last follow-up	140 (98.6%)	61 (42.9%)	<0.001
Follow up (months)	12.13 (2.96 to 12.1)	12.2 (11.43 to 12.03)	<0.001

All laboratory variables are expressed as median (interquartile range) and *p*-value was generated by Mann-Whitney U Test. uACR, urine albumin-to-creatinine ratio; RAASi, renin-angiotensin-aldosterone system inhibitors; SKS, Salford Kidney Study.

PO2370

Patiromer Enables Sustained RAAS Inhibitor Therapy over 52 Weeks: A Post Hoc Analysis of 246 Patients Who Completed the AMETHYST-DN Study

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Background: Hyperkalemia (HK) is a common electrolyte abnormality in CKD patients (pts) with type 2 diabetes mellitus (T2DM) and leads to underutilization of RAAS inhibitors (RAASi). KDIGO guidelines recommend RAASi dose should be reduced or discontinued only as a last resort in HK pts after measures to control serum potassium (sK) have failed. Patiromer (PAT) is a non-absorbed, sodium-free, K binder documented to reduce sK in pts with HK, and consequently enables sustained RAASi therapy. This post-hoc analysis of AMETHYST-DN analyzed in-depth the ability of PAT to maintain RAASi in a large cohort of pts with diabetic kidney disease (DKD) and HK who completed 1 year of treatment with PAT.

Methods: AMETHYST-DN was a multicenter, open-label trial of PAT in adult pts on RAASi with eGFR 15–<60 mL/min/1.73m^2, T2DM, hypertension, and HK (sK >5.0 mEq/L). Pts were randomized to PAT 8.4–33.6 g/d to start. The 52-wk study included an 8-wk treatment phase, followed, in pts on a stable PAT dose for ≥3 consecutive wks, by a 44-wk long-term maintenance phase (LTMP). This analysis evaluated dose modifications of RAASi among pts who completed the LTMP.

Results: 304 pts were randomized and received ≥1 PAT dose. Of these, 246 pts were on a stable PAT dose and entered the LTMP, and 197 pts completed 52 wks of treatment. All pts were receiving RAASi at baseline. By protocol, RAASi could not be downtitrated or discontinued because of HK during the study. In total, 195/197 pts who completed the LTMP remained on RAASi for the entire 44-wk LTMP period. Most pts (n=176) had no RAASi dose change, 14 had RAASi dose changes but remained stable or uptitrated, and 5 had their dose downtitrated. Of the 49 pts who withdrew early from the LTMP, 27 did so

for clinical reasons (AEs, 12; low sK, 5; death, 4; deterioration of renal function, 4; high sK, 2), whereas 22 had reasons related to investigator/patient factors (consent withdrawal, 12; noncompliance, 7; investigator decision, 1; other, 2). During the LTMP, ≥1 AE was reported for 158/246 pts.

Conclusions: This analysis of AMETHYST-DN demonstrates that the vast majority of hyperkalemic pts with DKD who completed the LTMP of the study were able to sustain their RAASi dose over an extended 44 weeks without downtitration or discontinuation of RAASi therapy. Only 2 pts withdrew early from the LTMP due to recurrent HK.

Funding: Commercial Support - Vifor Pharma

PO2371

Predict Hyperkalemia in Advanced CKD Patients Using Machine Learning Algorithms

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Background: Hyperkalemia is a common and fatal problem in advanced chronic kidney disease patients. The incidence rate was about 40-50%. It may cause muscle weakness, paralysis, and even cardiac arrhythmia. Our goal is to develop machine learning models to predict hyperkalemia in advanced chronic kidney disease patients, which could help physicians make clinical decisions.

Methods: We collected clinical data for advanced CKD (CKD stage 4 and 5, eGFR < 30 ml/min/1.73m2) patients receiving Output Patient Care in one medical center in Taiwan from January 2010 to December 2019. 1,965 patients were included. Four machine learning models (multilayer perceptron [MLP], logistic regression with regularization, XGBoost, and random forest [RF]) were used to estimate serum potassium concentration 3 months later. 2 Nephrologists participated in human-machine competition. Area under the receiver operating characteristic curves (AUCs), sensitivity, specificity, positive (PPV) and negative (NPV) predicted values, and accuracy were used to evaluate the performance of machine learning models with that of these physicians.

Results: In a test set including 2,074 records, the AUC of machine learning models was highest for XGBoost (0.843; 95% confidence interval [CI], 0.822–0.864). Moreover, the NPV and specificity were 0.875 and 0.943, respectively. The AUC for detecting hyperkalemia by humans was 0.602, 95% CI, 0.580–0.623. XGBoost model performed significantly better than humans ($P < 0.001$, using the DeLong test).

Conclusions: Machine learning models may help physicians make clinical decisions in advanced CKD patients who suffer from hyperkalemia in outpatient department care and possibly reduce cardiac arrhythmia.

PO2372

Association Between Dietary Potassium Intake and Abdominal Aortic Calcification in US Adults

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Background: In ApoE-deficient mice, low dietary potassium intake promoted vascular calcification and high dietary potassium intake attenuated vascular calcification. We hypothesized high dietary potassium intake was associated with lower abdominal aortic calcification (AAC) among adults in the US.

Methods: Cross-sectional analyses were performed on 2535 participants from the National Health and Nutrition Examination Survey 2013-2014. Dietary potassium intake was obtained from two 24-h recall interviews and were categorized into quartiles (Q1:0.3-1.9, Q2: 2.0-2.4, Q3: 2.5-3.1 and Q4: 3.2-6.8 g/day). AAC was measured using dual-energy X-ray absorptiometry in adults over 40 years old and quantified using the Kauppila score system. AAC scores were categorized into: no AAC (AAC=0, reference group), mild/moderate (AAC>0-≤6) and severe AAC (AAC>6). Multinomial logistic regression was used to study the association between AAC and dietary potassium intake. Model was adjusted for demographics, hypertension, diabetes, smoking, eGFR, albuminuria, BMI, energy intake and physical activity.

Results: In the entire cohort, mean dietary potassium intake was 2.4±0.9 g/day; 21% had mild/moderate AAC and 9.4% had severe AAC. Dietary potassium intake was not associated with mild-moderate AAC (table). For severe AAC, dietary potassium intake was only associated with AAC when comparing dietary potassium in Q2 with Q1: Q2 was associated with lower odds of having severe AAC (OR 0.65 (95% CI: 0.46-0.92), p=0.02). This association remained significant in the fully adjusted model (OR 0.50 (95% CI: 0.29-0.86), p=0.02).

Conclusions: We found that higher dietary potassium intake was associated with lower odds of having severe AAC, but the association is only significant when comparing dietary potassium intake in Q2 with Q1. This nonlinear relationship between dietary potassium intake and AAC requires further investigations.

Funding: NIDDK Support

Multinomial logistic regression models of AAC with dietary potassium intake(g/day) in quartiles, N=2535

Dietary potassium intake	Mild-moderate AAC versus no AAC		Severe AAC versus no AAC	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Q1	Reference		Reference	
Q2: Unadjusted	0.92 (0.54-1.56)	0.74	0.65 (0.46-0.92)	0.02
Adjusted	0.85 (0.48-1.50)	0.56	0.50 (0.29-0.86)	0.02
Q3: Unadjusted	0.78 (0.49-1.26)	0.29	0.99 (0.59-1.65)	0.97
Adjusted	0.79 (0.51-1.23)	0.27	0.92 (0.37-2.31)	0.85
Q4: Unadjusted	1.09 (0.65-1.82)	0.73	0.57 (0.28-1.14)	0.11
Adjusted	0.99 (0.56-1.72)	0.95	0.41 (0.11-1.51)	0.17

PO2373

Association of Rosuvastatin Use with Risk of Hematuria and Proteinuria

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Background: Early safety signals suggested potential nephrotoxicity with rosuvastatin, and the US FDA recommends a maximum dose of 10 mg for patients with severe CKD. Whether these recommendations are followed and whether rosuvastatin use is associated with nephrotoxicity in real-world practice is uncertain.

Methods: Using data from OptumLabs® Data Warehouse, a database that contains de-identified claims and electronic health record data, we identified adult patients who initiated rosuvastatin (N=155416) or atorvastatin (N=793513) in 44 health systems ("cohorts") between 2011-2019, were free of ESKD, and did not have history of hematuria or proteinuria at the time of prescription. The outcomes were hematuria (dipstick hematuria≥+ or presence of ≥3 red blood cells in urine microscopy) and proteinuria (dipstick proteinuria≥++ or urine albumin-to-creatinine ratio≥300 mg/g). We fit Cox models with inverse-probability of treatment weights within cohorts and then meta-analyzed using random-effects models.

Results: Overall, 2.6% and 0.8% of patients developed hematuria and proteinuria during a median follow-up of 2.6 years. Compared with atorvastatin, rosuvastatin was associated with an increased risk of hematuria (HR, 1.07 [95% CI, 1.03-1.11]) and proteinuria (1.18 [1.11-1.26]). Among those with eGFR<30 ml/min/1.73 m^2, rosuvastatin use was associated with greater risk of hematuria (1.78 [1.25-2.54]) and proteinuria (1.80 [1.15-2.83]) (**Figure**). Patients with eGFR<30 ml/min/1.73 m^2 frequently were prescribed a higher rosuvastatin dose than the maximum recommended dose of 10 mg; 30.5% received 20 mg while 14.4% received 40 mg.

Conclusions: Among patients with eGFR<30 ml/min/1.73 m^2, the use of higher-than-recommended dose rosuvastatin was common, and rosuvastatin was associated with an almost 2-fold increased risk of hematuria and proteinuria.

Funding: NIDDK Support

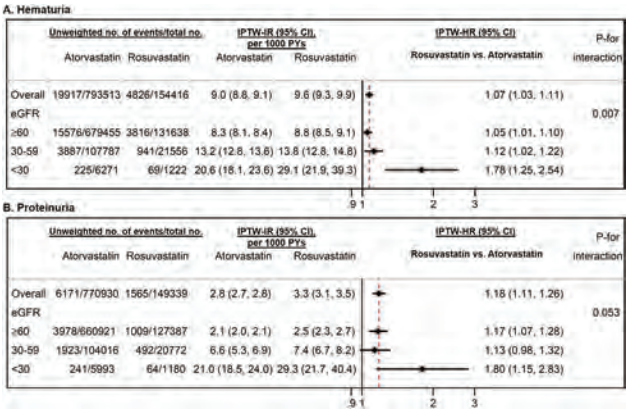

Figure. Risks of outcomes associated with rosuvastatin vs. atorvastatin, overall and across eGFR levels

PO2374

Hydrophilic vs. Lipophilic Statin Treatments in Patients with CKD After Acute Myocardial Infarction: A Propensity Score-Matched Comparison

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Background: Effect of statin treatment is critical to prevent major adverse cardiac and cerebrovascular events (MACEs) after acute myocardial infarction (AMI). Earlier studies demonstrated that the lipophilicity of statin did not affect prognosis in AMI patients without renal dysfunction. However, the effect of statin lipophilicity was not investigated in chronic kidney disease (CKD) patients.

Methods: We enrolled total 2,020 AMI patients with chronic kidney disease (CKD) from Korea Acute myocardial Infarction Registry between November 2011 and December 2015. CKD was defined as an eGFR < 60mL/min/1.73 m^2. Patients were divided into two groups based; hydrophilic (n = 663), lipophilic (n = 1399) statin treatment. The primary endpoint was a combination of 2-year major MACEs after AMI occurrence. Subsequently, a propensity score matched analysis was performed.

Results: The lowest cumulative event rate of MACE (HR 0.71 [95% CI 0.55-0.91], p=0.007), all-cause mortality (HR 0.68 [95% CI 0.50-0.94], p=0.018), recurrent MI (HR 0.42 [95% CI 0.23-0.76], p=0.005) was observed in patients treated with hydrophilic statin in propensity -matched population. In multivariable Cox-regression analysis, compared to patients treated with lipophilic statins, patients treated with hydrophilic statins were associated with lower risk for composite of MACEs (HR 0.70 [95%

CI 0.55-0.90], p=0.005), all-cause mortality (HR 0.67 [95% CI 0.49-0.93], p=0.016) and recurrent MI (HR 0.40 [95% CI 0.21-0.73], p=0.003), but not for composite of revascularization, and ischemic stroke.

Conclusions: Hydrophilic statin treatment was significantly better to reduce MACEs and all-cause mortality than lipophilic statins in CKD patients with AMI.

PO2375

The Effect of Fibrates on Kidney Function and CKD Progression: A Systematic Review and Meta-Analysis of Randomised Studies

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Background: Fibrates have proven efficacy in cardiovascular risk reduction and are commonly used, in addition to statins, to control hypertriglyceridemia. Their use is often limited due to reduction in glomerular filtration rate at treatment initiation. However, recent studies suggest benign change in kidney function and improvement of proteinuria; an established early marker of microvascular disease and kidney disease progression. We summarize the evidence from existing trials and provide summary effects of fibrates, alone or in combination, on kidney disease progression and proteinuria.

Methods: Systematic review and Meta-analysis of randomised controlled trials(PROSPERO CRD42020187764).

Results: Out of 12243 potentially eligible studies, 29 were included in qualitative and quantitative analysis, with a total of 20176 patients. Mean creatinine increased by 1.05 [95% CI(0.63 to 1.46)] units in patients receiving fibrates vs comparator, and this was similar in all other subgroups. eGFR showed a bigger decrease in the fibrates arm [SMD -1.99; 95% CI(-3.49 to -0.48)] when all studies were pooled together. Notably, short-term serum creatinine and eGFR changes remained constant in the long-term. Pool estimates show that fibrates improve albuminuria progression, RR 0.86; 95% CI(0.76 to 0.98); albuminuria regression, RR 1.19; 95% CI (1.08 to 1.310)]. Two studies showed reduction in progression to ESKD, albeit without statistical significance.

Conclusions: Fibrates improve albuminuria in patients with and without diabetes when used to treat hyperlipidaemia. The modest creatinine increase should not be a limiting factor for fibrate initiation in people with preserved renal function or mild CKD. The long-term effects on kidney disease progression warrant further study.

PO2376

The Effect of Atrasentan on Kidney and Heart Failure Outcomes by Baseline Albuminuria and Kidney Function: A Post Hoc Analysis of the SONAR Trial

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Background: Atrasentan reduces kidney failure risk, but increases risk of edema and possibly heart failure in patients with diabetic kidney disease. Patients with advanced chronic kidney disease (CKD) may obtain greater absolute renal benefit from atrasentan but may be at higher risk of fluid retention due to impaired renal excretory capacity. We assessed effects of atrasentan on kidney and heart failure events according to baseline eGFR and albumin:creatinine ratio (UACR) in a post-hoc analysis of the SONAR trial.

Methods: The effect of atrasentan versus placebo in 3668 patients with type 2 diabetes and CKD with elevated UACR was examined in SONAR. We used Cox regression to study effects on the primary kidney outcome (doubling of serum creatinine, end-stage kidney disease or renal death) and heart failure hospitalization across subgroups of eGFR (<30, ≥30-45, ≥45 ml/min/1.73m^2) and UACR (<1000, ≥1000-3000, ≥3000 mg/g).

Results: Atrasentan reduced the relative risk of the primary kidney outcome (HR 0.71, 95%CI 0.58-0.88) consistently across subgroups of baseline eGFR and UACR (table). Patients in the highest UACR and lowest eGFR subgroups showed the largest absolute benefit (all P-interaction <0.01). The relative (HR 1.39, 95%CI 0.97-1.99) and absolute risk of heart failure hospitalization was consistent across eGFR or UACR subgroups (all P-interaction >0.09).

Conclusions: Atrasentan reduced the relative risk of the primary kidney outcome consistently across baseline UACR and eGFR subgroups. The absolute risk reduction was greater among patients in the lowest eGFR and highest albuminuria subgroup who were at highest baseline risk. However, the relative and absolute risk of heart failure hospitalization were similar across baseline UACR and eGFR subgroups. These results support the initiation of atrasentan in high risk patients with CKD and significant albuminuria.

	Atrasentan n/N	Placebo n/N	HR (95% CI) for primary kidney outcome	P interaction
UACR <1000	36/1062	44/1065	0.82 (0.53-1.28)	0.208
UACR ≥1000 to < 3000	80/637	91/632	0.72 (0.53-0.98)	
UACR ≥3000	36/135	57/136	0.57 (0.37-0.88)	
eGFR <30	58/293	74/299	0.73 (0.51-1.03)	0.916
eGFR ≥30 to < 45	58/752	75/756	0.70 (0.50-1.00)	
eGFR ≥ 45	36/789	43/778	0.64 (0.41-1.02)	

PO2377

The Comparative Effectiveness and Safety of Rivaroxaban and Warfarin Initiation in Adults with Atrial Fibrillation (AF) by eGFR Category

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Background: The risk-benefit ratio of rivaroxaban, a commonly prescribed direct oral anticoagulant, relative to warfarin in patients with atrial fibrillation (AF) and CKD is uncertain.

Methods: We conducted an international multicenter cohort study(2011-2018) using healthcare data from 5 jurisdictions across Australia (530 participants of the 45 and Up Study [among 267153 recruited in 2006-09] with data, accessed via SURE, linked to hospital/laboratory data [by CHeReL] and the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data provided by Services Australia) and Canada (55038 patients in AB,BC,MB,ON; record linkage of provincial administrative/laboratory data). We propensity score matched adults with a new dispensation of rivaroxaban or warfarin, who had AF and a recorded eGFR grouped as≥60,45-59,30-44 and <30 ml/min/1.73m^2. Chronic dialysis or kidney transplant recipients were excluded. We assessed 2 composite outcomes within 1 year of initiating either therapy: ischemic (all-cause death, ischemic stroke or transient ischemic attack) and bleeding events (intracranial, gastrointestinal or other). We used Cox regression to estimate the hazard ratios of each outcome across eGFR categories and summarized centre data in random effects meta-analysis.

Results: Of the 55568 matched rivaroxaban and warfarin users, 4733(8.5%) experienced an ischemic event and 1144(2%) a bleeding event. As compared to warfarin initiation, rivaroxaban initiation was associated with lower or similar hazard for the ischemic outcome HR(95% CI) of 0.72(0.66-0.78), 0.82(0.58-1.16), 0.70(0.57-0.87) and 0.78(0.62-0.99), for eGFR ≥60, 45-59, 30-44 and <30ml/min/1.73m^2 respectively. Rivaroxaban initiation was also associated with lower or similar hazard for the bleeding outcome (0.70[0.49-1.00], 1.00[0.78-1.29], 0.85[0.64-1.12], 0.61[0.35-1.05]). We observed no evidence of heterogeneity across centers except for eGFR 45-59ml/min/1.73m^2 for the ischemic outcome(I^2=77%) and ≥60ml/min/1.73m^2 for the bleeding outcome(I^2=62%).

Conclusions: Compared to warfarin, rivaroxaban initiation was associated with lower or similar risk of both ischemic and bleeding outcomes independent of eGFR. Sufficiently powered randomized trials are needed to confirm findings from this large international cohort.

Funding: Government Support - Non-U.S.

PO2378

Risk of Bleeding Associated with Direct Oral Anticoagulants Is Higher Among Patients with Concomitant Use of Diltiazem in Patients with and without CKD

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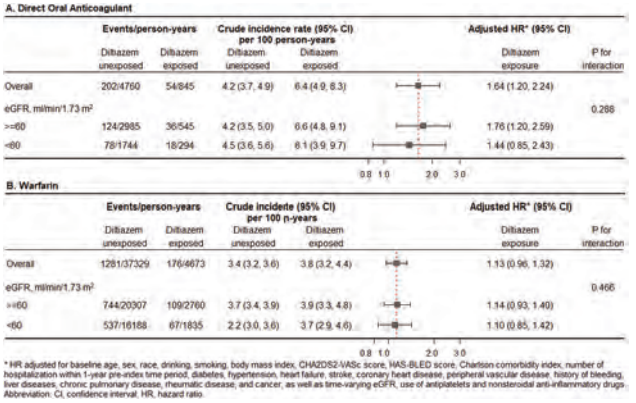
Background: Inhibitors of the cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) systems can increase blood levels of direct oral anticoagulants (DOACs). Diltiazem, a moderate CYP3A4/P-gp inhibitor, is commonly used for heart rate control in patients with atrial fibrillation (AF). We hypothesized that the co-administration of diltiazem with DOACs would be associated with bleeding events, particularly in patients with CKD.

Methods: We identified adult patients with AF and without end-stage kidney disease in the Geisinger Health System who initiated any DOAC between 2010-2018. We used Cox proportional hazard models with time-varying exposure to diltiazem, adjusting for characteristics at DOAC initiation as well as time-varying eGFR and use of antiplatelets and nonsteroidal anti-inflammatory drugs. We examined whether the risk of bleeding differed by CKD (eGFR <60 ml/min/1.73 m^2) status. As a negative control, we repeated the same analysis among warfarin users (n=13179), since there is no known interaction between warfarin and diltiazem.

Results: Among the 4544 patients who initiated apixaban (n=2373), rivaroxaban (n=1583), or dabigatran (n=588), the mean (SD) age was 72 (12) years, 45% were female, and the average eGFR was 69 (21) mL/min/1.73 m^2. At the time of DOAC initiation, 15% were on diltiazem and additional 4% initiated diltiazem during the follow-up. Among DOAC users, concomitant use of diltiazem was associated with a higher risk of bleeding (hazard ratio, 1.64; 95% confidence interval [CI]: 1.20-2.24), consistently across CKD status (**Figure A**). Among warfarin users (the negative control), concomitant use of diltiazem was not associated with bleeding (**Figure B**).

Conclusions: Concomitant use of diltiazem with DOACs was associated with a higher risk of bleeding in patients with AF, with similar risk with and without CKD.

Funding: NIDDK Support



PO2379

Association of Long-Term Aspirin Use with Progression of Kidney Disease

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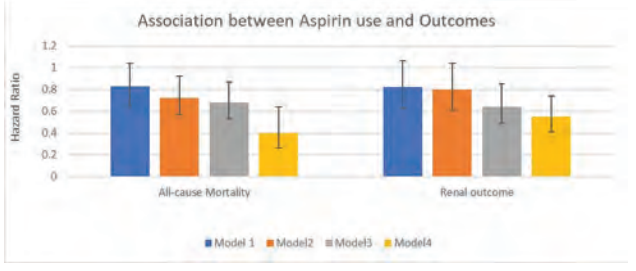
Background: Aspirin (ASA) has been used to control inflammation for over a century. Recently, chronic microinflammation was detected to be a major contributor to the progression of chronic diseases such as cancer and chronic kidney disease (CKD). However, it is unclear if long-term use of ASA could lower mortality and slow renal deterioration in patients with CKD.

Methods: We identified 860 US Veterans with non-dialysis dependent CKD followed at a single medical center between October 2014 to September 2015. Associations between long-term ASA use (at least 90 days) with mortality, and with a combined renal outcome (dialysis or eGFR dropping 40% from baseline) were examined in multivariable adjusted Cox proportional hazards models. Besides the crude model (model 1), we adjusted for demographics, BMI, smoking status, blood pressure (model 2), for comorbidities (Model3), and for antihypertensive medications, NSAIDs, steroids, baseline eGFR, medication adherence rate, and proteinuria (Model 4).

Results: The mean age (SD) of ASA users vs. non-users was 68.1 (9.9) vs. 64.2 (13.1) years, and the mean eGFR (SD) was 36.9 (0.7) ml/min/1.73m² vs. 43.7 (2.0). Over a 4.6-year median follow-up period, 37% of patients reached the combined renal endpoint (event rate: 102.8/1000 patient-years) and 372 (43%) patients died. ASA users demonstrated a lower risk of the renal outcome (Hazard Ratio [HR] 0.55[95%CI: 0.41, 0.74], p<0.001) and a lower mortality rate (HR 0.40[95%CI: 0.26, 0.64], p<0.001) in the fully adjusted model [Figure].

Conclusions: CKD patients receiving ASA for 90 days or longer had slower deterioration of kidney function and lower mortality. Further clinical trials are required to investigate the benefits of ASA in this population.



PO2380

Treatment of Hyperuricemia and Incident CKD in Patients with Normal Kidney Function

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Background: Hyperuricemia is associated with incident chronic kidney disease (CKD) independent of established metabolic risk factors. Treatment of hyperuricemia with uric-acid lowering therapy (ULT) was not beneficial in clinical trials of patients with CKD, but the effects of ULT on incident CKD in patients with no pre-existing CKD is unclear.

Methods: We identified a national cohort of US Veterans with normal kidney function (eGFR ≥60 ml/min/1.73m² and no proteinuria) and serum uric acid measurement. We examined the association of incident new ULT use (vs. no ULT), with the incidence of CKD (defined as 2 measurements of eGFR <60 ml/min/1.73m² or UACR >30 mg/gm at least 90 days apart), using time dependent Cox models adjusted for baseline demographic characteristics, comorbid conditions, and time dependent eGFR and serum uric acid concentration.

Results: We identified 1,152,040 patients with a serum uric acid measurement, of whom 111,508 (10%) patients received de novo ULT during 2006-2019. The overall mean (SD) age was 59 ±13 years, 94% were male, 76% were white, and the mean (SD) eGFR was 84 (17) ml/min/1.73m² at the cohort entry. There were 308,311 cases of incident CKD (event rate, 40.4/1000 PY; 95%CI, 40.3-41.6) over a median follow-up of 6.1 years. ULT was associated with higher risk of incident CKD in both crude models (hazard ratio, 2.57; 95%CI, 2.55-2.60) and after multivariable adjustments (HR, 1.45; 95%CI, 1.44-1.47) [table].

Conclusions: Although hyperuricemia is independently associated with risk of CKD, treatment of hyperuricemia with ULT was not associated with lower risk of incident CKD in patients with baseline normal kidney function and no proteinuria in a large national cohort.

Funding: Veterans Affairs Support

	N (%)	Incident CKD event rate	Crude hazard ratio (95% CI)	Multivariable adjusted hazard ratio (95% CI)
No ULT	1,040,532 (90)	36.5/1000 PY	Referent	Referent
ULT	111,508 (10)	91.8/1000 PY	2.57 (2.55-2.60)	1.45 (1.44-1.47)

PO2381

Trial Design of FRONTIER: Ferric Citrate for the Prevention of Renal Failure in Adults with Advanced CKD

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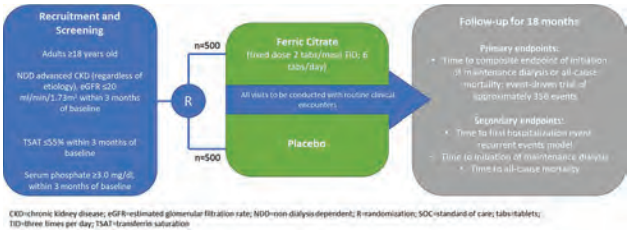
Background: There are no approved therapies to delay progression to RRT or improve survival specifically in patients with advanced CKD regardless of etiology. A pilot, open-label randomized trial in 200 patients with estimated GFR < 20 ml/min/1.73m2 demonstrated statistically significant reduction in the risk of the composite endpoint of death, dialysis or transplantation in patients randomized to fixed dose ferric citrate coordination complex (FCCC) as compared to standard of care (SOC). The current trial is designed to overcome the limitations of this open-label RCT by using a pragmatic, placebo-controlled, randomized trial design.

Methods: FRONTIER will enroll 1000 patients with estimated GFR < 20 ml/min/1.73m2 who will be randomized 1:1 to either fixed dose FCCC (2 tablets/meal) or matching placebo. Enrollment will not be based on serum concentrations reflecting iron sufficiency or phosphate. Subjects will be followed for 18 months using a pragmatic schedule based solely on SOC visits. No additional trial specific visits or laboratory tests will be required. The primary objective is to determine the effect of FCCC on the time to a composite endpoint of initiation of maintenance dialysis or all-cause mortality compared to placebo. The secondary objective is to evaluate the impact of FCCC on all-cause hospitalization and the individual components of the primary endpoint.

Results: FRONTIER is a collaboration between Industry (Akebia Therapeutics is providing study medication and funding), community nephrologists (planned for 42 sites in the US) and academia. An executive steering committee has designed the clinical trial protocol and US Renal Care, Inc will be acting as the Sponsor-Investigator.

Conclusions: Based on supportive pilot data, FRONTIER will utilize a novel trial design incorporating a pragmatic approach while maintaining a randomized, placebo-control arm and generating real-world evidence to determine the effects of FCCC on clinically meaningful patient outcomes (time to dialysis or all-cause mortality).

Funding: Commercial Support - Akebia Therapeutics



PO2382

Effect of Oral Sodium Bicarbonate on Biomarkers of Bone Turnover in CKD: A Secondary Analysis of the BASE Pilot Trial

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Background: CKD clinical practice guidelines recommend treatment with alkali to mitigate adverse effects of metabolic acidosis on several organ systems, including bone. The effect of alkali supplementation on bone turnover in CKD is unclear. We performed a secondary analysis of the Bicarbonate Administration to Stabilize eGFR (BASE) Pilot Trial to investigate the effect of $NaHCO_3$ on biomarkers of bone turnover.

Methods: BASE randomized 194 individuals with eGFR 20-59 ml/min/1.73m^2 to receive placebo (n=52) or one of two doses of $NaHCO_3$ (0.5 mEq/kg/d, n=52; 0.8 mEq/kg/d, n=90) for 28 weeks. We measured serum parathyroid hormone (PTH), bone-specific alkaline phosphatase (B-SAP), c-telopeptide (CTX, marker of bone resorption), and procollagen type I intact N-terminal propeptide (PINP, marker of bone formation) levels from stored samples collected at baseline, week 12, and week 28, and compared the mean change from baseline between placebo and those treated with $NaHCO_3$ using linear mixed models.

Results: 168 of 194 participants (86%) submitted samples for post-hoc measurements (placebo, n=46; lower-dose, n=47; higher-dose, n=75). Baseline characteristics were age 67±12 years, female 28%, Black, 32%, Hispanic 15%, eGFR 37±10 ml/min/1.73m^2, serum total CO_2 24±3 mEq/L, B-SAP 12.8±5.6 µg/L, CTX 0.36±0.38 ng/mL, PINP 57±31 ng/mL. $NaHCO_3$ treatment raised PTH and lowered B-SAP, however there was no significant difference when compared to placebo. $NaHCO_3$ treatment had no effect on CTX or PINP (Table).

Conclusions: $NaHCO_3$ treatment did not have consistent effects on biomarkers of bone turnover as assessed by PTH, B-SAP, CTX, or PINP, and no significant effects relative to placebo in patients with CKD.

Funding: NIDDK Support

Variable	Treatment	Baseline	Week 12	Week 28	Mean Δ (95% CI)	Within group p-value	Between group p-value
Intact PTH (pg/mL)	Placebo	70 (66)	84 (86)	69 (65)	0.41 (-0.51, 5.88)	0.883	0.140
	NaHCO3	64 (55)	71 (72)	71 (59)	5.25 (1.88, 8.61)	0.002	
B-SAP (µg/L)	Placebo	13.2 (6.4)	12.4 (5.5)	12.9 (5.1)	-0.16 (-0.51, 0.19)	0.366	0.621
	NaHCO3	12.7 (5.3)	12.6 (5.0)	12.3 (4.9)	-0.26 (-0.47, -0.05)	0.014	
CTX (ng/mL)	Placebo	0.35 (0.39)	0.36 (0.40)	0.34 (0.31)	-0.001 (-0.03, 0.03)	0.932	0.920
	NaHCO3	0.36 (0.37)	0.34 (0.38)	0.35 (0.33)	0 (-0.02, 0.02)	0.747	
PINP (ng/mL)	Placebo	55 (31)	58 (37)	53 (25)	-1.05 (-3.67, 1.56)	0.430	0.676
	NaHCO3	58 (31)	58 (31)	58 (31)	-0.39 (-2.03, 1.25)	0.640	

PO2383

Can Structured, Moderate Exercise Slow Kidney Function Decline in Sedentary Elders?

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Background: In numerous observational studies, higher physical activity is associated with slower declines in kidney function; however, no large trial has evaluated whether exercise can ameliorate kidney function decline in older adults. The Lifestyle Interventions and independence For Elders (LIFE) was a randomized clinical trial that demonstrated that a structured, moderate intensity physical activity (PA) intervention compared to a health education (HE) control intervention reduced the incidence of major disability among sedentary elders.

Methods: The LIFE-Kidney ancillary study evaluated whether this exercise intervention impacted the primary outcome of rate of eGFR change over two years. Participants were men and women aged 70-89 who reported being sedentary and were considered high risk for mobility impairment. Blood samples were collected pre-randomization (n=1,179), and at years 1 (n=1,155) and 2 (n=1,044) of follow-up; cystatin C was measured, and GFR was estimated by the CKD-EPI equation. Change in eGFR by cystatin C was the primary endpoint; rapid decline was defined by the high tertile threshold of 6.7%/year.

Results: At baseline, the two groups were well balanced by age, comorbidity and physical limitations, and had comparable eGFR. The PA group had eGFR values 0.5 and 1.5 ml/min/1.73m2 higher at years 1 and 2, respectively, and the average effect across the 2 follow-up visits was significantly different (p=0.04). Those in the PA arm were also less likely to experience a >6.7% annual eGFR decline compared to the HA arm (Table). In the PA arm, total steps completed was strongly associated with reduced eGFR decline (p=0.001), and mediated the effect of randomization to PA compared with HE (F statistic attenuated from 4.09 to 1.84).

Conclusions: Among sedentary elders, randomization to a program of moderate exercise slowed kidney function decline over 2 years compared with a control arm of health education.

Funding: NIDDK Support

	Physical Activity	Health Education Control	p-value
Baseline eGFRcys	54.0	53.4	0.52
Year 1 eGFRcys	52.6	52.1	0.33
Year 2 eGFRcys	51.5	50.0	0.02
eGFR decline >6.7%/year over 2 years	135 (25.9%)	167 (32.2%)	0.02
Adjusted* OR; 95% CI	0.81; 0.66-0.99	Ref.	0.04

*Adjusted for baseline eGFR

PO2384

Effect of Applying 6% Low-Protein Formula to Dietary Advice in Elderly CKD Patients: A Randomized Control Trial

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Background: The majority of researches have suggested the benefit of low-protein diet (LPD) could delay renal function progression in chronic kidney disease(CKD), but LPD increases the risk of malnutrition. The propose of this study to determine the effectiveness of dietary advices used by 6% low protein formula (6% LPF) for elderly CKD patients.

Methods: Patient were recruited aged over 65 years old who were diagnosed stages 3-5 CKD .There were randomized to general LPD advice (control group) or LPD advice combined with application 6% LPF (intervention group) for renal dietitian during 3 months treatment. 6% LPS were prescribed daily, providing 400 kcal energy, 6 g of protein. The data analyzed were measured body weight (BW), body mass index (BMI), hand grip strength (HGS)in nutrition status and blood urea nitrogen (BUN), creatinine and estimated glomerular filtration rate (eGFR) in kidney function parameter.

Results: 95 patients enrolled, and 47 completed of this study was distribution to intervention group (n=24) and control group (n=23). During the study period, HGS was maintain in intervention group but decreased significantly in control group (P<0.02) However, BW and BMI in both group were no significant differences. BUN was significantly reduced in intervention group (p = 0.003) but not control group (p = 0.059). There were no differences in creatinine and eGFR between groups at baseline to 3 months.

Conclusions: Compared with routine LPD prescription, which combined with supplement 6% LPF was associated with maintained nutrition status and prevention on of renal failure. Our findings suggested that 6% LPF was a complementary strategy routine LPD education protocol.

Table 1 Change in nutrition status and renal function parameters from intervention group and control group

	Intervention group (n=24)				Control group (n=23)			
	Baseline		3 month	[a]*P* value	Baseline		3 month	[b]*P* value
Nutrition Status								
Body weight(Kg)	61.0	(48.2- 68.1)	61.0	(50.1- 68.1)	0.841	67.3 (54.8- 73.2)	67.2 (57.1- 72.9)	0.131
BMI (kg/m^2)	25.5	(20.8- 25.2)	23.6	(20.7- 25.4)	0.280	24.2 (23.0- 27.4)	24.6 (23.0- 27.5)	0.649
HGS(kg)	24.1	(17.0- 30.6)	25.4	(17.3- 33.3)	0.103	26.9 (19.6- 31.4)	25.6 (18.0- 30.3)	0.022*
Renal function parameter								
BUN (mg/dL)	31	(25- 43)	29	(22- 43)	0.003**	31 (23- 46)	26 (19- 53)	0.059
eGFR (mL/min/1.73 m^2)	36	(19- 45)	38	(16- 44)	0.710	34 (22- 50)	31 (19- 50)	0.168
Creatinine(mg/dL)	1.7	(1.6- 3.4)	1.7	(1.5- 3.7)	0.587	1.9 (1.4- 3.0)	1.9 (1.4- 3.41)	0.053

eGFR. estimated glomerular ;BUN ,blood uren nitrogen: BMI ,body mass index: HGS, hand grip strength

[a]Comparisons within intervention groups were performed by Wilcoxon signed rank test.

[b]Comparisons within intervention groups were performed by Wilcoxon signed rank test.

* p<0 .05

** p< 0.01

PO2385

Incident Biologic Use and Risk of ESKD in Patients with Inflammatory Bowel Disease

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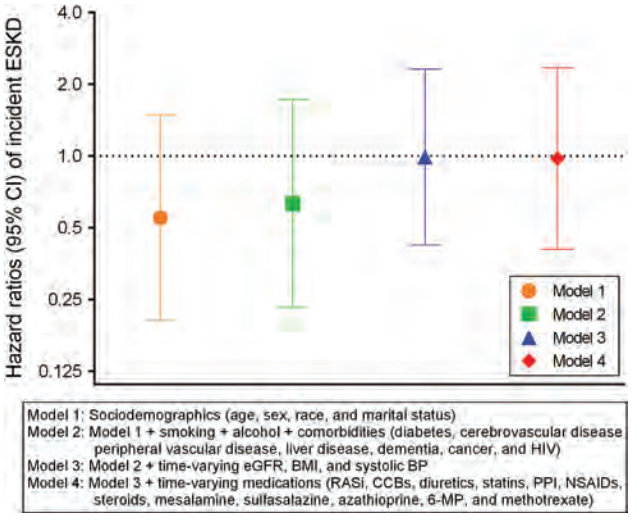
Background: Inflammatory bowel disease (IBD) is associated with reduced kidney function, possibly due to chronic inflammation or the use of nephrotoxic therapies. Little is known about the effects of IBD therapy using novel biologic agents on the risk of incident end-stage kidney disease (ESKD).

Methods: In a nationwide cohort of 66,602 US veterans with an eGFR ≥60 mL/min/1.73m^2 from 2004-2006 who were newly diagnosed with IBD (at least 2 IBD diagnoses that were 30-365 days apart) during follow-up through 2018, we examined the association of incident biologic use (as a time-dependent exposure) with incidence of ESKD, using time-dependent Cox models adjusted for sociodemographics, smoking and alcohol use, comorbidities, eGFR, vital signs, and relevant medications (e.g., antihypertensives, NSAIDs, steroids, nonbiologic DMARDs).

Results: Patients were 69±11 years old; 93% were male; 7.4% were African American; 30% were diabetic; and baseline eGFR was 77±16 mL/min/1.73m². Among 66,602 patients, 1,047 (1.6%) started biologic therapy, and 504 (0.8%) experienced an incident ESKD. In a sociodemographic-adjusted model, incident biologic use (vs. non-use) was associated with lower risk of incident ESKD (adjusted HRs [95%CI], 0.55 [0.20-1.49], in model 1) albeit not reaching statistical significance. This association was attenuated after further multivariable adjustment (0.98 [0.41-2.35], in model 4; **Figure**).

Conclusions: Biologic agent administration is not associated with higher risk of incident ESKD. Clinical trials are warranted to test whether active interventions with biologic agents are safe and effective in preventing adverse renal outcomes associated with IBD.

Funding: Veterans Affairs Support



PO2386

Decreased Progression of CKD in Patients Undergoing Fecal Microbiota Transplantation (FMT)

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Background: Prevalence of CKD is 8 to 16% in different stages, considered the main cause of emergency and hospital care in Mexico and catastrophic disease, its main causes: diabetes, arterial hypertension and glomerulonephritis. Treatment to prevent progression consists of inhibitors of the renin angiotensin aldosterone system, control of the underlying disease and blood pressure. The estimate of the loss of glomerular filtration rate is 2.3 to 4.5 ml/min per year in CKD patients. The intestinal microbiota has protective, structural and metabolic functions, there is a bidirectional interference of the microbiota and the host maintaining a symbiotic relationship, in CKD patients uremia affects the composition and metabolism of the microbiota, generating dysbiosis that is the absence of balance in the microbiological community generating an increase in the progression of CKD and an increase in the production of N-trimethylamine oxide, indoxyl sulfate and p-cresol sulfate associated with greater cardiovascular events in CKD patients, FMT has been used to correct dysbiosis in some pathologies.

Methods: A prospective, randomized, double-blind, comparative, placebo-controlled clinical trial, carried out at the University Hospital in Monterrey Mexico, in patients diagnosed with CKD due to diabetes and or hypertension, in stages 2, 3, 4 and 5 without renal replacement therapy, divided into 2 groups, MFT group: Microbiota fecal capsules, placebo group: placebo capsules, in both groups 15 capsules were administered every 12 hours for 2 days, on days 0, 10, 30, with a 6-month follow-up to demonstrate the difference in the progression of renal failure.

Results: 28 patients were randomized, the CKD of the placebo group progressed by 53.8% vs 13.3% of the TMF group Fisher's exact test *p* value = 0.0418 (Table 1).

Conclusions: The difference in the proportion of patients who did not decrease their GFR at 6 months was statistically significant, in the present study the patients who received FMT had less progression of CKD at 6 months. FMT was associated with a protective factor.

Funding: Private Foundation Support

Table. 1

	No progression CKD	Progression of CKD	Total
FMT group	13	2	15
Placebo group	6	7	13
Total	19	9	28

PO2387

Association of Kidney Measures with Cardiovascular Events, Kidney Outcomes, and Mortality Among Older Adults

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Background: Based on current criteria (glomerular filtration rate [GFR] <60 ml/min/1.73m² or urine albumin-to-creatinine ratio [UACR] ≥30 mg/g), the prevalence of CKD in U.S. older adults is up to 42% among those aged 65-79 years. However, the risk implications of this CKD definition in this population are controversial. We evaluated the risk of adverse outcomes among older adults across CKD stages based on the Kidney Disease Improving Global Outcomes (KDIGO) definition.

Methods: This study included 2640 older adults (age ≥75 years) without diabetes enrolled in the Systolic Blood Pressure Intervention Trial (SPRINT). We compared the risk of the primary composite SPRINT outcome, and all-cause death, across GFR and albuminuria categories based on KDIGO guidelines. To estimate GFR, we used the CKD Epidemiology Collaboration (CKD-EPI) equation and the Berlin Initiative Study (BIS1), a novel estimator of GFR in elderly persons.

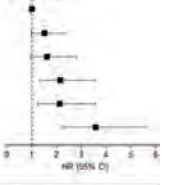
Results: Mean age was 79.8 years, 37.9% were female, 17.0% of participants self-identified as non-Hispanic Black, 6.6% as Hispanic, and 74.6% as non-Hispanic White. Mean estimated GFR was 63.3 ml/min/1.73 m², and median UACR 55 mg/g. In multivariable regression analysis, there was no statistically significant difference in the risk of the primary outcome among participants with UACR <30 mg/g, regardless of GFR level (**Table**). However, compared with participants with GFR ≥60 ml/min/1.73 m² and UACR <30 mg/g, those with UACR ≥30 mg/g had higher risk of the primary outcome at all levels of GFR, with the highest risk observed among those with GFR <45 ml/min/1.73 m². Similar results were observed with the BIS1 equation was used to estimate GFR.

Conclusions: Among older adults without diabetes, increased albuminuria was associated with adverse cardiovascular outcomes at all levels of GFR. However, low GFR was not associated with adverse outcomes in participants with normal albuminuria. These results support the proposal of an age-adapted definition of CKD.

Funding: NIDDK Support

Table. Primary composite SPRINT outcome by categories of GFR and albuminuria

GFR (ml/min/1.73 m²) and UACR (mg/g) categories	No. of events/ No. of participants (%)	Event Rate per 100 Person-Years	Hazard Ratio (95% CI)*
GFR ≥60 and UACR <30	44/1187 (3.7)	1.2	Referent
GFR 45-60 and UACR <30	34/538 (6.3)	1.99	1.53 (0.98, 2.41)
GFR <45 and UACR <30	19/242 (7.9)	2.49	1.62 (0.94, 2.81)
GFR ≥60 and UACR ≥30	24/282 (8.5)	2.91	2.16 (1.31, 3.56)
GFR 45-60 and UACR ≥30	21/210 (10.0)	3.31	2.12 (1.25, 3.59)
GFR <45 and UACR ≥30	35/181 (19.3)	6.47	3.57 (2.25, 5.65)



*Adjusted for age, sex, race/ethnicity, randomization arm, baseline systolic blood pressure, diastolic blood pressure, cardiovascular disease, total cholesterol and LDL-cholesterol.

Table

PO2388

Validation of Novel Cystatin C (CysC) Rapid Measurement Assay with Human Saliva

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Background: Rapid, frequent point-of-care (POC) monitoring of kidney filtration markers such as cystatin C (CysC) that does not require laborious blood specimen draws/processing can improve chronic kidney disease (CKD) patient outcomes and care. Saliva as a non-invasive biofluid for monitoring kidney function addresses a clinical need for rapid diagnostics in POC and home-based testing. Emerging data suggests CysC as a more reliable kidney filtration marker than creatinine because it is not affected by age, race, ethnicity, or body mass.

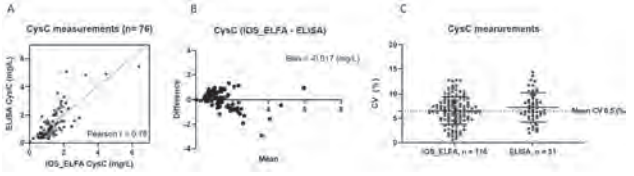
Methods: Our Enhanced Lateral Flow (ELF) immunoassays were validated against a commercial ELISA kit for quantitative measurement of CysC in 76 human healthy and CKD patient saliva samples. We applied Pearson correlation and Bland-Altman analysis to compare the two data sets, and assessed inter-assay repeatability by validating the coefficient of variation (CV) across measurements for the samples. Each sample was measured in triplicate (n=3) to obtain the CV value. The ELF assay was tested with 116 samples, and ELISA with 51 samples, due to limited resources.

Results: The ELF assay CysC assessment showed high correlation to the ELISA measurements, with Pearson r=0.78 (Fig. A). Bland-Altman analysis showed a minor bias of -0.017 mg/L between the two assays (Fig. B). Both assays demonstrated a <10% CV for most of the tests, with the ELF assay presenting a lower overall mean CV (6.5%) than the ELISA kit (7.2%) (Fig. C). Data from stability studies verified that the ELF assay maintains functionality at Day 510 when stored at room temperature.

Conclusions: We have demonstrated rapid measurement of CysC in human saliva with our novel ELF assay, with acceptable POC characteristics, and repeatability and reproducibility equivalent to ELISA. The ELF assay provided more accurate and faster

results (<30 min. vs. 3 hr. for ELISA), and also demonstrated a longer shelf life (stable at 510 days at ambient vs. ELISA requirements for storage at -20°C with a 1 yr. expiration date). Future validation studies could lead to a saliva testing framework for kidney function markers, and a potential paradigm shift in the monitoring and care of CKD patients.

Funding: NIDDK Support



PO2389

Kidney Filtration Markers: Accuracy and Reproducibility of Novel Serum Cystatin C Measurements in a Point-of-Care Rapid Test Platform

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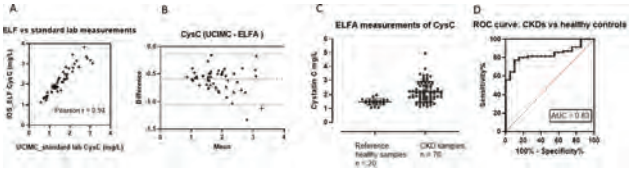
Background: Emerging data suggests cystatin C (CysC) as a more reliable kidney filtration marker than creatinine because it is unaffected by age, race, ethnicity, or body mass. In the US, the standard approach to assess blood-based CysC measurements is invasive phlebotomy followed by laborious blood specimen processing. There is a major unmet need for non-invasive point-of-care (POC) measurement of this kidney filtration marker. To fill this gap, we have recently developed and validated novel Enhanced Lateral Flow (ELF) immunoassays to measure CysC in human blood.

Methods: Validation of our ELF assays was performed in two steps. First, Pearson correlation and Bland-Altman analysis were used to assess the correlation, agreement and bias of ELF measurements to UCI Medical Center lab standard measurements from a set of 70 serum samples obtained from chronic kidney disease (CKD) patients. Then, Receiver Operating Characteristic (ROC) curve analysis was used to assess the medical diagnostic value of the ELF assay, with ELF assay measurements of 70 CKD samples and 20 healthy reference samples to determine ROC curve and Area Under Curve (AUC) of the assay.

Results: The ELF assay measurements showed high correlation to standard lab measurements, with Pearson r=0.94 (Figure A). Bland-Altman analysis showed bias of -0.5 mg/L for the ELF assay, which could be adjusted if it is consistent when we continue monitoring the assay on a broader concentration set of samples (Figure B). The ROC analysis showed excellent diagnostic value, with AUC=0.83, which shows potential for discriminating healthy and CKD subjects (Figure C and D).

Conclusions: We have demonstrated feasibility and validation of a novel POC assay to measure CysC in human blood-based samples. The ELF assay possesses acceptable POC characteristics, correlates well to standard laboratory measurements, and shows good diagnostic value. Future development could lead to a fully available POC measurement framework for CysC as a kidney function marker, and a potential paradigm shift in patient monitoring and care.

Funding: NIDDK Support



PO2390

Serum Creatinine Concentration and Estimates of Muscle Mass Among Race/Ethnicity Groups with End-Stage Kidney Failure

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Background: Racial differences in serum creatinine concentration have been attributed to differences in muscle mass. We examined this hypothesis among End Stage Kidney Disease patients receiving hemodialysis, whose serum creatinine concentration (SCr) should not be highly influenced by glomerular filtration.

Methods: 501 participants were enrolled from 2 centers who were at least 1 year post start of hemodialysis and for whom we measured SCr and body composition (including height-adjusted intracellular water [ICW] as a surrogate of muscle mass) using bioelectrical impedance spectroscopy. In multivariable linear regression we examined the independent association of race/ethnicity (Black, Asian, Non-Hispanic White (NHW), and Hispanic) with estimated muscle mass. We then examined whether race/ethnicity was associated with SCr with adjustment for demographics, clinical factors and body composition including ICW.

Results: Black (0.24 (-0.01,0.49)) and Hispanic (0.05 (-0.26, 0.37)) participants had similar ICW to that of NHW, but ICW was higher among Asians (0.42 (0.11, 0.72)). In contrast, SCr concentrations were significantly higher among Blacks, Hispanics and Asians compared with NHW. Adjustment for ICW did not change these associations or attenuate the difference in SCr between any racial/ethnic group and NHWs.

Conclusions: Among prevalent dialysis participants, ICW, a muscle mass surrogate, was higher among Asian, but not among Black, participants when compared to NHW. After adjusting for ICW, higher SCr was observed across all race ethnicity categories and muscle mass did not appear to explain differences in SCr by race/ethnicity.

Funding: NIDDK Support

Association between Race/Ethnicity and SCr in multivariable regression (N=501)

	SCr, mg/dl (Mean 7.09mg/dl, NHW)	
Race Ethnicity	Adjusted for demographics and clinical factors	Adjusted for demographics, clinical factors ECW, FM and ICW
Non-Hispanic White n=55	Reference	Reference
Black n=318	1.68 (1.09, 2.27)	1.71 (1.14, 2.28)
Hispanic n=58	0.83 (0.08, 1.57)	0.82 (0.11, 1.54)
Asian n=70	1.61 (0.90, 2.32)	1.52 (0.83, 2.22)

Demographics (age, sex); Clinical factors (phosphorus, albumin, adequacy (kt/v), hx Diabetes, Dialysis vintage; Bioelectrical Impedance Spectroscopy-Derived Body Composition (ECW= extracellular water; FM=fat mass; ICW=intracellular water)

PO2391

Patient-Reported Symptoms and Subsequent Risk of Myocardial Infarction in CKD

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Background: Patient-reported symptoms often precede clinical acute presentations of atherosclerotic cardiovascular disease (ASCVD), and include chest pain, shortness of breath, and inability to climb stairs. Patients on dialysis frequently have atypical or absent symptoms related to ASCVD; however, it is unknown whether these same findings are observed in patients with non-dialysis requiring chronic kidney disease. We examined time-updated symptoms of ASCVD and their associations with incident acute myocardial infarction (MI) in a large prospective CKD cohort.

Methods: We studied participants from the Chronic Renal Insufficiency Cohort (CRIC) study who had available symptom data. Chest pain, shortness of breath, and inability to climb stairs were evaluated using the Kidney Disease Quality of Life Instrument (KDQOL-36) at each annual study visit, and were categorized as "no symptoms", "mild symptoms", and "moderate or worse symptoms". Associations between categorical time-updated symptoms and interim MI were assessed using Cox regression models with adjustment for potential confounders. We tested for interaction by prior MI, eGFR, and diabetes.

Results: Among 3909 study participants, the mean age was 58 years, and the mean eGFR was 44.3 mL/min/1.73 m2; 22% had prior MI. There were 367 MIs over a median of 7.98 years; median time between symptom assessment and MI was 213 days (IQR 111 to 314 days). Moderate or worse shortness of breath was associated with 1.83-fold increased risk of MI (95% CI 1.25, 2.67) after adjustment. These associations were also seen for chest pain and inability to climb stairs (HR for moderate or worse chest pain 1.65, HR for severe limitation climbing stairs 1.85) (Table). P-values for interaction by prior MI, diabetes, and eGFR were all not statistically significant (p>0.05).

Conclusions: Chest pain, shortness of breath, and inability to climb stairs were significantly associated with increased risk of MI in a large cohort of participants with CKD. This highlights the importance of symptom assessment as early warning signs of ASCVD in patients with CKD.

Funding: NIDDK Support, Private Foundation Support

Associations between time-updated symptoms of ASCVD and incident MI compared to no symptoms

Chest Pain	**Unadjusted**	**Adjusted**
None	Referent	Referent
Mild	1.71 (1.30, 2.25)	1.44 (0.97, 2.12)
Moderate or worse	1.98 (1.43, 2.76)	1.65 (1.05, 2.59)
Shortness of Breath		
None	Referent	Referent
Mild	1.51 (1.18, 1.94)	1.27 (0.87, 1.84)
Moderate or worse	1.80 (1.39, 2.32)	1.83 (1.25, 2.67)
Inability to climb stairs		
No limitation	Referent	Referent
Mild limitation	1.97 (1.46, 2.67)	1.30 (0.84, 2.00)
Severe limitation	3.12 (2.33, 4.16)	1.85 (1.19, 2.87)

Adjusted for age, sex, race/ethnicity, prior MI or revascularization, prior stroke, DM, blood pressure, CHF, AF, BMI, COPD, eGFR, smoking, proteinuria, use of coronary vasodilators, CCBs, and beta blockers

PO2392

SGLT2 Inhibitors: Will They Change the Face of Kidney Care?

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Background: This research examines the evolving care and treatment of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), including the introduction and adoption of SGLT2 inhibitors. It includes trending on perceptions across specialists.

Methods: A total of 1,030 CKD non-dialysis patient records were collected from 183 nephrologists via an online, HIPAA-compliant form in October and November 2020

as part of an independent, retrospective chart audit. Data were also collected from an online survey of 74 endocrinologists, 75 cardiologists, and 76 primary care physicians in September and October 2020, and from 105 nephrologists in April 2021.

Results: CKD patients often experience a range of comorbidities and treatments throughout their disease. The optimal eGFR level nephrologists report they would initiate a CKD patient on an SGLT2 inhibitor is 57.1 ml/min/1.73m^2, or early in Stage 3, which is much earlier than the initiation of other treatments such as nutritional vitamin D and ESAs. Upon referral to a nephrologist, one-in-ten patients with CKD and T2D are already prescribed an SGLT2 inhibitor; this increases as the patient is under nephrology care, up to nearly one-in-five patients; however, there remains room for substantial growth - most notabably in CKD patients without T2D, with just 3% having ever been treated with an SGLT2 inhibitor. While nephrologists have been slow to adopt SGLT2 inhibitors firmly into their treatment paradigms, other physicians report a higher percentage of their DKD patients treated with an SGLT2 inhibitor, especially endocrinologists (34%). One-third of nephrologists report trepidation over prescribing SGLT2 inhibitors in their DKD patients, a percentage that has stayed remarkably consistent over the past year and is nearly mirrored by those who claim they have no trepidation in prescribing. This hinderance only increases (to 44%) when they consider prescribing the agents in non-diabetic CKD patients. However, anticipated use of SGLT2 inhibitors in DKD patients is high across specialists, highlighting the opportunity this class of drugs has to make an impact on the treatment of CKD non-dialysis patients.

Conclusions: As SGLT2 inhibitors offer benefits to diabetic and non-diabetic CKD patients, physicians are poised to begin treatment earlier in disease progression, especially with dapagliflozin now approved for CKD patients with and without diabetes.

PO2393

Prescribing Patterns of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with CKD

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Background: Since the publication of the EMPA-REG trial in 2015, sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have been demonstrated to slow chronic kidney disease (CKD) progression in patients with diabetic kidney disease (DKD). More recently in October 2010, the DAPA-CKD trial demonstrated SGLT-2i slows CKD progression regardless of diabetes (DM) status. We evaluated the adoption of these novel therapeutics in CKD patients, without and with DM.

Methods: A cross-sectional study of the Mass General Brigham Health System CKD registry was conducted in March 2021. All adult patients with non-dialysis CKD stages 3-5 were included. Multivariable logistic regression models were used to assess factors associated with SGLT-2i use in patients without and with DM.

Results: Among 49,587 non-DM, CKD patients, only 145 (0.3%) were taking SGLT-2i. Of 22,653 DM, CKD patients, 1,442 (6.4%) were taking SGLT-2i. As shown in the **Figure**, younger age, Male sex, Black race, history of heart failure, and cardiologist visit in the past year were associated with higher rates of SGLT-2i use in both cohorts. In patients with DM, nephrologist visit in the past year was associated with a higher rate of SGLT-2i use, whereas advanced CKD stages were associated with lower rates of SGLT-2i use.

Conclusions: Despite a well-demonstrated benefit of SGLT-2i, the adaption of these novel agents remained extremely low in the CKD population, particularly among patients without DM. Given the approval of SGLT-2i for CKD in May 2021, interventions to increase SGLT-2i usage and improve outcomes in patients with CKD are urgently needed.

Table. Factors associated with sodium-glucose cotransporter-2 inhibitor use among chronic kidney disease patients without and with diabetes mellitus

	Non-diabetic CKD cohort		Diabetic CKD cohort[1]	
Characteristic	**Adjusted OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Age, years	0.95 (0.94-0.96)	<0.001	0.96 (0.96-0.97)	<0.001
Male	3.48 (2.36-5.13)	<0.001	1.80 (1.60-2.02)	<0.001
Black compared to White	1.86 (1.04-3.31)	0.04	1.30 (1.06-1.60)	0.01
Asian compared to White	0.89 (0.22-3.66)	0.89	1.20 (0.86-1.66)	0.28
Other race compared to White	0.71 (0.36-1.48)	0.36	1.39 (1.13-1.70)	0.002
Hispanic ethnicity			0.82 (0.64-1.06)	0.14
English-speaking			0.73 (0.60-0.89)	0.002
Chronic kidney disease stages 3B compared to 3A	1.14 (0.79-1.63)	0.48	0.79 (0.70-0.89)	<0.001
Chronic kidney disease stages 4 compared to 3A	0.53 (0.26-1.08)	0.08	0.31 (0.24-0.39)	<0.001
Chronic kidney disease stages 5 compared to 3A	0.56 (0.13-2.43)	0.44	0.04 (0.01-0.17)	<0.001
Overweight or obesity compared to normal weight			1.49 (1.25-1.80)	<0.001
Heart failure	3.11 (2.09-4.62)	<0.001	1.20 (1.03-1.40)	0.02
Proteinuria screening	1.05 (0.65-1.69)	0.83	1.22 (1.08-1.38)	0.002
Nephrologist visit within one year	1.39 (0.82-2.34)	0.22	1.18 (1.00-1.39)	0.05
Cardiologist visit within one year	3.14 (2.16-4.56)	<0.001	1.48 (1.30-1.70)	<0.001
Endocrinologist visit within one year			2.36 (2.10-2.66)	<0.001
Renin-angiotensin-aldosterone system inhibitors	2.16 (1.53-3.06)	<0.001	1.87 (1.62-2.15)	<0.001
Diuretics	3.26 (2.14-4.99)	<0.001	0.99 (0.88-1.12)	0.88

[1] Other factors included in the multivariable analysis: coronary artery disease, hypertension, hemoglobin A1C at goal, primary care physician visit within one year, number of emergency room visits during last year, number of hospitalizations during last year, hospitalization during last 30 days, aspirin, beta-blockers, calcium channel blockers, and statins.

PO2394

Identification of Common Medication Therapy Problems in a High-Risk CKD Population

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Background: Medication therapy problems (MTPs) are commonly experienced by patients with chronic kidney disease (CKD) and have the potential to increase morbidity, mortality, and healthcare costs. As part of the Kidney Coordinated Health Management Partnership (Kidney CHAMP), an NIH funded, pragmatic randomized controlled trial testing an electronic health record- (EHR) based population health management approach to improve CKD care, we characterize the types and prevalence of MTPs in a population of high-risk CKD patients.

Methods: Eligible patients are 18 to 85 years old with CKD who have a high risk of progression to ESKD and are not being followed by a nephrologist. MTPs are identified through pharmacist-led telephonic medication therapy management (MTM) and electronic consult by nephrology specialists. Recommendations for resolution of MTPs are provided in the EHR to the primary care provider for review at the upcoming office visit.

Results: To date, in 493 intervention patients, 724 MTPs have been identified. Most patients (76%) experienced at least one MTP. The most common MTP identified was 'needs additional medication therapy,' followed by 'suboptimal medication,' and 'dosage too high.' New indications for SGLT2 inhibitors contributed largely to the 'needs additional medication therapy' category. The most common suboptimal medications identified were NSAIDs, with 15% of patients reporting over the counter or prescription use.

Conclusions: Patients with high-risk CKD experience a sizeable burden of MTPs. Identification of existing MTPs in the community setting is an important first step in the optimization of a medication regimen, with the succeeding goal to resolve and prevent MTPs and improve CKD care and outcomes.

Funding: NIDDK Support

MTP category	n	% with regard to MTPs (N=724)
Needs additional med therapy	214	29.6%
Suboptimal medication	138	19.1%
Dosage too high	105	14.5%
Dosage too low	82	11.3%
Drug interaction	53	7.3%
Needs additional monitoring	47	6.5%
Unnecessary med therapy	44	6.1%
Adverse med event	25	3.5%
Failure to receive drug	16	2.2%

PO2395

Treatment with IL-17 Inhibitors Is Associated with Reduced eGFR in Patients with Psoriasis or Psoriatic Arthritis: A Retrospective Cohort Study

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Background: The complex interplay of the cytokines within the IL family can both mediate and modulate inflammation. Specifically, the cytokine IL-17 has been implicated in several disease processes including hypertension, cardiovascular, autoimmune, and chronic inflammatory diseases. However, there is emerging evidence that IL-17 can also favorably modulate inflammation. It has been demonstrated that low-dose IL-17 therapy may prevent and reverse diabetic nephropathy in mouse models. We aimed to study the effect of IL-17 inhibitors on eGFR in human subjects.

Methods: We conducted a single-center retrospective cohort study of patients who had been treated with an IL-17 inhibitor (ixekuzumab or secukinumab), for the treatment of psoriasis (P) or psoriatic arthritis (PA). Demographics and serum creatinine values were extracted from the electronic medical record. Aggregated data in a 6 month window at 6-months prior to initiation of the IL-17 inhibitor and 12 months after initiation of the IL-17 inhibitor were analyzed using paired t-test. Estimated GFR was calculated using the CKD-Epi equation.

Results: We identified 307 patients who had been treated with IL-17 inhibitors. We included 65 patients who had serum creatinine values at pre-specified time periods before and after initiation of treatment. At baseline, the mean age was 50.3±12 years, 43% were men, 51(78%) had a diagnosis of hypertension, 11(17%) had a diagnosis of diabetes, and mean eGFR was 83.6 mL/minute/1.73 m^2. One year after initiation of IL-17 inhibitor therapy, mean eGFR was significantly lower at 78.7 mL/minute/1.73 m^2 ($p < 0.001$). After excluding patients taking medications known to affect eGFR (n=26), there was still a significant decrease in eGFR after 1 year (88.4 versus 83.2 ml/minute/1.73 m^2, $p < 0.01$).

Conclusions: In patients with P or PA, IL-17 inhibitor therapy is associated with a reduction in eGFR at 1 year after initiation of treatment. Prospective study with longer follow-up is needed to determine the long-term effect of IL-17 inhibitor therapy on kidney function.

PO2396

Network Meta-Analysis for Prevention of Kidney Function Decline Using Uric-Acid-Lowering Therapy in CKD Patients

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Background: Several previous studies have suggested that uric-acid-lowering therapy (ULT) can slow the progression of chronic kidney disease (CKD). However, few studies have evaluated the effects of each ULT treatment on kidney function, although this topic is crucial for CKD patients. This systematic review aimed to summarize evidence from randomized controlled trials (RCTs) concerning the effects of ULT on kidney function.

Methods: We performed a systematic search and selected RCTs in CKD patients comparing the effects of ULT on kidney function. We performed a network meta-analysis to compare each ULT indirectly. The primary outcome was change in estimated glomerular filtration rate (eGFR) from baseline. Treatment effects were summarized using random-effects model.

Results: Ten studies were selected with a total of 1480 patients. Topiroxostat significantly improved eGFR compared to placebo (MD [95% CI]; 1.49 [0.08; 2.90], $P = 0.038$) (Fig. 1). Although Febuxostat did not show a positive effect overall, it significantly improved renal function (eGFR) in a subgroup analysis of CKD patients with hyperuricemia (MD [95% CI]; 0.85 [0.02; 1.67], $P = 0.045$) (Fig. 2). Allopurinol and pegloticase did not show good effects.

Conclusions: Topiroxostat and febuxostat have better renoprotective effects in CKD patients. we believe that the results of this study allow us to recommend ULT with topiroxostat or febuxostat for patients with CKD.

Figure 1

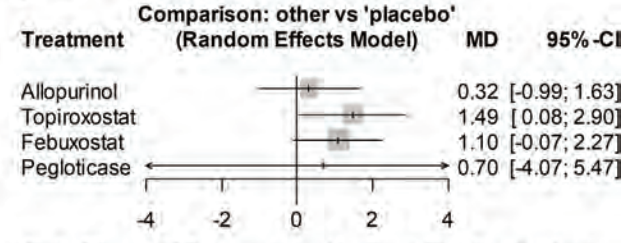


Fig.1. Effects of ULT; change in renal function (eGFR) from baseline in CKD patients.

Figure 2

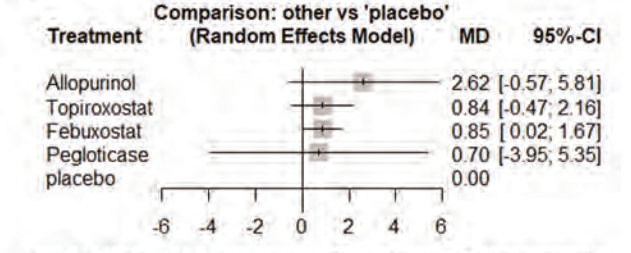


Fig.2. Effects of ULT; change in renal function (eGFR) from baseline in CKD patients with hyperuricemia.

PO2397

Prevalence of Polypharmacy and Associated Adverse Health Outcomes in Patients with CKD: A Systematic Review and Meta-Analysis

Mohammed M. Tinwala,[1] Deenaz Zaidi,[1] Feng Ye,[1] Shezel Muneer,[1] Anukul Ghimire,[1] Maryam Khan,[1] Naima Sultana,[1] Ikechi G. Okpechi,[1] Paul E. Ronksley,[2] Neil Drummond,[1] Dee Mangin,[3] Aminu K. Bello.[1] *[1]University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; [2]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [3]McMaster University Faculty of Health Sciences, Hamilton, ON, Canada.*

Background: Patients with chronic kidney disease (CKD) are at increased risk of adverse health outcomes associated with excessive medication use (polypharmacy) due to impaired kidney function and multimorbidity. However, data on the associations of polypharmacy and adverse health outcomes in this population are limited. We conducted a systematic review and meta-analysis to determine the prevalence of polypharmacy and its associated health consequences in CKD.

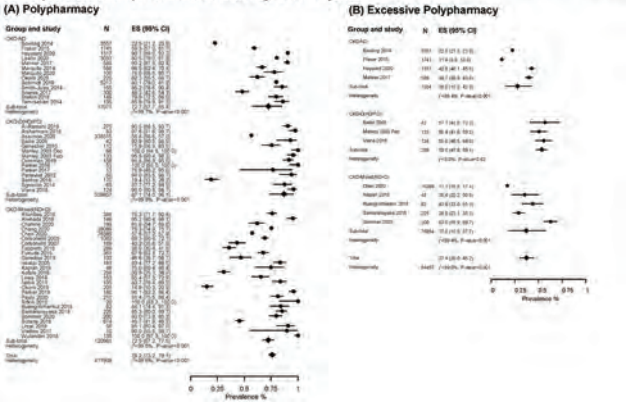
Methods: The study was conducted using a pre-specified study protocol and adheres to PRISMA reporting guidelines. Six electronic databases were searched from inception to September 2020 for studies that included patients with CKD, use of polypharmacy, and associated adverse health outcomes. Random effects models were used to pool the prevalence of polypharmacy and associations with health outcomes.

Results: 53 eligible articles (n = 477,909 patients) met criteria for inclusion. The pooled prevalence of polypharmacy and excessive polypharmacy was 76.2% (95% CI 73.2%-79.1%; range 14.9% to 100%) and 37.4% (95% CI 30.0%-45.2%; range 11.4% to 63.0%), respectively (Figure 1). The prevalence of polypharmacy was 72.7% and 87.1% in non-dialysis CKD and dialysis populations, respectively. 17 studies reported significant associations between polypharmacy and adverse health outcomes. These studies found an increased risk for potentially inappropriate medication use, drug-drug interactions, drug-related problems, medication-related problems, adverse drug reactions, decreased quality of life, decreased kidney function, hospitalization, and mortality.

Conclusions: Polypharmacy is common in CKD and linked to adverse health outcomes. Our findings highlight the need for improved prescribing practices in CKD and the development of strategies to reduce polypharmacy.

Funding: Government Support - Non-U.S.

Figure 1: Forest plot and meta-analysis depicting the pooled prevalence of polypharmacy and excessive polypharmacy in patients with CKD according to dialysis status.
Abbreviations: CKD-ND, non-dialysis CKD; CKD-D (HD/PD), hemodialysis and/or peritoneal dialysis; CKD-Mixed (ND+D), non-dialysis CKD and dialysis combined, or CKD stage was not reported.



PO2398

Risk of Bias in Observational Studies Assessing the Relationship Between Proton Pump Inhibitors and Adverse Kidney Outcomes

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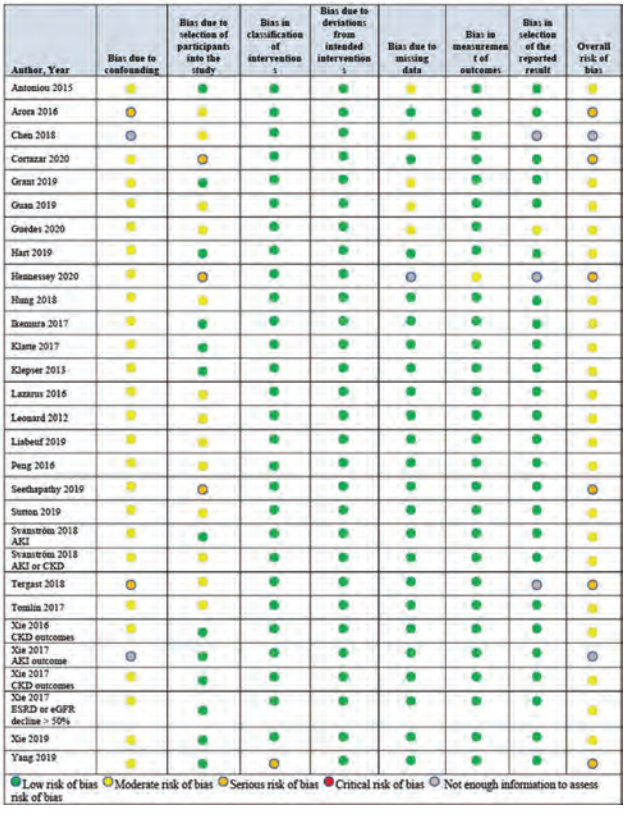
Background: Proton pump inhibitors (PPIs) are widely prescribed as acid-suppression therapy. However, some observational studies suggest that long term use of PPIs is potentially associated with adverse kidney outcomes. We assessed potential bias in observational studies reporting on putative associations between PPIs and adverse kidney outcomes: AKI, acute interstitial nephritis, acute tubular necrosis, CKD, ESRD.

Methods: Searches in EMBASE and PubMed identified relevant English language articles published in the last 10 years. Risk of bias on an outcome-specific basis was evaluated using Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) by 2 independent reviewers (PROSPERO Registration: CRD42021227555).

Results: Of 620 identified records, 26 studies met *a priori* eligibility criteria and underwent risk of bias assessment. 19 studies were rated as having a moderate risk of bias for the reported adverse kidney outcomes, while 6 studies were rated as having a serious risk of bias (mainly due to inadequate control of confounders and selection bias) (Table 1). Effect estimates for the association between PPI and adverse kidney outcomes varied widely (0.24-7.34) but were mostly positive.

Conclusions: Observational studies suggesting kidney harm by PPIs were found to have a moderate to serious risk of bias using the ROBINS-I tool, making it challenging to establish causality. Additional high-quality, real-world evidence among generalizable populations is needed to better understand the relation between PPI treatment and acute/chronic kidney outcomes, taking into account the effects of varying time periods of PPI treatment, potential self-treatment with over-the-counter PPIs, and adequate control for potential critical confounders.

Funding: Commercial Support - Takeda



ROBINS-I

PO2399

Treatment Adherence Support and Relationships with CKD Providers: A Qualitative Analysis

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Background: Adherence is critical in chronic kidney disease (CKD) to delay progression to kidney failure. Treatment plans for CKD can include medications, diet, and exercise. Overall adherence to treatment is low in CKD, and also as few as 40% of new kidney failure patients have any documented CKD-related care. The purpose of this study was to explore CKD patients' experiences of adherence to treatment plans and what role their healthcare providers had in supporting adherence.

Methods: As part of a larger mixed-methods study of Chronic Renal Insufficiency Cohort (CRIC) study participants, a subset was randomly selected for 1:1 interviews. All CRIC participants are >45 years with CKD stages 1-4, and this sample consisted of University of Pennsylvania participants interviewed in 2019-2020. Participants described their experiences with adherence and what they have done when experiencing difficulty. Interviews were recorded, transcribed, and coded using conventional content analysis.

Results: The sample (n=32) had a mean age of 67 years, 53% women, 59% non-white. After analysis of factors relevant to treatment planning and adherence, four themes emerged: patient factors (multiple chronic conditions, motivation, outlook), provider factors (attentiveness, availability, communication), treatment planning factors (lack of plan, proactive patient research, provider-focused goals, and shared decision making), and patient responses to the treatment plan (disagreeing with treatment, frustration with their lack of adherence ["I know what to do"], lack of information, and positive feedback). Patients also described the impact of COVID on access to care and the positive impact of family, ancillary providers, and routines/habits.

Conclusions: These themes align with behavioral learning theory, which includes: internal antecedents (patient factors), external antecedents (provider factors), behavior (treatment planning and attempts at adherence), and consequences (adherence and responses to the treatment plan). Our results provide many potential points of intervention to support treatment adherence in CKD, and a tailored approach is needed to address patients' specific adherence factors.

Funding: Other NIH Support - NINR, NIA

PO2400

The Association Between the Adherence of Self-Management and Prognosis of Non-Dialysis CKD Stages 3-5 Patients

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Background: Self-management plays a very important role in the prognosis of patients with CKD. However, there is a lack of evidence-based results to support this. This study aimed to evaluate the association between the adherence of self-management and prognosis of non-dialysis CKD stages 3-5 patients.

Methods: Data including basic information, laboratory test results, oral drugs, time of endpoint events were retrospectively collected. Patients were divided into good or poor adherence according to whether they participated in self-management education on time every month. Endpoints were the initiation of renal replacement therapy and death.

Results: 785 patients were included in this study. 111 and 674 patients were considered to have good and poor adherence, respectively. 12 and 162 endpoint events occurred in the good and poor adherence groups. Propensity score matching was performed. After 1:2 matching, the outcomes of 315 patients were analyzed(109 : 206). Univariate Cox regression was performed to screen variables with $P < 0.05$, then we further performed Cox proportional hazards regression with three adjusted models. The results of the 3 models all showed that the good adherence of self-management was an independent factor associated with reduced risk of incident endpoints(HR95%CI: Model 1: 0.47(0.25, 0.89); Model 2: 0.31(0.15, 0.64); Model 3: 0.26(0.12, 0.60)). The Kaplan-Meier analysis demonstrated that the cumulative incidence of endpoint events in the good adherence group was significantly lower than that in the poor adherence group (log-rank test, $P < 0.05$).

Conclusions: This study suggests that good adherence with self-management could effectively reduce the incidence of endpoint events in CKD stages 3-5 patients

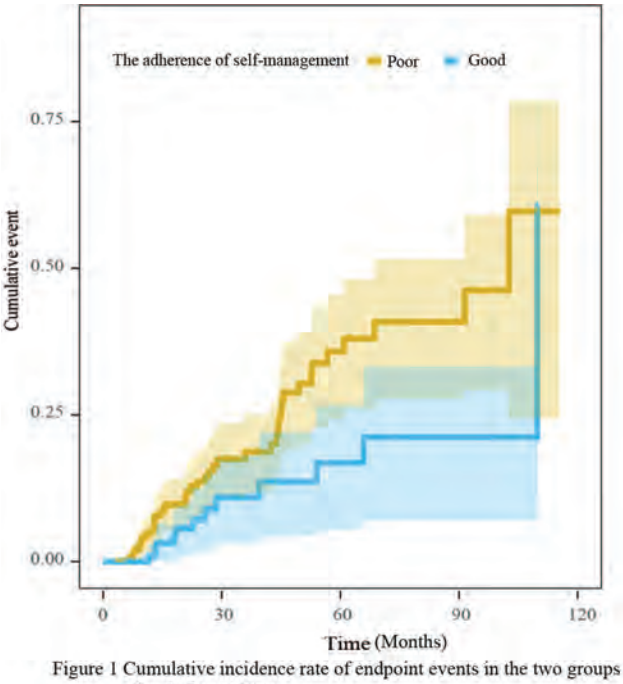

Figure 1 Cumulative incidence rate of endpoint events in the two groups after 1: 2 matching.

PO2401

Impact and Outcomes of Advance Care Planning in CKD

Shanti Tan, Timothy J. Koh, Eileen Pang, Wan Limm Looi, See Cheng Yeo. *Tan Tock Seng Hospital, Singapore, Singapore.*

Background: The incidence of chronic kidney disease (CKD) is rising, with patients being older and having more chronic disease at time of dialysis initiation. Advance care planning (ACP) has been advocated to better align treatment with patient preferences, facilitate shared decision making and improve patient-centred care. We aim to evaluate the impact of ACP on patient-centred outcomes and describe patient preferences expressed during ACP.

Methods: We conducted a retrospective cohort study of patients who underwent ACP from January 2013 to March 2021, comparing outcomes with age-, gender-, aetiology- & renal replacement therapy (RRT) decision-matched patients without ACP. Outcome

measures include intensive care unit (ICU) admissions, number of hospitalisations per year, change in decision for renal palliative care (RPC) and referral to palliative physician.

Results: 198 patients underwent ACP during the study period, with a median age of 77 years old. 52.5% of patients in the ACP cohort were referred as they chose RPC. Other reasons for ACP included patients with difficulty tolerating dialysis, vascular access issues, long-term catheter-based dialysis and significant comorbidities. Majority of patients who underwent ACP elected not for cardio-pulmonary resuscitation (80.8%) or admission to ICU (77.8%), 9.6% of the cohort changed their mind about subsequent treatment plan. Compared to 197 patients in the matched-control group, patients with ACP were less likely to be admitted to ICU (5.0% vs 14.7%, p=0.001). In patients who chose RPC, those with ACP were less likely to have a change in decision for conservative management of CKD (8.6% vs 20.2%, p=0.018), had fewer hospital admissions a year (1.21 vs 1.92, p=0.001) and were less likely to require palliative referral (44.2% vs 61.5%, p=0.013).

Conclusions: ACP should be considered in CKD patients to help align goals of care and treatment preferences. When considering patients who chose RPC, patients who undergo ACP are more likely to be consistent with their plan for conservative management of CKD, including a reduced utilization of resources like ICU care, palliative care involvement and hospital admissions. This ensures appropriate diversion of resources and allows alignment to patient's treatment preferences.

PO2402

Well-Managed CKD and Its Association with Healthcare Resource Utilization and Costs

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Background: Diabetes and hypertension are prevalent in CKD. The association of coordinated care with outcomes in the setting of these coexisting comorbidities is not well understood. This study evaluated the association between well-managed care and healthcare resource utilization (HCRU) and costs.

Methods: Using the Humana Research Database, this retrospective cohort study identified 241,628 patients with CKD Stage ≥ 3a (3% diabetes, 40% hypertension, 50% diabetes and hypertension, 7% neither diabetes nor hypertension) in 2017. Eligible patients were indexed on first evidence of CKD and required to be enrolled in a Medicare Advantage Prescription Drug plan for ≥ 12 months pre- and post-index date. Patients who had kidney transplant or hospice election pre-index were excluded. Well-managed care measures included hemoglobin A1c (HbA1c) monitoring, adherence to glucose medications, cardiovascular (CV) therapy, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACEi/ARBs), and routine primary care provider (PCP)/ nephrologist visits. HCRU and costs were evaluated within 12-months post-index.

Results: The cohort was 55% female, 77% White, average age of 75 years, and comprised of 67%, 23%, 10%, and 1% patients with Stages 3a, 3b, 4 and 5 CKD, respectively. Patients with diabetes and hypertension who were adherent to well-managed care were significantly less likely to experience an inpatient (IP) admission or emergency department (ED) visit (Table 1) and incurred lower mean monthly costs compared with patients who were not adherent to well-managed care. Similar results were observed for patients with diabetes only, hypertension only, or neither condition.

Conclusions: Well-managed diabetes and/or hypertension in patients with CKD was associated with lower HCRU and costs. Findings may inform innovative models of CKD care coordination.

Measures of well-managed care*

	Odds ratio [95% Confidence Interval]				
Outcomes	> 2 HbA1c lab values	< 60 days not covered, glucose therapy	< 60 days not covered, CV therapy	> 3 yearly nephrology visits	> 2 yearly PCP visits
IP admission	0.60 [0.58-0.62]	0.90 [0.87-0.92]	0.93 [0.90-0.96]	0.74 [0.68-0.80]	0.90 [0.87-0.94]
ED visit	0.70 [0.68-0.73]	0.89 [0.87-0.91]	0.96 [0.93-0.99]	0.84 [0.78-0.91]	0.93 [0.90-0.97]

* ACEi/ARBs not significant

PO2403

Opt-In vs. Opt-Out Approach for Kidney Disease Education and Associated Research

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Background: Clinical research mail-invites require patients to call back for their ability to participate (opt-in). This patient-initiative need reduces efficiency, requires more effort, and limits external validity. Opt-out approach, where research team actively contacts those not choosing to call back, can improve efficiency, especially when evaluating recommended but uncommonly used interventions. Current guidelines recommend comprehensive pre-end stage kidney disease (ESKD) education (CPE) for all advanced, stage 4/5 CKD patients but, CPE is uncommonly used prompting patient preference research. Evaluating enrollment statistics for the initial year of randomized controlled Trial to Evaluate and Assess the effects of CPE on Home dialysis among VETerans(TEACH-VET), we report the effectiveness and efficiency of the 'opt-out' approach in CKD education research.

Methods: TEACH-VET (NCT04064086) aims to evaluate universal CPE strategy on Veteran outcomes, including home dialysis. It uses an EHR-based source cohort to mail-invite advanced CKD Veterans; those who do not call-back within 15 days to opt-out, are telephoned for upto 3 times for their interest. Staff surveys(n=6) are used to determine effort (time) associated with each study activity and aggregated for opt-in/opt-out processes. We examined approach success rates, and study enrollments and efficiency(time per enrollments) as outcomes.

Results: Of the total of 226 randomly selected Veterans mail-invited for study participation over the initial 15 months, approach success rate was 3.9%(n=9) for opt-in method, resulting in 2(22%) enrollments, while 4(44.3%) requested additional time for decision. Of the remaining 217, study staff were able to approach 157 invitees(success rate of 72.4%), resulting in 86(54.8%) enrollments, while 18(10.8%) requested additional time. Significant differences in personnel efforts were seen with an estimated 147±69.2 and 183±70 min, minutes per enrollments($p<0.05$) in the opt-in vs. opt-out respectively though, efficiency for enrollment was signficantly better for opt-out vs. opt-in (60.2 vs. 30.7min) approach.

Conclusions: Patient driven opt-in approaches are less effective and efficient for enrollments in clinical and research activities involving the universally recommended services like kidney disease education.

Funding: Veterans Affairs Support

PO2404

CKD Healthcare Utilization Preceding Unplanned Dialysis in a Large Accountable Care Organization

Leslie P. Wong, Anindita Ghosh. *Cleveland Clinic, Cleveland, OH.*

Background: Unplanned dialysis initiation or "crash starts" is associated with worse outcomes and higher costs in chronic kidney disease (CKD). Avoiding these events should be a quality improvement priority for accountable care organizations (ACOs). We examined care utilization associated with unplanned dialysis initiation in a large ACO.

Methods: Cleveland Clinic is an academic health system with a 100,000+ member ACO and value-based care (VBC) program. A claims analysis of CKD patients who transitioned to dialysis attributed to the ACO or a VBC contract in 2020 with a lookback 2017-2020 was done. Crash start patients initiated hemodialysis (HD) with a central venous catheter in the hospital. Optimal start patients initiated dialysis with outpatient HD or peritoneal dialysis (PD). Those with acute kidney injury, hospital death, urgent start PD, or preemptive transplant were excluded.

Results: A total of 261 patients met criteria for crash starts and 133 for optimal starts. Outpatient utilization and average visits per specialty by patient category are shown in Table 1. Forty percent of crash start patients had no preceding nephrology care in the 12 months prior to dialysis. Optimal start HD patients had more visits with nephrologists and vascular surgery than crash start patients. PD patients had the highest percentage and number of nephrologist visits. Crash start patients with outpatient pre-dialysis care saw a mix of employed nephrologists (45%), independent nephrologists (35%), and non-ACO nephrologists (20%). Average total cost of care was $95,036 for crash starts versus $25,671 for optimal starts in the 12 months prior to dialysis start date including the index admission.

Conclusions: In a large ACO, unplanned dialysis initiation was associated with lower pre-dialysis nephrology and vascular surgery utilization and substantially higher costs. ACOs managing CKD population risk should address the systemic factors leading to crash dialysis starts.

CKD care utilization in 12 months prior to dialysis initiation

	Crash start n=261	Optimal HD start n=96	Optimal PD start n=37
Any PCP visit	88%	74%	80%
Average PCP visits	7.3	7.7	6.2
Any nephrologist visit	60%	61%	73%
Average nephrologist visits	2.2	3.1	3.8
Any vascular surgeon visit	23%	62%	10%
Average vascular surgeon visits	0.4	1.1	0.2

PCP = primary care provider

PO2405

Comparing Telenephrology (TN) vs. Face-to-Face (F2F) Visits: A Comprehensive Outpatient Nephrology Patient Perspective-Based Cohort Study

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Background: Little is known about patient perspectives on the quality of care provided via TN compared to F2F visits. We aimed to use objective survey data to study patients' perspectives on outpatient nephrology care received via TN (phone and video) versus F2F visits

Methods: We retrospectively studied adults who received outpatient nephrology care at Mayo Clinic, Rochester, MN, from March 1st - July 31st 2020. We used a standardized structured survey methodology to evaluate patient satisfaction across TN versus F2F visits. The primary outcome was the percent of patients who responded with a composite of a score of *good (4)* or *very good (5)* on a 5-point Likert scale on survey questions that asked their perspectives with regard to *access* to their nephrologist, their relationship with *care provider*, and when relevant – their opinions on the *telenephrology technology*, and

their *overall assessment* of the care they received during the nephrology visit. Wilcoxon rank sum tests and chi-square tests were used as appropriate to compare telenephrology versus face-to-face visits

Results: 3,486 of the patient encounters were face-to-face, 808 via phone and 317 via video. 443 patients responded to satisfaction surveys, and 21% of these had TN encounters. Established patients made up 79.6% of TN and 60.9% of F2F visits. There was no statistically significant difference in patient perceived *access* to health care, satisfaction with their *care provider*, or *overall quality* of care between patients who received care via TN versus F2F

Conclusions: Patient satisfaction was equally high amongst those patients seen face-to-face or via telenephrology

Table 1: Patient Survey Results

		Very Poor 1	Poor 2	Fair 3	Good 4	Very Good 5	Frequency of Top Box =4 or 5 responses			
							Telenephrology			F2F
							Phone	Video	Combined	
		0	0	0	0	0	n (%)	n (%)	n (%)	n (%)	P-value
ACCESS	Ease of scheduling your appointment						49 (90.7%)	38 (100%)	87 (94.6%)	327 (95.1%)	0.056
	Ease of contacting us (e.g. email, phone, web portal)						53 (98.1%)	37 (97.4%)	90 (97.8%)	324 (94.7%)	0.523
CARE PROVIDER	Concern the care provider showed for your questions or worries						53 (98.1%)	36 (94.7%)	89 (96.7%)	342 (98.6%)	0.692
	Explanations the care provider gave you about your problem or condition						54 (100.0%)	35 (92.1%)	89 (96.7%)	341 (98.0%)	0.637
	Care provider's efforts to include you in decisions about your care						53 (98.1%)	34 (89.5%)	87 (94.6%)	341 (98.3%)	0.839
	Care provider's discussion of any proposed treatment (options, risks, benefits, etc.)						53 (100.0%)	34 (89.5%)	87 (95.6%)	342 (99.1%)	0.400
	Likelihood of your recommending this care provider to others						53 (98.1%)	35 (92.1%)	88 (95.7%)	339 (96.9%)	0.977
TELEMEDICINE TECHNOLOGY	Ease of talking with the care provider over the video or audio connection						52 (96.3%)	36 (94.7%)	88 (95.7%)		
	How well the audio connection worked during your visit, whether by phone or video						53 (98.1%)	36 (94.7%)	89 (96.7%)		
	If you had a video visit, how well the video connection worked							37 (97.4%)	37 (97.4%)		
OVERALL ASSESSMENT	How well the staff worked together to care for you						53 (98.1%)	36 (94.7%)	89 (96.7%)	337 (98.3%)	0.998
	Likelihood of your recommending our practice to others						54 (100.0%)	37 (97.4%)	91 (98.9%)	340 (98.3%)	0.674

*p-values reflect continuous scales and are compared between telehealth and F2F visits. A Wilcoxon Rank Sum test was used. F2F = face to face; Telenephrology (Combined) = Phone + Video

Patient Responses to Press Ganey/ Mayo Clinic Survey

PO2406

Depressive Symptom Trajectory and CKD Progression: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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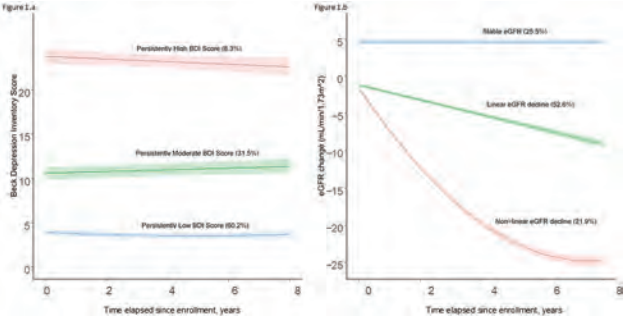
Background: While depressive symptoms (DS) are highly prevalent in adults with early-stage chronic kidney disease (CKD), little is known about its course over time. We identified trajectories of DS and evaluated their association with CKD progression in adults with CKD enrolled in the CRIC study.

Methods: DS were assessed using the Beck Depression Inventory (BDI), at baseline and biennially. Higher BDI scores are consistent with more severe DS. Glomerular filtration rate (GFR) was estimated at baseline and annually. Group-based trajectory models were used to determine trajectories of BDI and eGFR over time. The association between these trajectories was assessed using multinomial logistic regression, adjusting for socio-demographics, lifestyle factors, and comorbidities.

Results: Among 3113 participants at baseline: μ_{age}=58 years, 45.5% female, μ_{eGFR}=47 mL/min/1.73 m^2 and μ_{BDI}=7.6. We identified three BDI trajectory patterns (persistently low, persistently moderate, and persistently high [Figure 1a]), and three trajectory patterns for eGFR (non-linear decline, linear decline, and stable [Figure 1b]). Odds of non-linear eGFR decline were higher for adults with persistently moderate BDI (OR, 1.51; 95% CI, 1.11-2.06) and those with persistently high BDI (OR, 1.75; 95% CI, 0.99-3.07), compared to counterparts with persistently low BDI scores. No association was evident between BDI scores and linear eGFR decline.

Conclusions: In this CKD cohort, moderate and high DS that persisted over time were associated with non-linear eGFR decline. Intervention studies are warranted to test the effect of depression prevention and treatment on CKD progression.



PO2407

Health-Related Quality of Life and Depression Score Differences in Brazilian and US CKD Patients

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Background: CKD patients suffer from many issues, increasing in prevalence and severity as disease progresses, that may affect their perceptions of health-related quality of life (HRQOL) and increase depression symptoms (DS). A patient-centered care approach including systematic assessment of self-reported HRQOL and DS as CKD progresses facilitates tailoring the treatment to individual patient concerns. This study examines the relationship at baseline between CKD stage and patient responses to the KDQOL-36 and CESD-10.

Methods: We studied 1901 CKDOPPS participants (629 Stage 3, 1009 Stage 4, and 263 Stage 5) from Brazil (n=598) and the U.S. (n=1310). Patients at different CKD stages at study selection were compared for differences at baseline in scores of DS (CESD-10 [Kohout], higher score worse, max 40) and HRQOL (KDQOL-36, higher score better, each scale max 100). The KDQOL-36 yields the Physical Component Summary (PCS) and Mental Component Summary (MCS) from the SF-12v1; Burden of Kidney Disease (BKD); Symptoms of Kidney Disease (SKD); and Effects of Kidney Disease (EKD). The Kruskal-Wallis Test assessed differences among groups.

Results: Patients' mean age, albumin, and BP did not differ in the 3 CKD groups. Mean Hb was lower for CKD 5 (10.8) and 4 (11.9) than for CKD 3 (12.7) patients, but only slight mean difference occurred in DS and MCS by CKD stage. Mean PCS score was 39.8 and 37.9 in CKD 3 and 5 respectively. The largest mean difference in HRQOL scores by CKD stage was for BKD: 77.7 in CKD 3, 69.4 in CKD 4, and 58.0 in CKD 5 ($p < 0.0001$). Lower HRQOL scores for more advanced CKD stage occurred for EKD: (85.13, 79.7, and 76.0 in CKD 3, 4, and 5, $p<.0001$) and SKD (79.95, 77.8, 77.1, $p=0.0007$). Compared to U.S. patients, those in Brazil had higher PCS scores (40.1 vs 37.5) but lower BKD scores (62.3 vs 74.4); other scores did not differ by country.

Conclusions: HRQOL baseline scores for CKD patients show a greater difference in the BKD scores; differences by CKD stage were not seen in MCS and CESD-10 scores; and minimal difference occurred for PCS scores. These results potentially can help address patients' problems and concerns at different CKD stages.

Funding: Other U.S. Government Support, Commercial Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/AboutUs/Support.aspx, Private Foundation Support, Government Support - Non-U.S.

PO2408

The Spectrum of Kidney Disease and Outcomes in US Veterans with Inflammatory Bowel Disease

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Background: Glomerular and tubulointerstitial diseases have been associated with inflammatory bowel disease (ulcerative colitis, UC and Crohn's disease, CD). However, the clinical outcomes of UC and CD patients who underwent kidney biopsy are not well described. We present a case series of the kidney biopsy findings and clinical outcomes of veterans with UC and CD from the US department of Veteran's Affairs (VA) health system.

Methods: We performed a retrospective review of the VA electronic health record. Patients were included if they had UC or CD diagnosed by gastroenterology evaluation and biopsy. Kidney biopsy data including primary and secondary diagnoses, degree of interstitial fibrosis and tubular atrophy (IFTA), and degree of arteriosclerosis were extracted from biopsy reports. Incident end-stage kidney disease (ESKD) was defined as requirement of renal replacement therapy. All analyses were performed using SAS.

Results: Of 59,007 patients with an ICD code of inflammatory bowel disease, 66 patients had kidney tumor biopsies and 140 patients (91 with UC and 49 with CD) underwent biopsy to evaluate intrinsic kidney disease. At the time of kidney biopsy, the mean serum creatinine was 2.9 mg/dL for UC and 3.4 mg/dL for CD and the mean

urine protein to creatinine ratio was 3.8 g/g for UC and 3.0 g/g for CD. The 5 most common primary diagnoses were IgA nephropathy (16%), diabetic nephropathy (14%), acute interstitial nephritis (12%), FSGS (8%), and membranous glomerulopathy (6%). Additionally, 13% of patients had interstitial nephritis (acute or chronic) as a secondary diagnosis. Moderate or severe IFTA was seen in 45% of biopsies. 24 UC patients (26%) and 10 CD patients (20%) progressed to ESKD, with a mean time from kidney biopsy of 3.1 and 1.9 years, respectively. 41 UC patients (45%) and 17 CD patients (34%) died, with a mean time from kidney biopsy of 4.3 and 4.6 years, respectively.

Conclusions: Among US Veterans with UC or CD who underwent kidney biopsy, the most common findings were: IgA nephropathy, interstitial nephritis, and diabetic nephropathy. Patients had advanced kidney disease at biopsy, and subsequent ESKD or death were common within a relatively short time period. These findings suggest a delay in diagnosis and possibly a low rate of diagnosis. Greater provider awareness may lead to earlier detection and improve outcomes.

PO2409

Healthcare Costs Associated with Systemic Lupus Erythematosus (SLE) in the Year Prior to Diagnosis of ESKD: Real-World Evidence from Two Databases in the United States

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Background: Approximately 40% of patients with SLE develop lupus nephritis (LN), many of whom may progress to ESKD[1]; however, data on of the economic burden of ESKD in patients with SLE are scarce. This study described healthcare resource utilization (HCRU) and costs for patients with SLE in the 12 months before ESKD diagnosis in the US.

Methods: This was a retrospective study (GSK Study 215295) of 2 US administrative claims databases (IBM MarketScan [DB#1], Optum Research [DB#2]), conducted from March 1, 2011, to December 31, 2019. Patients were adults with SLE and newly diagnosed ESKD. Study results focus on patients with 12-month continuous enrollment pre ESKD diagnosis reporting on HCRU and costs (2019 US$) during this period.

Results: In total, 1356 (DB#1) and 425 (DB#2) patients with SLE and ESKD were identified (DB#1/DB#2): female 81.8%/79.3%; mean (standard deviation [SD]) age: 46.7 (12.3)/46.3 (14.0) years. Mean (SD) Quan-Charlson Comorbidity Index score in the 12 months pre ESKD was 2.95 (1.9) and 3.05 (2.0) in DB#1 and DB#2, respectively. The mean (SD) healthcare cost in the 12 months pre ESKD was $64,887 (106,822) (DB#1) and $68,219 (137,704) (DB#2) (**Table**). In the 12-month pre-ESKD period, HCRU was similar across databases and oral corticosteroids were the most commonly prescribed SLE-related medications (**Table**).

Conclusions: Patients with SLE incur substantial HCRU and costs 1 year before ESKD diagnosis, reflecting the clinical and economic burden of SLE and ESKD.

Reference: 1. Menez SP, *et al. Rev Recent Clin Trials* 2018;13:105–13

Funding: Commercial Support - GSK

Table. HCRU, costs, and SLE-related medications in the 12 months before ESKD diagnosis

	DB#1 (N=1356)	DB#2 (N=425)
All-cause HCRU, mean (SD)		
Any visit	78.0 (64.1)	87.5 (60.0)
Ambulatory	24.1 (18.1)	22.6 (15.5)
Physician office	16.3 (13.9)	16.5 (12.7)
Hospital outpatient	7.8 (10.3)	6.0 (7.1)
Inpatient	1.8 (3.0)	2.2 (3.3)
Emergency room	1.0 (1.8)	1.2 (2.6)
Other*	9.4 (35.3)	9.8 (29.9)
Pharmacy fills	41.7 (39.2)	51.7 (37.1)
Healthcare costs (US$), mean (SD)		
Total	64,887 (106,822)	68,219 (137,704)
Medical	51,764 (96,458)	55,492 (132,350)
Pharmacy	13,122 (39,075)	12,728 (25,367)
Medication, n (%)		
Antimalarials	478 (35.3)	182 (42.8)
Oral corticosteroids	786 (58.0)	301 (70.8)
Immunosuppressants	637 (47.0)	231 (54.4)
Biologics	86 (6.3)	36 (8.5)

*Ambulance, hospice/home care services; and assisted living, comprehensive rehabilitation, custodial care, intermediate care, psychiatric, and skilled nursing facilities

PO2410

Patterns of Progression of Stage 2 CKD and Associated Costs in Medicare Advantage Enrollees

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Background: The prevalence of chronic kidney disease (CKD) in Medicare beneficiaries has quadrupled in the past two decades. Little is known about patterns of progression in older adults with early CKD. We identify CKD progression trajectories, risk factors and health care costs for these trajectories in a large cohort of Medicare Advantage (MA) enrollees with stage 2 CKD.

Methods: In a cohort of 418,930 MA enrollees, we identified trajectories of stage 2 CKD progression (measured by estimated glomerular filtration rate (eGFR)) from 2014-2018 via group-based trajectory modeling. Multinomial logistic regression was used to identify patient factors associated with each trajectory. Mean total costs one year before and two years after baseline are described.

Results: The cohort had a mean age of 72.6 years, was predominantly female (57.2%) and White (67.8%), with mean baseline eGFR of 75.3 ml/min/1.73m^2. Median follow-up was 2.6 years. We identified 5 trajectories of kidney function: stable kidney function (22.1%); slow decline with mean baseline eGFR 78.3 (30.1%), slow decline with mean baseline eGFR 71.0 (28.5%); steep decline (16.4%); accelerated decline (2.9%). In adjusted analyses, higher odds of accelerated decline (vs. stable kidney function) were found in those age 75 and older, (odds ratio (OR)=2.84, 95% confidence interval (CI): 2.38-3.38), living in a non-metropolitan area (OR=1.26, 95% CI: 1.18-1.35), with lower eGFR at baseline (OR=0.64, 95% CI: 0.63-0.64), greater comorbidity (OR=1.28, 95% CI: 1.27-1.29), having a nephrologist visit (OR=2.06, 95% CI: 1.81-2.34) or clinical diagnosis of CKD (OR=4.41, 95% CI: 4.11-4.74) during the year prior to baseline. Mean total MA costs of enrollees with accelerated kidney function decline were nearly twice as high as costs of MA enrollees in the other 4 trajectories in every year ($27,856 versus $13,507) for stable kidney function during the first year.

Conclusions: The small fraction of MA enrollees with accelerated loss of kidney function have disproportionately higher costs than other enrollees with stage 2 CKD and may benefit from closer clinical management to minimize progression and contain costs.

Funding: Other U.S. Government Support

PO2411

The Kidney Failure Risk Equation as a Predictor of Healthcare Costs

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Background: The Kidney Failure Risk Equations (KFRE) are accurate and validated to predict the risk of kidney failure in individuals with CKD, but little is known about their potential to predict healthcare costs. We assessed the 4- and 8-variable 2-year KFRE models as independent predictors of monthly healthcare costs in patients with CKD stages 3-4.

Methods: Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007-2017) was queried to identify patients with non-dialysis CKD stages 3-4 (90-day average eGFR ≥15 to <60 mL/min/1.73 m^2) followed by 2 consecutive serum bicarbonate 12 to <30 mEq/L, 28–365 days apart, with 6 months pre-index data and ≥2 years of post-index or death within 2 years, plus concurrent medical claims. The first qualifying serum bicarbonate test established the index date. KFRE elements were evaluated during the pre-index period and predicted risk scores of 2-year kidney failure were computed for each patient. Monthly medical costs were calculated for each patient from individual healthcare insurance claims and log-transformed due to skew. Patients were also stratified by index CKD stage. Generalized linear regression models were used to examine the association of KFRE score and costs. The individual components of the KFRE were similarly analyzed.

Results: 1721 patients qualified for this observational study (1475 and 246 with CKD stage 3 and 4 at index, respectively). Both the 4- and 8-variable KFRE assessments were associated with log monthly medical costs. Per 1% increased risk for 2-year kidney failure risk predicted by KFRE, costs were increased significantly: for CKD stage 3 (parameter estimates: 0.065 [P=0.016] and 0.126 [P<0.0001]) and for CKD stage 4 (parameter estimates: 0.029 [P=0.001] and 0.040 [P<0.0001]). Of the individual components, lower serum albumin and lower serum bicarbonate were consistently associated with higher monthly medical costs.

Conclusions: Both the 4- and 8-variable KFRE were associated with higher medical costs for patients with CKD stages 3 or 4, with monthly medical cost increases of 6.7% - 13.5% for CKD stage 3 and 2.9% - 4.1% for CKD stage 4, respectively, for each 1% increase in 2-year kidney failure risk. The KFRE may be a useful tool to anticipate medical costs for patients at risk of kidney failure.

Funding: Commercial Support - Tricida, Inc.

PO2412

Applying Predictive and Causal Analytics to Design Intelligently Targeted Outreach to Address Underrecognition of CKD

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Background: 43% of adults with advanced Chronic Kidney Disease (CKD) are unaware of their diagnosis. 2 priorities for The National Institute of Diabetes and Digestive and Kidney Research are to create diagnostic models of kidney function, and to promote studies with responsive outcomes. We propose a novel approach to identify undiagnosed members and increase CKD testing.

Methods: To target Commercial and Medicare members for CKD testing, we combined 3 techniques: i) machine learning, ii) causal inference, and iii) clinical practice. Our machine learning model predicted members' risk of stage 3b+ CKD. With causal inference, we calculated the average per member per year costs-difference over 6 years between an early or late CKD test. Using the members' risk score, their associated costs, and their expected behavior change we created a targeting threshold. When the cost-difference of testing a member was larger than the threshold, we enrolled those members into the study. Our intervention consisted of low-cost member outreach like emails and

direct mailers (Dir. M). Members were randomized into a i) control group for Dir. M, ii) a control group for email and Dir. M, iii) Dir. M with interactive voice response (IVR), iv) Dir. M only, v) Dir. M and email, and vi) Dir. M and email with IVR. Logistic regression was used for the primary outcome of testing for CKD.

Results: We enrolled 76,388 members of which 35,933 were allocated to the control group. Baseline features were comparable across test and control (age: 80.4±8.3 vs 80.4±8.3, male: 36% [36.3-36.4%] vs 35.9% [35-36%], diabetes: 40.8% [40.3-41.2%] vs 41.1% [40.5-41.6%], hypertension: 88.8% [88.5-89.1%] vs 88.6% [88.3-88.9%]). Members that received only Dir. M were not ever statistically different from control. In the other test arms, testing increased by 1.6-2.1 percentage points at 90 days ($p < 0.05$). Post-hoc analysis found an increase in laboratory services, PCP and Nephrologist usage, nephroprotective drug claims, and new or updated CKD diagnosis at 90 and 180 days (all $p<0.05$). Direct medical costs were unchanged.

Conclusions: Low-cost outreach with individualized targeting led to significant increases in CKD stage diagnosis and care-gap closure. The study was under powered to observe direct medical cost savings.

Funding: Commercial Support - CVS and Aetna a CVS Health Company

PO2413

Association of Kidney Function with Major Postoperative Events After Noncardiac Ambulatory Surgeries: A Population-Based Cohort Study

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Background: Though people with chronic kidney disease (CKD) frequently receive outpatient surgical procedures, the associated risks of major perioperative outcomes is unknown. In this study, we estimated the association between estimated glomerular filtration rate (eGFR) and a composite of acute myocardial infarction (AMI) or death after ambulatory non-cardiac surgery.

Methods: This retrospective population-based cohort study used administrative health and laboratory data from Alberta, Canada, and included adults with measured preoperative kidney function undergoing ambulatory non-cardiac surgery between April 2005 and February 2017. We categorized participants into six eGFR categories (in mL/min/1.73m^2) of ≥ 60 (G1-2), 45-59 (G3a), 30-44 (G3b), 15-29 (G4), < 15 not receiving dialysis (G5ND), and those receiving chronic dialysis (G5D). The odds of AMI or death within 30 days of surgery were estimated using multivariable generalized estimating equations. Secondary outcomes included the odds of hospitalization, emergency department (ED) and urgent care center (UCC) visits.

Results: We identified 543,160 procedures in 323,521 people with a median age of 66 years (IQR 56-76); 52% were female. Overall, 2,338 people (0.7%) died or had an AMI within 30 days of surgery. Compared with the G1-2 category, the adjusted odds ratio (OR) of death or AMI increased from 1.1 (95% Confidence interval [CI]: 1.0, 1.3) for G3a to 3.1 (CI: 2.6, 3.6) for G5D. The associations between eGFR and the independent components of this outcome were consistent for both death and AMI, and similar for 30-day hospitalization. ED and UCC visits within 30 days were frequent (17%), though similar across eGFR categories.

Conclusions: We found that ambulatory surgery was associated with a low overall risk of major postoperative events, though was significantly higher for people with CKD. This study may inform their perioperative shared decision-making and management, and suggests that more refined risk stratification approaches based on eGFR may be warranted.

Funding: Government Support - Non-U.S.

PO2414

Association of Multimorbidity and Mortality Risk in US Veterans with New-Onset CKD

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Background: Many patients with CKD live with multiple chronic conditions. We examined the association of multimorbidity at CKD onset and the 10-year risk of death in US veterans with incident CKD.

Methods: The cohort included 892,005 veterans with new-onset CKD (estimated GFR<60 mL/min/1.73 m^2 for >3 months) between 2004 and 2018 in the US Veterans Health Administration, followed for up to 10 years or December 31, 2018. Multimorbidity was measured by the total number of comorbidities among 16 conditions based on ICD-9/ICD-10 codes during the 2 years before and up to 6 months after CKD onset, and categorized as 0–1, 2, 3, 4, 5, 6, 7, and ≥8 conditions. We estimated mortality risk by age groups at CKD onset.

Results: The median number of comorbidities at CKD onset was 4 (interquartile range: 3-6). After multivariable adjustment, the association between increasing multimorbidity and mortality risk was seen in all age groups, but was stronger in younger than older groups (Table). Death risk when having ≥5 comorbidities was >8-fold higher in ages 18-44, but only >2-fold higher in ages 85-100, compared to their age counterparts with 0-1 comorbidity. Multimorbidity patterns also differed by age. For example, among those with only 2 concurrent comorbidities, hypertension and depression co-occurred most frequently in ages 18-44, as compared to hypertension and cardiovascular disease in older age groups.

Conclusions: At CKD onset, 95% of patients had multiple comorbidities. The association of multimorbidity and mortality was greater for younger patients. Effective plans for early CKD diagnosis and timely treatment of comorbidities may improve survival in CKD, especially for younger patients.

Funding: NIDDK Support, Other U.S. Government Support

Hazard ratios (95% CI) of death across multimorbidity categories at CKD onset

Number of comorbidities at CKD onset	Percent of patients in each category	Ages 18-44	Ages 45-64	Ages 65-84	Ages ≥85-100
0-1	5.2	1	1	1	1
2	11.8	2.7 (1.4-5.5)	1.8 (1.6-1.9)	1.4 (1.4-1.5)	1.2 (1.1-1.2)
3	18.0	3.8 (2.0-7.5)	2.6 (2.4-2.8)	1.9 (1.8-1.9)	1.4 (1.4-1.5)
4	19.3	5.9 (3.1-11.4)	3.5 (3.3-3.8)	2.4 (2.3-2.4)	1.7 (1.6-1.8)
5	16.7	8.5 (4.4-16.2)	4.6 (4.3-5.0)	3.0 (3.0-3.1)	2.1 (2.0-2.2)
6	12.4	10.5 (5.4-20.2)	5.8 (5.4-6.3)	3.7 (3.6-3.8)	2.5 (2.3-2.6)
7	8.1	13.1 (6.7-25.5)	7.4 (6.9-8.0)	4.6 (4.5-4.8)	3.0 (2.8-3.2)
≥8	8.5	15.6 (8.1-30.1)	10.8 (10.0-11.7)	6.5 (6.3-6.7)	3.9 (3.7-4.1)

PO2415

Self-Reported Walk Pace and Cardiovascular Events in Adults with CKD

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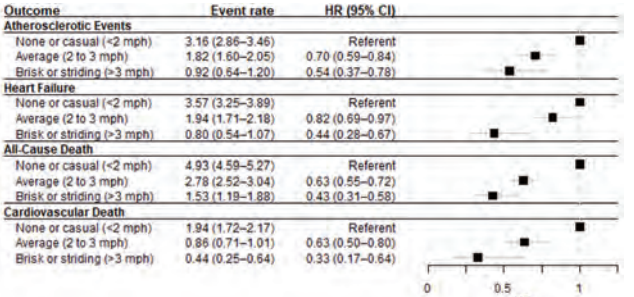
Background: Physical function, as measured by self-reported walk pace, is lower in patients with CKD compared to the general population. While slower walk pace has been found to be associated with cardiovascular outcomes in non-CKD populations, its relationship to cardiovascular outcomes in CKD patients has not been fully explored.

Methods: We used data from 3925 adults with mild-to-moderate CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study. Walk pace (scored 0-4) was self-reported using the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey. Outcomes included atherosclerotic events (a composite of myocardial infarction, stroke or peripheral arterial disease), incident heart failure, all-cause death, and cardiovascular death. Multivariable Cox proportional hazard models with time-updated covariates were used to evaluate the association of walk pace with outcomes.

Results: At baseline, mean age was 58 years, 45% were women, 33% had self-reported cardiovascular disease, mean eGFR was 45 ml/min/m^2, 12% reported brisk or striding walk pace (>3 mph), 39% reported average walk pace (2-3 mph), and 48% reported walk pace of none or casual (<2 mph). During a median follow-up of 11.5 years, there were 725 atherosclerotic events, 790 incident heart failure events, 1333 deaths from any cause, and 434 cardiovascular deaths. In fully adjusted models, there was a graded association between walk pace and risk for each outcome (**Figure**).

Conclusions: In this cohort of adults with CKD, faster self-reported walk pace was associated with lower risk of cardiovascular events and mortality. These findings may have implications for risk stratification, as well as for future interventions targeting physical function in patients with CKD.

Funding: NIDDK Support



PO2416

Low Magnesium Predicts Cardiovascular Outcomes in Pre-Dialysis CKD Patients: Results from the KNOW-CKD Study

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Background: There are few large-scale studies of the association between magnesium (Mg) and cardiovascular (CV) outcomes in pre-dialysis chronic kidney disease (CKD) patients. Therefore, we analyzed the effects of Mg on CV outcomes in a large-scale cohort of pre-dialysis CKD patients.

Methods: We investigated the association between serum Mg and CV outcomes in a prospective, multi-center cohort of pre-dialysis CKD patients (n=1,646). Patients were divided into four groups according to serum Mg concentration. The primary endpoint was composite outcome, defined as either a CV event and/or all-cause death. Secondary outcomes were coronary artery calcification (CAC) progression and arterial stiffness progression as assessed by mean brachial-ankle pulse wave velocity (baPWV).

Results: During a median follow-up of 6.0 years, 196 (11.9%) patients had the composite outcome of a CV event and/or all-cause death. In a multivariable cause-specific model, patients in the lowest Mg group (serum Mg ≤2.0 mg/dL) had an elevated risk of a composite outcome (hazard ratio (HR) 1.71 [1.02–2.84]; *P*=0.038; serum Mg =2.2 mg/dL as the reference group). Subgroup analyses showed that low Mg was particularly associated with risk of a composite outcome in patients with early CKD and those who were male. Patients in the lowest Mg group also had increased risks of progression to CAC and arterial stiffness relative to the reference group (Mg =2.2 mg/dL).

Conclusions: Low Mg level is a predictor of cardiovascular outcomes in pre-dialysis CKD patients.

PO2417

Baseline Renal Function and Left Ventricular Assist Device Outcomes Among Patients with CKD

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Background: Chronic kidney disease (CKD) is associated with increased risk of cardiovascular disease. Coronary artery disease is one of the most important causes of heart failure with reduced ejection fraction, a condition for which advanced therapies such as left ventricular assist device (LVAD) and orthotopic heart transplant (OHT) are increasingly utilized. Information about outcomes of CKD patients with LVAD is limited. We studied the outcomes of patients with CKD who had received LVAD in a large cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated electronic medical records network, to identify 4939 patients≥ 18 years from 31 healthcare organizations, from the United States, who had undergone LVAD implantation between 1/1/2010 and 12/31/2019. We excluded 1552 patients with estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2. We grouped the eligible patients into stages of CKD, based on eGFR: [stages: 2 (n=1140), 3a (n=821), 3b (n=563), 4 (n=182), and 5 (n=681)]. The primary and secondary outcomes were survival and receiving an OHT within one year of LVAD implantation, respectively. We used CKD stage 2 as the reference and calculated the odds ratio (OR) [with 95% confidence interval (CI)] of each of the two outcomes.

Results: A total of 172 patients died within one year of LVAD implantation. When compared with Stage 2 CKD, and after propensity score matching, there was a decrease in the OR of survival at one year with higher stages of CKD: —Stage 3b: OR: 0.64 (CI: 0.41, 0.99); —Stage 4: OR: 0.42 (CI: 0.24, 0.73); —Stage 5: OR: 0.57 (0.38, 0.86). There was no significant difference in the odds of survival between stage 3a and the reference group. A total of 274 heart transplants were performed within the first year after LVAD implantation. Patients in the reference group were more likely to receive an OHT within the first year in comparison with CKD stage 5 patients (OR: 1.61; CI: 1.06, 2.45).

Conclusions: Presence of a more advanced stage of CKD is associated with decreased survival in LVAD patients. Patients with CKD stage 2 are more likely to undergo OHT compared to those with CKD stage 5.

PO2418

Associations of eGFR and Albuminuria with Physical Performance

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Background: Reduced physical performance is associated with increased all-cause mortality, and individuals with chronic kidney disease (CKD) are at an increased risk of suffering from impaired physical function. However, most studies have not included assessment of albuminuria. We hypothesized that eGFR and albuminuria would be independently associated with physical performance.

Methods: The Brain in Kidney Disease (BRINK) cohort was designed to examine cognitive and physical function among adults with CKD. Intentional recruitment ensured participants with an eGFR (ml/min/1.73m^2) range from <30 to 59 were included, in addition to a control group with eGFR ≥60. We estimated GFR using creatinine ($eGFR_{Cr}$) and, in separate analyses, cystatin C ($eGFR_{CysC}$), and measured urine albumin to creatinine ration (UACR). We assessed physical performance using the Short Physical Performance Battery (SPPB; range 0-12). 571 community-dwelling adults with baseline SPPB scores were included. Univariate and multivariable logistic regression models, adjusted for demographics and comorbidity, examined associations of eGFR and UACR with SPPB <10.

Results: Mean age was 69.3 years. 157 (27.5%) participants had $eGFR_{Cr}$ <30, 276 (48.3%) 30 to <60, and 138 (24.2%) ≥60. In separate univariate analyses, both lower $eGFR_{Cr}$ and higher UACR were associated with higher odds of low SPPB (Table). In the adjusted model with $eGFR_{Cr}$, UACR and covariates, UACR retained a significant association with low SPPB, but $eGFR_{Cr}$ did not. Similar results were found in models with $eGFR_{CysC}$ and UACR.

Conclusions: Both low $eGFR_{Cr}$ and high UACR were associated with poor physical performance in univariate analyses, but only UACR remained associated in the fully adjusted model. Similar results with $eGFR_{CysC}$ suggest that confounding based on muscle mass does not explain the lack of association between $eGFR_{Cr}$ and physical performance and raises the possibility that vascular or endothelial function may be important factors.

Funding: NIDDK Support, Other NIH Support - NIA

	Unadjusted models for SPPB < 10		Adjusted model for SPPB < 10*	
Predictor	OR (95% CI)	p-value	OR (95% CI)	p-value
$eGFR_{Cr}$, ml/min/1.73m^2				
≥60	Reference		Reference	
45 to <60	2.0 (1.1, 3.7)	0.02	1.1 (0.5, 2.1)	0.85
30 to <45	1.8 (1.1, 2.9)	0.02	0.6 (0.3, 1.1)	0.12
<30	3.2 (2.0, 5.3)	< 0.001	0.9 (0.4, 1.8)	0.72
UACR, mg/g				
<30	Reference		Reference	
30 to 300	2.6 (1.8, 3.9)	< 0.001	2.3 (1.3, 3.9)	0.002
>300	2.1 (1.3, 3.2)	0.001	1.9 (1.0, 3.6)	0.06

* Model with both $eGFR_{Cr}$, and UACR and adjusted for low hemoglobin, low bicarbonate, low albumin, pulse pressure, diabetes, BMI group, CVD, CHF, Stroke/TIA, smoking, Black race, gender, age, and years of education.

PO2419

Association Between Estimated Glomerular Filtration Rate Decline and Clinical Outcomes in Nondiabetic CKD

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Background: There is limited evidence on association between surrogate laboratory endpoints and hard clinical outcomes in chronic kidney disease (CKD). This real-world data analysis investigated dependence between relative estimated glomerular filtration rate (eGFR) decline of ≥30%, 40%, 57% and cardio-renal outcomes in non-diabetic CKD patients treated in routine clinical practice.

Methods: Individual-level data from the US claims database, Optum Clinformatics Data Mart (CDM), for years 2008 – 2018 were analysed. Adult individuals were required to have CKD stage 3 or 4 (index date), 365 days of continuous insurance prior to index (baseline period). Individuals with diabetes mellitus, CKD stage 5 or end-stage kidney disease (ESKD) prior index or kidney failure, transplant or dialysis in the baseline period were excluded. Patients were followed until insurance/data end, or death. Two selected hard clinical outcomes were hospitalisation for heart failure (HHF) and a composite of ESKD/kidney failure/need for dialysis. To investigate the association between eGFR decrease and clinical outcomes, an intercurrent event analysis was performed using eGFR decline of ≥30%, ≥40% or ≥57% as an intercurrent event.

Results: Of 64 million individuals in Optum CDM, 504,924 satisfied the selection criteria, median age 75 years, 60% female, 10% black. At baseline, eGFR values were available for 62% of individuals; median eGFR was 53; 94% of those patients had at least one eGFR value in the follow-up period of a median 744 days. Proportion of the patients with eGFR decline of ≥30%, 40%, 57% was 5%, 3% and 1%. More rapid eGFR decline was associated with increased risk of the outcome. The hazard ratio for HHF was 3.03, 3.41, 3.86 and for ESKD/kidney failure/need for dialysis it was 5.61, 8.29 and 18.63 in patients with eGFR decline of ≥30%, 40%, 57% as compared to those with no such decline, respectively.

Conclusions: In this analysis of the US non-diabetic CKD patients treated in routine clinical practice, a relative eGFR decline of ≥30%, ≥40%, ≥57% was associated with a subsequent HHF and ESKD/kidney failure/need for dialysis, supporting that carefully selected lab-based surrogate measures may be used as early indicators of hard clinical outcomes.

Funding: Commercial Support - Bayer AG

PO2420

Effect of Obesity and Metabolic Dysfunction on Cardiovascular Events and Progression to ESRD in CKD

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Background: Obesity and metabolic dysfunction increased the risk of cardiovascular event and chronic kidney disease (CKD) progression. However, there are conflicting results on clinical outcomes in obese patients without metabolic dysfunction and it is unclear whether metabolically healthy obesity increases the risk of cardiovascular events and progression to end-stage renal disease in CKD patients.

Methods: We enrolled 166,397 CKD patients from Korea National Health Insurance Service Health Examinee Cohort between January 2009 and December 2011. Obesity is defined as body mass index greater than 23kg/m^2. Metabolic dysfunction was assessed using following components: waist circumference, blood pressure, fasting blood sugar, triglyceride level, high-density lipoprotein cholesterol level. The primary endpoint was the ischemic heart disease, ischemic stroke and progression to end-stage renal disease (ESRD).

Results: Of total CKD patients, the proportion of patients with metabolic dysfunction was significantly higher in obese patients than in non-obese patients (25.1% vs. 5.4%; $p < 0.001$). In multivariable Cox-regression analysis, compared to metabolically healthy non-obese patients, metabolic dysfunction significantly increased the risk of ischemic heart disease and progression to ESRD in patients with and without obesity. Patients with metabolically healthy obesity were significantly associated with increased risk of ischemic heart disease (HR 1.22; 95% CI 1.00-1.50) and ischemic stroke (HR 1.48; 95% CI 1.10-1.19). However, the risk of progression to ESRD was not significantly increased (HR 0.98; 95% CI 0.87-1.10).

Conclusions: The metabolic dysfunction was significantly associated with worse clinical outcomes in CKD patients, irrespective of obesity. The metabolically healthy obesity increased risk for ischemic heart disease and ischemic stroke, but not for progression to ESRD.

PO2421

Diet Quality and Kidney Outcomes in Adolescent and Adult American Indians: The Strong Heart Family Study

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Background: The burden of chronic and end stage kidney disease (CKD and ESKD), is exceedingly high amongst American Indians (AIs). We sought to examine the relationship of diet quality, a modifiable risk factor, and kidney outcomes in AI adolescents and adults, hypothesizing that poorer quality diets would be associated with incident albuminuria and accelerated eGFR decline in this population.

Methods: This is a secondary analysis of data from the Strong Heart Family Study, a longitudinal study of cardiovascular disease and its risk factors among AIs from Arizona, North and South Dakota, and Oklahoma (n=1721, mean age 39 +/- 16 years, 16% adolescents aged 14-21 years, 61% female, 28% with hypertension, 13% with diabetes, 52% with obesity, 4% with CKD at baseline). Participants completed two exams (baseline: 2001-2003; follow-up: 2007-2009). The primary exposure (at baseline) was the Alternative Healthy Eating Index (AHEI), a measure of diet quality on a 110-point scale (assessed using a 119-item Block food frequency questionnaire). The primary outcomes (at follow-up) were: 1) incident albuminuria (albumin to creatinine ratio 30mg/g); 2) eGFR decline of 30%. Generalized estimating equations were used to examine the association of AHEI (in quartiles) with incident albuminuria and eGFR decline.

Results: In total, 9.9% (5.6% of adolescents) had incident albuminuria and 5.6% of participants (9.2% of adolescents) had eGFR decline of 30%. Median AHEI for the poorest diet quartile was 34 compared to 55 for the healthiest diet quartile, each 10-20 points lower than AHEI scores from studies of the general population. The unadjusted odds ratio (OR) for incident albuminuria comparing extreme quartiles of diet quality (poorest versus healthiest [reference] quartiles) was 1.32 (95%CI 0.92, 1.89). After adjustment for baseline diabetes, eGFR and age, the OR for incident albuminuria was 1.79 (95% CI 1.24, 2.58). There were no significant unadjusted or adjusted associations of diet quality with eGFR decline.

Conclusions: These preliminary results suggest an association of diet quality and incident albuminuria in AI. Given the high burden of CKD in this population, further research is required to determine whether interventions to improve diet quality may improve kidney outcomes.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung and Blood Institute, National Institute of Health, Department of Health and Human Services

PO2422

Renal Function and Effect of Body Mass Index on Mortality Risk After Acute Myocardial Infarction

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Background: Obesity is paradoxically linked to greater survival benefit after acute myocardial infarction (AMI). In patients with renal impairment, higher body mass index (BMI) is also associated with protective effects against cardiovascular and all-cause mortality. However, there are no studies investigating the interactive effects of BMI and renal function on mortality risk after AMI.

Methods: We enrolled 12,647 AMI patients from Korea Acute myocardial Infarction Registry between November 2011 and December 2015. Patients were categorized based on renal function; normal (≥90 mL/min/1.73m^2), mild (90-45 mL/min/1.73m^2), and moderate impairment (<45 mL/min/1.73m^2). BMI was divided into four groups; underweight (<18.5 kg/m^2), ideal (18.5-23 kg/m^2), overweight (23-25 kg/m^2) and obesity (≥25 kg/m^2). The primary endpoint was 2-year mortality after AMI treatment.

Results: In multivariable Cox-regression analysis, compared to Ideal weight patients, overweight and obese patients were associated lower risk of mortality and underweight patients had the increased risk of mortality in all renal function categories. However, the survival effect of each BMI stratum was decreased as renal function worsened. The adjusted mortality risk of obesity was 0.63 (95% CI 0.0.41-0.99), 0.76 (95% CI 0.59-0.97) and 0.84 (95% CI 0.65-1.08) for patients with normal, mild and moderate renal function impairment, respectively. There was a significant interaction between BMI and renal function ($P = 0.010$). We found that the survival benefit of obesity for noncardiac death was decreased with decreasing renal function (P for interaction = 0.03), but obesity-related advantage was not changed between different renal function (P for interaction = 0.03).

Conclusions: The effect of BMI on mortality risk after AMI was dependent on renal function. The association between greater BMI and survival benefit was weakened as renal function was worsened. We suggest that the association between renal function and effect of BMI on mortality originated in non-cardiac death, not cardiac death.

PO2423

Steroid-Resistant Retroperitoneal Fibrosis in the Elderly

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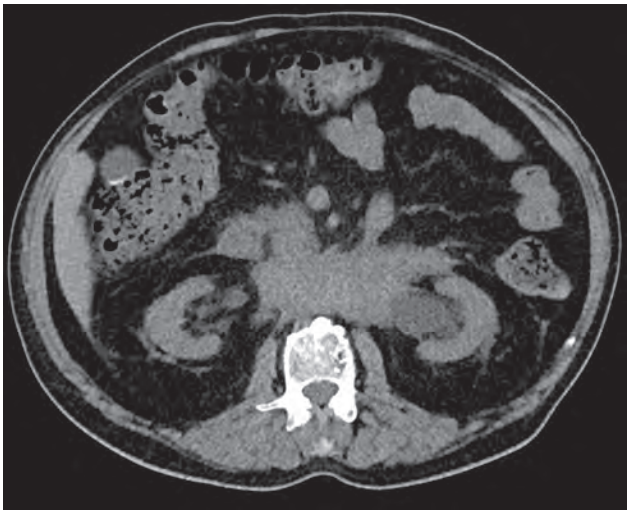
Introduction: Retroperitoneal fibrosis (RPF) is a rare disease characterized by chronic inflammation and fibrosis that involve multiple organs, including the ureters leading to obstructive uropathy. IgG4-related RPF accounts for the majority of cases. We present a case of obstructive uropathy secondary to RPF that is steroids resistant

Case Description: A 71-year-old male known case of atrial fibrillation on warfarin presents with urinary hesitancy and decrease output. No history of fever, weight loss or night sweats. His creatinine was 1.8mg/dL from baseline of 0.9mg/dL. A CT scan of the abdomen revealed a 15x14cm retroperitoneal lesion extending from aortic bifurcation and obstructing both ureters with moderate left-sided hydronephrosis. The patient required double J-stent (DJS) placement with no improvement in creatinine. Workup revealed elevated IgG4 levels (1215mg/L), normal CBC, negative quantiferon test. Chest X-ray, malignancy screening and PET scan were unremarkable. The patient refused the biopsy given the risk of bleeding. He was started on prednisolone 80 mg for one month with no improvement of hydronephrosis. The patient developed hypertension, hyperglycemia, and edema, hence switching to mycophenolate mofetil (MMF) with low-dose prednisone. Repeated CT scan showed a partial reduction in retroperitoneal fibrosis (12x13cm) with mild hydronephrosis

Discussion: Although rare, secondary causes of RPF such as tuberculosis, Castleman disease, Erdheim-Chester disease, lymphoma and bladder carcinoma should be identified. In idiopathic RPF, high-dose glucocorticoids are the first line of treatment. Several studies have shown the effectiveness of low-dose steroids in combination with immunosuppressive drugs like MMF or rituximab. The use of a combination treatment as a first-line treatment is still debatable, however, patients who cannot tolerate high doses of prednisolone and have poor treatment response should be considered for alternative therapy



PO2424

Peripheral Blood Mononuclear Cell Mitochondrial Bioenergetics Is Associated with Physical Performance in Patients with CKD

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Background: Patients with CKD suffer from skeletal muscle dysfunction and impaired physical performance. Impaired muscle and systemic mitochondrial metabolism are central candidate mechanisms of skeletal muscle impairment in CKD. Live peripheral blood mononuclear cells (PBMC) mitochondrial bioenergetics may link altered metabolism in CKD with exercise intolerance. The association of PBMC bioenergetics with physical performance in CKD is unknown.

Methods: We recruited 13 participants with eGFR<60 ml/min/1.73m2. Cardiopulmonary fitness (absolute VO2 peak), total work performed, and work efficiency were measured using COSMED K5 wearable metabolic system during cycle ergometry testing. PBMC bioenergetics analysis were performed using the high resolution respirometry (Oroboros O2k). PBMC oxygen consumption rate was measured with sequential additions of pyruvate, oligomycin, FCCP, and antimycin A. We estimated basal, maximal uncoupled respiration (MUR) and spare respiratory capacity (SRC). SRC was defined as the difference between basal respiration and MUR. Pearson correlation coefficient was used to assess correlation of PBMC bioenergetics with muscle performance.

Results: The mean age of participants was 60.6 +/-9.5 years, eGFR was 35 +/-12.5 ml/min/1.73m^2 and 53% were females. PBMC MUR correlated with total work (r= 0.57, *P*-value=0.041) and efficiency (absolute) (r=0.58, *P*-value=0.034). PBMC SRC correlated with total work (r=0.58, *P*-value=0.036) and efficiency (r=0.60, *P*-value=0.029). VO2 peak correlated with PBMC basal respiration (r=0.56, *P*-value=0.044), MUR (r=0.69, *P*-value=0.007), and SRC (r= 0.71, *P*-value=0.006).

Conclusions: These results suggest that PBMC respiration is strongly associated with exercise capacity and efficiency. Further studies are needed to investigate biologic determinants of PBMC bioenergetic health and its validity as a surrogate marker of skeletal muscle metabolic health in CKD.

Funding: NIDDK Support, Commercial Support - Dialysis Clinics Incorporated

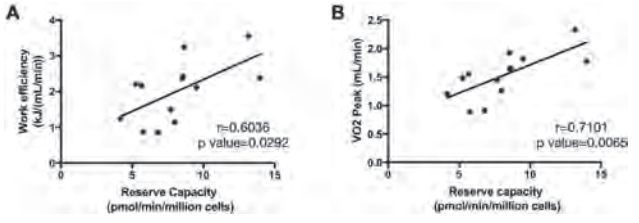

Figure 1. Association of PBMC reserve capacity with A) total work efficiency and B) cardiorespiratory function (VO2 peak).

PO2425

Association of Proximal Tubular Secretory Clearance with Decline in Cognitive Function

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Background: Persons with chronic kidney disease (CKD) are at risk for cognitive decline. The retention of protein bound organic solutes, normally cleared by renal tubular secretion, is hypothesized to contribute to cognitive dysfunction in CKD. We tested whether lower kidney clearance of secretory solutes is associated with cognitive decline in a multi-center CKD cohort.

Methods: We studied participants from the Chronic Renal Insufficiency Cohort (CRIC) study, excluding persons with prior stroke or baseline cognitive impairment. We estimated tubular secretory clearance by 24-hour kidney clearance of eight solutes primarily eliminated by tubular secretion. Cognitive function was measured by annual Modified Mini Mental Status (3MS) exams. We defined cognitive decline as a sustained >5 point decrease in the 3MS score from baseline. Associations were assessed with Cox survival models; we controlled for multiple comparisons by calculating q-values compared to the false discovery rate.

Results: Among 2366 study participants, the mean age was 58 years, mean eGFR was 46 mL/min/1.73 m2, and median baseline 3MS score was 96; 235 developed cognitive decline over a median of 7.22 years of follow-up (1.48 events per 100 person-years). Lower kidney clearance of five of the eight solutes was associated with cognitive decline after adjustment for baseline eGFR, urinary albumin excretion, and other potential confounders (Table).

Conclusions: Lower kidney clearance of secreted solutes was associated with cognitive decline over long-term follow-up in a prospective CKD cohort. The retention of secretory solutes may be a novel cause of impaired cognition in persons with CKD.

Funding: NIDDK Support

Associations of baseline 24-hour secretory solute clearances with cognitive decline over follow-up (Hazard Ratios per 50% lower secretory clearance)

Secretory clearance	Unadjusted	Adjusted	q-value
Cinnamoylglycine	1.18 (1.07, 1.29)	1.17 (1.05, 1.29)	0.013*
Indoxyl sulfate	1.20 (1.04, 1.38)	1.23 (1.03, 1.46)	0.038*
Isovalerylglycine	1.31 (1.15, 1.48)	1.31 (1.13, 1.51)	0.002*
Kynurenic acid	1.29 (1.11, 1.49)	1.29 (1.07, 1.55)	0.023*
p-cresol sulfate	1.06 (0.94, 1.19)	1.00 (0.87, 1.16)	0.986
Pyridoxic acid	1.16 (1.03, 1.31)	1.15 (0.99, 1.38)	0.094
Tiglylglycine	1.20 (1.07, 1.35)	1.19 (1.03, 1.38)	0.038*
Xanthosine	1.10 (0.98, 1.23)	1.08 (0.95, 1.23)	0.265

Adjusted for age, sex, race/ethnicity, education, baseline 3MS, diabetes, coronary artery disease, peripheral arterial disease, systolic blood pressure, diastolic blood pressure, BMI, HDL, LDL, hemoglobin, CRP, use of use of statins, aspirin, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, eGFR, and 24-hour proteinuria

* Denotes statistical significance after correction for multiple comparisons, q-value < FDR value 0.05

PO2426

Clinical Features and Outcomes of Immunoglobulin G4-Related Disease Including Kidney Involvement

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Background: Immunoglobulin G4-related disease (IgG4-RD) is a newly recognized disease, and a few epidemiologic studies about this disorder have been published. This research aimed to describe the clinical, laboratory, and histopathological features and outcomes of IgG4-RD.

Methods: Ninety-four patients who satisfied the comprehensive diagnostic criteria on IgG4-RD were included in this study. Fifty-eight (61.7%) were men. The mean age was 54.8 years, and the median follow-up duration was 32.9 months. The clinical feature between single and multiple organ involvement and with or without kidney involvement groups were evaluated based on symptoms and laboratory findings. The clinical outcome was assessed according to treatment strategies and response.

Results: Of 94 patients, 56 (59.6%) had multiple organs involvement. It showed a variety of symptoms and organs involved. Patients with multiple organ involvement had higher serum IgG and IgG4 levels than those with single organ involvement. Those with IgG4-related kidney disease (IgG4-RKD) had worse renal function. The incidence of peripheral blood eosinophilia and hypocomplementemia was higher in patients with renal involvement than in those without. Glucocorticoids-based therapy was most commonly used. (79.8%). Thirty-nine (41.5%) achieved complete remission. Eighteen (19.1%) relapsed after response to treatment. Eight (61.5%) of 13 patients with IgG4-RKD experienced improvement in renal function after treatment. None of the patients died during the follow-up period.

Conclusions: Kidney or other organ involvement is not significantly associated with clinical outcomes. Since IgG4-RD has different clinical features, it should be accurately diagnosed. Therefore, all physicians must actively diagnose and treat the condition.

Figure 1. Distribution of organs involvement

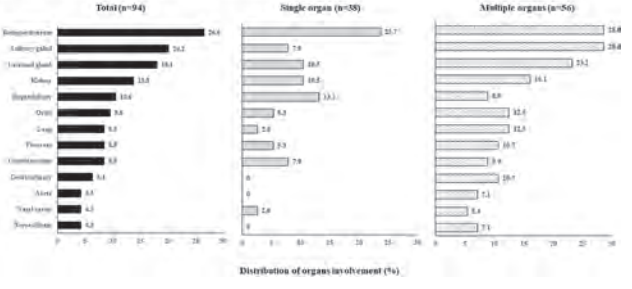
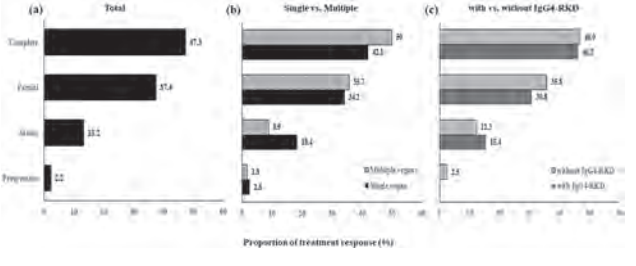


Figure 2. Treatment response



PO2427

Evaluation of Changes in Renal Microperfusion in Hyperuricemic-Induced Kidney Injury by Contrast-Enhanced Ultrasound Imaging

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Background: The diagnostic tools for early detection of renal injury caused by hyperuricemia are particularly lacking. Our study investigated the application of contrast-enhanced ultrasound (CEUS) in both hyperuricemic nephropathy (HN) rats and patients with hyperuricemia induced kidney injury.

Methods: Animal study was performed in hyperuricemic rat induced by feeding with a mixture of adenine and potassium oxonate for 4 weeks. In addition, 10 healthy volunteers and 40 patients with hyperuricemia induced kidney injury from CKD 1 to 4 stage were enrolled. CEUS was performed and low acoustic power contrast-specific imaging was used for quantitative analysis. Time-intensity curves (TICs) and quantitative indexes were created by Qlab software.

Results: In HN rat model monitored by CEUS technique, a significant decline in renal cortical perfusion as reflected by lower Peak Intensity (PI) value (25.43±1.31 vs. 37.9±1.75db) and longer time to reach peak (TTP) intensity (34.5±5.9 vs. 8.58±1.6s) was found when compared to control rats one week after administration of adenine and potassium oxonate, with more pronounced decline in HN rats at 4 weeks. Quantitative assessment of PI was well corelated with the serum Kim-1 level as well as the fibrosis scores in hyperuricemic rats from mild to advanced disease stage. Clinically, an early decline of PI in renal cortical perfusion was found in CKD stage 1 patients with hyperuricemia induced kidney injury as compared to the control group (61.1±4.52 vs. 65.80±7.10 db), which became progressively less visible in patients with more severe kidney injury in these patients of CKD 4 stage (40.93±13.36 db). An early increase of TTP could also be detected in HN patients with CKD 1 stage as compared to normal control (15.14±1.75 vs. 14.52±4.75s), which became the most pronounced in these patients of CKD 4 stage (67.32±3.29s). In addition, Peak value measured by CEUS was correlated with renal function in patients with hyperuricemia induced kidney injury.

Conclusions: CEUS is able to detect the renal perfusion in a dynamic way. Renal perfusion measured by CEUS correlates with the renal functional impairment and tubulointerstitial fibrosis, suggesting a sensitive, reliable and non-invasive method that could be applied in the diagnosis of hyperuricemia induced kidney injury in clinical practice.

Funding: Government Support - Non-U.S.

PO2428

The Effect of Kidney Function on Reference Intervals of Serum-Free Light Chains and Free Light Chain Kappa/Lambda Ratio

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Background: A kidney reference interval has previously been published for serum free light chain (FLC) ratio (0.37–3.10) but does not take into account the degree of kidney failure. The aim of this study was to establish a kidney reference interval for FLC and validate the current and propose new kidney reference interval for FLC ratio.

Methods: A total of 80,759 participants of the Iceland Screens, Treats or Prevents Multiple Myeloma (iStopMM) study were included. Participants were screened with serum FLC (FREELITE) measurements and serum protein electrophoresis (SPEP) and immunofixation (IFE). Serum creatinine (SCr) value closest to the screening was used to calculate eGFR. Participants with M-protein, eGFR > 59 mL/min/1.73 m^2, missing SCr measurement or > 1 year from the iStopMM screening were excluded. A nonparametric method was used to calculate the 95% CI. Partitioning was determined based on the proportion in each subgroup outside reference interval.

Results: Serum FLC were measured in 4885 (12%) participants with eGFR <60 mL/min/1.73 m^2, without evidence of monoclonality on SPEP or IFE. Median (IQR) kappa level was 20.6 mg/L (16.0–27.7), lambda level 18.6 mg/L (14.7–24.2) and FLC ratio 1.13 (0.95–1.35). Using current reference intervals, 58% and 20% of persons had values outside the normal range for kappa and lambda, respectively. The FLC ratio was outside the standard reference interval (0.26–1.65) in 8% and the kidney reference interval (0.37–3.10) in 0.6% of persons. Based on these findings, new reference intervals for FLC and FLC ratio have been established (Table).

Conclusions: Current reference intervals for FLC and FLC ratio are inaccurate for patients with decreased kidney function. We propose new reference intervals for FLC and FLC ratio for use in patients with chronic kidney disease.

Funding: Government Support - Non-U.S.

Reference intervals for kappa, lambda, and FLC ratio depending on kidney function

	New reference interval (2.5 - 97.5th percentile)		
Kidney function (ml/min/1.73 m2)	Kappa (2.5–97.5 percentile)	Lambda (2.5–97.5 percentile)	FLC ratio (2.5–97.5 percentile)
eGFR 45 – 59	10.0 – 45.3	9.2 – 37.7	0.63 – 1.88
eGFR 30 – 44	11.8 – 67.6	10.2 – 50.7	0.67 – 2.05
eGFR < 30	17.9 – 109.6	14.4 – 87.9	0.67 – 2.14

eGFR: estimated glomerular filtration rate

PO2429

Molecular Stratification of CKD

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Background: Current classification of chronic kidney disease (CKD) into stages based on the indirect measures of kidney functional state, estimated glomerular filtration rate and albuminuria, is agnostic to the heterogeneity of underlying etiologies, histopathology, and molecular processes. We used genome-wide transcriptomics from patients' kidney biopsies, directly reflecting kidney biological processes, to stratify patients from three independent CKD cohorts.

Methods: Self-Organizing Maps (SOM), an artificial neural network machine-learning algorithm, assembled CKD patients into four novel subgroups, molecular categories, based on the similarity of their kidney transcriptomics profiles.

Results: The unbiased, molecular categories were present across CKD stages and histopathological diagnoses, highlighting heterogeneity of conventional clinical subgroups at the molecular level. CKD molecular categories were distinct in terms of biological pathways, transcriptional regulation and associated kidney cell types, indicating that the molecular categorization is founded on biologically meaningful mechanisms. Importantly, our results revealed that not all biological pathways are equally activated in all patients; instead, different pathways could be more dominant in different subgroups and thereby differentially influencing disease progression and outcomes.

Conclusions: This first kidney-centric unbiased categorization of CKD paves the way to an integrated clinical, morphological and molecular diagnosis. This is a key step towards enabling precision medicine for this heterogeneous condition with the potential to advance biological understanding, clinical management, and drug development, as well as establish a roadmap for molecular reclassification of CKD and other complex diseases.

Funding: Commercial Support - This work was done as part of Renal Precompetitive Consortium (RPC2) collaboration (Tomilo et al, Drug Discov Today 2018) and was jointly funded by the participating members: AstraZeneca, Eli Lilly, NovoNordisk, Gilead, Janssen

PO2430

Determinants of Serum β2 Microglobulin and β-Trace Protein in South Asians

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Background: β2-Microglobulin (B2M) and β-trace protein (BTP) are being considered for use with creatinine and cystatin C to improve the GFR estimation (Inker, AJKD 2020). In a Pakistani population, we showed that B2M and BTP did not improve the performance of eGFRcys and eGFRcr-cys (Wang, Kidney Week 2021). We aimed to evaluate non-GFR determinants of B2M and BTP in a general population in Pakistan.

Methods: We used linear regression models to assess associations between possible determinants and log-transformed levels of B2M and BTP adjusting for measured GFR among 557 participants (≥40 years) from Pakistan. The strength of significant associations was defined as strong, intermediate, or weak if the absolute percent difference in B2M or BTP levels was >10%, 5%-10% and <5%, respectively. R^2 was calculated in a model including all determinants.

Results: Non-GFR determinants with intermediate and strong associations with higher BTP included male sex, history of heart disease, and lower waist circumference. Non-GFR determinants of higher B2M included male sex, higher total body fat, and lower serum albumin. As shown in Table below, the non-GFR determinants assessed in our study along with measured GFR could explain 64.2% and 78.2% variance of BTP and B2M, respectively.

Conclusions: Factors associated with non-GFR determinants of BTP and B2M differ from those of cystatin C and creatinine. These and unidentified factors limit their usefulness in improving eGFR among South Asians.

Funding: NIDDK Support, Other NIH Support - Fogarty International Center (1R03TW007588-01A1)

Factor of interest	IQR	Average percent difference (95% CI) in BTP	Average percent difference (95% CI) in B2M	Average percent difference (95% CI) in cystatin C	Average percent difference (95% CI) in creatinine
		Multivariate model	Multivariate model	Multivariate model	Multivariate model
Measured GFR (mGFR)	36.6	-52.4 (-55.5 to -49.0)	-47.8 (-51.1 to -44.2)	-42.6 (-45.1 to -40.0)	-50.0 (-53.0 to -46.9)
Age (year)	13.0	3.56 (-2.63 to 10.2)	0.002 (-3.67 to 3.82)	3.02 (-0.14 to 6.30)	-1.00 (-4.41 to 2.52)
Sex (men vs. women)	-	20.7 (9.22 to 30.6)	10.1 (2.33 to 17.2)	13.1 (7.07 to 18.7)	24.8 (17.8 to 31.2)
Smoking (yes vs. no)	-	4.91 (-3.61 to 14.2)	5.04 (-0.36 to 10.7)	5.14 (0.72 to 9.74)	-0.66 (-5.37 to 4.28)
Body mass index (kg/m²)	8.6	7.10 (-0.98 to 15.8)	0.63 (-4.35 to 5.88)	4.49 (0.36 to 8.80)	12.4 (7.03 to 18.1)
Waist circumference (cm)	15.0	-7.39 (-13.2 to -1.10)	0.12 (-4.04 to 4.46)	0.35 (-2.88 to 3.69)	-3.07 (-6.98 to 1.01)
Total body fat (kg)	10.6	3.81 (0.22 to 7.52)	6.40 (3.70 to 9.18)	2.65 (0.67 to 4.67)	-0.19 (-2.93 to 2.62)
Lean body mass (kg)	14.7	-1.43 (-7.17 to 4.67)	2.55 (-1.46 to 6.73)	1.08 (-2.05 to 4.31)	7.33 (2.71 to 12.1)
History of heart disease	-	13.6 (1.84 to 22.5)	7.25 (-1.13 to 16.3)	8.32 (2.38 to 14.6)	6.62 (-0.42 to 14.2)
Serum albumin (g/dL)	0.4	-6.49 (-10.1 to -2.69)	-7.39 (-9.84 to -4.88)	-3.93 (-6.05 to -1.77)	-6.60 (-2.85 to 1.71)
LDL cholesterol (mmol/L)	37.0	-2.25 (-5.98 to 1.63)	-3.61 (-6.06 to -1.10)	-2.10 (-4.14 to -0.02)	-1.22 (-3.63 to 1.26)
Dietary protein intake (g/day)	19.0	0.18 (-0.49 to 0.85)	0.39 (-0.34 to 1.14)	0.27 (-0.05 to 0.59)	-0.25 (-0.90 to 0.41)
Urine creatinine (mg/kg/d)	6.4	0.90 (-4.72 to 26.8)	-1.82 (-10.2 to 7.43)	0.67 (-5.47 to 7.21)	17.5 (5.11 to 27.7)
R^2 for the multivariate model with mGFR measurement error		64.2%	78.2%	81.4%	80.5%
R^2 for mGFR with mGFR measurement error		59.5%	74.6%	75.3%	65.4%
R^2 for mGFR without mGFR measurement error		58.5%	73.4%	74.2%	64.4%

Average percent difference in serum B2M, BTP, cystatin C and creatinine levels for an IQR (difference between the 25th and 75th percentiles) higher level in continuous variables was calculated as $100 \times (e^{\beta_{IQR\ difference}} - 1)$ using error-in-variables regression models assuming log-transformed mGFR was measured with 98.5% reliability. The multivariate model included all variables presented in the table and corrected for measurement error of mGFR.
Strength of association for statistically significant results is indicated by color: red, strong (absolute average percent difference in B2M/BTP levels >10%); blue, intermediate (absolute average percent difference in B2M/BTP levels 5%-10% inclusive); and yellow, weak (absolute average percent difference in B2M/BTP levels <5%). R^2 was based on all the non-GFR determinants presented in the table.

Table. Determinants and log-transformed filtration markers (N=557).

PO2431

Performance of Serum β2 Microglobulin and β-Trace Protein-Based Glomerular Filtration Rate Estimating Equations in South Asians

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Background: Previously we showed that glomerular filtration rate (GFR) estimation based on cystatin C alone (eGFRcys) had a large bias in a general population in Pakistan, and the GFR estimation based on cystatin C and creatinine (eGFRcr-cys) was not substantially better than eGFRcr-PK (Wang, KI Reports 2021). β2-Microglobulin (B2M) and β-trace protein (BTP) are being considered for use in a panel including creatinine and/or cystatin C to improve GFR estimation (Inker, AJKD 2020). We aimed to evaluate whether adding B2M and BTP would improve the performance of eGFRcys and eGFRcr-cys in a general population in Pakistan.

Methods: We assessed panel eGFR equations using B2M and BTP in addition to cystatin C (3-marker panel) or creatinine and cystatin C (4-marker panel) in a cross-sectional study of 557 participants (≥40 years) from Pakistan. We compared bias (median difference in measured GFR [mGFR] and eGFR), precision (interquartile range of differences), and accuracy (percentage of eGFR within 30% of mGFR [P_{30}] and root mean square error [RMSE]).

Results: As shown in the Table, the 4-panel equation (addition of BTP and B2M to creatinine and cystatin C) had lesser bias, better precision, and better accuracy (all *P*s<0.001) compared to the 3-panel equation (addition of BTP and B2M to cystatin C). The 3-panel equation worsened bias (*P*<0.001) and did not improve precision or accuracy (*P*>0.05 for both) relative to eGFRcys. Similarly, the 4-panel equation worsened bias (*P*<0.001) and did not improve precision or accuracy (*P*>0.05 for both) compared to eGFRcr-cys.

Conclusions: B2M and BTP did not improve the performance of eGFRcys and eGFRcr-cys in South Asians. Evaluation of non-GFR determinants of BTP and B2M would be of interest.

Funding: NIDDK Support, Other NIH Support - Fogarty International Center (1R03TW007588-01A1)

Equation	Filtration marker	Demographics	Bias[a], median difference (ml/min/1.73 m²)	Precision[b], IQR (ml/min/1.73 m²)	Accuracy[c], P_{30} (%)	Accuracy[d], RMSE
CKD-EPI eGFRcr	Creatinine	Age, sex, race	-6.76 (-9.10 to -5.90)	22.6 (20.3 to 25.4)	76.1 (72.4 to 79.6)	0.269 (0.263 to 0.323)
CKD-EPI eGFRcr-PK	Creatinine	Age, sex, race	NA	22.7 (20.6 to 25.8)	82.4 (79.0 to 85.5)	0.265 (0.243 to 0.297)
CKD-EPI eGFRcys[e]	Cystatin C	Age, sex, race	12.7 (10.7 to 15.2)	25.6 (23.2 to 28.3)	75.3 (69.4 to 76.9)	0.322 (0.303 to 0.349)
CKD-EPI eGFRcr-cys[f]	Creatinine, Cystatin C	Age, sex, race	2.73 (1.16 to 4.58)	21.2 (18.6 to 24.3)	83.1 (79.8 to 86.1)	0.253 (0.231 to 0.255)
2020 Cystatin C-B2M-BTP equation[g]	Cystatin C, B2M, BTP	Age, sex	15.3 (13.6 to 18.1)	26.7 (25.0 to 29.0)	70.7 (66.8 to 74.5)	0.331 (0.312 to 0.355)
2020 Creatinine-Cystatin C-B2M-BTP equation[h]	Creatinine, Cystatin C, B2M, BTP	Age, sex	5.12 (3.49 to 7.20)	22.1 (19.5 to 25.7)	81.3 (77.8 to 84.5)	0.256 (0.235 to 0.288)

[a]Bias was expressed as the median difference in measured GFR minus estimated GFR (95% confidence interval). A negative bias indicates overestimation of the measured GFR, and a positive bias indicates underestimation of the measured GFR. NA, not applicable because bias was expected to be zero (the equation was developed in the study population).
[b]Precision was expressed as the interquartile range (IQR) of differences between measured GFR and estimated GFR (95% confidence interval).
[c]P_{30} was defined as the percentage of individuals with estimated GFRs within 30% of measured GFR (95% confidence interval). The 95% CI of P_{30} was calculated using the Clopper-Pearson (Exact) method.
[d]RMSE was defined as the square root of the average squared different of measured GFR and estimated GFR on the logarithmic scale.
[e]The significance of differences among equations was determined with the use of the Wilcoxon sign rank test for bias, the McNemar test for P_{30}, and the bootstrap method for IQR and RMSE with 10,000 replications. *P* values for the 4-panel equation compared to the 3-panel equation were *P*<0.001 for bias, *P*<0.001 for precision, *P*<0.001 for accuracy, and *P*=0.24 for RMSE. *P* values for the 3-panel compared to eGFRcys were *P*<0.001 for bias, *P*=0.32 for precision, *P*=0.08 for accuracy, and *P*=0.55 for RMSE. *P* values for the 4-panel equation compared to eGFRcr-cys were *P*<0.001 for bias, *P*=0.71 for precision, *P*=0.12 for accuracy, and *P*=0.84 for RMSE.

Table. The performances of GFR estimating equations in comparison with measured GFR (N=557).

PO2432

Rare Variant Analyses in 171,172 UK Biobank Participants Reveals Novel Genetic Associations with Renal Function and Kidney Diseases

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Background: GWASs have identified hundreds of common genetic variants associated with chronic kidney disease (CKD), but the burden of rare loss-of-function (LoF) or pathogenic/likely pathogenic (P/LP) variants has not been systematically examined.

Methods: We tested gene-based and variant-level association for 5 renal biomarkers (Glomerular Filtration Rate estimated from serum creatinine and/or cystatin-C, Blood Urea Nitrogen, Urine Albumin-to-Creatinine Ratio) measured at enrollment and kidney-related diseases (e.g. End-Stage Renal Disease and stage4/5 CKD, CKD defined by biomarker and/or diagnosis from NHS data, Cystic kidney disease and Renal calculi) in 171,172 UK Biobank participants of genetically assessed European ancestry and with whole exome sequencing (WES). For each trait, we fit a genome-wide regression model and tested for association using REGENIE V2.0, adjusting for age, sex, 10 ancestry PCs, assessment center, and BMI where appropriate. For gene-based analyses, we generated 15 models to collapse ClinVar-classified P/LP, putative LoF and deleterious variants predicted by 16 *in silico* scores (SIFT, Polyphen, BayesDel, etc.) from dbNSFP 4.1c.

Results: We identified 33 and 18 genes associated with ≥2 biomarkers and ≥1 kidney diseases across collapsing models (FDR<0.05), respectively. *PKD1/2, COL4A3/4, CUBN, IFT140* were associated with both biomarkers and kidney diseases. Association analyses also highlighted genes including: *COL4A1, CST3, LAMC1, LRP2, SLC22A2, SLC34A3* and *SH2B3*. Variant-level analyses further informed impact on protein, e.g. the *SLC22A2* association signal was mainly driven by a frameshift (rs8177505) with lowering effects on eGFR (p=1e-27, beta=-6.2, MAF=0.12%). The exome-wide variant analyses revealed 29 genes (eg. *UMOD*) with variant associations (p<5e-8) with >3 biomarkers or ≥1 endpoint, including 2 that were also implicated from gene-based analyses (*COL4A4* and *CUBN*).

Conclusions: This large-scale study elucidates the genetic landscape of kidney diseases. Our findings validate established genes and reveal novel genetic associations with renal function and kidney diseases.

Funding: Commercial Support - Janssen R&D

PO2433

High Dietary Phosphate Intake Causes Inflammatory Tubular Injury and Fibrosis in Mice

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Background: Due to the increasing consumption of processed food, the dietary inorganic phosphate intake clearly exceeds the recommended daily allowance. Elevated phosphate levels are associated with a higher cardiovascular and all-cause mortality in the general population and accelerated progression of chronic kidney disease (CKD). It is under investigation whether chronic phosphate load represents a renal health risk in the absence of CKD.

Methods: Male C57BL/6 mice were fed with a 2% high phosphate diet (HPD) or respective 0.8 % normal phosphate diet (NPD) for six months. We collected blood, urine and kidneys to investigate phosphate metabolism, kidney function, tissue alterations and inflammation.

Results: Six months HPD significantly increased plasma levels of the phosphaturic hormone fibroblast growth factor (FGF) 23 resulting in enhanced phosphaturia and elevated serum phosphate level. HPD in mice caused albuminuria and increased plasma creatinine level. Histological analyses revealed that mice on HPD develop proximal tubular injury characterized by loss of cell polarity and brush border membranes, flattened

epithelia, increased proliferation, mononuclear interstitial infiltration and fibrosis. The kidney damage in HPD was accompanied by increased renal expression of the kidney injury marker *Kim-1* und *Ngal* mice. Kim-1 accumulated in regions of tubular lesions. Flow cytometry analysis demonstrated that the HPD reduced storage of $Ly6C^{hi}$ monocytes in the spleen and concurrently, enhanced accumulation of $F4/80^{+}$ macrophages and dendritic cells in the kidney. Histological analyses proofed accumulation of $F4/80^{+}$ macrophages and $CD3^{+}$ T-cells in areas of tubular injury that associated with increased renal expression of chemotaxis and growth factors for monocytes and macrophages *Ccl2, Csf1* and *Il34* in HPD mice. Finally, HPD caused renal fibrosis associated with increased *collagen 1, Ctgf*, and *Tgfb1* expression.

Conclusions: Chronic high phosphate load impairs kidney function by causing a strong inflammatory response and proximal tubular injury in healthy mice. Our results indicate that chronic high phosphate intake might be a renal health risk not only for CKD patients but also for the general population.

PO2434

Apabetalone Downregulates Fibrotic, Inflammatory and Calcific Processes in Renal Mesangial Cells: Mechanism for Reduced Cardiac Events in CKD Patients

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Background: Major adverse cardiac events (MACE) are prevalent in patients with chronic kidney disease (CKD). Apabetalone inhibits BET proteins, which regulate expression of genes involved in fibrosis, inflammation & calcification. In the phase 3 BETonMACE trial, apabetalone reduced MACE in patients with CKD (eGFR<60) implying favorable effects on the kidney-heart axis. Here we examine apabetalone's impact on pathways of nephropathy in human renal mesangial cells (HRMCs).

Methods: HRMCs were stimulated with TGF-β1 or LPS ± 1-25μM apabetalone. Gene expression was measured by real-time PCR & RNA-seq. Smooth muscle actin (a-SMA) was examined by immunofluorescence & alkaline phosphatase (TNALP) activity in biochemical assays. RNA-seq from TGF-β1 stimulated HRMC was evaluated by GO and Ingenuity Pathway Analysis (IPA).

Results: In HRMCs, apabetalone suppressed TGF-b1 induced pro-fibrotic gene expression including (a) a-SMA, a fibrotic marker, by 90% $p<0.001$ & de novo a-SMA protein production (b) fibronectin, an extracellular matrix (ECM) component, by 44% $p<0.001$ (c) NOX4, promoting reactive oxygen species (ROS) production, by 82% $p<0.001$ (d) TNALP, promoting calcification, by 96% & TNALP activity by 96% $p<0.001$. Apabetalone opposed LPS induced inflammatory gene expression: IL6 by 94%, IL1B by 95% & PTGS2 (COX2) by 94% $p<0.001$. In GO, ECM gene sets were in the top 20 affected by apabetalone, indicating reduced fibrosis. IPA predicted inhibition of NfkB-RelA and NFkB complex to suppress inflammation, and activation of glucose utilization & tolerance of ROS production pathways, such as Oxidative Phosphorylation (z-score 5.7 $p<0.01$ at 25μM; z-score 3.5 $p>0.05$ at 5μM) and NRF2-Mediated Oxidative Stress Response (z score 2.3 $p<0.001$ at 25μM; z-score 1.6 $p<0.001$ at 5μM).

Conclusions: Apabetalone downregulates responses to TGF-β1 or LPS that promote fibrosis, inflammation & calcification in HRMCs. Changes in energy metabolism pathways predict apabetalone enables HRMC to cope with elevated glucose. Our results provide mechanistic insight into reduced MACE in CKD patients receiving apabetalone in the BETonMACE trial, & predict efficacy in the upcoming phase 3 BETonMACE2 trial.

Funding: Commercial Support - Resverlogix Corp.

PO2435

Characterization of Nano-Sized Silica in Sugarcane Ash and Its Potential Role in the Pathogenesis of CKD of an Unknown Etiology

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Background: Sugarcane burning by farmers in developing countries is hypothesized to contribute to an endemic kidney pathology called chronic kidney disease of an unknown etiology (CKDu). Further, elemental analysis of the sugarcane stalks was shown to have a high percentage of amorphous silica (SiO_2). We hypothesized that burning of sugarcane generates nano-sized particles that are easily inhaled and translocated to the kidney thereby contributing to CKDu in sugarcane workers.

Methods: To determine if nano-sized particles are present in sugarcane ash, we utilized single particle inductively coupled plasma mass spectrometry (ICP-MS) and dynamic light scattering (DLS). To determine the effects of SiNPs on the kidney, we used a human proximal convoluted tubule cell line (HK-2) to recapitulate the nephron's exposure to sugarcane ash, desilicated ash, sugarcane ash derived SiNPs, and pristine 200 nm SiNPs at 0.25, 2.5, and 25 μg/mL.

Results: Using single particle ICP-MS, we identified silica nanoparticles (SiNPs) within digested sugarcane ash which ranged in size from 190-212 nm. DLS analysis of digested ash confirmed the presence of nanoparticles with a hydrodynamic diameter of ~180 nm and Despite not being directly cytotoxic to HK-2 cells at 6 hours at any dose, SiNPs are taken up leading to significant production of reactive oxygen species and mitochondrial superoxide within the first hour of exposure at all doses.

Conclusions: This indicates that the presence of silica nanoparticles from sugarcane ash in the kidney may lead to NLRP3 inflammasome activation and epithelial mesenchymal transition occurring which will lead to a CKDu phenotype and disease pathogenesis.

Funding: NIDDK Support

PO2436

Release of ATP from Renal Tubular Epithelial Cells via Connexin 43 Deteriorates Renal Fibrosis After Unilateral Ureteral Obstruction

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Background: As a kind of DAMPs (Danger associated molecular patterns), ATP is released after stress or injury through ATP-permeable channels, most likely to be connexin hemichannel proteins. Among which, connexin 43 (Cx43) is the most common member. However, its role on renal injury and the following fibrosis has not been examined.

Methods: We analyzed renal samples from patients with obstructive nephropathy and applied unilateral ureteral obstruction (UUO) to induce renal fibrosis in mice. Cx43-KSP mice were generated to deplete the Cx43 gene of renal tubular epithelial cells (TECs). Through transcriptomics, metabolomics, and single-cell sequencing multi-omics analysis, the relationship among Cx43, ATP, and macrophage in renal fibrosis was explored.

Results: The expression of Cx43 upregulated in TECs after UUO in mice or in patients with obstructive nephropathy. Knockdown of Cx43 in TECs or using Cx43 specific inhibitors reduced UUO induced-inflammation and fibrosis. Single cell RNA sequencing and immunoflurence showed that the distribution of ATP specific receptors is mainly on macrophages, including P2rx4 and P2rx7. These receptor positive macrophages were undergoing pyroptosis after UUO. In vitro, ATP directly induced macrophage pyroptosis. The administration of P2 receptor and P2rx7 receptor inhibitors to UUO mice inhibited macrophage pyroptosis and demonstrated a similar renoprotection as the Cx43 knocking out. Further, we found the GAP19/26 (Cx43 hemichannel inhibitor peptide) and A-839977 (the inhibitor of pyroptosis receptor) alleviated UUO induced fibrosis, while BzATP (the agonist of pyroptosis receptor) exacerbated fibrosis. Single cell sequencing demonstrated that the pyroptotic macrophages upregulated the expression of CXCL 10, which in turn activated fibroblasts.

Conclusions: Cx43 hemichannel mediates the outflow of ATP in TECs inducing macrophage pyroptosis, which subsequently secretes CXCL 10 promoting fibroblast activation and renal fibrosis.

PO2437

Single-Nucleus RNA-Sequencing Analysis Elucidates Intercellular Interactions Between Inflammatory Parenchymal Cells and Immune Cells in the Kidneys with Tertiary Lymphoid Tissues

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Background: After acute kidney injury (AKI), elderly patients sometimes fail to recover and develop chronic kidney disease (CKD). We previously demonstrated that tertiary lymphoid tissues (TLTs) are formed in aged kidneys after AKI, resulting in prolonged inflammation and impaired regeneration, leading to CKD. However, the mechanism of TLT formation in aged kidneys remains unknown.

Methods: Single nucleus RNA-sequencing (snRNA-seq) for three aged murine kidneys 30 days after ischemic reperfusion injury (IRI) as well as an aged kidney after sham operation was performed using the 10X platform. Computational analysis including subset analysis, ligand-receptor analysis, and pseudotime trajectory analysis were performed. Gene expression was validated by immunostaining and high sensitivity in situ hybridization.

Results: SnRNA-seq generated 15968 and 7485 nuclei transcriptomics from IRI kidneys and a sham kidney, respectively, and demonstrated heterogeneous cell populations including parenchymal cells and immune cells in IRI kidneys with TLTs. We identified a subset of proinflammatory proximal tubules with sustained injury in IRI kidneys with TLTs, and confirmed that some of them surrounded TLTs. Ligand-receptor analysis suggested that this proinflammatory proximal tubules intensively interact with immune cells and fibroblasts. We also identified subsets of profibrotic fibroblasts and proinflammatory fibroblasts, and validated that the latter population being TLT-associated fibroblasts. Pseudotime trajectory analysis of fibroblasts showed that these two types of fibroblasts acquired distinct transcription factors and gene expression patterns along differentiation into distinct populations. Ligand-receptor analysis suggested that proinflammatory fibroblasts possibly contribute to survival and proliferation of B cells through BAFF production in TLT formation.

Conclusions: SnRNA-seq elucidated proinflammatory populations both in proximal tubules and fibroblasts in aged injured kidneys. Various intercellular interactions between the proinflammatory parenchymal cells and immune cells might contribute to TLT formation and these interactions have the potential to be promising therapeutic targets for AKI to CKD transition in the elderly.

Funding: Government Support - Non-U.S.

PO2438

NGAL Is Necessary for Antigen-Presenting Cells Recruitment and Proteinuria in the Mouse Kidney with Ureteral Obstruction

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Background: Elevated levels of proteinuria are present in patients with chronic kidney disease (CKD) even with preserved kidney function. In this line, immune cells play a major role in the development and progression of renal inflammation in CKD. In particular, antigen presenting cells (APCs), such as macrophages (MØ) and dendritic cells (DCs) may play a pivotal role. Previous studies have demonstrated that neutrophil gelatinase-associated lipocalin, NGAL, is overexpressed during renal lesion. However, it is unknown whether there is a relationship between proteinuria and the APCs recruitment, and if it is dependent on NGAL. Our objective was to determine whether NGAL promotes proteinuria and APCs recruitment during the unilateral ureteral obstruction (UUO).

Methods: Male C57BL/6 Wild type (WT) and NGAL-KO mice (8-12 w.o.) were undergoing to UUO and to Sham surgery (Control) during 14 days (n=8). Creatinine and proteinuria were measured from pelvis urine of obstructed kidney. DCs ($MHC\text{-}II^+/CD11c^+/F4/80^-/CD11b^+$ for DCs type-2 phenotype) and MØ ($MHC\text{-}II^+/CD11c^+/F4/80^+/CD11b^+/CD80^+$ for M1 phenotype) recruitment were measured by flow cytometry. Additionally, WT-MØ were stimulated with albumin (10mg/mL, 24 h) and M1 genes evaluated by real-time PCR.

Results: We observed that the increased protein/creatinine ratio in the obstructed kidney of UUO WT mice was reduced in NGAL-KO mice (24.4±9.0 vs. 12.2±5.6 $p<0.01$). *In vitro* stimulation with albumin on macrophages from WT mice increased the mRNA levels of pro-inflammatory M1 markers (IL-12b, IL-23a, TNFα and iNOS; $p<0.001$). We did not observe changes in the M2 profile. Finally, we observed an early increase in the recruitment of DCs and M1 macrophages in WT UUO ($MØ_{Sham}$=6.9±1.2 vs $MØ_{UUO}$=60.0±24.4 cell/mg renal tissue; DCs_{Sham}=54.7±20.0 vs DCs_{UUO}=242±99.9 cell/mg renal tissue; $p<0.01$), which was prevented in UUO NGAL-KO mice ($MØ_{WT}$=60.0±24.4 vs $MØ_{NGAL\text{-}KO}$=30.2±7.8 cell/mg renal tissue; DCs_{WT}=242±99.9 vs $DCs_{NGAL\text{-}KO}$=83.1±9.6 cell/mg renal tissue; $p<0.05$).

Conclusions: Our results show that NGAL is necessary for DCs and MØ recruitment, in addition for the proteinuria increment in the obstructed kidney, suggesting a new pro-inflammatory mechanism of NGAL in CKD. Supported by Fondecyt #1201251 and #3201016

Funding: Government Support - Non-U.S.

PO2439

Role of Mast Cells in the Progression of Peritoneal Fibrosis in Rats with Chronic Renal Failure

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Background: Mast cells, that are originally derived from hematopoietic stem cells, secrete inflammatory cytokines besides their exocytotic release of chemical mediators. Recent studies also demonstrated that mast cells synthesize fibroblast-activating factors in chronic inflammatory diseases, thereby facilitating the progression of organ fibrosis.

Methods: Using rat models with chronic renal failure (CRF) induced by 5/6 nephrectomy, the histopathological features of CRF rat peritoneum were examined. We also treated the CRF rats with tranilast, a mast cell stabilizer, to reveal the involvement of mast cells in the progression of peritoneal fibrosis.

Results: In fibrotic areas of CRF rat peritoneum, mast cells proliferated *in situ* and increased their activity by producing fibroblast growth factors. Therapeutic intervention with tranilast, a potent mast cell stabilizer, actually slowed the progression of peritoneal fibrosis. Therefore, the activation of mast cells were considered to be responsible for the progression of peritoneal fibrosis in uremic condition. Additionally, we employed the standard patch-clamp whole-cell recording technique in mast cells to examine the effects of other mast cell stabilizers, since the process of exocytosis in mast cells can continuously be monitored electrophysiologically by the changes in the membrane capacitance (Cm). Second generation anti-histamine drugs, such as olopatadine and loratadine, markedly suppressed the increase in the Cm and directly inhibited the exocytotic process, suggesting their potency as mast cell stabilizers. In additional morphological studies, these drugs actually caused inward bending of mast cell membranes and counteracted the exocytosis-induced cellular surface deformation.

Conclusions: Taken together these *in vivo* and *in vitro* evidence, our results strongly indicated the therapeutic efficacy of targeting mast cells to ameliorate organ fibrosis in chronic diseases, besides the treatment of allergic diseases.

PO2440

Pro-Inflammatory HLA-DRhi Intermediate Monocytes Are Increased in CKD

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Background: People with Chronic Kidney Disease (CKD) suffer high rates of cardiovascular disease and have high numbers of circulating intermediate monocytes (IMs). IM numbers are associated with cardiovascular risk. We previously defined novel IM subpopulations termed $HLA\text{-}DR^{mid}$ and $HLA\text{-}DR^{hi}$ IMs, of which $HLA\text{-}DR^{hi}$ IMs are increased in CKD. To understand how these cell populations contribute to endothelial damage in CKD we determined the functional properties of $HLA\text{-}DR^{hi}$ IMs.

Methods: People with CKD, age-matched patient controls (PC) and healthy volunteers (HV) were recruited. Blood samples were used for profiling of IM subpopulation number and phenotype, functional assays and serum isolation. Intracellular cytokine production, migration and endothelial adhesion assays were performed using *ex vivo* cells.

Results: Numbers and proportions of circulating $HLA\text{-}DR^{hi}$ IMs were higher in CKD compared to PC ($3.0x10^4$ vs. $1.9x10^4$ cells/ml, $p=0.007$). Following LPS stimulation in vitro, $HLA\text{-}DR^{hi}$ IMs from both HV and CKD patients produced markedly higher amounts of TNF-α ($p<0.0001$) and IL-1β ($p<0.0001$) than other monocyte subpopulations. LPS-stimulated cytokine levels of $HLA\text{-}DR^{hi}$ IMs did not differ for HV vs. CKD. Surface profiling revealed that $HLA\text{-}DR^{hi}$ IMs expressed relatively high levels of specific chemokine receptors (CCR5, CX3CR1) and adhesion proteins (CD11a, CD11b, CD11c). Total monocyte migration toward CCL5 and CX3CL1 was increased in CKD vs. HV. Total monocyte adhesion to both resting and TNF-α-activated endothelial cells was increased in CKD vs. HV. Monocyte adhesion to TNF-α activated endothelial cells was partially dependent on CX3CR1-CX3CL1 binding. Finally, serum CX3CL1 was increased in CKD compared to PC ($p=0.004$) and correlated with CKD-EPI eGFR ($R=0.33$, $p=0.002$).

Conclusions: CKD-associated monocytosis is characterised by increased circulating $HLA\text{-}DR^{hi}$ IMs with high capacity for inflammatory cytokine production and high surface levels of specific adhesion proteins and chemokine receptors. CCL5 and CX3CL1-dependent chemo-attraction and CX3CL1-dependent endothelial adhesion of monocytes are increased in CKD. The results highlight targetable mechanistic links between intermediate monocytosis, accelerated atherosclerosis and progressive renal injury in CKD.

Funding: Private Foundation Support

PO2441

Parenteral Iron Therapy Alters Polarization of Kidney Macrophages and Mitigates Kidney Fibrosis in Mice

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Background: Iron therapy is common in patients with chronic kidney disease (CKD). Macrophages are a major cell type capable of handling and storing iron. At the same time, macrophages play a critical role in the pathogenesis of kidney fibrosis. Iron has been shown to modulate macrophage polarization in other pathologic conditions. However, the effect of iron therapy on polarization of kidney macrophages during kidney fibrosis is unclear.

Methods: To elucidate this, we took advantage of two mouse models of kidney fibrosis: adenine and the unilateral ureteral obstruction (UUO) models. A subset of mice received weekly intraperitoneal injections of iron dextran (0.5 g/kg body weight) in addition to adenine. Same iron administration regimen was used to treat a sub-group of mice for 4 weeks prior to UUO. Mice were euthanized after 8 weeks of adenine diet or 7 days after UUO. Blood for serum creatinine and CBC measurements and kidneys were collected at euthanasia.

Results: Iron therapy improved anemia and mitigated kidney function decline in CKD mice, as indicated by serum creatinine improvement. Kidney fibrosis was less severe in mice treated with iron compared to untreated mice in both the adenine and UUO models, as indicated by Masson trichrome staining and reduced kidney expression of fibronectin. Prussian blue staining identified iron accumulation in the kidney interstitium of CKD mice treated with iron, specifically within kidney macrophages, as confirmed by electron microscopy. Flow cytometry demonstrated reduced infiltration of kidney tissue by $Ly6C^{high}$ monocytes and neutrophils and lower percentage of kidney $CCR2^+$ and $CX3CR1^+$ myeloid cells in CKD mice treated with iron compared to untreated CKD mice. While macrophage surface markers MHCII, CD86, and CD206 were altered by iron therapy, they did not follow the classical M1/M2 dichotomy. However, expression of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β by kidney macrophages was reduced in CKD mice treated with iron compared to untreated CKD mice.

Conclusions: Chronic parenteral administration of iron mitigated kidney fibrosis in two different mouse models, which, at least in part, was likely mediated by iron-induced kidney macrophage skewing towards an anti-inflammatory phenotype and reduced recruitment of pro-inflammatory cells into the kidney.

Funding: NIDDK Support

PO2442

Loss of Macrophage Mitofusin 2 but Not Mitofusin 1 Suppresses Mitochondrial Biogenesis and Promotes Kidney Fibrosis

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Background: Mitochondrial biogenesis, dynamics (fusion/fission) and mitophagy exert critical roles in maintaining mitochondrial function and protect against oxidative stress. Macrophages are well-known to aggravate kidney injury-induced inflammation and fibrosis in the pathogenesis of chronic kidney disease (CKD). We studied the effects of macrophage mitofusins: *Mfn1* and/or *Mfn2* deficiency on mitochondrial biogenesis during CKD.

Methods: Myeloid-specific *Mfn1* (*Mfn1$^{fl/fl}$, LysM-Cre$^{+/-}$*), *Mfn2* (*Mfn2$^{fl/fl}$, LysM-Cre$^{+/-}$*), & double knockout (DKO) mice and corresponding controls were fed with control (Ctl) or adenine diet (AD) for 28-days. Kidneys, kidney macrophages, bone marrow-derived macrophages (BMDM) were analyzed by western blot, flow cytometry, immunohistochemistry. Blood urea nitrogen (BUN), creatinine were measured.

Results: Expression of mitochondrial biogenesis regulator: PGC-1α, antioxidant enzyme: superoxide dismutase-2, mitochondrial fusion proteins: *Mfn1*, *Mfn2*, and *OPA-1* decreased while fission proteins: DRP-1 and phospo-DRP-1-Serine-616 increased in the kidneys after AD and BMDM after TGF-β1 treatment. Kidney macrophage superoxide levels increased after AD. However, kidney macrophages from AD-fed *Mfn2$^{fl/fl}$, LysM-Cre$^{+/-}$* and DKO mice but not *Mfn1$^{fl/fl}$, LysM-Cre$^{+/-}$* mice displayed higher superoxide & increased expression of galectin-3, TGF-β1, & CD206 than corresponding controls. In addition, *Mfn2$^{fl/fl}$, LysM-Cre$^{+/-}$* and DKO mice displayed greater collagen accumulation, and increased BUN and creatinine after AD than wild-type and *Mfn1$^{fl/fl}$, LysM-Cre$^{+/-}$* mice. Wild-type and *Mfn1$^{fl/fl}$, LysM-Cre$^{+/-}$* mice showed similar increases in collagen deposition in the kidney and worsening of kidney function after AD. BMDM from *Mfn1$^{fl/fl}$, LysM-Cre$^{+/-}$* and wild-type mice also showed similar expression of profibrotic macrophage marker, arginase-I after TGF-β1-treatment. However, TGF-β1-treated *Mfn2$^{fl/fl}$, LysM-Cre$^{+/-}$* and DKO BMDM and kidney macrophages displayed greater polarization towards profibrotic phenotype while lower expression of PGC-1α and defective mitophagy than *Mfn1$^{fl/fl}$, LysM-Cre$^{+/-}$* and wild-type macrophages.

Conclusions: Macrophage-specific deficiency of *Mfn2* but not *Mfn1* causes impairments in mitochondrial biogenesis and mitophagy, thereby promoting polarization towards profibrotic macrophage phenotype and kidney fibrosis.

Funding: Other NIH Support - NHLBI

PO2443

F4/80hi Resident Macrophages Contribute to Cisplatin-Induced Kidney Fibrosis and M2 Polarization in C57BL/6 Mice

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Background: Cisplatin is a mainstay in the treatment of many solid-organ cancers. Its therapeutic benefits, however, are hindered by dose-limiting nephrotoxicity. Cisplatin causes acute kidney injury (AKI) in 30% of patients. Development of AKI puts patients at risk for development of fibrosis and chronic kidney disease (CKD). Cisplatin-induced kidney fibrosis can be modeled in rodents using repeated, low doses of cisplatin once a week for four weeks. Understanding the mechanisms that promote fibrosis in this model could improve long-term care of cancer patients who receive cisplatin. Macrophages are known to respond to kidney injury and correlate with progression of fibrosis in CKD patients, indicating they may be key regulators of fibrosis development following kidney insults. We hypothesize that chronic macrophage activity promotes cisplatin-induced kidney fibrosis.

Methods: In this study, we depleted populations of F4/80^{hi} resident macrophages and F4/80^{lo} infiltrating macrophages in C57BL/6 mice using either clodronate encapsulated liposomes or CCR2 genetic knockout, respectively. In parallel with this macrophage depletion, mice were given 4 weekly doses of 9 mg/kg cisplatin. After euthanization, we evaluated kidney function, injury, and fibrosis development.

Results: Our data suggests that F4/80^{hi} resident macrophage depletion ameliorates development of cisplatin-induced fibrosis, as measured by statistically significant decreased collagen deposition and myofibroblast accumulation. In contrast, CCR2 knockout and subsequent F4/80^{lo} infiltrating macrophage depletion did not alter pathological outcomes after cisplatin treatment. Additionally, depletion of resident macrophages, but not infiltrating macrophages, decreased accumulation of CD206+ M2 macrophages in cisplatin treated kidneys.

Conclusions: Taken together, these data suggest that F4/80^{hi} resident macrophages may be key drivers in the development of cisplatin-induced kidney fibrosis and the primary source of M2 macrophages in the kidney. Therefore, kidney resident macrophages represent a possible target for preventing long-term kidney damage associated with cisplatin treatment.

Funding: NIDDK Support

PO2444

Lactate Dehydrogenase A Influences Pro-Inflammatory Polarization of Murine Bone Marrow-Derived Macrophages

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Background: Excessive inflammation is a major underlying pathogenic process in the progression of chronic kidney disease (CKD). Infiltration of pro-inflammatory macrophages can provoke such inflammatory responses. Macrophages undergo transcriptomic and metabolic reprogramming and rely heavily on glycolysis. Lactate Dehydrogenase A (LDHA) is a key enzyme involved in the glycolytic switch which catalyzes the conversion of pyruvate to lactate and regenerates NAD+ from NADH. Utilizing LDHA deletion, we investigated the effect of suppression of the glycolytic switch in macrophages and its effect on CKD.

Methods: Mature bone marrow-derived macrophages (BMDMs) from wild-type and LDHA knockout mice (KO) mice were cultured and then polarized for 24 hours using IFN-γ. Bulk RNA-seq (transcriptomic) and LC-MS/MS (metabolomic) experiments were performed. For in vivo studies, wild-type littermate and myeloid deficient LDHA KO were treated with aristolochic acid (AA) for 6 weeks as a model of CKD.

Results: BMDMs lacking LDHA showed a significant decrease in transcript counts of key metabolic genes involved in the glycolytic switch (HIF1a and GLUT1). LDHA deletion resulted in significantly decreased levels of aspartate indicating the arginine-succinate shunt is affected. Carnitine levels and fatty acid metabolism were significantly downregulated in the LDHA deficient macrophages. In contrast, mannose-6-phosphate levels were significantly upregulated. Combined, these changes suggest an anti-inflammatory shift. The Multi-omics approach of combining metabolomics and transcriptomic data revealed significant changes in multiple pathways including purine, nicotinate and nicotinamide metabolism. Lastly, mice lacking LDHA in myeloid cells showed a significant decrease in renal fibrosis 6 weeks post-exposure to AA in the model of CKD.

Conclusions: LDHA deficient BMDMs exhibited diminished pro-inflammatory profile in vitro and decreased renal fibrosis in vivo. These results highlight LDHA's role as a potential target for manipulation in immunometabolism and may have a significant impact on approach to CKD.

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

PO2445

Major Vault Protein Promotes Macrophage-to-Myofibroblast Transition and Tubulointerstitial Fibrosis in a Murine Model of CKD

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Background: Chronic kidney disease (CKD) is characterized by progressive interstitial fibrosis and tubular atrophy, and inflammatory cell infiltration. We found that major vault protein (MVP), a key component of the vault complex, contributed to increased matrix protein deposition in an adenine-induced murine CKD model. We continued to investigate whether MVP contributes to interstitial fibrosis.

Methods: CKD was induced in MVP wild-type (WT) and knockout (KO) mice by feeding with casein-based chow containing 0.2% adenine for 8 weeks, and mice were sacrificed and renal cortical tissue harvested for qPCR, immunohistochemistry and flow cytometry analysis. Mice fed casein-based chow served as controls.

Results: MVP WT mice with CKD showed increased MVP mRNA compared to control WT mice. In MVP WT mice with CKD there was increased macrophage infiltration in the tubulo-interstitium that co-localized with collagen I, fibronectin and a-smooth muscle actin, suggesting macrophage-to-myofibroblast transition. Flow cytometric data showed increased CD45^{+} cells and F4/80^{+} / CD11b^{+} macrophages in MVP WT mice with CKD. MVP KO mice with CKD showed reduced infiltration of macrophages in the tubulo-interstitium, with lower transition to myofibroblasts (P<0.01); and there was decreased MCP-1, MCP-1 receptor and TNF-a mRNA expression, with better preservation of normal renal histology.

Conclusions: The findings suggest that MVP may contribute to the pathogenesis of CKD by promoting macrophage infiltration and their transition to myofibroblasts.

Funding: Government Support - Non-U.S.

PO2446

Classical Dendritic Cells Mediate Nephrotoxic Serum Nephritis by Activating T Cells

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Background: Glomerulonephritis is a prominent cause of chronic kidney disease (CKD) and features robust chronic inflammation. Following an inflammatory insult, myeloid cells infiltrate the kidney and drive CKD progression. Flt3L-expressing classical dendritic cells (DCs) are the most potent antigen-presenting cells, and heterozygous deletion of the ubiquitin editor A20 spontaneously activates DCs. However, the role of Flt3L-expressing classical DCs in the regulation of inflammatory CKD requires elucidation. We hypothesized that classical dendritic cells exacerbate inflammatory kidney injury by promoting the activation of renal T cells.

Methods: We induced nephrotoxic serum nephritis (NTS) in flt3L-deficient mice lacking DCs (DC KO), mice with spontaneous DC activation (CD11c Cre^{+} A20$^{flox/wt}$ = DC ACT), and wild-type (WT) controls. After 14 days of NTS, kidney injury was assessed by pathology scoring and ACRs. In addition, mRNA levels of renal injury biomarkers were determined by RT-PCR and western blot. NTS kidneys were harvested for flow cytometric analysis to determine intra-renal immune cell lineage distributions and test their mRNA levels of inflammatory cytokines.

Results: On day 14 of NTS, DC KO mice had attenuated kidney injury scores compared to WTs (1.6±0.3 vs 3.0±0.3 au, p=0.01), while kidney injury was more severe in DC ACTs than in WTs (2.3±0.3 vs 1.4±0.2 au, p=0.02). Compared to WTs, DC KOs had lower ACRs (432±36 vs 267±11, p=0.001) and reduced renal mRNA levels for NGAL (1.0±0.1 vs 0.2±0.1 au, p=0.001), collagen-I (1.0±0.1 vs 0.4±0.1, p=0.003), and fibronectin (1.0±0.1 vs 0.5±0.1, p=0.01). In contrast, DC ACTs had higher ACRs (623±84 vs 1171±243, p=0.001) and upregulated mRNA for NGAL (29.2±7.4 vs 1.0±0.3 au, p=0.004), collagen-I (6.5±0.9 vs 1.0±0.2, p=0.001), and fibronectin (3.9±0.4 vs. 1.0±0.1, p=0.001). Renal protein levels for collagen-I and fibronectin recapitulated the mRNA patterns. In DC ACT kidneys, absolute numbers of CD8^{+} effector memory T cells, marked by a CD62L^{lo}CD44^{hi} surface expression were higher (2864±648 vs 836±107 cells, p=0.006) and had higher cytokine mRNA levels for TNFα (4.2±0.5 vs 1.0±0.1, p=0.001) and IL1β (2.0±0.3 vs 1.0±0.1, p=0.02) than in WTs at day 14 of NTS.

Conclusions: The pathogenesis of CKD requires classical DC-mediated T cell activation. Inhibition of classical DCs may ameliorate autoimmune nephritis.

Funding: NIDDK Support

PO2447

Targeting Innate Immune-Polyamine Axis Prevents CKD-Associated Cardiac Hypertrophy

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Background: It is well recognized in clinic that patients with chronic kidney disease (CKD) have a higher risk for developing cardiovascular diseases including cardiac hypertrophy. However, the pathogenetic mechanisms remain poorly understood.

Methods: The hypertrophic phenotype changes and metabolic characteristics of neonatal rat cardiomyocytes were studied after incubated with serum from 5 stage CKD patients, as well as myocardium from mice with or without CKD, accompanied by bulk RNA-seq analysis. The role and mechanism of CKD in inducing cardiac hypertrophy were evaluated in vivo and ex vivo, and confirming in targeted gene knockout and cardiomyocyte-specific knockout mice.

Results: Here, we show that adult cardiomyocytes are characterized by restrained polyamine metabolism, while CKD activates polyamine metabolism especially ornithine decarboxylase (ODC1)-putrescine metabolic axis in cardiomyocytes. Then, we reveal that nuclear factor kappa B (NFκB) in cardiomyocytes not only drives hypertrophic program under CKD milieu, but also conservatively dominates the transcriptional activation of ODC1-putrescine metabolic axis. Meanwhile, activation of ODC1-putrescine metabolic axis in cardiomyocytes acts as a prerequisite for the efficient initiation of NFκB-driven hypertrophic program, rather than a pathogenic factor for cardiac hypertrophy. Furthermore, mitochondrial oxidative damage is a prominent feature of cardiomyocytes under CKD milieu. The damaged mitochondria release mitochondrial DNA into the cytosol and stimulates the innate immune cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway in cardiomyocytes, which subsequently activates NFκB. Therefore, myocardial cGAS-STING-NFκB pathway plays a critical role in CKD-associated cardiac hypertrophy through immune surveillance of mitochondrial fitness as well as integrating hypertrophic program and polyamine metabolism.

Conclusions: Our study uncovers a previously unrecognized role of innate immune-polyamine axis in CKD-associated cardiac hypertrophy. Targeting innate immune-polyamine axis may represent a promising strategy to prevent and treat CKD-associated cardiac hypertrophy.

Funding: Government Support - Non-U.S.

PO2448

The Active Ingredient in the Nuphar lutea Plant, 6,6′-Dihydroxythiobinupharidine (DTBN), Ameliorates Kidney Fibrosis, Inflammation, and Anemia in a Mouse Model of CKD

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Background: EPO resistance and iron deficiency in CKD-related anemia are associated with an increase in inflammatory cytokines associated with the innate immune response, such as IL-6, IL-1, and TNF-α. Recently (Bandach et al, Sci Reports 2021) we reported that kidney fibrosis and anemia of CKD can be worsened or relieved when IL1 effects are enhanced or inhibited respectively. The Water lily (*Nuphar lutea)* plant has been widely used as a traditional remedy for the treatment of rheumatism, scars, pain, and more. Gopas, Golan-Goldhirsh et al (Cancer Biology Therapy 2009) extracted an active ingredient from the family of nupharidines: 6,6′-Dihydroxythiobinupharidine (DTBN) which showed anti-inflammatory properties, mainly through the inhibition of NF-κB. The purpose of this study was to test the effects of DTBN in a mouse model of CKD-associated anemia.

Methods: 8 weeks old male C57BL/6 mice were divided into 3 groups: Control, CKD (induced by adenine diet) and CKD- DTBN. CKD groups were injected with saline-DMSO or 30 μg DTBN, every two days and sacrificed after 3 weeks from dietary intervention.

Results: Serum urea and kidney TGFβ mRNA were significantly decreased in CKD- DTBN Vs CKD. Kidney histology in CKD mice showed macrophage infiltration and renal fibrosis, which was ameliorated in CKD-DTBN. A significant improvement in inflammation indices (blood lymphocytes, kidney and liver IL-6 and p-STAT3, liver CRP), as well as kidney immunoreactive NF-κB and F4\80, which were increased in CKD, were decreased in CKD-DTBN. CKD anemia indices (hemoglobin, hematocrit, and RBC count) significantly improved in CKD-DTBN. Kidney HIF-2α and EPO mRNA were significantly decreased in both uremic groups, but was unchanged in CKD- DTBN Vs CKD. However, serum iron and transferrin saturation significantly increased in CKD-DTBN Vs CKD.

Conclusions: Uremic mice treated with DTBN show improvement in kidney fibrosis, inflammation and anemia indices. Thus, DTBN may be a novel therapeutic alternative for CKD and its complications.

PO2449

Exploring the Presence of Endogenous Retroviruses in CKD

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Background: Chronic kidney disease (CKD) affects more than 1 in 7 US adults and is the fourth leading cause of death worldwide. However, the mechanism of CKD is poorly understood. Endogenous retroviruses (ERVs) are transposable elements (TEs) that have integrated into mammalian genomes millions of years ago, accounting for about 8% of the human genome. ERVs remain inactive in the genome due to mutations and deletions during evolution, however recent studies have found that reactivation of ERVs is possible and their increased expression has been identified in a variety of human diseases. Here, we examine ERVs in human and mouse kidneys and their potential role in CKD.

Methods: We performed RNA sequencing and collected clinical and histopathological data from 300 human kidney samples, both healthy and with varying degrees of CKD. We mapped the genomic landscape of TEs, including LINE, SINE and ERVs, using RepeatMasker and quantified their expression in healthy and diseased kidney tissues. Associations between ERV expression, gene expression and methylation level were analyzed. Similar analyses were performed on three kidney disease mouse models.

Results: We found increased expression of several ERV elements in diseased human kidney tissues. Using a linear regression model adjusted for 7 covariates, we identified 2,486 TEs whose expression showed a significant linear correlation with interstitial fibrosis. We also found that ERVs trigger a strong interferon response through the activation of cytosolic nucleic acid sensors such as RIG-I and STING. Furthermore, ERV expression was correlated with methylation level of overlapping methylation sites and we found that loss of cytosine methylation and epigenetic repression may have contributed to the increase in ERV level. We also identified several differentially expressed TEs between healthy and diseased kidney tissues in three kidney disease mouse models, many overlapping between models. An increase in expression of cytosolic nucleic acid sensors was also observed in mice. Furthermore, genetic deletion of RIG-I and STING ameliorated kidney inflammation and fibrosis in mouse disease models.

Conclusions: Our study provides the first comprehensive analysis of ERVs in the kidneys of both humans and mice and suggests the potential role of ERVs in kidney disease by aggravating immune response during disease progression.

Funding: NIDDK Support

PO2450

Interleukin 1α (IL-1α) Is a Central Regulator of Leukocyte-Endothelial Adhesion in Myocardial Infarction and in CKD

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Background: Cardiovascular diseases (CVD) and chronic kidney disease (CKD) are highly prevalent, aggravate each other, and account for substantial mortality. Both conditions are characterized by activation of the innate immune system. The alarmin IL-1α is expressed in a variety of cell types promoting (sterile) systemic inflammation. The aim of the present study is to examine the role of IL-1α in mediating inflammation in the setting of cardiorenal diseases.

Methods: We assessed the expression of IL-1α on the surface of monocytes from patients with acute myocardial infarction (AMI) and patients with CKD and determined its association with atherosclerotic CVD events during follow-up in an explorative clinical study. Furthermore, we assessed the inflammatory effects of IL-1α in several organ injury models in *Il1a*$^{-/-}$ and *Il1b*$^{-/-}$ mice and investigated the underlying mechanisms *in vitro* in monocytes and endothelial cells.

Results: IL-1a is strongly expressed on the surface of monocytes from patients with AMI and CKD compared to healthy controls. Higher IL-1α surface expression on monocytes from patients with AMI was associated with a higher risk for atherosclerotic CVD events, which underlines the clinical relevance of IL-1α. In mice, IL-1α, but not IL-1β, mediates leukocyte-endothelial adhesion as determined by intravital microscopy. IL-1α promotes accumulation of macrophages and neutrophils in inflamed tissue *in-vivo*. Furthermore, IL-1α on monocytes stimulates their homing at sites of vascular injury. A variety of stimuli such as free fatty acids or oxalate crystals induce IL-1α surface expression and release by monocytes, which then mediates their adhesion to the endothelium via IL-1 receptor-1. Besides, IL-1α promotes expression of the vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells thereby fostering the adhesion of circulating leukocytes. IL-1α induces inflammatory injury after experimental AMI and abrogation of IL-1α prevents the development of CKD in oxalate or adenine-fed mice.

Conclusions: IL-1α represents a key mediator of leukocyte-endothelial adhesion and inflammation in cardiorenal diseases. Inhibition of IL-1α may serve as a novel anti-inflammatory treatment strategy.

PO2451

Complement C5a Receptor in Macrophage-Mediated Renal Inflammation and Fibrosis in Lupus Nephritis

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Background: Lupus nephritis (LN) is caused by autoimmune responses and is a significant driver of end-stage renal disease in systemic lupus erythematosus patients. Complement activation, pro-inflammatory cytokine production, and the influx of macrophages have all been implicated in LN pathogenesis. The anaphylatoxin complement 5a (C5a) receptor 1 (C5aR) is a major driver of the pro-inflammatory functions of complement activation. We examined C5aR's expression in kidney in lupus nephritis and investigated its role in controlling pro-fibrotic functions of macrophages.

Methods: C5aR expression, infiltrating immune cells, and fibrosis were examined by immunohistochemistry in LN patient kidney biopsies. M1 and M2 macrophages derived from human peripheral blood monocytes were used in in vitro assays to examine the effect of C5a stimulation and avacopan, a specific C5aR inhibitor, on the secretion of cytokines and other factors.

Results: In LN kidney biopsies, large numbers of macrophages, identified by CD68 staining, were observed in areas with severe fibrosis, and expressed C5aR. In addition, C5aR was detected on distal tubules in biopsies of both normal and lupus nephritis kidneys. C5a increased the production of inflammatory cytokines TNFa and IL-6 from both M1 and M2 macrophages in vitro. Chemokines (MCP-3, MIP-1a, MIP-1b and MIP-3a), matrix metalloproteinases (MMP3 and MMP8), and pro-fibrotic growth factors (fibroblast activation protein, platelet-derived growth factor-AA) were strongly increased in M2 macrophages with C5a stimulation, and these increases were blocked by the C5aR inhibitor avacopan.

Conclusions: C5aR activation induced macrophage secretion of factors that are known to drive inflammation, fibroblast activation and tissue fibrosis, and thus may contribute to LN disease progression. Inhibiting C5aR activity with avacopan blocks these pathological changes, and may provide therapeutic benefit to LN patients.

PO2452

Remdesivir Inhibits Tubulointerstitial Fibrosis in Obstructed Kidneys

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Background: Kidney impairment is observed in patients with COVID-19. The effect of anti-COVID-19 agent remdesivir on kidneys is currently unknown. We aimed to determine the effect of remdesivir on renal fibrosis and its downstream mechanisms.

Methods: Remdesivir and its active nucleoside metabolite GS-441524 were used to treat TGF-β stimulated renal fibroblasts (NRK-49F) and human renal epithelial (HK2) cells. Vehicle or remdesivir were given by intraperitoneal injection or renal injection through the left ureter in unilateral ureteral obstruction (UUO) mice. Serum and kidneys were harvested. The concentrations of remdesivir and GS-441524 were measured using LC-MS/MS. Renal and liver function were assessed. Renal fibrosis was evaluated by Masson's trichrome staining and Western blotting.

Results: Remdesivir and GS-441524 inhibited the expression of fibrotic markers (fibronectin and aSMA) in NRK-49F and HK2 cells. Intraperitoneal injection or renal injection of remdesivir attenuated renal fibrosis in UUO kidneys. Renal and liver function were unchanged in remdesivir treated UUO mice. Two remdesivir metabolites were detected after injection. Phosphorylation of Smad3 that was enhanced in cell and animal models for renal fibrosis was attenuated by remdesivir. In addition, the expression of Smad7, an anti-fibrotic factor, was increased after remdesivir treatment *in vitro* and *in vivo*.

Conclusions: Remdesivir inhibits renal fibrosis in obstructed kidneys.

Funding: Government Support - Non-U.S.

PO2453

Heightened Innate Immune Response to COVID-19 Infection in CKD: Implications to Poorer Outcome During CKD

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Background: Meta-analyses reveal show a significant association of chronic kidney disease (CKD) with severe COVID-19. The double stranded RNA virus SARS-CoV-2 can evoke a damaging inflammatory response. To understand the mechanism for the greater severity of the disease in patients with CKD, we studied an animal model of CKD exposed to polyinosinic-polycytidylic acid [poly(I:C), a synthetic analog of double-stranded RNA that recapitulates the innate immune response provoked by SARS-CoV-2].

Methods: C57Bl6j mice were injected with 2 doses of cisplatin at 15 mg / kg or vehicle control subcutaneously, 2 weeks apart. After CKD established, control and CKD mice were subsequently injected with poly(I:C) at 30 mg/kg intravenously and monitored for body weight loss and mortality. Bone marrow cells were isolated 2 weeks post poly(I:C) treatment and grown in serum-free medium supplemented with macrophage colony stimulation factor for 7 days to obtain bone marrow derived macrophages (BMDM). These cells were stimulated with 10 ug / ml poly (I:C), followed by measurement of proinflammatory cytokines. Single cell RNA sequencing was used to compare transcriptome between normal and CKD kidneys.

Results: CKD animals had elevated plasma creatinine (0.14 ± 0.02 mg / dL, n=8, control mice 0.09 ± 0.01 mg / dL, n=5, $p<0.05$) and elevated plasma levels kidney injury marker 1 (KIM-1; 133.6 ± 29.9 pg /ml, vs undetectable, n=5, $p<0.05$). Poly (I:C) treatment induced a greater body weight loss in CKD animals (9.9± 2.9 %, n=8 vs control mice 6.8 ± 2.0 %, n=5, $p<0.0005$) and greater mortality of CKD mice (46% mortality within 24h in CDK mice vs no mortality in control mice). BMDMs from CKD mice produced greater levels of IL-6 than control BMDM upon poly (I:C) stimulation at both the mRNA and protein levels. In addition, Single cell RNA sequencing revealed that there is 3-fold higher relative number of macrophages in CKD kidneys.

Conclusions: Our results show that CKD mice are more sensitive to foreign double strand RNA insult. BMDM isolated from cisplatin-induced CKD demonstrated a greater innate immune response during CKD. We propose that the inherent hyperinflammatory nature of CKD drives a greater innate immune response in this model of viral injury and may be responsible, at least partially, for the poor outcomes in CKD patients with Covid-19 infection.

Funding: NIDDK Support

PO2454

Combined Soluble Epoxide Hydrolase Inhibition and Epoxyeicosatrienoic Acid Administration Attenuates the Renal Fibrogenesis Without Additivity or Synergy

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Background: Epoxyeicosatrienoic acids (EETs) are arachidonic acid metabolites with biological effects, including anti-apoptotic, anti-inflammatory, and anti-fibrotic functions. Soluble epoxide hydrolase (sEH)-mediated hydrolysis of EETs to dihydroxyeicosatrienoic acids (DHET) attenuates these effects. Recent studies have demonstrated inhibition of sEH prevents renal tubulointerstitial fibrosis and inflammation in chronic kidney disease (CKD) model. Here, we demonstrated the role and underlying mechanism of EETs in unilateral ureteral obstruction (UUO)-induced renal fibrogenesis.

Methods: Eight-week-old male wild type (*Ephx2*$^{+/+}$) and *Ephx2*$^{-/-}$ mice underwent sham or UUO surgical procedures and were treated with the combination of 11,12- and 14,15-EETs (15 μg/kg/day, respectively) using osmotic pump for 7 days following UUO surgery.

Results: EETs administration abolished tubulointerstitial fibrogenesis, as demonstrated by reduced fibroblast activation and collagen deposition after UUO. Furthermore, inflammatory response was prevented as demonstrated by decreased macrophage infiltration and expression of inflammatory cytokines (TGF-β, IL-1β and IL-6) in EETs-administered UUO kidneys. The genetic inhibition of sEH also mitigated UUO-induced renal inflammation and interstitial fibrogenesis. The combination of EET administration and genetic sEH inhibition also attenuated inflammation and renal interstitial fibrogenesis after UUO, but no additive or synergic effect of combined sEH inhibition and EETs administration.

Conclusions: Taken together, our findings provide that the underlying mechanism of EETs in kidney fibrogenesis during obstructive nephropathy, suggesting EETs as a potential therapeutic target of kidney fibrosis progression.

Funding: NIDDK Support

PO2455

EP1 Receptor Antagonism Mitigates Early and Late-Stage Renal Fibrosis

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Background: Renal fibrosis is a hallmark of Chronic Kidney Disease (CKD), which affects 10-16% of the world's adult population. Yet current treatment strategies are ineffective in attenuating renal fibrogenesis. Therefore, we are in urgent need for new therapeutic strategies against renal fibrosis. The cyclooxygenase/prostaglandin (COX/PG) system plays a key role in renal fibrosis and holds great promise as a suitable therapeutic target. Here, we used a translational approach to evaluate the role of the PGE_2-EP_1 receptor in the pathogenesis of renal fibrosis in several models of kidney injury, including human (fibrotic) kidney slices.

Methods: The anti-fibrotic effect of SC-19220 - an EP_1 receptor antagonist - was studied in Madin-Darby Canine Kidney (MDCK) cells, mice subjected to seven days of unilateral ureteral obstruction (UUO), and healthy and fibrotic human precision-cut kidney slices (PCKS). Progression of fibrosis was evaluated on gene and protein level using qPCR, Western blot and immunohistochemistry.

Results: Pharmacological inhibition of the EP_1 receptor using SC-19220 reduced TGF-β-induced fibronectin (FN) expression, ERK1/2 phosphorylation and epithelial-to-mesenchymal transition in MDCK cells. Moreover, SC-19220 diminished fibrosis in UUO mice, measured by decreased protein expression of FN and α-smooth muscle actin (αSMA), and a reduction in collagen deposition. In addition, treatment of healthy human PCKS with SC-19220 reduced TGF-β-induced fibrosis as shown by decreased gene levels of collagen 1A1, FN and αSMA as well as reduced collagen deposition. Moreover, similar observations were made using fibrotic human PCKS.

Conclusions: This study highlights that the EP_1 receptor is a promising target for preventing both the onset and late stage of renal fibrosis. Moreover, we provide strong evidence that the effect of SC-19220 may translate to clinical care since its effects were observed in UUO mice and human kidney slices.

PO2456

Selective Activation of the Prostaglandin E2-EP4 Receptor Can Slow or Reverse the Fibrotic Process in Human Kidney Slices

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Background: Chronic kidney disease (CKD) affects approximately 10% of the population, and renal fibrosis, *i.e.* excessive scar formation in the kidney, is one of the major pathological processes leading to end-stage renal disease (ESRD). Despite overwhelming efforts to find therapies to reduce renal fibrosis, current management strategies are ineffective at preventing disease progression in CKD patients. Activation of the prostaglandin E2-EP4 receptor has been shown to have renoprotective effects in cell and animal studies. However, translational studies using human kidney tissue are lacking.

Methods: In this project, we studied the anti-fibrotic effect of the selective EP4 receptor agonist Rivenprost using a translational model of renal fibrosis, namely human precision-cut kidney slices (PCKS). This model is ideal to study multicellular pathological processes, *e.g.* fibrosis, directly in human tissue, since cellular diversity and organ architecture is maintained in the slices. Macroscopically healthy renal tissue (n = 13) was obtained from tumor nephrectomies, whereas fibrotic renal tissue (n = 6) was obtained from ESRD nephrectomies. Subsequently, PCKS were incubated with Rivenprost (75μM) to evaluate its anti-fibrotic effect directly in human tissue. Fibrogenesis was evaluated on a gene level using qPCR. Viability was assessed by ATP measurements using ELISA. Protein and histological analyses are ongoing.

Results: The expression of the EP4 receptor in PCKS was increased twofold after 48h of incubation with the pro-fibrotic cytokine TGFβ, suggesting that the EP4 receptor might play a role in the fibrotic process. Treatment with Rivenprost mitigated TGFβ-induced fibrogenesis in healthy tissue. Moreover, Rivenprost halted disease progression in fibrotic PCKS and appeared to partly reverse fibrosis, as illustrated by a reduction in the gene expression of α-smooth muscle actin, fibronectin and collagen 1A1 by at least 50%, without affecting the viability of the human PCKS.

Conclusions: Selective stimulation of the PGE2-EP4 receptor can slow and reverse the process of fibrosis directly in human renal tissue. These findings warrant further research into the clinical application of Rivenprost, or other EP4 receptor agonists, as a treatment for (established) renal fibrosis.

PO2457

Mice with a Deficient Myeloid COX-2/EP4 Axis Developed More Severe Kidney Dysfunction in Response to a High-Fat Diet

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Background: Obesity leads to a state of chronic, low-grade inflammation that contributes to insulin resistance and type 2 diabetes as well as chronic kidney injury. Macrophages are major contributors to obesity-associated adipose inflammation and dysregulated metabolism. When fed a high fat diet (HFD), cyclooxygenase-2 (COX-2) expression increased in adipose tissue macrophages (ATMs). Mice with myeloid deletion of COX-2 or its EP4 receptors resulted in increased obesity after the HFD. The current studies investigated whether kidney dysfunction was exacerbated in mice with myeloid COX-2 or EP4 deletion fed a HFD.

Methods: αααWe developed myeloid COX-2-/- mice (CD11b-Cre; COX-2$^{f/f}$) and myeloid EP4-/- mice (CD11b-Cre; EP4$^{f/f}$). COX-2$^{f/f}$ mice and EP4$^{f/f}$ mice were used as corresponding WT controls. The mice were fed a HFD (36% fat accounting for 60% of calories) for 12 weeks.

Results: The HFD induced greater increases in body weight, fasting blood glucose, and plasma concentrations of insulin, free fatty acids, TNF-a, and leptin. The HFD-treated myeloid COX-2-/- mice and myeloid EP4-/- mice had albuminuria, kidney weight, and kidney weight vs. body weight ratio, compared to WT mice. Histologically, HFD-treated myeloid COX-2-/- mice and myeloid EP4-/- mice had more mesangial expansion, increased glomerular volume and lipid deposition in epithelial cells as well as increased immune cell infiltration. Flow cytometry and qPCR analysis showed increased renal macrophages and cytotoxic CD8 T cells and increased mRNA levels of renal proinflammatory cytokines such as *Ccl2* and *Il6* and profibrotic and fibrotic components including *Col1α1, Col3α1, Col4α1, Fn,* and *Tgfb1*.

Conclusions: These studies found that mice with myeloid cell deletion of COX-2 and EP4 are more sensitive to high fat diet-induced obesity and develop more severe kidney dysfunction and immune cell infiltration. The potential role of increased adipokines, insulin, free fatty acids, and leptin in the observed exacerbated kidney dysfunction are under investigation.

Funding: NIDDK Support, Veterans Affairs Support

PO2458

Functional Role of Tumor Necrosis Factor α Pathway in Aristolochic Acid-Induced Kidney Injury Model

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Background: Tumor necrosis factor (TNF)-α is a potent mediator of inflammatory responses and is suggested to be involved in the pathogenesis of kidney injuries. However, little is known about modulating effects of TNF-α inhibition on the development of kidney fibrosis. The aim of this study is to examine the effects of TNF-α inhibition on kidney inflammation and fibrosis in a mouse model of chronic kidney disease (CKD) with fibrosis.

Methods: Aristolochic acid nephropathy (AAN) was employed as the mouse model of CKD with fibrosis. To induce AAN, C57BL/6J mice were intraperitoneally administered 3 mg/kg AA twice a week followed by 4-week remodeling period. Meanwhile, 5 mg/kg etanercept (ETN) or saline were subcutaneously administered twice a week for a total of 8 weeks. At the end of experimental period, 24-hour urine samples were collected in metabolic cages, and then kidneys and blood samples were collected.

Results: TNF-α inhibition by ETN partially but significantly attenuated kidney fibrosis estimated by the picrosirius red staining, and ameliorated albuminuria without affecting kidney function in the AAN model. Treatment with ETN significantly suppressed an AA-induced increase in kidney expression of pro-inflammatory cytokines and fibrosis-related genes, including IL-1b, IL-6, type I and III collagen. Moreover, the TNF-α inhibition tended to reduce an AA-induced increase in renal interstitial TUNEL positive cells along with the suppression of kidney Bax mRNA expression. Although the kidney phosphorylated-p38 MAPK, a key mediator activated by TNF-α, was significantly up-regulated by the AA administration, this pathological up-regulation was ameliorated upon the TNF-α inhibition by ETN.

Conclusions: TNF-α inhibition by ETN significantly attenuated the development of albuminuria and kidney fibrosis, concomitant with suppression of kidney inflammation and interstitial cell apoptosis in the mouse model of CKD with fibrosis. These findings indicate that the TNF-α pathway plays a role in the pathogenesis of kidney fibrosis, and further suggest that TNF-α inhibition could become an adjunct therapeutic strategy to treat CKD.

PO2459

Endoglin Is Upregulated in CKD and Is Associated with Increased Extracellular Matrix Production

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Background: Chronic kidney disease (CKD) may result from any cause of renal dysfunction of sufficient magnitude, including diabetic nephropathy (DN) and different glomerulopathies like IgA nephropathy or focal segmental glomerulosclerosis (FSGS). Irrespective of the etiology, the common pathway in the pathophysiology of CKD involves glomerular sclerosis and tubulointerstitial fibrosis. TGF-β is an important cytokine in the development of renal fibrosis. Transmembrane glycoprotein endoglin, a TGF-β co-receptor could be a possible new therapeutic strategy to counteract the development of renal fibrosis in CKD.

Methods: Biopsies of patients with chronic kidney diseases including chronic allograft dysfunction (n=43), DN (n=11), FSGS (n=48), IgA nephropathy (n=85) and were selected; kidneys excluded for transplantation for technical reasons were used as controls (n=8). Sequential sections were stained for endoglin and Sirius Red. Human kidney fibroblasts were lentivirally transduced with either an empty vector or an endoglin knock-in construct and mRNA levels of genes involved in extra cellular matrix (ECM) production were measured with qPCR after TGF-β1 stimulation.

Results: The endoglin-positive area was significantly increased in the interstitium of patients with chronic allograft dysfunction, DN, FSGS and IgA-nephropathy compared to the controls ($p<0.05$). Endoglin-positive areas also co-localized with the Sirius Red-positive areas. The knock-in cell line showed an 7 times upregulation of the endoglin protein level compared to control cells. SERPINE-1 ($p<0.05$) and fibronectin ($p<0.05$) mRNA levels were significantly upregulated (respectively 2.5 and 2.8 times) after stimulation with TGF-β1 in endoglin overexpressing cells compared to controls.

Conclusions: Endoglin was upregulated in different chronic kidney diseases, which were characterized by interstitial fibrosis. We also showed that upregulation of endoglin increases TGF-β-dependent ECM production. This indicates that endoglin could be a potential target in reducing the development of fibrosis and offers an interesting opportunity to slow formation of fibrosis in CKD.

PO2460

Guanidinylated Apolipoprotein C3 (ApoC3) Causes Kidney and Vascular Injury

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Background: Cardiovascular diseases (CVD) and chronic kidney diseases (CKD) are highly prevalent in Western populations and account for a substantial proportion of mortality. We found that apolipoprotein C-3 (ApoC3), a constituent of triglyceride-rich lipoproteins, induces alternative NLRP3 inflammasome activation in human monocytes and thus causes sterile inflammation. The aim of the present study was to screen ApoC3 for the presence of posttranslational protein modifications and to assess its relevance in vitro, in vivo, as well as in a prospective cohort of CKD patients.

Methods: ApoC3 was subjected to proteomic analysis. The proinflammatory properties of ApoC3 were assessed in human monocytes and in humanized mice. Moreover, posttranslationally modified ApoC3 was quantified in prospective cohort of 543 patients with various etiologies of CKD and linked to kidney and cardiovascular outcomes.

Results: We identified posttranslational guanidinylation of lysine residues of ApoC3 (gApoC3) in patients after acute myocardial infarction and in patients with CKD. gApoC3 accumulates in kidneys and hearts after injury as determined by 2D-proteomic analyses. In human monocytes, guanidinylation enhanced the binding of ApoC3 to the cell surface and exerted substantially stronger pro-inflammatory effects as compared native ApoC3. In humanized mice, gApoC3 strongly induced kidney fibrosis and abolished the regeneration after vascular injury. In a prospective clinical trial of 543 patients, higher gApoC3 blood levels as determined by mass spectrometry were associated with increased mortality as well as cardiovascular and renal events during a long-term follow-up.

Conclusions: The present study provides evidence from preclinical models and a prospective clinical trial that gApoC3 plays an important role in the development of organ injury in patients with CKD, myocardial infarction and other clinical conditions. The clinical study represents one of the largest trials, in which the association of a specific PTM and clinically relevant outcomes was assessed. These findings highlight gApoC3 as a pathophysiologically relevant factor in development of organ dysfunction.

PO2461

Endothelial Function, Oxidative Stress, and Cognitive Performance in CKD

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Background: Cognitive impairment, common in patients with chronic kidney disease (CKD), can be explained at least partially by the high prevalence of cerebrovascular disease in the population. Here, we hypothesized that endothelial dysfunction associates with reduced cognition in patients with CKD.

Methods: We conducted a cross-sectional study of 63 middle-aged/older adults with CKD stage 3b and 4. Cognitive function domains including executive function, memory, language, and processing speed were assessed via the NIH-Toolbox. Endothelial function of the brachial artery was assessed via flow-mediated dilation (FMD) using Doppler ultrasound. The influence of oxidative stress on FMD was determined by infusing a supraphysiological dose of ascorbic acid vs. isovolumetric saline (control). Regression models evaluated if measures of vascular function associated with each domain of cognition, and were adjusted for education (< college degree vs. ≥ college degree).

Results: The mean(SD) age, estimated glomerular filtration rate (eGFR), and FMD of the participants were 64(9), 34(11), and 2.6(1.4). Ascorbic acid increased FMD by 4.5±1.7 as compared to saline which increased FMD by 2.5±1.3 ($p<0.001$). Table 1 illustrates the age-adjusted standard scores for each cognitive domain. We found no association between FMD and any of the cognitive domains. However, a greater response to ascorbic acid correlated with better age-adjusted memory performance independently of education (95% CI: 2.08: 0.51,3.65; $p<0.05$).

Conclusions: Oxidative stress contributes to endothelial dysfunction in CKD and a greater response to ascorbic acid is associated with better memory performance. More studies are needed to understand the role of oxidative stress in cognitive impairment in patients with stage 3b/4 CKD.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

Table 1: NIH Toolbox Cognitive Domain Standard Scores

Executive function	95.9±9.5
Memory	99.5±10.4
Language	100.6±11.1
Processing speed	98.8±11.0

Normatively age-adjusted standard sores are presented. Standard scores have a mean of 100 and SD of 15.

PO2462

Key Role for EphB2 Receptor in Kidney Fibrosis

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Background: Eph-Ephrin receptor-ligand signaling has been implicated in the development of tissue fibrosis, though it has not been well defined in the kidney.

Methods: We then firstly made use of male EphB2-knockout and littermate control mice (n=5/per group) to receive unilateral renal ischemia-reperfusion (IR) surgery for 35min. In addition, EphB2 signaling was further determined in varied kidney disease models, particullary in diabetes- or hypertension-induced kidney disease models and in the kidney biopsy tissue from IgA nephropathy with glomerulosclerosis and tubular fibrosis.

Results: We detected substantial upregulation of expression and phosphorylation of the EphB2 receptor tyrosine kinase in fibrotic kidney tissue obtained both from mice subjected to either the unilateral renal IR model at 14 days or type 2 diabates or DOCA & Ang II-infused hypertension and in patients suffering from chronic kidney disease (CKD). Knockout mice lacking EphB2 expression exhibited a normal renal structure and function, indicating no major role for this receptor in kidney development or action. Although IR injury is well known to cause tissue damage, fibrosis, and renal dysfunction, we found that kidneys from *EphB2* knockout mice showed much less renal tubular injury and retained a more preserved renal function. IR-injured kidneys from *EphB2* knockouts exhibited greatly reduced fibrosis and inflammation compared to injured wild-type (WT) littermates, and this correlated with a significant reduction in renal expression of pro-fibrotic molecules, inflammatory cytokines, NADPH oxidases, and markers for cell proliferation, tubular epithelial-to-mesenchymal transition, myofibroblast activation, and apoptosis. A panel of 760 fibrosis-associated genes were further assessed, revealing that 506 genes in WT mouse kidney following IR injury changed their expression. However, 70.9% of those genes were back to or close to normal in expression when *EphB2* was deleted.

Conclusions: These data indicate endogenous EphB2 expression and signaling are abnormally activated after kidney injury and subsequently contributes to the development of renal fibrosis via regulation of multiple pro-fibrotic pathways.

Funding: NIDDK Support

PO2463

Apelin, a Novel Apelin Receptor Analog, Improves Endothelial Dysfunction in Uremic Rats with 5/6 Nephrectomy

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Background: Endothelial dysfunction (ED), characterized by a reduction in vasodilation as a response to endothelial stimuli, has been reported in patients at almost all stages of chronic kidney disease (CKD). Considering that apelin is a vasoactive molecule causing nitric oxide release from endothelial cells, we aimed to investigate the regulatory role of apelin receptor on CKD-induced ED.

Methods: Adult Sprague Dawley male rats were randomized into sham-operation or 5/6-nephrectomy (CKD) groups. CKD groups were treated subcutaneously with saline (S-CKD) or 100 μg/day (each) of apelin (A-CKD), ala-apelin (Ala-CKD) or apelin+ala-apelin (A+Ala-CKD) for eight weeks. Isolated aortas were mounted in organ baths and their vasorelaxatory responses to carbachol (CCh) and apelin were evaluated following pre-contraction with phenylephrine.

Results: Aortas of S-CKD group demonstrated an impaired CCh-induced relaxation as compared to sham group ($P<0.05$), while pre-incubation with L-NAME further inhibited CCh-induced vasorelaxation in both sham and S-CKD groups ($P<0.05$) (Fig A). In A-CKD group, CCh-relaxation response was significantly improved compared to S-CKD group, but L-NAME attenuated the improvement in relaxation (Fig B-C). When apelin was added to organ bath, despite that S-CKD group showed no relaxation, a dose-dependent relaxation was observed in sham group, which was abolished in the presence of L-NAME (Fig D). In A-CKD, Ala-CKD and A+Ala-CKD groups, the relaxation response to apelin was enhanced as compared to S-CKD, while L-NAME pre-incubation abolished the relaxation (Fig E-F).

Conclusions: Apelin, which directly relaxes aortic rings of intact rats in an endothelium-dependent manner, ameliorates CKD-induced endothelial dysfunction when given as a treatment. Moreover, this beneficial effect of apelin treatment on endothelial vasomotor function appears to act by the preserving the activity of nitric oxide-signaling pathway.

Funding: Government Support - Non-U.S.

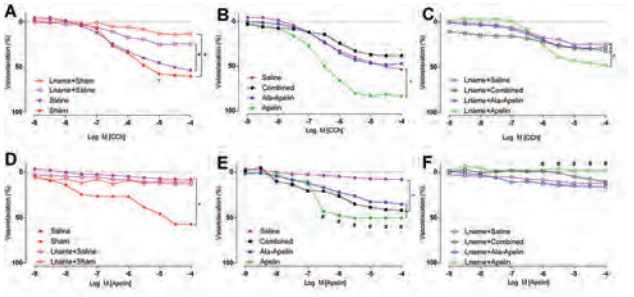

Figure. A, B, C. Impaired endothelial-dependent relaxation of aortic segments in Saline, Losartan, Apelin, Ala-Apelin and Combined groups under the L-NAME incubation or not. D, E, F. Vasorelaxant response of the Saline, Losartan, Apelin, Ala-Apelin and Combined groups under the L-NAME incubation or not. *p<0.05 vs. Saline; +p<0.05 vs. L-NAME incubated groups; #p<0.05 vs. Ala-Apelin group.

PO2464

Apelin and FGF-23 as Biomarkers for Vascular Calcification in Type 2 Diabetic Patients with CKD

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Background: Cardiovascular disease is the leading cause of death in chronic kidney disease (CKD) patients. CKD-Mineral and Bone Disorder occur from the earliest stages of estimated glomerular filtration rate (eGFR) loss and is associated with an increased risk of vascular calcification (VC), which is one of the strongest predictors of cardiovascular risk and mortality in patients with CKD. Apelin and FGF-23 have emerged as potential markers of VC. The main objective of this study is to evaluate the role of apelin and fibroblast growth factor 23 (FGF-23) in the development of VC in type 2 diabetic CKD patients

Methods: Observational prospective study enrolling 150 type 2 diabetes mellitus patients with CKD. Sample characteristics were analyzed using descriptive statistics. Independent-samples t-test, Pearson's correlation test and partial correlations were used to evaluate the association and correlation of several demographic and clinical parameters with vascular calcification score (VCS). Univariate logistic regression and multivariate logistic regression were used to find out predictors of VC.

Results: Lower levels of apelin, 1,25-dihydroxycholecalciferol and eGFR were negatively associated with higher VCS and higher levels of phosphate, calcium × phosphate, parathyroid hormone, interleukin-6 and FGF-23 were positively associated with higher VCS. A negative correlation was found between VCS and apelin ($r = -0.429$, $p<0.0001$), and between apelin and FGF-23 ($r = -0.483$, $p<0.0001$), while a positive correlation was found between VCS and FGF-23 ($r = 0.232$, $p=0.005$). Variables significantly associated with VCS in univariate logistic regression analysis were used in multivariable logistic regression analysis. Multivariable logistic regression analysis demonstrated that lower apelin levels and diminished eGFR were associated with a higher VCS. Contrarily, higher levels of inorganic phosphorus and FGF-23 were linked with a higher VCSA.

Conclusions: The results suggest that apelin and FGF-23 are predictors of VC on type 2 diabetic patients with CKD. Therefore, these osteo-mineral markers might be used as diagnostic/therapeutic targets in order to improve management of CKD complications.

PO2465

Endothelial Dysfunction in Dermal Biopsies of Patients with CKD Associates with Markers of Inflammation and Volume Overload

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Background: Cardiovascular (CV) morbidity is a major health problem in patients with chronic kidney disease (CKD). Besides traditional risk factors, CKD-induced endothelial dysfunction (ED) is involved in CV pathology. Of note, the luminal side of the vascular endothelium is covered by a protective endothelial glycocalyx (eGC) and indirect evidence indicates eGC loss and/or ED in CKD patients. So far, no direct endothelial profiling in non-renal tissue from renal patients has been performed. We aimed to investigate possible eGC loss and ED in CKD patients and its association with inflammation and volume overload.

Methods: During kidney transplantation, abdominal skin biopsies were taken from 11 kidney transplant recipients, of which 4 received hemodialysis. Abdominal skin biopsies from 9 healthy kidney donors served as control. Biopsies were stained for the eGC marker *Ulex Eur I* and the endothelial markers VEGFR2 and vWF. Subsequently, they were quantified and normalized in an immunofluorescence double staining for the pan-endothelial marker CD31. We also studied associations between the quantified endothelial markers and plasma markers of inflammation (CRP) and volume overload (NT-proBNP).

Results: Compared to healthy subjects, there was severe loss of eGC marker *Ulex Eur I* in renal patients (P=0.0008). Conversely, VEGFR2 was increased in renal patients, especially in those on dialysis (P=0.01). The same trend was seen for vWF, although this did not reach statistical significance. Skin water content was identical in all groups, which excluded dermal edema in patients with CKD. Compared with controls, plasma levels of CRP were increased in dialysis patients (P=0.02), whereas NT-proBNP was highly upregulated in all renal patients (P=0.03) which associated with VEGFR2 (R=0.29; P=0.03) and vWF (R=0.63; P<0.0001). Also, VEGFR2 and vWF were correlated (R=0.97; P<0.0001).

Conclusions: This study is the first to show direct evidence of dermal ED in patients with CKD. eGC damage has been shown by loss of *Ulex Eur I* and endothelial activation by increased VEGFR2 and vWF levels. In line with previous research, our results show ED to associate with inflammation and volume overload. More research is needed to further explore this pathophysiology.

PO2466

CCN2/CTGF Causes Renal Fibrosis Progression Through the Integrin/FAK Signal Pathway

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Background: Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that accumulates with integrins at focal adhesions and is involved in intracellular signal transduction. We have focused on CCN2, and demonstrated that FAK phosphorylation is also reduced when the progression of fibrosis is suppressed in a tubular cell-specific CCN2 knockdown mouse. In this study, we examined in greater detail the relationship between CCN2 and FAK.

Methods: A mouse ischemia-reperfusion (IRI) model, cultured human renal tubular epithelial cells (HK-2), 3 types of anti-phosphorylated FAK antibody (Y397, Y576 / 577, Y925), and anti-total FAK antibody were used to perform Western blotting. Furthermore, we examined what subunits of the integrin were expressed in HK-2 by using RT-PCR. A specific neutralizing antibody against integrin was also used to suppress the binding of CCN2 to integrins.

Results: A significant increase in total FAK was observed in the chronic phase (day 12) as fibrosis progressed (total FAK/GAPDH; control 0.81 ± 0.10 vs. day 12 1.96 ± 0.20). Among the phosphorylated FAK (pFAK), Y397 was particularly significant (pFAK/FAK: control 0.39 ± 0.01 vs. day 12 0.75 ± 0.17). Positive staining for pFAK was observed in tubular epithelial cells. In serum-stimulated HK-2, FAK was phosphorylated, but the addition of the decoy peptide of the CCN2 VI-module decreased the amount of Y397. Results of RT-PCR confirmed the expression of several integrin subunits. The results of studies using neutralizing antibodies revealed that the decrease in pFAK was most remarkable when the anti-integrin αv antibody was added (pFAK/FAK: control 0.99 ± 0.13 vs. 0.48 ± 0.06 after addition of the antibody).

Conclusions: By using the IRI model, we found that not only the expression of FAK was increased but also its phosphorylation was promoted in the injured kidney. CCN2 produced in tubular epithelial cells acts via cellular integrin αv in autocrine/paracrine manner, and promotes renal fibrosis through phosphorylation of the tyrosine 397 residue of FAK. CCN2 has been previously shown to activate Wnt/β-catenin and TGF-β/Smad pathways. However, here we identified another pathway for CCN2 in relation to kidney fibrosis. Several FAK inhibitors have already been investigated as anticancer agents. Further clarification of the pathways may prove the therapeutic effects of these inhibitors on CKD.

Funding: Government Support - Non-U.S.

PO2467

Multitarget Soluble Epoxide Hydrolase/Farnesoid X Receptor Agonist Combats CKD

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Background: Chronic kidney disease (CKD) is characterized by progressive fibrosis leading to end-stage renal disease. There has been little success in developing agents that can slow the progression of CKD to ESRD. The current study investigated the efficacy of an innovative multi-target ligand drug, DM509, in mitigating renal fibrosis using the unilateral ureteral obstruction (UUO) mouse CKD model.

Methods: DM509 acts concurrently as a soluble epoxide hydrolase inhibitor and farnesoid X receptor agonist. UUO or sham surgery was conducted in C57BL/6J male mice (n=8/group). Interventional DM509 treatment (10 mg/kg/d p.o.) or vehicle was started three days after UUO induction and continued for 7 days. Plasma and kidney tissue were collected at the end of the experimental protocol. Several biochemical, histopathological, immunohistopathological, and gene expression studies were carried out to determine the antifibrotic actions for DM509

Results: UUO mice demonstrated fibrosis with higher kidney hydroxyproline content (267±46 vs. 53±14 μg/mg protein), collagen area (4.3±0.1% vs. 0.7±0.3%). DM509 reduced hydroxyproline by 41% and collagen area by 65%. Renal inflammation was evident in UUO mice with elevated MCP-1, increased CD45 immune cells, and increased TNF-a, IL-6, IL-1b expression. Interventional DM509 treatment markedly reduced renal inflammation in UUO mice. Vascular inflammation was evident in UUO mice with increased higher ICAM and VCAM expression. DM509 reduced vascular inflammation by 40-50% in UUO mice. In addition, peritubular vascular density assessed by CD31 was reduced by 35% in UUO mice and DM509 attenuated vascular loss. Kidney fibrosis in UUO mice was associated with epithelial-to-mesenchymal transition (EMT) with higher expression of mesenchymal markers a-SMA, FSP-1, and FN, as well as a marked decrease in the epithelial marker, E-cadherin. UUO mice treated with DM509 had markedly reduced EMT. UUO mice also had tubular epithelial barrier injury with increased renal KIM-1, NGAL expression and lower claudin-1, -2 and -4 expression. DM509 treatment reduced tubular injury markers by 25-50% and maintained tubular epithelial integrity by restoring claudin expression in UUO mice.

Conclusions: These data reveal that DM509 is a promising multi-target antifibrotic drug that combats epithelial and vascular kidney fibrotic disease and CKD progression.

Funding: NIDDK Support

PO2468

Single-Nucleus Transcriptional Profiling of CKD After Repeated Low-Dose Cisplatin Treatment

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Background: Cisplatin induces both acute and chronic kidney problems during chemotherapy. Recent studies have established the models of chronic kidney problems after repeated low dose cisplatin treatment (RLDC). RLDC-induced global transcriptional changes in specific renal cells associated with the development of chronic kidney problems is unclear.

Methods: Male C57BL/6 mice were given 4 consecutive weekly injections of 8 mg/kg cisplatin. Renal function was measured at 5 and 9 weeks after the first cisplatin injection. Kidney tissues were collected for histology and single-nucleus RNA sequencing (Sn-RNA-seq). Cell-type-specific changes in gene expression were compared between the samples from control and cisplatin treated mice. Transcriptional regulators in proximal tubular cells were identified and qPCR was used to validate the critical genes involved in renal fibrotic and inflammation.

Results: RLDC induced decreases in eGFR and kidney weight in mice at 5 and 9 weeks. The kidneys of these mice showed tubular degeneration and dilation. There was also increases in KIM-1 positive tubules and atubular glomeruli. Sn-RNA-seq identified transcripts corresponding to 23021 genes. The markers for 11 cell types and 12 cell clusters were detected. Cluster-by-cluster comparison demonstrated cell-type-specific changes in gene expression that are important for transport, fibrosis and inflammation in RLDC mouse kidneys. In particular, compared with the untreated control, RLDC resulted in 425 differentially expressed genes ($log2FC>1$, $p<0.05$) in proximal tubular cells. >400 and >300 genes displaying altered expression were enriched in profibrotic and proinflammatory pathways, respectively. Consistently, RLDC induced NF-κB activation and proinflammatory cytokines (TNFa, IL6 and IL7), and the expression of fibrosis markers (fibronectin, collagen I, vimentin and α-SMA). Furthermore, Runx1 and Spp1 were identified as critical transcriptional factors that drive inflammation and fibrosis progression after repeated cisplatin treatment.

Conclusions: Single-nucleus RNA sequencing revealed altered gene expression and identified critical transcriptional regulators that promote renal inflammation and fibrosis during the development of chronic kidney problems after repeated low dose cisplatin treatment.

Funding: NIDDK Support, Veterans Affairs Support

PO2469

Activation of EGFR in Myofibroblasts Promotes Renal Fibrosis in Unilateral Ureteral Obstruction

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Background: In response to injury, renal fibroblasts and pericytes differentiate into highly specialized myofibroblasts, which are essential for maintaining kidney structural integrity. It is imperative to identify the molecular mechanism initiating and sustaining myofibroblast activation in order to identify novel therapeutics to stop or reverse kidney fibrosis. The activation of epidermal growth factor receptor (EGFR) plays an important role in mediation of recovery of epithelial integrity following ischemic acute kidney injury (AKI). However, sustained activation of EGFR triggers renal fibrogenesis after AKI. The role of EGFR in fibroblasts/myofibroblasts in development of renal fibrosis after severe AKI has not been previously investigated.

Methods: Both PDGFRβ-Cre/ERT2; mCherry mice (WT) and PDGFRβ-Cre/ERT2; mCherry; $EGFR^{f/f}$ mice (PDGFRβ EGFR-/-) were treated with tamoxifen 2 weeks before unilateral ureteral obstruction (UUO) was performed for 3 or 7 days. Quantification of proliferation of PDGFRβ-positive cells was determined at day 3 after UUO. PDGFRβ-positive cells were isolated using PDGFRβ antibody/IgG microbeads.

Results: EGFR mRNA in isolated renal PDGFRβ+ cells was increased >5-fold after 7d UUO. In PDGFRβ EGFR-/- mice, selective EGFR deletion was confirmed by >80% EGFR mRNA reduction in isolated renal PDGFRβ+ cells as well as absence of immunofluorescent EGFR expression in α-SMA+ myofibroblasts. Flow cytometry determined that renal $CD45^{-}CD31^{-}$PDGFRβ+EdU+ cells were markedly lower in PDGFRβ EGFR-/- mice than WT mice 3d after UUO. PDGFRβ EGFR-/- mice had markedly decreased renal fibrosis, indicated by Sirius red and Masson's Trichrome staining, and increased mRNA and protein levels of profibrotic and fibrotic components including α-SMA, collagen I, collagen IV, IL-11, fibronectin, and PDGFRβ. Isolated PDGFRβ+ cells from PDGFRβ EGFR-/- mice also expressed less *col1α1* and *col4α1*. Unexpectedly, the mRNA levels of proinflammatory cytokines, including *Tnf, Il6, Il1α,Il1b, Ccl2, Ccl3, Il23α, Infγ,* and *Il12* in whole kidney tissue as well as in isolated renal myeloid cells were comparable between WT mice and PDGFRβ EGFR-/- mice.

Conclusions: In response to UUO, increased EGFR expression in PDGFRβ+ cells induces myofibroblast proliferation and differentiation to promote subsequent fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

PO2470

Activins Facilitate TGF-β1 Profibrotic Signaling in Kidneys

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Background: Chronic kidney disease (CKD) is a rising health issue in North America. It is characterized by progressive renal fibrosis leading to end-stage kidney disease requiring dialysis or transplantation. TGFβ1 is a central mediator of kidney fibrosis in CKD of diverse etiology. Directly blocking it is unfeasible due to adverse effects. Alternate approaches to inhibit TGFβ1 signaling are needed to develop tolerable antifibrotic therapies. Recent studies suggest that TGFβ1 requires activins for its profibrotic effects. Interesingly, both signal through the same canonical Smad pathway. Here we study the mechanisms by which activins enable TGFβ1-induced fibrosis and assess efficacy of specific activin inhibition *in vivo*.

Methods: Primary mouse kidney mesangial cells (MC) were used. Activin A and B (AA, AB), the predominant activins, were inhibited with a neutralizing antibody or follistatin. ELISA, IF and IB were used to assess cytokine levels, signaling pathways and profibrotic responses. Smad3 transcriptional activity was assessed by CAGA12 luciferase reporter and the alpha smooth muscle actin (αSMA) promoter luciferase. Unilateral ureteral obstruction (UUO) was created in mice overexpressing (OE) TGFβ1 or wild-type controls, and effects of neutralizing anti-AA antibody on kidney fibrosis was assessed.

Results: TGFβ1 stimulated the production of AA more than AB, and AA neutralization inhibited the profibrotic effects of TGFβ1. TGFβ1 provoked strong early Smad3 activation (30-60min), while AA did so later (24-48h). Inhibition of AA decreased TGFβ1 (24h)-induced Smad3 activation, assessed by its phosphorylation, nuclear accumulation, and transcriptional activity. Cells retained responsiveness to AA signaling even after becoming refractory to TGFβ1 restimulation, enabling ongoing Smad3 activation. AA additionally regulated noncanonical TGFβ1 signaling. Its inhibition reduced nuclear accumulation of MRTFA, a Smad3 co-mediator of αSMA induction by TGFβ1. Fibrosis was augmented in TGFβ1 OE mice. Neutralizing AA attenuated Smad3 activation and fibrosis in both wild-type and TGFβ1 OE mice.

Conclusions: AA facilitates TGFβ1 profibrotic effects through regulation of both canonical (Smad3) and non-canonical (MRTFA) signaling. Importantly, AA inhibition reduced fibrosis in vivo, suggesting a novel potential therapeutic for fibrosis in CKD.

PO2471

CircHIPK3 Aggravates Folic Acid-Induced Renal Interstitial Fibrosis by Sponging miR-30a

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Background: Renal interstitial fibrosis is a major pathological feature of end stage kidney disease and currently lacks effective treatment. CircHIPK3 is reported to participate in various diseases. However, the role of circHIPK3 in renal fibrosis is unreported. We aimed to verify whether circHIPK3 participates in the pathogenesis of renal fibrosis and its corresponding.

Methods: C57BL/6 mice were intraperitoneally injected with folic acid (FA) (250 mg/kg) for 30 days. Renal tissue samples were used for paraffin section PAS and Masson staining to confirm the occurrence of renal fibrosis. The expressions of circHIPK3, miR-30a, Transforming growth factor β (TGF-β1),Fibronectin (FN) and Collagen 1 (COL1) in kidney were detected. Those three parameters were further confirmed by immunoblotting. Then the expressions of miR-30a, TGF-β1, FN and COL-1 were detected in immortalized human tubular epithelial cells HK-2 cells overexpressed of circHIPK3 and stimulated with TGF-β1. Finally, fluorescence in situ hybridization (FISH) to measure the localization of circHIPK3 and miR-30a, and immunofluorescence was to detect the expressions of TGF-β1, FN and COL1.

Results: In mice, renal fibrosis features and expression of profibrotic FN and COL1 were increased at day 30 after peritoneal injection of FA. Renal circHIPK3 was up-regulated while miR-30a was down-downregulated in FA-induced kidney injury, as shown by qPCR and FISH. TGF-β1 expression was increased. In addition, renal circHIPK3 negatively correlated with miR-30a and kidney miR-30a also negatively correlated with TGF-β1 mRNA expression. In HK-2 cells, circHIPK3, miR-30a, and TGF-β1 co-localized in the cytoplasm on FISH and immunofluorescence staining. Importantly, transient transfection of circHIPK3 down-regulated miR-30a and up-regulated TGF-β1, FN, and COL1 assessed by qPCR and immunoblotting. Furthermore, exposure of HK-2 cells to human TGF-β1 resulted in increased circHIPK3, decreased miR-30a, and increased expression of profibrotic fibronectin and collagen 1 protein. Kidney biopsies from patients with chronic tubulointerstitial nephritis manifested the same directional changes of circHIPK3, miR-30a, and profibrotic proteins including TGF-β1, FN and COL 1.

Conclusions: A pro-fibrotic feedback involving in circHIPK3, miR-30a, and TGF-β1 and further indicated that circHIPK3 might contribute to renal fibrosis by sponging miR-30a.

Funding: Government Support - Non-U.S.

PO2472

ROCK-Binding ASD2-Domain of Shroom3 Has a Profibrotic Role

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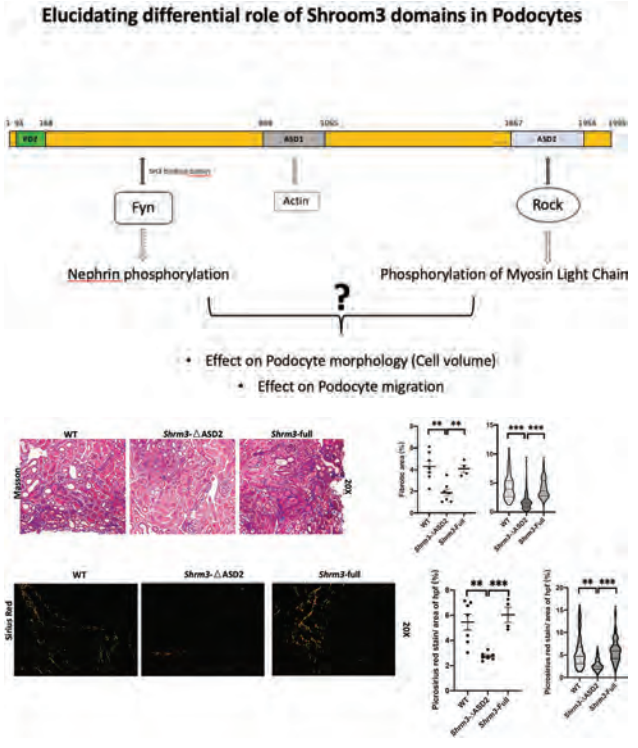
Background: We previously showed that a CKD-associated Shroom3 allele was a quantitative trait locus for *SHROOM3* expression and promoted CKD and allograft nephropathy.

Methods: Here we investigated the mechanism of increased fibrosis downstream of Shroom3. We systematically deleted consensus domains in Shroom3 and evaluated profibrotic signaling in tubular cells (Fig-1).

Results: Overexpression of ASD2-domain deleted SHROOM3 mutant (ASD2-SH3 with deficient ROCK binding) consistently reduced TGF-B signaling responses in TGF-B reporter 293-Tcells and in Smad-reporter luciferase assays (vs ASD1-, PDZ-, Fyn-binding domain deletion mutants and intact SHROOM3; n=3 sets each). Based on these data we generated doxycycline inducible transgenic mice for SHROOM3 and ASD2-SH3 mutants. Two founder lines of each transgene crossed with CAGS-rTTA mice were selected based on transgene expression in kidney tissues upon DOX-feeding. Adult CAGS-rTTA:SHROOM3-Tg, ASD2-S3-Tg and control mice were dox fed, and UUO surgery performed (n=5 each). At 7 days, UUO kidneys from ASD2-SH3-Tg mice showed reduced Phospho-Smad3, and reduced profibrotic transcripts (Col1a1, Fn1) vs other groups. ASD2-SH3 UUO kidneys had significantly reduced interstitial fibrosis (masson trichrome and sirius red), and reduced COL1A1 immunofluorescence (fig 2).

Conclusions: Our sequential findings show that the profibrotic role of Shroom3 excess is mediated via its ASD2-domain.

Funding: NIDDK Support



PO2473

EPAC1-Mediated cAMP Signaling in Podocytes Protects Kidneys from the Progression of Glomerulonephritis

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Background: Many efforts are made to identify new therapeutic targets to slow down, prevent or even reverse Chronic Kidney Disease (CKD) progression. One of the therapeutic approaches is the targeting of the renoprotective cAMP pathway, especially by stimulation of its downstream effector, the protein kinase A (PKA). PKA was considered as the unique cAMP effector, however, the exchange factor directly activated by cAMP 1 (EPAC1) has been recently identified as a novel, PKA-independent, mediator of cAMP signaling. Epac1 is a guanidine exchange factor that promotes the exchange of GDP for GTP regulating important cellular functions. Of the two isoforms described, Epac1 is the most expressed in the kidney. Epac1 activation exerts a renoprotective effect during acute kidney injury, via maintenance of epithelial adhesion and protection from oxidative stress. However, the role of EPAC1 in CKD remains poorly understood.

Methods: Here we aim to determine the role of EPAC1 in CKD progression, by inducing nephrotoxic serum glomerulonephritis (NTS-GN) in genetically modified mice with total and conditional EPAC1 deletion.

Results: Following the induction of NTS-GN, genetic deletion of EPAC1 aggravates renal disease, characterized by increased proteinuria, glomerular damage, tissue inflammation and fibrosis compared to wild-type mice. Conversely, pharmacological activation of Epac1, with the agonist 8-pCPT-2-OMe-cAMP, delays NTS-GN progression. Since in normal mouse kidney tissues we have observed EPAC1 expression in podocytes, mice with conditional deletion of EPAC1 in podocytes (Nphs2Cre:epac$^{fl/fl}$) are generated. Similar to the whole-body knockout, mice with EPAC1 deletion in podocytes show increased renal damage and worsened disease progression compared to control mice.

Conclusions: Our results suggest a protective role of podocytes-derived EPAC1 against the development of GN. Targeting the cAMP-EPAC1 signaling axis could represent a new therapeutic option to delay the development of CKD. Further investigations are needed to better define the molecular mechanisms involved, and to define its relevance in human CKD.

Funding: Government Support - Non-U.S.

PO2474

A Novel Allosteric HIPK2 Inhibitor Attenuates Renal Fibrosis with Superior Pharmacokinetic, Selectivity, and Safety Profiles

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Background: Renal fibrosis is considered the final convergent pathway for progressive CKD, regardless of the original etiologies of the disease. Although much has been learned of the molecular mechanisms underlying renal fibrogenesis, there is still a paucity of success in translating this knowledge to clinical application. We previously demonstrated HIPK2 as a multifunctional activator of TGF-β/Smad3, NF-κB, and p53 pathways and that the global knockout of HIPK2 in mice attenuated kidney fibrosis in vivo. We recently developed a small molecule inhibitor of HIPK2, BT173, that specifically blocked TGF-β/Smad3 pathway to attenuate renal fibrosis without causing adverse systemic effects. Importantly, BT173 did not alter the activity of p53 to produce unwanted oncogenic side effects. However, the in vivo use of BT173 was limited by its poor solubility and potency.

Methods: Based on BT173, we used iterative cycles of chemical synthesis and biological assays to optimize the solubility, bioavailability and potency of TGF-β/Smad3 pathway inhibition. ADME, selectivity, and safety profiling were performed on the optimized HIPK2 inhibitor compounds. The lead inhibitor was then tested in CKD models to test its efficacy in reducing renal fibrosis.

Results: 1) Repeated iteration and in vitro screening assay led to a lead compound, HIPK2i-174. 2) HIPK2i-174 showed greater potency (IC50<200nM) to disrupt the HIPK2-Smad3 interaction in vitro with enhanced solubility. 3) It showed pharmacokinetics suitable for oral *qd* dosing. 4) No appreciable kinase inhibition was observed when tested against a panel of 30 diverse kinases. Acceptable selectivity profiles were observed with Eurofins Safety 44 and CEREP selectivity panels. 5) Safety profiling did not show any relevant CYP inhibition, hERG, or other cardiac ion channel liabilities. 6) Daily *qd* dosing of HIPK2i-174 in mouse models of proteinuric CKD significantly reduced proteinuria and renal fibrosis development.

Conclusions: The optimized HIPK2i-174 effectively improved renal function, reduced renal fibrosis development and CKD progression in vivo. Moreover, its enhanced selectivity, bioavailability, and biological activity demonstrate a favorable safety profile in preclinical species for IND-enabling studies.

Funding: Commercial Support - Shang Pharma Innovation Inc.

PO2475

Inhibition of RNA-Binding Protein HuR Protects Kidney from Ischemia-Reperfusion-Induced Injury and Fibrosis

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Background: Upregulation of an RNA-binding protein HuR has been implicated in glomerular diseases both in patients and in animal models. Herein, we further evaluated whether upregulation of HuR occurs in and promotes renal tubular injury and subsequent fibrosis by using a renal ischemia/reperfusion (IR) mouse model and a selective HuR inhibitor, KH3.

Methods: All mice were received unilateral renal IR surgery for 35 min. The contralateral kidneys without surgery served as controls. Mice were then randomly assigned into either vehicle or KH3-treated groups (n=5/group). KH3 was given via daily intraperitoneal injection from day 3 after IR at the dose of 50 mg/kgWB/day to day 14. In additon the effect of HuR inhibition on TGFß-induced tubular cell injury was further investigated in vitro.

Results: IR-injured kidneys showed a significant upregulation of HuR in tubular and tubulointerstitial cells determined by postive cytoplasmic staining of HuR and western blot assay, which was accompanied by extensive tubular damage and fibrosis. However, KH3-treated and IR-injured kidneys exhibited greatly reduced damage and fibrosis, and this correlated with a reduction in renal expression of profibrotic molecules, inflammatory cytokines, NADPH oxidases, and markers for cell proliferation, tubular epithelial-to-mesenchymal transition (EMT), and apoptosis. A panel of 760 fibrosis-associated genes were further assessed, revealing that 519 genes in mouse kidney following IR injury changed their expression and 71.3% of those genes that are involved in 50 annotated

pathways were ameliorated when treated with KH3. Among those, TGFß1 as a HuR target was elevated in the IR-injured kidney. KH3 abrogated TGFβ1-induced tubular HuR cytoplasmic translocation and subsequent tubular EMT in cultured HK-2 cells.

Conclusions: These results suggest that upregulation of HuR contributes to renal tubular injury and fibrosis by dysregulating multiple pro-fibrotic pathways. HuR-targeted inhibitory therapeutics offer a promising novel treatment in the future for preventing or reversing the progression of CKD.

Funding: NIDDK Support

PO2476

Spiny Mice (Acomys cahirinus) Activate Unique Transcriptional Programs After Severe Kidney Injuries and Regenerate Organ Function Without Fibrosis

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Background: Fibrosis-driven solid organ failure is a pervasive burden on global health. Muroid rodents of the genus *Acomys* (spiny mice) are terrestrial mammals that evolved remarkable abilities to regenerate severe skin wounds without scar formation to avoid predation. Whether regenerative wound healing extends beyond skin to vital internal organs in spiny mice is not known.

Methods: Models of acute and chronic kidney injury (UUO, unilateral IRI, unilateral IRI+nephrectomy) were utilized in *Acomys* and compared to C57Bl6/J and CD-1 mice. Fibrosis, myofibroblasts, macrophages were measured. Total kidney RNA Seq, western blotting and confocal image analysis was performed.

Results: Using two aggressive kidney injury models, we show that despite equivalent kidney injury there was rapid regeneration of nephron structure and function without fibrosis in *Acomys* compared to extensive fibrosis and renal failure in *Mus*. Comparative genome-wide analysis of gene expression after injury suggested that the *Acomys* genome is poised to initiate and sustain regenerative wound healing. Among the 843 differentially regulated genes between *Acomys* and *Mus* were metabolic enzymes, transcription factors, and nephrogenic genes such as *Osr1*, *Ror1/2* and *Cdh6*. Interaction analyses revealed 6 clusters of genes that were differentially regulated with injury between *Mus* and *Acomys*. Clusters 1 and 4 represented *Mus*-specific genomic responses to UUO injury whereas the response to injury in *Acomys* is to maintain expression at homeostatic levels. In contrast, clusters 2 and 3 represent *Acomys*-specific kidney response gene sets which are unchanged or downregulated in *Mus*. Early after injury, a cluster 3 gene, *Cdh6* appeared in rapidly expanding renal tubular mosaic patches throughout the injured *Acomys*, but not *Mus*. Regeneration of nephron function was accompanied by cell cycle entry and DNA replication in tubular and glomerular cells, including podocytes and endothelial cells.

Conclusions: Our findings have important implications for an evolutionary solution to mammalian regenerative repair of the kidney, and by extension, to the heart and coronary vessels, lungs, liver, and other internal organs similarly prone to organ failure as a result of progressive tissue fibrosis.

Funding: NIDDK Support, Other NIH Support - DiaComp

PO2477

Graphene Quantum Dots Protects Against Renal Fibrosis After Restoring Mitochondria Function in Rat 5/6 Nephrectomy

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Background: Graphene Quantum Dots (GQDs) are carbon-based nanoparticles and spotlighted in biological application due to their biocompatibility, quantum confinement and low toxicity. Rat with subtotal 5/6 nephrectomy exhibit mitochondrial dysfunction mediated by TRPC5 channel, a core calcium channel in podocytes and tubular cells. With current limited understanding of the interaction on between nanomaterials and renal cells, we show GQDs as a potential therapeutic nano-sized material in 5/6 nephrectomy rat model.

Methods: To evaluate GQDs therapeutic effect on 5/6 nephrectomy Sprague Dawley (8-week; male) rat model, GQDs (4mg/kg) was administered by intraperitoneal for 3 times per week up to 8 weeks. *In vitro* stimulation, recombinant TGF-beta (2mg/mL) was treated in both human primary podocytes and tubular cells with GQDs in dose-dependent manner (0.1ug/mL, 0.5ug/mL, 1ug/mL). Renoprotection in 5/6 nephrectomy were assessed through combination of flow cytometry, Annexin V – FTIC Apoptosis staining, histomorphometry, functional manipulations, protein and mRNA expressions. Intracellular Calcium permeability was measured from Fura 2-AM.

Results: GQDs pivotal role in 5/6 nephrectomy led to identification of the partial proteinuria recovery and antihypertensive effects. *In Vivo* study discloses GQDs anti-fibrosis role as impeding MMT process that co-express macrophage (CD68) and myofibroblast (a-SMA). Thus, *in vitro* study after TGF-beta induction show similar results. GQDs-treated group in rats have increased potential cell viability by downregulating the cyclin kinase inhibitors after decreasing Bax-2, P53, P21 but increasing BCL2 expression. Next, Annexin staining result shows GQDs-treated group have a higher viable cells population (-/-) than 5/6 nephrectomy. Computing differential gene expression (DGE), RNA sequencing (RNA-seq) highlights the significant folding changes in *TRPC5* gene from GQDs-treated group. Acute stimulation of calcium movement measured by Fura 2-AM was lowered in GQDs group and TRPC5 protein function expression. Interestingly, after TRPC5 modulation by GQDs, mitochondrial dysfunction is repaired.

Conclusions: GQDs restores mitochondrial function associated with TRPC5 activation pathways. This gratitude of GQDs for renal preservation will promote next generation of CKD treatments.

PO2478

Critical Role of Histone Demethylase JMJD3 in the Regulation of Macrophage Polarization and Renal Fibrosis

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Background: Chronic kidney disease is characterized by macrophage infiltration and fibrosis. Macrophage infiltration and polarization play an important role in the development of renal fibrosis. However, the mechanisms underlying macrophage polarization and development of renal fibrosis are not fully understood. In this study, we examined the role of histone demethylase JMJD3 in the regulation of macrophage polarization and renal fibrosis.

Methods: To examine the role of JMJD3 in vivo, we generated mice with global or myeloid cell-specific deletion of JMJD3, and we treated wild-type mice with vehicle or GSK-J4, a selective JMJD3 inhibitor. Unilateral ureteral obstruction (UUO) model were used to induce renal fibrosis.

Results: JMJD3 expression was increased in the kidneys during the development of renal fibrosis. Mice with tamoxifen-inducible deletion of JMJD3 (CAG-Cre, floxed JMJD3) or myeloid cell specific deletion of JMJD3 (LysM-Cre, floxed JMJD3) were born normal and had no obvious morphological abnormality in the kidney. Compared with Cre negative, floxed JMJD3 mice, mice with global or myeloid cell-specific deletion of JMJD3 displayed fewer F4/80-positive macrophages, CD206-positive M2 macrophages, and myofibroblasts, and expressed less α-SMA protein in the kidneys following UUO. Furthermore, global or myeloid cell-specific deletion of JMJD3 significantly reduced total collagen deposition and ECM protein production in the kidneys after UUO injury. Real-time RT-PCR showed that global or myeloid cell-specific deletion of JMJD3 attenuated M2 macrophage polarization, fibroblast activation, and extracellular matrix protein production. Moreover, genetic deletion of JMJD3 increased histone Lys 27 dimethylation. Wild-type mice treated with GSK-J4 exhibited fewer M2 macrophages and myofibroblasts and produced less amounts of extracellular matrix proteins in the kidney following UUO.

Conclusions: Our study identifies JMJD3 as a critical regulator of macrophage polarization and development of renal fibrosis. Therefore, JMJD3 may represent a novel therapeutic target for chronic kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

PO2479

DNA Methylation in Repeated Low-Dose Repeated Cisplatin-Induced CKD

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Background: DNA methylation is an epigenetic mechanism that regulates gene expression by adding methyl groups to DNA molecules via DNA methyltransferases (DNMTs). Aberrant DNA methylation changes have been implicated in the pathogenesis of kidney diseases. Recent work indicates that DNA methylation protects against cisplatin-induced acute kidney injury partially through hypomethylation of interferon regulatory factor 8 (Irf8). However, little is known about DNA methylation in chronic kidney problems following cisplatin exposure.

Methods: Mice and HK2 cells were subjected to repeated low-dose cisplatin treatment (RLDC). We analyzed the expression of DNMTs and the methylation marker 5-methyl-cytosine following RLDC. We further conducted representation bisulfite sequencing (RRBS) to analyze the genome-wide DNA methylation changes. To explore the pathogenic role of DNA methylation, we initially tested the effects of 5-aza, a pharmacological DNMT inhibitor. We further established and tested a conditional knockout mouse model in which DNMT3a is specifically ablated from kidney proximal tubules (PT-DNMT3a-KO).

Results: RLDC induced notable increases in DNMT1 and DNMT3a (but not DNMT3b) expression, which were accompanied by an overall increase in DNA methylation as shown by 5-methyl-cytosine staining. Genome-wide DNA methylation assay identified differentially methylated regions (DMRs) in 171 genes after RLDC. Five of these genes (*Oxgr1, Smim22, Sec61a2, lhx1, Nsd1)* had hypermethylation in their promoter regions, which was associated with decreased mRNA expression, suggesting the regulation of these genes by DNA methylation. Functionally, 5-aza reduced the expression of fibrosis-related proteins in cisplatin-treated HK2 cells including collagen I and CTGF. In vivo, 5-aza and ablation of proximal tubule DNMT3a both alleviated the decline of renal function, kidney atrophy, and renal fibrosis after repeated cisplatin treatment.

Conclusions: DNMTs are induced in renal tubular cells after cisplatin exposure, accompanied by an overall increase of DNA methylation. Under this condition, DNA methylation contributes to the development of chronic kidney problems. Inhibition of DNMTs may afford therapeutic effects against cisplatin-induced chronic kidney disease.

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

PO2480

Targeting Histone Demethylase LDS1 Inhibits Renal Epithelial-Mesenchymal Transition and Attenuates Renal Fibrosis

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Background: Lysine-specific histone demethylase 1 (LSD1) as the first identified protein demethylase plays a special role in the regulation of gene expression by removing methyl groups from mono- and di-methylated lysine 4 and 9 on histone H3 and functions as an oncogenic factor in cancers. However, its role in renal fibrosis is unknown.

Methods: To evaluate the role and mechanisms of LSD1 in the development of renal epithelial–mesenchymal transition (EMT) and renal fibrosis, we inhibited LSD1 with its inhibitor, ORY1001, in mouse unilateral ureter obstruction (UUO) model and rat kidney fibroblasts (NRK-49F) and rat kidney proximal tubular (NRK-52E) cells stimulated by TGF-β1.

Results: We found that the expression of LSD1 was increased and the methylation of its histone targets were decreased in mouse kidneys with unilateral ureteral obstruction and NRK-52E cells undergoing EMT. Inhibition of LSD1 with ORY1001 decreased the deposition of extracellular matrix proteins and the expression of fibrotic markers, including α-smooth muscle actin (α-SMA) and fibronectin, which was associated with preserving E-cadherin expression and inhibiting N-cadherin upregulation in the obstructed kidney. Injury to the kidney enhanced the phosphorylation and activation of Smad2/3, AKT and Stat3, and that could be prevented by ORY1001 administration. Targeting LSD1 with ORY1001 and siRNAs inhibited TGFβ1 induced the activation of renal fibroblasts, NRK-49F, and EMT of NRK-52E cells. The expression of Snail family transcriptional repressor 1 (Snail-1) was upregulated in UUO kidneys and cultured NRK-52E cells treated with TGFβ1. Snail-1 repressed the expression of E-cadherin via the interaction of its N-terminal SNAG domain with LSD1. LSD1 inhibition with ORY1001 or siRNA silencing prevented the upregulation of Snail-1 and disrupted Snail/LSD1 interaction, resulting in the expression of E-cadherin. ORY1001 was also effective in suppressing TGF-β1-induced renal epithelial cells arrest at the G2/M phase.

Conclusions: This study indicates that LSD1 participates in the expression of profibrotic genes and contributes to renal EMT and fibrosis through activation of diverse signaling pathways, and places an emphasis that LSD1 has potential as a therapeutic target for the treatment of renal fibrosis.

Funding: Other NIH Support - R01 DK084097, R01 DK126662 and NIH P30 DK106912

PO2481

Does Senescence Induce Muscle Wasting in CKD?

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Background: Muscle wasting is a common complication of CKD and associated with higher mortality and morbidity. The mechanism of muscle wasting in uremia has been widely studied; however, uremic stress-induced senescence might be a missing connection between chronic kidney disease and muscle wasting. Senescent cells are capable of producing and secreting various growth and proinflammatory factors, cytokines, and chemokines, which is known as the S-ASP. We hypothesized that senescence and senescence associated secretary phenotype (S-ASP) play important roles in the CKD-induced muscle loss.

Methods: CKD mice were induced by 5/6 nephrectomy. Senescence was confirmed by using senescence associated beta gal (SA-βgal). The levels of S-ASP (interleukin 6 (IL-6), TNFα, TGFβ and IL-8) were measured by immunohistochemistry and ELISA. Senescence pathway markers p16, p21 and p53 were measured by Western blots. To limit senescence, dasatinib (5 mg/kg BW) + quercetin (50 mg/kg BW) (D&Q) were given by oral gavage 2 days per week for 8 weeks. Muscle function was measured with a grip force detector.

Results: CKD stress-induced premature senescence phenomena have been evidenced in the skeletal muscle of uremic mice by 1) the increases in senescence pathway indicators p21 and p16, but not p53 protein; 2) phosphorylated histone H2AX (γH2AX, DNA damage marker); 3) the level of the senescence biomarker SA-β gal; and 4) S-ASP components present in the uremic muscle, which include high levels of interleukin 6 (IL-6), TNFα, TGFβ and IL-8. The D&Q treatment eliminated CKD-induced elevation of p21, p16 and γH2AX, abolished positive SA-β gal, and depressed the high levels of S-ASP cytokines. The muscle cross-sectional area was increased by D&Q treatment compared with the vehicle treatment in 5/6 nephrectomy mice. Skeletal muscle function was also improved with D&Q treatment in uremic mice.

Conclusions: Senescence and S-ASP are important factors in development of muscle wasting during CKD progression. Limiting senescence with D&Q ameliorates muscle wasting and improves muscle function. These results provide new approaches for developing therapeutic strategies to improve muscle health in chronic kidney diseases.

Funding: Veterans Affairs Support

PO2482

Chronic Aristolochic Acid Administrations Induce Renal Senescence in Mice

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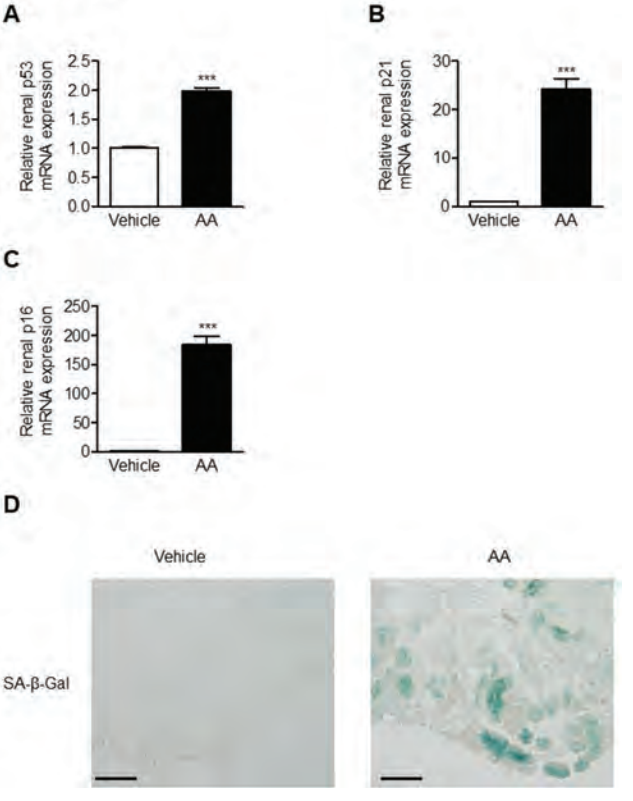
Background: The kidneys are one of the most susceptible organs to age-associated impairments. Recently, although renal aging research has been extensively performed, appropriate models of renal aging are still limited. Generally, renal aging is strongly associated with renal fibrosis, which is the final common pathway of chronic kidney disease. Aristolochic acid (AA), a renal toxic agent, causes aristolochic acid nephropathy (AAN) characterized by progressive renal fibrosis and functional decline. Here, we examined the potential of AAN as a model of renal senescence using chronic AA administrations into C57BL/6 mice.

Methods: 8-week-old male C57BL/6 mice were assigned to AA or vehicle control group after 1-week acclimatization. Mice were intraperitoneally administered with AA (3mg/kg) or vehicle (75% dimethyl sulfoxide) twice a week for 4 weeks, followed by a 4-week recovery period.

Results: Compared to controls, the AA group showed aged kidney-like phenotypes such as renal atrophy, renal functional decline, and tubulointerstitial fibrosis. In addition, AA provoked cellular senescence specifically in the kidneys, concomitant with an increase in renal p16 mRNA expression and senescence-associated β-galactosidase activity. Additionally, AA-induced mice exhibited proximal tubular mitochondrial abnormalities, followed by accumulation of reactive oxygen species.

Conclusions: Collectively, the results of the present study indicates that AAN partially mimics aged kidney and could become a useful mouse model for kidney aging research.

Figure 4



PO2483

Hypervitaminosis A Contributes to Kidney Injury Through Excessive Endoplasmic Reticulum Stress in CKD

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Background: Endoplasmic reticulum (ER) stress is activated upon the accumulation of misfolded proteins in the ER. PERK signal, one of the downstream pathways of ER stress response, mediates some transcription factors such as activating transcription

factor 4 (ATF4) and C/EBP-homologous protein (CHOP). It has been known CHOP induces renal dysfunction and leads to chronic kidney disease (CKD) via apoptosis. ATF4 promotes transcriptional activation of DNA damage-inducible protein 34 (GADD34/Ppp1r15a), which is the negative-feedback protein of PERK signaling and essential for cell survival. It is reported that the levels of plasma vitamin A and its metabolites, all-trans retinoic acid (ATRA), increase in CKD patients from the early CKD stage. One recent report shows excessive vitamin A in CKD patients induces renal dysfunction, however, the effects of ATRA on ER stress have been unclear. In this study, we investigated the role of ATRA on ER stress in the kidney of CKD.

Methods: NIH3T3 cells were treated with 100 nM ATRA and 100 nM thapsigargin (Tg), a major ER stress inducer, for 12 to 48 hours. Eight-week-old male C57BL/6J mice were fed a control diet (control) or adenine-contained diet (0.2%) and treated with either vehicle (CKD) or ATRA (10 mg/kg/3 days) for 8 weeks (CKD + ATRA). Gene and protein expressions were evaluated by real-time qPCR and western blotting.

Results: Although ATRA did not change the mRNA and protein expressions of ATF4 and CHOP in NIH3T3 cells, ATRA additively increased ATF4 and CHOP induced by Tg. Interestingly, ATRA decreased GADD34 protein expression induced by Tg, even though ATRA increased Tg-induced expression of ATF4, the positive upstream regulator of GADD34. The evaluation of protein levels of cleaved-Caspase 3, a major apoptosis marker, and flow cytometry indicated ATRA increases Tg-induced apoptosis. ATRA did not change CKD-induced high plasma levels of phosphate and BUN. However, ATRA increased the protein expression of BiP, CHOP, and cleaved-Caspase 3, but decreased GADD34 expression in CKD mice. Furthermore, the evaluations of Masson's Trichrome staining in the kidney suggested ATRA increase CKD-induced fibrosis.

Conclusions: These results indicate hypervitaminosis A on CKD exacerbates ER stress via decreasing GADD34, which induces kidney injury.

PO2484

Time-Restricted Feeding Ameliorates Fibrosis by Restoring Disrupted Peripheral Clock in Adenine-Induced CKD Model

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Background: Circadian disruption has recently been demonstrated to be closely associated with various metabolic diseases. Time restricted feeding (TRF) is a dietary strategy that limit the time of eating to a window of 4-12hr per day and has been shown to resynchronize peripheral clock. In this study, we aimed to investigate the relationship between circadian disruption and chronic kidney disease (CKD). We also tested whether TRF confer renoprotective effect via restoration of peripheral clock.

Methods: First, to determine the effect of CKD on circadian rhythm in the kidney, oscillation of several peripheral clock genes (*Bmal1, Per1, CLOCK* and *Rev-erbα*) as well as physiologic parameters (GFR, transporter protein expression and urine output) were compared between control and adenine induced CKD mice. To determine the role of circadian disruption on CKD progression, renal function and fibrosis were compared between WT and Bmal-1 knockout mice. In addition, adenine-induced CKD mice were given either a 24-hour ad libitum diet or a TRF for 8 weeks and the effect of TRF on CKD progression as well as oscillation of peripheral clock genes were measured.

Results: Adenine induced CKD mice showed disrupted oscillation of peripheral clock genes (*Bmal1, Per1, CLOCK* and *Rev-erbα*) and this was associated with loss of rhythmic oscillations of glomerular filtration rate, tubular functions and urine output. Meanwhile, more severe fibrosis and lower GFR were observed in Bmal1 (principal driver of molecular clock) knockout mice compared to WT mice, showing a bidirectional relationship between disturbed circadian rhythm and CKD progression. TRF in adenine induced CKD mice significantly suppressed interstitial inflammation as well as cell cycle arrest and ultimately ameliorated worsening of renal function and fibrosis. These changes were accompanied by partial restoration of disturbed oscillation of peripheral clock genes, suggesting that renoprotective effect of TRF is partially mediated by restoration of peripheral clock.

Conclusions: Our data demonstrated a unique bidirectional relationship between the circadian disruption and CKD and suggest that disruption of peripheral clock might contribute to CKD progression. The renoprotective effect of TRF might be mediated via resynchronizing disrupted peripheral clock in the kidney.

PO2485

The Role of Abnormal Expression of Clock Gene DBP Mediated by Gut Microbiota Dysbiosis in Cognitive Dysfunction in ESRD and the Underlying Mechanism

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Background: The objective of this study is to explore whether gut microbiota dysbiosis is one of the main cause of cognitive dysfunction (CD) in CKD and to reveal its specific mechanism, bringing a new insight for its pathogenesis.

Methods: The fecal microbiota of normal rats was transplanted into CKD rats by intragastric gavage for 4 weeks. The gut microbiota was analyzed by 16S rRNA sequencing. The cognitive function (CF) was evaluated by Morris Water Maze. The level of microinflammatory biomarkers were detected by ELISA, and their correlation with CF was analyzed. The expression of DBP in rat macrophages was detected by qPCR. Further, the level of DBP in macrophages was verified in CKD patients, and the serum of CKD patients was used to stimulate the differentiation of THP-1 cells into macrophages. The proportion of M1 and M2 macrophages was detected by flow cytometry. The expression of DBP and cytokines in THP-1 was detected by qPCR. Finally, DBP in THP-1 cells was knocked down and overexpressed before treating with PMA, respectively, to measure the expression of cytokines.

Results: The ability to search the target quadrant decreased significantly in CKD rats, which were partially reversed by FMT. FMT improved the β-diversity of CKD microbiota, and increased the abundance of Prevotella_9, Prevotella_1 and Roseburia. Compared with sham rats, serum levels of IL-6, TNF-α and hsCRP were significantly increased in CKD rats, while they were decreased after FMT. The levels of above markers were negatively correlated with CF. DBP expression was higher in CKD rats macrophages, which was reversed by FMT. The percentage of M1 macrophages was increased in CKD patients, and DBP expression in macrophages was increased. Moreover, the serum of CKD patients induced the differentiation of THP-1 cells into M1 macrophages, during which the expression of DBP and cytokines was increased. Furthermore, DBP knockdown decrease the expression of proinflammatory cytokines, while DBP overexpression induced the expression of these cytokines significantly.

Conclusions: The microinflammation mediated by gut microbiota dysbiosis is an important cause of CD in CKD. DBP, induced by dysbiosis, positively regulates the expression of inflammatory factors in macrophages differentiation, leading to microinflammation, which may be involved in the pathogenesis of CD in CKD.

Funding: Government Support - Non-U.S.

PO2486

Circadian Cycle Exaggerates Sympathoexcitatory Responses to Activation of Chemosensitive Renal Sensory Nerves

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Background: Renal sensory nerves contribute to renovascular hypertension and renal dysfunction in chronic kidney disease. These sensory nerves are activated by chemokines (e.g., bradykinin and capsaicin) and produce reflexive changes in efferent sympathetic nerve activity (SNA) and arterial blood pressure (ABP). SNA, renal function, and ABP exhibit clear circadian patterns. Yet, it is unknown whether the circadian cycle alters renal-reflex responses to chemosensitive stimuli. We hypothesized renal sensory nerve activation would elicit larger SNA and hemodynamic responses during the dark versus the light periods.

Methods: To test this hypothesis, male and female Sprague-Dawley rats (250-400g) were anesthetized with Inactin and prepared for simultaneous nerve recordings of renal and splanchnic SNA and ABP at dark (D; 20:00-04:00; n= 12M, 10F) and light (L; 09:00-16:00; n= 8M, 8F) periods.

Results: Intrarenal capsaicin infusion (0.1μM – 30.0μM; 50μl over 15s) produced concentration-dependent increases in renal and splanchnic SNA in both the dark and light periods. Interestingly, a greater increase in renal SNA in dark versus light groups occured with 10 μM (D: 723±136 vs L: 409±79 %; p=0.03) and 30 μM (D: 826±181 vs L: 509±80 %; p=0.03) capsaicin. Intrarenal capsaicin produced greater increases in splanchnic SNA between dark versus light periods at 10 μM (D: 501±117 vs L: 204±53 %, p=0.03) and 30 μM (D: 537±101 vs L: 295±68 %; p=0.03). ABP was similarly increased during the dark (7±1 mmHg; 30 μM) and light (6±1 mmHg; 30 μM) periods. Intrarenal bradykinin infusion (0.1μM – 30.0μM; 50μl over 15s) produced concentration-dependent increases in renal and splanchnic SNA in both the dark and light periods. A greater increase in renal SNA during the dark versus light periods occured at 10 μM (D: 1773±216 vs L: 1249±112 %; p=0.01) and 30uM (D: 2605±263 vs L: 1783±163 %; p=0.001). Splanchnic SNA responses were also greater during the dark versus light periods at 0.1 μM (D: 163±65 vs L: 0±0 %; p=0.02), 1.0 μM (D: 566±114 vs L: 184±52 %; p=0.005), 10 μM (D: 1110±193 vs L: 583±87 %; p=0.006) and 30 μM (D: 2008±193 vs L: 1044±162 %; p<0.001). ABP was similarly increased between the dark (10±2 mmHg; 30 μM) and light (6±1 mmHg; 30 μM) periods.

Conclusions: Thus, the circadian cycle exaggerates sympathoexcitatory responses produced by activation of chemosensitive renal sensory nerves.

Funding: NIDDK Support, Other NIH Support - NHLBI

PO2487

D-Serine Promotes Kidney Remodeling via an mTOR-Related Pathway

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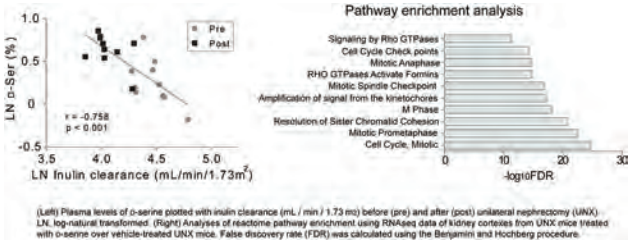
Background: D-Serine, a long-term undetected enantiomer of serine, is a biomarker that reflects kidney function and disease activity, whereas the physiological functions of D-serine have been unclear. Here, we investigated the physiological functions of D-serine in human living kidney donors and in unilateral nephrectomy (UNX) mice model.

Methods: Dynamics of D-serine was assessed by measuring D-serine in human samples of living kidney donors using two-dimensional high-performance liquid chromatography before and after UNX. Effects of D-serine on kidney from UNX mice and genetically modified cells were examined by gene expression profiling and histological studies.

Results: Human living kidney donors after UNX decreased urinary excretion and thus increased the blood level of D-serine. The plasma ratio of D-serine correlated well with glomerular filtration rate (GFR). Treatment of D-serine at physiological dose promoted the enlargement of remnant kidney in UNX mouse model. Profiling of pathway enrichment analysis using RNAseq in the kidney of UNX mice revealed dominant activation of the cell cycle-related pathways by D-serine treatment. Mechanistically, D-serine activated the cell cycle for tissue remodeling through an mTOR-related pathway, and inhibition of mTOR suppressed D-serine-induced cellular proliferation.

Conclusions: D-Serine is a physiological molecule that promotes kidney remodeling. Besides its function as a biomarker, D-serine has a physiological activity that influences kidney function.

Funding: Commercial Support - Shiseido Company, Limited, Government Support - Non-U.S.



(Left) Plasma levels of D-serine plotted with inulin clearance (mL / min / 1.73 m2) before (pre) and after (post) unilateral nephrectomy (UNX). LN, log-natural transformed. (Right) Analyses of reactome pathway enrichment using RNAseq data of kidney cortexes from UNX mice treated with D-serine over vehicle-treated UNX mice. False discovery rate (FDR) was calculated using the Benjamini and Hochberg procedure.

PO2488

First-in-Class PRS Inhibitor DWN12088 Ameliorates Folic Acid-Induced Kidney Fibrosis

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Background: Fibrosis is characterized by the upregulated extracelluar matrix (ECM), which drives organ damage and abnormal cell proliferation. According to recent studies, PRS (prolyl- tRNA synthetase) is known to play a role in synthesizing collagen during ECM components. It has been reported that PRS is greatly increased in the lung and liver fibrosis animal model, but the role of PRS in the renal fibrosis model has not been elucidated.

Methods: In this study, we investigated the protective effect of novel PRS inhibitor (Daewoong Pharmaceutical Co., Ltd, Korea), in folic acid (FA)-induced kidney fibrosis and aimed to determine whether this role depends on the inhibition of mitochondria dysfunction and the STAT3 signaling pathway. Renal fibrosis was induced by FA (250 mg/kg) intraperitoneal injection in C57BL/6 mice. DWN12088 (10, 30 mg/kg) was administered by intraperitoneal daily injection for 4 weeks. Histological changes were examined by Masson's trichrome staining. The expression of ECM markers was evaluated by immunohistochemistry, western blot analysis and real time-PCR. Mitochondria was also examined by electron microscopy.

Results: FA induced renal fibrosis and mitochondria dysfunction and upregulated PRS expression. When the FA induced decreased weight in mice, there was an effect on body weight by administering the DWN12088. We also examined the blood urea nitrogen (BUN), serum creatinine (Cr), creatinine clearance (CCr) and urine protein creatinine ratio (UPCR) levels. DWN12088 attenuated the levels of clinical data of renal injury (it decreased the BUN levels, Cr levels and UPCR levels, and increased the CCr levels). The administration of DWN12088 decreased the PRS levels and improved FA-induced renal fibrosis and mitochondria. Moreover, DWN12088 effectively inhibited the ECM markers (FN and Collagen 1A1) and the levels of SIRT1/STAT3 induced by TGF- β1 induced fibrotic condition in HK-2 cells. DWN12088 also improved mitochondria function in HK-2 cells.

Conclusions: This study provides evidence for the detrimental role of upregulated PRS in the pathogenesis of renal fibrosis. The findings highlight a DWN12088 that improves renal fibrosis and mitochondria dysfunction. As a result, blockade of PRS is a potential therapeutic intervention to prevent renal fibrosis (NRF-2020R1A2C2003438).

Funding: Government Support - Non-U.S.

PO2489

AIM2 Modulates Renal Metabolic Profile and Inflammation in Acute and Chronic Kidney Injury

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Background: The absent in melanoma 2 (AIM2) is cytosolic double-stranded DNA receptor expressed in the kidney. AIM2 activation initiates the assembly of the inflammasome, culminating in inflammatory response. Inflammasomes cause metabolic dysregulation and drive pathology in a wide variety of human diseases. So far, the function and how AIM2 affects inflammatory and renal metabolic profile in acute and chronic injury is poorly described.

Methods: The wild-type (WT) and AIM2 KO mice were submitted to cisplatin-induced acute kidney injury or unilateral ureter obstruction (UUO), a chronic kidney disease model. We evaluated renal structure and function, fibrotic molecules, fibronectin (FN) and type I collagen (COL1) and inflammation (IL-1β, IL-6). The expression of carnitine palmitoyltransferase 1 (CPT1a), involved in fatty acid oxidation (the main energy source of kidneys), and glycolytic enzyme expression, pyruvate kinase M2 (PKM2) were used as an indicative of metabolic alteration. The AIM2 activation was also investigated in proximal tubular cells (PTCs).

Results: The severe tissue injury induced in WT mice by cisplatin was markedly attenuated in AIM2 KO mice, evidenced by reduction in tubular dilatation and amelioration of renal function. Moreover, AIM2 deletion impaired the reduction of CPT1a expression. In mice model of UUO, we observed an increase of AIM2 expression, concomitantly with increase of IL-1β, IL-6, FN and COL1. Moreover, the animals presented reduction of CPT1a and increase of PKM2, suggesting a metabolic reprogramming in the kidneys. The AIM2 deficiency attenuated the renal injury, fibrosis, inflammation, and CPT1a levels did not change after kidney injury. In vitro study, the AIM2 activation caused metabolic reprogramming in PTCs, accompanied by increase of proinflammatory and profibrotic markers.

Conclusions: AIM2 activation drives acute e chronic kidney injuries. However, a better understand on how AIM2 affects PTCs metabolism and its connection with inflammation and kidney injury is needed.

Funding: Government Support - Non-U.S.

PO2490

Identification of Post-Translational Guanidinylated Proteins in the Context of Systemic Lupus Erythematosus by Using Mass-Spectrometric Methods

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Background: With continuous identification of post-translational modified isoforms of proteins, it is becoming increasingly clear that post-translational modifications limit or modify the biological functions of native proteins are majorly involved in development of various chronic disease. This is mostly due to technically advanced molecular identification and quantification methods, mainly based on mass spectrometry. Mass spectrometry has become one of the most powerful tools for the identification of proteins and lipids.

Methods: In this study, we used sophisticated high-resolution mass-spectrometric methods to analyze the soluble ligand of receptor Notch-3, namely the Y-*box* protein (YB)-1, in serum from systemic lupus erythematosus (SLE) patients. In addition, kidneys of lupus-prone (MRL.*lpr*) mice were analyzed by mass-spectrometric imaging techniques to identify the underlying pathomechanisms. Serum YB-1 was isolated by chromatographic methods, afterwards digested by trypsin and analyzed by matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS). The kidneys were fixed in paraffin, then kidney sections were deparaffinized, tryptic digested and analyzed by mass-spectrometric imaging techniques

Results: Mass-spectrometry of extracellular YB-1 in SLE patient serum revealed post-translational guanidinylation of two lysine's within the highly conserved cold shock domain (CSD) of the YB-1 protein (YB-1-2G). Patients with increased disease activity and those with active renal involvement (lupus nephritis, LN) had a higher degree of dual-guanidinylation within the CSD. Of note, at least one of these modifications was present in all analyzed LN patients, whereas single-guanidinylated YB-1 was present in only one and double modification in none of the control individuals. Mass-spectrometric imaging analyses specifically localized YB-1-2G and increases Notch-3 expression in kidney sections from MRL.*lpr* mice.

Conclusions: The data from this study clearly demonstrate the high potential of high-resolution mass spectrometric methods as well as mass spectrometric imaging techniques to identify pathomechanisms of diseases like SLE/LN.

PO2491

Deletion of Tubular Cpt1a Does Not Worsen Kidney Aging or Response to Injury

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Background: Proximal tubules (PT) preferentially use fatty acid oxidation to generate the energy necessary to support their high reasborptive capacity. Carnitine palmitoyltransferase 1 (CPT1) is required for long chain fatty acids to enter mitochondria, and CPT1a is considered the rate-limiting enzyme for PT fatty acid oxidation. CPT1a expression is decreased in kidney injury and its overexpression reduces fibrosis, so we hypothesized that Cpt1a deletion would exacerbate kidney aging and injury.

Methods: We inducibly deleted Cpt1a in adult mouse tubules using Pax8-rTTA;tetO-Cre mice and confirmed robust recombination. Mice were aged for 2 years or injured by either aristolochic acid nephropathy (AAN) or unilateral ureteral obstruction (UUO). Primary PT-enriched cell populations were generated from aged mice, and fatty acid-dependent respiration and glycolysis were measured using Seahorse bioflux analyzer.

Results: Old mice lacking tubular Cpt1a ($Cpt1a^{CKO}$) had increased intracellular fatty acid accumulation (Oil Red O staining) and inflammation (F4/80 staining), but there were no significant differences in oxidative stress, fibrosis or renal function (GFR, proteinuria) compared with aged floxed controls. Similarly, $Cpt1a^{CKO}$ mice had no differences in tubular injury or fibrosis after either AAN or UUO-induced injury. Palmitate-dependent respiration was reduced but not blocked in primary cells from $Cpt1a^{CKO}$ aged mice, and glycolytic capacity was significantly increased. RNAseq from aged $Cpt1a^{CKO}$ revealed significantly upregulated genes in several pathways including PPARα that may compensate for Cpt1a loss.

Conclusions: Surprisingly, tubular deletion of Cpt1a did not worsen aging or response to kidney injury in mice, suggesting that compensatory responses can partially correct the metabolic impairment. A better understanding of these compensatory responses may inform future treatments for kidney injury.

Funding: NIDDK Support, Veterans Affairs Support

PO2492

Multi-Omic Analysis of Mouse Renal Tubule Cell Responses Following Unilateral Nephrectomy

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Background: The kidney increases in size following resection of the contralateral kidney. Modern '-omics' methods provide an opportunity to understand this response at a cellular level.

Methods: Experiments were done in mice after unilateral nephrectomy (UNx) or sham nephrectomy. MRI was used to measure kidney volume. The earliest portion of the kidney proximal tubule (PCT) and the cortical collecting duct (CCD) were microdissected at different time points (24 hours and 72 hours). Microdissected tubules were analyzed by quantitative immunofluorescence microscopy to determine cell size and number, and by RNA-seq to identify gene expression changes. Quantitative protein mass spectrometry was used to identify proteomic changes.

Results: Increased kidney volume was already detectable at the 24 hour-time point after UNx (versus sham), and was increased further at 72 hours. Morphometry of microdissected PCT and CCD, labeled with apical and basolateral markers and DAPI, revealed a marked increase in total cell volume per unit length, but no significant change in mean cell volume in both PCT and CCD, revealing that the increase in total cell volume was due to cellular proliferation rather than hypertrophy of individual cells. Consistent with this observation, RNA-Seq at 72 hours after surgery showed significant increases in the abundance of transcripts associated with cell cycle regulation in both segments (Gene Ontology enrichment analysis) such as Cdk1 and Cdc20 among many others. To identify the earliest signaling events, RNA-seq was employed at 24 hours after UNx revealing that in PCT, UNx produced upregulation of numerous transcripts associated with free fatty acid generation and sterol metabolism including many genes that are known targets of the transcription factor PPARa such as Angptl4, Acot1 and Cyp4a14. Protein mass spectrometry of whole kidneys at 24 hours, composed chiefly of proximal tubule cells, confirmed upregulation of many PPARa-regulated proteins such as HMGCS2, CYP4A14 and ANGPTL4.

Conclusions: Increased kidney size in response to UNx was due to cellular proliferation not hypertrophy of individual cells. Many lipid-metabolism related mRNAs were highly upregulated that predict increased free fatty acid levels in proximal tubule cells. Lipid mediators, including those derived from the fatty acid arachidonic acid, may be involved the cellular proliferation.

Funding: Other NIH Support - Division of Intramural Research, National Heart, Lung, and Blood Institute(project ZIA-HL001285 and ZIA-HL006129, M.A.K.)

PO2493

Calponin 2 Determines AKI to CKD Transition Through Alternating Fatty Acid Oxidation

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Background: Calponin 2 (CNN2) is an actin filament-associated regulatory protein that plays a central role in numerous fundamental biological processes, including cell proliferation, motility, and adhesion to substrates and others cells. Emerging evidence suggests that cell mechanics can have direct, non-transcriptional influences on cell metabolism. The kidney is a highly metabolically active organ. Fatty acid oxidation is one of the major metabolic processes that occurred in the kidney under pathophysiological conditions. It remains unknown whether CNN2 plays a role in mediating kidney disease progression from the perspective of cell metabolism.

Methods: We constructed ischemic reperfusion injury (IRI) and unilateral ureter obstruction (UUO) animal models in this study. *In vitro* and *in vivo* translational experiments and proteomics were performed.

Results: Our quantitative proteomics revealed that CNN2 was induced at 1d and peaked at 10d after ischemic injury. In AKI or CKD patients' kidney biopsy specimens, CNN2 expression was markedly induced and predominantly localized in the interstitial compartment. *In vivo*, knockdown CNN2 significantly preserved kidney function after ischemic AKI at 1 day. In two classic CKD models induced by 10-d IRI or 7-d UUO, the mice with CNN2 knockdown exhibited reduced expression of fibronectin, α-SMA, and collagen type I, compared to controls. In the meantime, Oil-Red staining showed reduced lipid accumulation in CNN2 knockdown mice kidneys than in controls. Mechanistically, we revealed that knockdown CNN2 could promote fatty acid oxidation to repair injured kidneys and subsequently halt disease progression, as assessed by the increased expression of PPARα, CPT1α, and ACOX1.

Conclusions: Our findings suggested that CNN2 is a crucial determinant in mediating the transition from AKI to CKD through alternating fatty acid oxidation.

Funding: NIDDK Support

PO2494

Decreased Renal Gluconeogenesis Is a Hallmark of CKD

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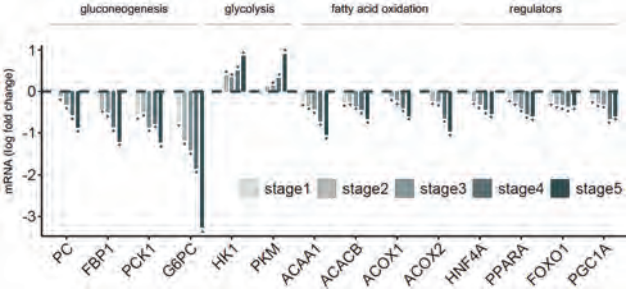
Background: Chronic kidney disease (CKD) is associated with alterations of tubular function. Renal gluconeogenesis is responsible for 40% of systemic gluconeogenesis during fasting, but how and why this process is affected by CKD and the repercussions of such regulations are unknown.

Methods: We used data from more than 200 renal biopsies performed in CKD patients and from 43 kidney allograft patients. We studied three complementary mice models of chronic kidney disease *in vivo* and *ex vivo*. We analyzed a cohort of patients having benefitted from renal catheterization and a retrospective cohort of patients hospitalized in the intensive care unit (ICU).

Results: Renal biopsies of CKD and kidney allograft patients revealed a stage-dependent decrease in the renal gluconeogenic pathway. Three different animal models of CKD confirm a proximal tubular cell-specific gluconeogenic down-regulation. This resulted in an alteration of renal glucose production and lactate clearance during an exogenous lactate load. Decreased renal glucose production and lactate clearance were confirmed by the isolated perfused kidney technique in animal models, and by renal venous catheterization in CKD patients. In CKD patients hospitalized in the ICU, systemic alterations of glucose and lactate levels were more prevalent and associated with increased mortality and worse renal prognosis at follow-up. Decreased expression of the gluconeogenesis pathway and its regulators predicted faster histological progression of renal disease in kidney allograft biopsies.

Conclusions: Renal gluconeogenic function is impaired during CKD. Altered renal gluconeogenesis leads to systemic metabolic changes with a decrease in glucose and increase in lactate level, and associates with a worse renal prognosis.

Funding: Private Foundation Support, Government Support - Non-U.S.



PO2495

Localization of Metabolites in Tubulointerstitial Disease

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Background: Tubulointerstitial (TI) disease plays a critical role in the outcome of patients with chronic kidney disease, however the basic biochemical pathways that generate the TI damage remain unclear. The application of metabolomics in chronic kidney disease (CKD) studies provide researchers the opportunity to gain new insights into metabolic profiling and pathophysiological mechanisms. Mass spectrometry imaging (MSI) is a promising approach that has the potential in reveal spatially-resolved metabolic information within kidney tissue across different disease states.

Methods: In the current study, we employed a high-resolution matrix-assisted laser desorption/ionization (MALDI)-MSI approach to characterize small molecules in human kidney biopsy core samples (n=6) were received from KPMP recruitment sites (CCF, JOS, UTSW, CLU, JHMI, YLE, UPMC, BMC, CIN-HRT and UMI-CBR). The data output was uploaded to METASPACE for molecular annotation, and SCiLS Lab, Metaboanalyst, and Cytoscape were utilized for data processing and statistical analyses.

Results: In total, 600 small metabolites (*m/z* 80-1000) were annotated by METASPACE using the human metabolome database (20% FDR) in human kidney biopsy core sections. MALDI-MSI of human kidney biopsy core sections exhibited different spatial distributions of intermediates in the tricarboxylic acid cycle, glutamate-glutamine cycle, malate-aspartate shuttle, and phospholipid metabolism, simultaneously. Specifically, D-4′-phosphopantothenate (*m/z* 298.0697) was identified as a new glomerular-enriched marker in normal glomeruli but was also present in atrophic tubule. The glycolytic metabolite glucose-6-phosphate (*m/z* 259.0224) was enriched in normal tubules and not over expressed in atrophic tubule.

Conclusions: MALDI MSI is potentially an effective tool for small molecule *in situ* analysis of human kidney tissue. MALDI-MSI technology, coupled with METASPACE, shed new light on omics data integration studies. In summary, from an individual patient with CKD, we found spatial restrictions of metabolites to normal tubule and potentially with atrophic tubule.

Funding: NIDDK Support

PO2496

Blockade of Transglutaminase 2 Ameliorates CKD Progression

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Background: Transglutaminase 2 (TG2) is a calcium dependent enzyme of the protein- glutamine γ-glutamyltransferases family that associated with fibrosis in CKD. The purpose of this study is to identify the relationship between expression of TG2 and the CKD progression in human kidney tissues, and to determine the biological activity of TG2 and TGFβ associated pathways in vitro and in vivo models.

Methods: We conducted immunohistochemistry staining of TG2 on kidney biopsy core derived from who were diagnosed chronic kidney disease. Plasma TG2 concentrations were measured by ELISA. Analyses were performed to reveal the relationship between TG2 and pathologic, functional markers of kidney disease. TG2 mRNA were evaluated at 3, 7, 14 days after from unilateral ureteral obstruction (UUO) mice model establishment with the fibrosis aggravation. To investigate the effect of TG2 inhibition on CKD progression, we used cystamine, well known TG2 inhibitor that induces the oxidation of vicinal cysteine residues of TG2 in primary cultured human tubular epithelial cells (hTECs) that injured with rTGFβ.

Results: Plasma TG2 concentrations showed positive relationships with CKD progression. Samples from progressed CKD patients showed higher plasma TG2 level. The tissue expression of TG2 were increased with CKD progression in human samples. After the establishment of the UUO model, elevation of TG2 mRNA levels were observed over time. TG2 inhibition by cystamine reduced 5.4% of apoptosis in hTECs that injured with rTGFβ (rTGFβ vs. rTGFβ+cystamine; 12.47% vs. 7.033%). Inhibiting TG2 using cystamine were associated with decreased fibronectin and increased E cadherin in rTGFβ inducted hTECs in a dose dependent manners.

Conclusions: The increased expression of TG2 were associated CKD progression in kidney. Suppressing TG2 activity could protect kidney cells from CKD deterioration through its anti-apoptotic and anti-fibrotic effect.

PO2497

Glutathione-Specific Gamma-Glutamylcyclotransferase 1 (Chac-1) Is a CKD Risk Gene

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Background: Genome-wide association studies (GWAS) have identified more than 300 loci where genetic variants associated with CKD development, however the causal variant, gene, cell type and the disease mechanism remain mostly unknown

Methods: We used expression of quantitative trait loci (eQTL) and computational integration coloc and transcriptome wide association analysis, to identify target genes for GWAS variants. We integrated human kidney single cell RNA and ATAC-seq to fine map likely causal variants. Using CRISPR technology we generated mice with genetic deletion of Chac1. Kidney injury was induced by folic acid injection, and uninephrectomy followed by streptozotocin injection. We have also analyzed primary tubule cells isolated from control (Chac1 +/+) and heterozygous (Chac1 +/-) mice.

Results: Integration of GWAS and human kidney eQTL dataset prioritized Chac1 as potential kidney disease risk gene. Lower CHAC1 level was protective. Single cell and immunofluorescence studies highlighted strong Chac1 expression in kidney tubules. Mice with a heterozygous deletion in C showed no phenotypic differences at baseline, however exhibited less fibrosis both in the folic acid and diabetic injury models compared to wild type animals. In vitro, Chac1 heterozygous cells showed improved survival following cisplatin treatment compared to wild type cells, but no difference in apoptosis or necroptosis. Chac1 +/- cells showed protection from cisplatin induced ferroptosis, including preserved cell viability, less lipid peroxidation and higher expression of ferroptosis inhibitors such as Aifm2 and Gpx4. Gluthathione levels were also higher in kidneys of Chac1 heterozygous mice when compared to controls potentially explaining their ferroptosis resistance.

Conclusions: Via the integration of kidney function GWAS and eQTL, mouse model and cell culture studies we identified Chac1 as a new kidney disease risk gene.

Funding: Other NIH Support - Pediatric Scientist Development Program

PO2498

Association of Metabolic Syndrome with Hyperfiltration in a General Non-Diabetic Population: The Renal Iohexol Clearance Survey

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Background: Metabolic syndrome (MS) affects approximately one quarter of the world, making it a global epidemic. Although MS has been associated with increased risk of rapid decline in the glomerular filtration rate (GFR), only a few studies have investigated the association of MS with abnormally elevated GFR, known as hyperfiltration. Previous studies of MS and hyperfiltration were limited by the use of estimated GFR and the results were divergent. As there are promising treatment options for hyperfiltration, establishing the relationship between MS and hyperfiltration is of clinical importance.

Methods: In the Renal Iohexol Clearence Survey (RENIS) we included 1551 subjects from the population based Tromsø survey (2007-2009). The participants were 50-62 years old without known diabetes, cardiovascular disease or kidney disease. The GFR was measured using iohexol clearance. The aim was to investigate the relationship between MS and RHF. The dichotomous variable for RHF was defined as an absolute mGFR (ml/min) above the 90th percentile after adjusting for gender, age and height.

Results: Metabolic syndrome was associated with increased absolute GFR (ml/min) and renal hyperfiltration (yes/no) independent of age, sex and height (OR 2.44 95% CI; 1.71 – 3.46, p<0.001). All risk factors except for hypertension were independently associated with RHF and increased absolute GFR. The risk of renal hyperfiltration was highest in subjects fulfilling 5 out of 5 criteria (OR 4.06, 95% CI; 1.54-10.67, p=0.005) compared to those fulfilling 0 or 1 criteria. Conversely, MS was not associated with higher estimated GFR based on creatinine or cystatin C.

Conclusions: Subjects with MS have a higher absolute GFR and increased risk of renal hyperfiltration compared to subjects without MS. RCTs are needed to explore whether treatment of hyperfiltration can prevent accelerated GFR decline and CKD in persons with MS.

PO2499

Hydrogen Sulfide Ameliorates High Fat Diet-Induced Hypertension and Kidney Injury in Mice

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Background: The role of hyperinsulinemia caused by high fat diet (HFD) in kidney injury is not known. Employing kidney proximal tubule specific insulin receptor (IR) KO mice, we have shown recently that HFD-induced kidney injury requires hyperinsulinemia-induced IR activation (Lee et al., JCI insight, 2021, 6(3): e143619). Furthermore, HFD reduced kidney hydrogen sulfide (H_2S) generation in an IR-dependent manner. We tested if H_2S administration ameliorates HFD-induced kidney injury in mice and cell models.

Methods: 5 month-old C57BL6 male mice were placed on normal fat diet (NFD) or HFD for 2 months followed by randomization to receive for 2 months, H_2S as sodium hydrosulfide (NaHS) 30 μmoles/L in drinking water or. water alone (n=5-6 in each group).

Results: HFD or NaHS did not affect blood glucose level. HFD increased body weight, and induced systolic hypertension (NFD: 118 ± 8 vs. HFD: 144 ± 10 mmHg), albuminuria (25.5 ±16 vs. 139.7 ±48 μg/mg), and kidney accumulation of matrix proteins. NaHS reversed these HFD-induced changes (systolic hypertension: 112 ± 7 mmHg, urinary ACR: 76.1 ± 29 μg/mg) without affecting body weight. In the renal cortex, HFD reduced level of H_2S, which was restored by NaHS administration. HFD stimulated IR phosphorylation and inhibited AMPK activity, which promotes synthesis of proteins including matrix proteins. NaHS did not affect IR phosphorylation but increased AMPK activity. We employed proximal tubule cells to test the effect of H_2S on insulin-induced matrix synthesis. Insulin increased fibronectin synthesis likely through stimulation of its mRNA translation by inhibiting AMPK and activating mTORC1. This effect of insulin was abolished by NaHS.

Conclusions: Taking in vivo and in vitro data together, we conclude: (1) HFD induces kidney IR activation and reduces H_2S generation in association with kidney injury. (2) H_2S acts as a signling molecule to activate AMPK, downstream of IR, and inhibits mTORC1 to ameliorate HFD-induced kidney injury. (3) H_2S could be a therapeutic agent for obesity-related kidney injury.

PO2500

Proximal Tubule Cyclophilin D Mediates Kidney Fibrogenesis in Obstructive Nephropathy

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Background: Proximal tubule (PT) is highly vulnerable to acute injury, including ischemic insult and nephrotoxins, and chronic kidney injury. It is established that PT injury is a primary cause of development of chronic kidney disease, but the underlying molecular mechanism remains to be defined.

Methods: Here, we tested whether PT cyclophilin D (CypD), a mitochondrial matrix protein, is a critical factor to cause kidney fibrosis progression. To define the role of CypD in kidney fibrosis, we used an established mouse model for kidney fibrosis, unilateral ureteral obstruction (UUO) model in global and PT-specific CypD knockout (KO).

Results: Global CypD KO blunted kidney fibrosis progression with inhibition of myofibroblast activation and fibrosis. UUO-induced tubular atrophy was suppressed in kidneys of global CypD KO, but not tubular dilation or apoptotic cell death. PT cell cycle arrest was highly increased in WT-UUO kidneys, but markedly attenuated in global CypD KO-UUO kidneys. The number of macrophages and neutrophils was less in UUO kidneys of global CypD KO than those of WT. The pro-inflammatory and -fibrotic factors were all inhibited in global CypD KO. In line with those of global CypD KO, PT-specific CypD KO also blunted kidney fibrosis progression, along with less tubular atrophy, renal parenchymal loss, cell cycle arrest in PT and inflammation, indicating a critical role for PT CypD in fibrogenesis.

Conclusions: Collectively, our data demonstrate that CypD in PT is a critical factor contributing to kidney fibrosis in UUO, providing a new paradigm for mitochondria-targeted therapeutics of fibrotic diseases.

Funding: NIDDK Support

PO2501

Reduction of Hnf4α Expression in CKD Accelerates Disease Progression

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Background: Renal mitochondrial dysfunction is a common feature of Chronic Kidney Disease (CKD) and is associated with cardiovascular disease. HNF4α is highly expressed in proximal tubules and controls the expression of genes involved in various metabolic pathways. Mutations in *Hnf4α* are associated with mitochondrial defects. We tested the hypotheses that renal *Hnf4α* decline in CKD contributes to mitochondrial dysfunction, CKD progression and onset of cardiovascular outcomes and that *Hnf4α* reduction in CKD is result of hyperphosphatemia.

Methods: We confirmed *Hnf4α* expression was reduced in the kidneys Col4a3^{KO} mice, model of progressive CKD. Next, we performed RNA sequencing (RNAseq) on kidneys collected from WT and Col4a3^{KO} mice to identify genes and molecular pathways altered by HNF4α reduction in CKD. We treated mice with a continuous administration of HNF4α antagonist (BI-6015, 3µg/g/day) for 8 weeks to study the effects of HNF4α suppression on renal and cardiac functions. To further evaluate the role of HNF4α reduction in CKD progression, we injected 30µg/g BI-6015 to Col4a3^{KO} mice for 5 days. We also generated WT and Col4a3^{KO} mice with a *Hnf4α* deletion in kidney proximal tubules (Hnf4α^{Pax8cKO} and Col4a3^{KO}/Hnf4α^{Pax8cKO}). Finally, to demonstrate that hyperphosphatemia reduces *Hnf4a* expression in the kidney, we fed WT mice a control and a high phosphate diet (HPi) for 6 weeks.

Results: RNAseq of Col4a3^{KO} mice kidneys showed impaired molecular pathways regulated by HNF4α, including increased mitochondrial dysfunction and reduced oxidative phosphorylation. Inhibition of HNF4α in WT mice led to kidney interstitial fibrosis and left ventricular hypertrophy, while in Col4a3^{KO} mice a shorter administration of HNF4α antagonist accelerated the decline in kidney function (+450% serum creatinine vs. Col4a3^{KO}-Ctr mice), demonstrating the crucial role of HNF4α in CKD progression. Similarly, *Hnf4α* deletion in proximal tubules impaired kidney function in WT mice and further worsened it in CKD animals. WT mice fed a HPi diet showed a 70% reduction in renal *Hnf4α* expression, suggesting that hyperphosphatemia contributes to renal HNF4α suppression.

Conclusions: Our results suggest that HNF4α is a master regulator of kidney mitochondrial function and might represent a novel therapeutic target to improve renal and cardiovascular outcomes in CKD.

Funding: Other NIH Support - R01DK102815 and R01DK114158

PO2502

Wasp Homologue Associated with Membranes and Microtubules Is a Kidney Disease Risk Gene

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Background: Genome-wide association studies identified hundreds of risk variants that are associated with kidney function traits. More than 90% of these variants are located in non-coding region of the genome and therefore their target genes, target cell type and encoded molecular pathways remain not known.

Methods: Here we used human kidney expression and methylation of quantitative trait (eQTL and mQTL) information and complex computational integration to identify target cell types for genetic variants. We obtained mice with genetic loss of *WHAMM*. We induced acute kidney injury by cisplatin injection and chronic disease by folic acid injection. Kidney function was analyzed by serum creatinine and blood urea nitrogen, real time PCR, western blotting, and histology analyses. We cultured primary kidney tubule epithelial cells, in addition, autophagy was assessed by *ptf-LC3B GFP-RFP* plasmid and mitophagy was assessed by using *mitoCox- VIII GFP-RFP* plasmid.

Results: Using Bayesian colocalization, summary mendelian randomization, and transcriptome-wide association studies we prioritized *WHAMM* as a kidney disease risk gene. Risk variant rs12903411 was associated with higher WHAMM expression. WHAMM is an Arp2/3 complex activator protein that is associated with membrane dynamics by utilizing microtubules. WHAMM heterozygous and knock-out mice subjected to cisplatin and folic acid injury presented with improved kidney function (BUN, creatinine) and lower expression of injury markers (Kim1, N-gal) and fibrosis markers. Primary tubular cells with *WHAMM* loss showed increased autophagy flux compared to wild type. Furthermore, WHAMM heterozygous and knock-out mice and cells showed improved mitophagy and reduced expression of inflammatory markers such as *IL-1β, IL-18* and *Nlrp3*. Mice with genetic deletion of *WHAMM* showed lower pyroptosis indicated by cleaved caspase1 and gasdermin D levels compared to WT mice in the folic acid model.

Conclusions: In summary, this study identified *WHAMM* as a new kidney disease risk gene.

Funding: NIDDK Support

PO2503

Autophagy Gene ATG7 Regulates Albumin Transcytosis in Renal Tubule Epithelial Cells

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Background: Receptor-mediated albumin transport in renal proximal tubule epithelial cells (PTECs) is important to control proteinuria. Autophagy is an evolutionarily conserved degradation pathway and its role in intracellular trafficking through interaction with the endocytic pathway has recently been highlighted. In this study, we determined whether autophagy regulates albumin transcytosis in PTECs and suppresses albumin-induced cytotoxicity.

Methods: Human tubular epithelial cell line (HK-2) was used for all experiments. The cells were exposed to 10 mg/mL BSA for 6 h or 24 h as required. For autophagy related 7 (*ATG7*) knockdown (KD), cells were transfected with *ATG7* siRNA. The intracellular trafficking of FcRn was examined by biotin-labeled recycling assay. Immunofluorescence of FcRn and Rab7 or Rab11 was observed by confocal microscopy. The transcytosis of albumin in HK-2 was evaluated using FITC-BSA-based transcytosis assay. The release of IL-8 and KIM-1 caused by excess albumin were measured by ELISA, and mitochondrial damage was measured by MitotrackerCMXRos.

Results: FcRn partially co-localized with autophagosomes. FcRn was accumulated and recycling of FcRn was attenuated in *ATG7* KD cells. Colocalizations of FcRn with RAB7-positive late endosome or RAB11-positive recycling endosomes were reduced in *ATG7* KD cells. In *ATG7* KD cells, albumin transcytosis was significantly reduced, and albumin accumulated in the cells. Exposure to excess albumin reduced autophagic flux in HK-2. Consequently, excess albumin-induced mitochondrial damage is enhanced in *Atg7* KD cells. The release of IL-8 and KIM-1 from *ATG7* KD cells was increased in response to excess albumin.

Conclusions: In PTECs exposed to excess albumin, autophagy is decreased and intracellular transport of FcRn is impaired, resulting in decreased albumin transcytosis. The resulting accumulation of albumin induces cytotoxicity in tubules. Preventing dysfunctional autophagy in PTECs might be beneficial in the clinical management of nephropathies with proteinuria.

Funding: Government Support - Non-U.S.

PO2504

Leveraging High-Content Imaging Platforms for Drug Discovery

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Background: Disruption of the structure and function of the glomerular filtration barrier leading to proteinuria is a hallmark of several podocytopathies. Efficacy in translatable *in vitro* models is a critical first step to develop new therapies. For example, free fatty acids such as palmitic acid and protamine sulfate are well characterized in-vitro models to model DN and FSGS. However, these models are low throughput, making them unsuitable for target and compound screening.

Methods: We used immortalized murine podocytes and adapted the readouts of *in vitro* assays to a high content imaging /screening (HCS) platform. Readouts in response to Palmitic Acid (PA) included: apoptosis and cell viability by annexinV and propidium iodide staining or MTT; mitochondrial membrane potential by JC-1 and Mitotracker Deep Red; and mitochondrial and cytosolic reactive oxygen species by MitoSOX and DCF. Actin cytoskeleton dynamics were assessed by quantification of actin aggregation (Phalloidin) and synaptopodin reduction in response to Protamine Sulfate (PS). Fluorescent staining followed by high content imaging and custom image analysis were performed on the BioTek-Cytation 5 cell imaging reader.

Results: Podocyte apoptosis and cell death was comparable to the readout by FACS, but capacity was increased by at least 4x. We observed a dose-dependent, incremental change in mitochondrial ROS and membrane depolarization. Mitotracker Deep Red was less sensitive than other assays for PA injury. PS treatment resulted in loss of Synaptopodin and increase of Phalloidin aggregation, and is usually assessed by confocal microscopy, which is difficult to quantify. We developed an automated imaging pipeline to quantify 9 fields per well of a 96-well plate. We showed that there was a dose- and time-dependent actin aggregation that was partially rescued by cyclosporin A, a known positive control.

Conclusions: We established a reliable and semi-automated high-content imaging platform, which will facilitate a better mechanistic understanding of podocyte injury, as well as drug discovery, including target validation and compound screening in podocytes.

Funding: Commercial Support - Goldfinch Bio

PO2505

The eNOS–NO Pathway Attenuates the Progression of Age-Related Kidney Diseases via Suppression of C/EBPβ-Associated Inflammaging

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Background: Chronic kidney disease (CKD) is a very common clinical problem in elderly patients and is associated with increased mortality. As life expectancy continues to improve worldwide, the prevalence of comorbidities and risk factors, such as hypertension and diabetes, that predispose this population to a high burden of CKD is rising. Chronic inflammation (inflammaging) is also an important cause of age-related organ damage, such as kidney disease, and we hypothesized that endothelial dysfunction accelerates the progression of age-related kidney injury.

Methods: We evaluated the anti-inflammatory effects of nitric oxide (NO) as an endothelial function in bone marrow–derived macrophages (BMDM) using in vitro experiments. BMDM derived from Wild Type (C57BL/6J; WT) were stimulated through NLRP3 inflammasome activation using LPS-ATP, and the IL-1β secretion was examined. To determine the importance of inflammasome activation in age-related kidney diseases, we used mice deficient in apoptosis-associated speck-like protein containing CARD (ASC) —which is an essential molecule for inflammasome activation—in vivo. We evaluated those mice (ASCKO), eNOS knockout (eNOSKO) mice, and eNOS-ASC double-knockout mice (eNOS-ASC-DKO).

Results: S-nitrosoglutathione (GSNO) attenuated the NLRP3 inflammasome activation that followed treatment with LPS-ATP. This indicates that NO directly inhibits NLRP3 inflammasome activation. GSNO also decreased the expression of inflammasome-related genes. To investigate the detailed mechanisms (epigenetic regulation), we performed ATAC-seq using BMDM. The binding region of the transcription factor CCAAT/enhancer-binding protein (C/EBP) β was significantly closed in the LPS+GSNO, compared with the LPS; it has recently been reported that C/EBP is associated with the NLRP3 inflammasome and is activated in aging kidneys. These mice were sacrificed at 15 months of age; the glomerular injury was found to be exacerbated, and serum Crn was elevated in the eNOSKO-15M, but not in the WT-15M. These changes were improved in the eNOS-ASC-DKO-15M.

Conclusions: The eNOS–NO pathway ameliorated the progression of renal injury by regulating the inflammaging of the aging kidney. NO directly inhibits NLRP3 inflammasome activation via the suppression of C/EBP β activation.

PO2506

Symmetric Dimethylarginine Inhibits Renal Fibrosis in Obstructive Kidneys

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Background: Symmetric dimethylarginine (SDMA) is regarded as an independent cardiovascular risk factor in patients with chronic kidney diseases. Renal interstitial fibrosis is a common pathway of all kinds of chronic kidney diseases progressing to the end stage of renal diseases. In this study we investigated the role of SDMA in renal fibrosis and its underlining mechanisms.

Methods: Normal saline (NS) and SDMA (2.50 μmol/kg) were administered into the kidney through the left ureter in a mouse model of unilateral ureteral obstruction (UUO). UUO kidneys were harvested at day 7. Western blotting and Masson's trichrome staining were performed to evaluate renal fibrosis. Moreover, human kidney 2 (HK2) cells were treated with various concentrations of SDMA (0.01 μM to 10 μM) in the presence of 2.5 ng/ml TGF-β. Protein samples were collected from cells to measure the expression of fibrotic markers.

Results: We observed that intrarenal administration of SDMA attenuated renal fibrosis as shown by Masson staining and Western blotting analysis of the expression of fibronectin, collagen-I and α smooth muscle actin (αSMA). In parallel, SDMA dose-dependently reduced the expression of pro-fibrotic proteins in TGF-β stimulated HK2 cells. Phosphorylation of Smad3 protein was analyzed in vivo and in vitro, which showed that SDMA inhibited phosphorylation of Smad3 in UUO kidneys and TGF-β stimulated HK2 cells.

Conclusions: Thus, our data suggest that renal SDMA exerts direct anti-fibrotic effects in fibrotic kidneys probably through inhibition of Smad3 signaling pathway.

PO2507

Targeting ARG1+ Macrophages Slows the Progression of AKI to CKD

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Background: Recently, $ARG1^+$ myeloid cells were defined as a new subgroup that express a large number of pro-inflammatory and pro-fibrotic genes. However, its function and clinical application in kidney disease has not yet been identified.

Methods: We clarified the source of $ARG1^+$ macrophages via the bone marrow transplantation and the parabiosis, and constructed macrophage-specific ARG1 knockout mice ($ARG1^{fl/fl}$; $CX3CR1^{creERT2}$) and $CX3CR1^{CreERT2}$-DTR mice. Kidney samples were analyzed through 10X single-cell sequencing technology. The arginase inhibitor nor-NOHA and RNAi lentiviral vector of ARG1 were applied to ischemia-induced kidney injury.

Results: Most of the intra-renal $ARG1^+$ macrophages were from bone marrow. Knocking down ARG1 in macrophages alleviated ischemia-induced AKI and the subsequent chronic fibrosis, and reduced the infiltration of macrophages in the kidney, while depletion of $CX3CR1^+$ cells aggravated ischemia-induced renal injury. GSEA analysis found that the function of $ARG1^+$ macrophages significantly enriched in the regulation of the release of inflammatory factors, activation of immune inflammatory response, and secretion of extracellular matrix. More biological macrophage ligand–mesenchymal receptor pairs expressed in $ARG1^+$ macrophages between mesenchymal cells, compared to $ARG1^-$ macrophages. Inhibiting ARG1 activity alleviated the proliferation of $ARG1^+$ macrophages and reduced ischemia-induced renal fibrosis. The application of RNAi lentiviral vector of ARG1 via the tail vein injection alleviated the renal fibrosis, reduced ARG1 expression and macrophage infiltration.

Conclusions: $ARG1^+$ macrophages accelerated the development of AKI to CKD by promoting inflammation response, activating fibroblasts and secreting extracellular matrix proteins. Inhibiting the activity or expression of ARG1 in macrophages alleviate IR-induced renal fibrosis.

PO2508

UBE-1099, a Novel Non-Covalent Keap1-Nrf2 Inhibitor, Protects Against Renal Ischemia-Reperfusion Injury via Nrf2 Activation

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Background: Patients with chronic kidney disease (CKD) showed a decline in renal function, as represented by glomerular filtration rate (GFR), as the disease progresses. A covalent Kelch-like ECH-associated protein 1 (Keap1) - Nuclear factor erythroid 2-related factor (Nrf2) inhibitor, bardoxolone methyl, has been reported to increase the estimated GFR in patients with advanced CKD. However, it is unclear how the Nrf2 activator improved GFR. Previous studies have shown that bardoxolone imidazole suppresses tubular damage in a mouse model of unilateral ischemic reperfusion without contralateral nephrectomy (U-IR). In this study, we evaluated in detail the effect of a novel non-covalent Keap1-Nrf2 inhibitor UBE-1099 on U-IR model.

Methods: A fluorescence polarization-based (FP) assay and NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme activity-inducting assay on murine Hepa1c1c7 hepatoma cell were used to investigate a non-covalent Keap1-Nrf2 inhibitor. U-IR model was established using 10 week old male C57BL/6 mice. These mice were orally administered either the inhibitor (30 mg/kg, 10 mL/kg, once a day) or vehicle for 14 days. Renal damage was then evaluated by histopathological analysis and measurement of GFR using a percutaneous GFR measurement system (MediBeacon, St. Louis, Missouri). Protein and mRNA expression in the whole kidney were assessed by Western blot analysis and real-time PCR, respectively.

Results: UBE-1099 directly inhibited Keap1-Nrf2 interaction as assessed by the FP assay, and induced NQO1 enzyme activity at Hepa1c1c7. UBE-1099 showed *Nqo1* mRNA induction activity as well as bardoxolone imidazole in the kidney of a normal mice by single oral administration. Oral administration of UBE-1099 to U-IR model mice increased NQO1 protein and mRNA expression in the kidney and improved the atrophic pathology, including renal tubular damage. More surprisingly, UBE-1099 also showed an increasing trend in GFR in that model.

Conclusions: A novel non-covalent Keap1-Nrf2 inhibitor UBE-1099 improved the atrophic pathology and reduced tubular damage resulting from Nrf2 activation in U-IR model mice. UBE-1099 has been suggested to be a promising drug for renal diseases associated with oxidative stress.

PO2509

Peroxiredoxin 5 Regulates Cyst Growth and Ciliogenesis via Modulating Aurora A and Plk1 Stability and Wnt Signaling Activation

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Background: Peroxiredoxin 5 (Prdx5) is an antioxidant enzyme that catalyzes the reduction of H_2O_2 and alkyl hydroperoxide and plays a protective role in neurological and cardiovascular disorders. However, the role and mechanism of Prdx5 in autosomal dominant polycystic kidney disease (ADPKD) is unknown.

Methods: To investigate the role and mechanism of Prdx5 on cyst growth and cilia biogenesis in ADPKD, we knocked down Prdx5 in mIMCD3 and RPE cells with siRNA and shRNA, and performed Western blot, qRT-PCR and immunostaining analysis in renal epithelial cells and tissues. A 3-dimensional cell culture system was used to evaluate the effect of Prdx5 knockdown on cyst growth.

Results: We found that Prdx5 was downregulated in cystic renal epithelial cells and tissues. Knockdown of Prdx5 resulted in: 1) abnormal centrosome amplification and multipolar spindle formation in mIMCD3 cells; 2) the upregulation of Polo-like kinase 1 (Plk1) and Aurora kinase A (AurA), essential in cell division and checkpoint regulation of mitosis; 3) the formation of cysts in a three-dimensional matrigel culture system using IMCD3 cells, which correlated with the phosphorylation and activation of PKD associated proliferation signaling, including ERK and mTOR; and 4) impaired primary cilia formation in mIMCD3 and RPE cells, which could be rescued by inhibition of Plk1 activity. In addition, we show that Prdx5 plays a crucial role in the regulation of Wnt signaling pathway activity in renal epithelial cells. Stimulation of Wnt3a ligand had no effect on ciliogenesis in Prdx5 knockdown cells. In contrast, stimulation of Wnt5a exacerbated ciliogenesis defect in Prdx5 knockdown cells. Consistent with Wnt5a activity on regulating primary cilia biogenesis, knockdown of Prdx5 decreased the recruitment of centriolar satellites PCM1 and CEP290, to the centrosome/basal body.

Conclusions: This is the first study to show that Prdx5 regulates cyst formation and cilia biogenesis via affecting the stability of Plk1 and AurA, and the activation of PKD associated signaling pathways. Prdx5 could also control noncanonical Wnt5a-dependent regulation of ciliogenesis, a cascade of events that regulate the recruitment of centriolar satellites necessary for, primary cilia biogenesis.

Funding: Other NIH Support - R01 DK084097 and NIH P30 DK106912

PO2510

Comparison of the Renal Effects of Heme-Dependent and Independent Soluble Guanylate Cyclase Targeting Drugs in 5/6 Nephrectomized Rats on High-Salt Diet

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Background: Soluble guanylate cyclase (sGC) targeting drugs were reported to have beneficial renal effects in chronic kidney disease (CKD). The sGC stimulators bind to reduced, heme-containing sGC, while sGC activators bind to oxidized, heme-free sGC and their actions are heme-independent. Regarding renal outcomes, the potential differences between these two classes of drugs are unknown so far. This study aimed to provide a head-to-head comparison of the renal effects of BAY 41-8543 (sGC stimulator) and BAY 60-2770 (sGC activator) in 5/6 nephrectomized rats on high salt diet as a model of CKD.

Methods: Rats were allocated to the following groups: Sham + normal diet + placebo (PBO); 5/6Nx + 2 % high salt diet (HSD) + PBO; 5/6Nx + HSD + Telmisartan (5mg/kg/day); 5/6Nx + HSD + BAY 60-2770 (1mg/kg/day); 5/6Nx + HSD + BAY 41-8543 (1mg/kg/day). The treatment period was 8 weeks.

Results: Blood pressure was significantly decreased by BAY 60-2770 and BAY 41-8543 versus placebo (-32.52/-27.20 mmHg, $p<0.001$; -23.83/-29.90 mmHg, $p<0.001$, respectively), which was also comparable to the effects of telmisartan (-24.24/-31.90 mmHg, $p<0.001$). Plasma creatinine was not altered by any of the 3 drugs, however, renal fibrosis was significantly decreased by Bay 60-2770 (44.76%, $p<0.05$) and telmisartan (43.96%, $p<0.05$) versus placebo. On the other hand, BAY 41-8543 did not ameliorate renal fibrosis. RNA-sequencing in renal tissues revealed that 144 genes were differentially regulated among the groups. Interestingly, 23 genes including collagen type VI alpha 5 (*Col6a5*), phospholipase C Eta 1 (*Plch1*) and claudin 19 (*Cldn19*) were exclusively differentially regulated by BAY 60-2770 and these genes might explain anti-fibrotic renal effects.

Conclusions: Only the sGC activator BAY60-2770 ameliorated renal fibrosis comparable to the gold-standard treatment of CKD with an ARB (telmisartan). These effects were blood pressure independent since blood pressure was similar in all treatment groups. Inactivation of the sGC by oxidative stress in our CKD model may explain the failure of the sGC stimulator in reducing kidney fibrosis. The mechanisms underlying the renal anti-fibrotic effects of BAY60-2770 might involve the differential regulation of *Col6a5*, *Plch1* and *Cldn19*.

PO2511

In-Depth Proteomic Analysis to Identify the Cellular Proteins and Secretome of Human Tubular Epithelial Cells with Fibrotic Injury

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Background: Fibrosis is the major pathophysiology in the development of chronic kidney disease. While there are several proteomic studies to reveal the mechanism of renal fibrosis, the in-depth analysis which elucidate the repertoire of proteins expressed on cell or released into extracellular space are lacking.

Methods: To induce the fibrosis on kidney cells in stages, two different dose (1ng/ml and 2ng/ml) of TGFbeta were treated on primary cultured human renal proximal tubular epithelial cells (TECs). For global proteome and secretome profiling, liquid chromatography-tandem mass spectrometry based quantitative proteomic analysis were performed on isolated TECs and their media, respectively.

Results: When comparing the cellular proteins expressed in control and in cells with fibrotic damage, we identified 691 and 1344 differentially expressed proteins (DEP) in low and high dose treated cells, respectively. And the DEPs in secretomes from low and high dose treated cells were 168 and 283, respectively. Then we identified overlapping 74 DEPs which showed significant difference in both cell and secretome analysis. Eleven proteins including NAMPT and KRT18 were decreased in same manner in both cell and secretome analysis, suggesting overall decrease in expression of these proteins with fibrosis. Seventeen proteins including STRAP and EIF3B were significantly decreased in cells while increased in secretome, representing the possible extracellular release of proteins with the response to fibrosis injury. There were 25 proteins including SERPINE1 and CTGF significantly elevated in both cell and secretome identified. And the other proteins which increased in cells and decreased in secretome were identified as 15 including PIEZO1 and ABCD4, which are presumably translocated into the cells with damage.

Conclusions: We identified different protein expression changes in cells and secretomes following fibrotic injury. Further studies are needed to validate the pathophysiological role of these proteins on kidney tubulointerstitial fibrosis.

PO2512

Hyaluronan Synthase-2 Antisense (HAS2-AS1) Is a Novel Long Non-Coding RNA That Regulates Pro-Fibrotic Cell Responses in the Kidney

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Background: Renal interstitial fibrosis drives CKD and increased synthesis of hyaluronan (HA) in the tubulointerstitium correlates with fibrosis and renal outcomes. Our work shows that of the three HA synthase enzymes, HAS2 expression is causally linked with fibrosis *in vivo*, a pro-fibrotic cell phenotype *in vitro*, and is regulated by a long non-coding RNA, *HAS2-AS1*. Here we investigated the mechanisms that regulate *HAS2-AS1* expression and function and influence HA-dependent regulation of pro-fibrotic cell phenotype.

Methods: Primary human fibroblasts were used to test effects of siRNA-mediated *HAS2-AS1* knockdown on TGFβ1-driven myofibroblast differentiation and HA levels by ELISA, RT-qPCR and immunofluorescence. ChIP-Seq determined binding of HYAL2 to *HAS2-AS1* and *HAS2* promoters. Alterations in *HAS2-AS1* expression were assessed from acute to chronic kidney injury and in fibrosis prevention using kidneys from a rat-model of bilateral ischaemia-reperfusion-injury (IRI) or from rats that underwent ischaemic-preconditioning prior to IRI (prevention model).

Results: In fibroblasts, TGFβ1 increased *HAS2-AS1* expression concomitantly with *HAS2*. *HAS2-AS1* knockdown resulted in significant attenuation of *HAS2* expression demonstrating that *HAS2-AS1* is a positive regulator of HAS2. *HAS2-AS1* knockdown led to a decrease in soluble and cell-surface HA, attenuated TGFβ1-driven expression of pro-fibrotic markers, and modified expression of the principal HA receptor, CD44 and its variant isoforms suggesting a link between *HAS2-AS1* and CD44 alternative splicing relevant to progression of renal disease. In turn, we showed that HYAL2 (a novel regulator of DNA/RNA processing) regulates *HAS2-AS1* expression. Anti-HYAL2 ChIP-Seq analysis identified enrichment of *HAS2-AS1*, but not *HAS2* promoter sequence, and HYAL2 knockdown resulted in attenuation of TGFβ1-driven *HAS2-AS1* and decrease in myofibroblast marker expression. Kidneys with progressive fibrosis had significantly increased *HAS2-AS1* expression versus kidneys that were protected from fibrosis through IPC, suggesting an *in vivo* role for *HAS2-AS1* in modulation of pro-fibrotic renal responses.

Conclusions: *HAS2-AS1* is a novel lncRNA causally-linked with pro-fibrotic responses both *in vitro* and *in vivo* and a new potential therapeutic target for intervention in fibrosis.

PO2513

Renoprotective Effects of Soluble Guanylate Cyclase (sGC) Activation vs. ACE Inhibition in a CKD Model with Volume/Salt-Dependent Hypertension

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Background: BP control using renin-angiotensin system (RAS) blockade is the current standard of care for CKD. However, outcomes remain suboptimal in part because adequate BP reductions are difficult to achieve in the volume expanded CKD states with RAS blockade even with additional antihypertensives. Given that endothelial dysfunction and/or NO loss accelerate the progression of both diabetic and non-diabetic CKD, sGC activators represent potential novel therapeutic interventions in CKD.

Methods: Two weeks after 3/4 nephrectomy and instrumentation for chronic BP radiotelemetry, male Sprague-Dawley rats were switched to a 4% NaCl diet after proteinuria measurements. After 2 weeks on the 4% NaCl diet and repeat proteinuria measurements, the rats started receiving vehicle only (5 ml/kg), the ACE inhibitor, enalapril (50 mg/kg), the sGC activator (BR-11257) (10 mg/kg), or the combination of BR11257 + enalapril by daily gavage. After 6 weeks of therapy and final proteinuria measurements, the rats were sacrificed for a blinded histologic assessment of % glomerulosclerosis (GS).

Results: In this CKD model with volume (salt) dependent hypertension (HTN), BR-11257 alone or in combination with enalapril but not enalapril alone, significantly lowered BP, ameliorated proteinuria and reduced the development of GS (Table). Linear regression analysis showed a strong correlation between individual systolic BP (SBP) and % GS ($r=0.69$, $n=63$, $p < 0.0001$), without a significant difference in the slope of the relationship (0.3 ± 0.04) between treatment groups.

Conclusions: These data strongly support the therapeutic potential of sGC activators alone or in combination with RAS blockade in hypertensive and proteinuric CKD states.

Funding: Commercial Support - Bayer AG

Group	Before Treatment (2 weeks) 4% NaCl diet		On Treatment (6 weeks) 4% NaCl diet		OS
(n)	Average SBP (mmHg)	Proteinuria (mg/24 hours)	Average SBP (mmHg)	Final Proteinuria (mg/24 hours)	%
Vehicle (n=16)	142.2 ± 2.4	26.8 ± 5.3	170.4 ± 4.3	77.6 ± 13.5	11.8 ± 3.0
Enalapril (n=17)	143.9 ± 4.2	44.0 ± 10.6	168.2 ± 6.4	99.8 ± 19.8	15.9 ± 3.2
BR 11257 (n=15)	143.1 ± 3.5	40.0 ± 10.0	140.4*δ ± 4.6	42.6*δ ± 10.7	7.1 ± 1.8
BR 11257 + Enalapril (n=15)	149.2 ± 2.9	35.2 ± 7.5	133.1*δ ± 2.6	29.4*δ ± 7.8	3.2*δ ± 1.4

*p < 0.01 maximum vs. vehicle δ; p < 0.05 maximum vs. compound D

PO2514

Oxysterol-Binding Protein Like 7 in CKD

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Background: ATP-binding cassette transporter A1 (ABCA1)-mediated, cholesterol ester-induced podocyte injury plays a major role in the progression of glomerular disease and pharmacological inducers of ABCA1 (ABCA1i) are sufficient to partially rescue glomerular injury in proteinuric mice. Interestingly, these ABCA1i's compete specifically with oxysterol binding to oxysterol-binding protein (OSBP) like 7 (OSBPL7), a member of a group of lipid-binding proteins involved in lipid transport between intracellular membranes. OSBPs are implicated in cholesterol transfer from the endoplasmic reticulum (ER) to the Golgi, in cholesterol efflux and in the regulation of ABCA1 expression. However, if OSBPL7 is expressed in the kidney and if it is involved in the preservation of ER function has not been explored.

Methods: In this study, we utilized podocytes and tissues obtained from wildtype and Col4a3$^{-/-}$ mice, an experimental model of CKD. siOSBPL7 Podocytes and HEK293 cell lines were established using siRNA yielding these cells deficient in OSBPL7. HEK cells do not express ABCA1 making them a valuable tool to study the ABCA1 independent effects of OSBPL7. OSBPL7 levels were determined from kidney cortex and isolated podocytes from WT and Col4a3$^{-/-}$ mice by western blot, immunohistochemistry, and RT-PCR. siOSBPL7 podocytes and HEK cells were analyzed for changes in ER stress markers, reactive oxygen species (ROS), cytotoxicity, and apoptosis.

Results: OSBPL7 is expressed in podocytes isolated from wildtype and Col4a3$^{-/-}$ mice, an experimental mouse model of chronic kidney disease. Western blot analysis revealed that OSBPL7 protein levels are reduced in kidney cortex of Col4a3$^{-/-}$ mice. siOSBPL7 podocytes and HEK293 cells show increased levels of ER stress, ROS, cytotoxicity, and apoptosis. Overexpression of OSBPL7 in Col4a3$^{-/-}$ podocytes lead to a reduction in apoptosis levels further indicating a beneficial role of OSBPL7 in podocytes.

Conclusions: This study represents the first time that OSBPL7 has been implicated in CKD. OSBPL7 deficiency in podocytes leads to ER stress and ultimately apoptosis suggesting that OSBPL7 levels are beneficial to podocyte function. Future studies will address the role of OSBPL7 in podocyte lipid trafficking in chronic kidney disease that may lead to the identification of novel therapeutic targets for the treatment of this prevalent and costly disease.

Funding: NIDDK Support

PO2515

Determinants of Serum Phosphate Concentration in CKD

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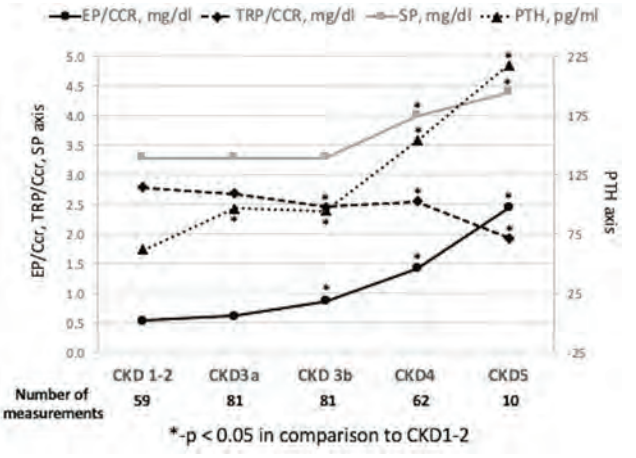
Background: The serum phosphorus concentration (SP) is the sum of rates of P excretion and reabsorption per volume of filtrate (EP/Ccr and TRP/Ccr). EP/Ccr is calculated as UPxScr/Ucr (U-urine, S-serum, P-phosphorus, cr-creatinine). In a steady state, EP/Ccr rises as P intake rises or Ccr falls. TRP/Ccr, calculated as SP – EP/Ccr, is hormonally regulated. We aimed to analyze the evolution of SP and its determinants over CKD stages G1-G5 (dialysis excluded).

Methods: This was a retrospective study involving 200 US veterans followed in the nephrology clinic of the Albany VAMC from 1/2020 to 4/2021. CKD stages were based on 4-variable MDRD eGFR. There were 293 simultaneous random measurements of SP, UP, Scr, Ucr, PTH, and eGFR. Means of these parameters were plotted against CKD stage. Correlations among variables were determined with linear regression models.

Results: The mean age (SD) of the cohort was 73 (10) years. 96% were male, and 48% had diabetes. In comparison to stages G1-2, EP/Ccr rose and TRP/Ccr fell significantly starting at stage G3b (Figure). EP/Ccr correlated with eGFR (R^2 = 0.28, p < 0.001), but TRP/Ccr and SP did not. SP correlated with EP/Ccr (R^2=0.24, p<0.001) and TRP/Ccr (R^2=0.38, p<0.001). PTH correlated with EP/Ccr (R^2= 0.32, p<0.001), and TRP/Ccr correlated with [PTH] (R^2= 0.10, p< 0.001).

Conclusions: EP/Ccr rises consistently as eGFR falls. At stage G3b, the decrement in TRP/Ccr equals the increment in EP/Ccr, and SP remains stable. In stages G4 and G5, the rise in EP/Ccr is greater than the fall in TRP/Ccr, and SP ascends accordingly. As eGFR declines, PTH rises, but its apparent effect on TRP/Ccr is blunted. As CKD progresses, maintenance of stable SP depends primarily on reduction of intestinal P absorption.

Funding: Veterans Affairs Support



PO2516

Tubular Urate Controls Intracellular Lactate in the Proximal Tubule with Implications for CKD

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Background: Alterations in cell metabolism in the proximal tubule are a recognized component in the initiation and progression of chronic kidney disease (CKD). Previously, a mouse model of hyperuricemia revealed elevated serum urate was associated with hyperglycemia and altered expression of key mitochondrial complex I and complex IV genes in the kidney, changes implicated in human CKD. Further, a recent human trial showed that blockade of proximal tubule urate transporter, URAT1, in conjunction with urate lowering therapy, slowed the progression of CKD as defined by change in albuminuria. Here, we focused on the role of renal urate handling in controlling the intracellular levels of lactate, a key metabolite and substrate of cellular respiration. Lactate is a substrate of URAT1 (*SLC22A12*) moving in *trans* with the apical entry of urate from the renal tubule lumen. We hypothesized that increased extracellular urate would promote the secretion of lactate and lower intracellular levels.

Methods: We used cultured primary normal human cortical renal epithelial cells (NHCRE) and a new hyperuricemia mouse model, produced by the inducible inactivation of the uricase gene, *Uox*, to explore the relationship between urate and CKD.

Results: In NHCRE cells we found that increasing the extracellular urate to 500μM significantly lowered intracellular lactate with high (4.5g/l) or reduced levels of glucose (1g/l) in the culture media, and that additional extracellular lactate could rescue intracellular levels. Further, the application of probenecid, a general anion transporter blocker with affinity for URAT1 abolishes the effects of extracellular urate on lactate levels, though probenecid alone has no effect. Finally, we sought to confirm the mechanistic connection between urate and lactate handling in the mammalian nephron. In the inducible *Uox* knockout hyperuricemia mouse model we found the increased plasma urate and resulting increased urinary urate excretion was associated with an increased urinary lactate excretion as well as a significant increase in the fractional excretion of lactate.

Conclusions: We conclude that increased tubular urate alters intracellular lactate levels, which potentially alters cellular respiration in the proximal tubule and affects kidney disease progression.

Funding: NIDDK Support, Commercial Support - AstraZeneca

PO2517

A Severe Case of Secondary Hyperoxaluria Successfully Treated

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Introduction: Bariatric Surgery for the treatment of obesity is categorized as either restrictive or malabsorptive. Malabsorption procedures are often used for long lasting weight loss in morbidly obese patients. The Biliopancreatic Diversion and Duodenal Switch (BPD/DS) is preferred for patients with more severe comorbidities as it provides best durability, minimal dumping syndrome and less dietary restriction. Malabsorption weight loss surgeries have been associated with AKI, CKD, nephrolithiasis and metabolic and nutritional derangements. Here we report a patient with history of BPD/DS with CKD due to hyperoxaluria.

Case Description: A 70-year-old female with history of morbid obesity since childhood, status post BPD/DS surgery in 2004 with persistent hypocalcemia, severe osteoporosis and newly recognized chronic kidney disease (CKD) was referred for nephrology consultation. Serum creatinine pre-surgery was 0.9. Her eGFR at the time of referral was 42cc/min and her urinalysis was without proteinuria. Renal Ultrasound was without nephrolithiasis. As part of her work up, a 24-hour urine collection for oxalate was obtained and revealed severe oxaluria at 168mg/day. Patient's medications included 4 grams a day of Calcium Citrate along with multiple other supplements. Patient admitted to non-compliance with her calcium supplements. After two months of strict compliance

with low oxalate diet and calcium supplements a 24-hour urine collection showed improvement of oxaluria to 62 mg/day. Her renal function remains stable.

Discussion: Patients who undergo malabsorptive weight loss surgery are at risk for AKI, CKD and nephrolithiasis from hyperoxaluria. Kidney damage can continue years after the surgical procedure. Treatment involves low oxalate diet and aggressive oxalate binding with use of calcium supplements. Bariatric surgery reversal is the definitive treatment if conservative management fails. Bariatric patients should be referred promptly to a nephrologist if change in renal function is noted.

PO2518

Increasing Acid Retention with Progressive GFR Decline Is Associated with Decreasing Urine Ammonium Excretion

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Background: Our laboratory showed that acid (H^+) retention without metabolic acidosis increased as eGFR declined while plasma total CO_2 ($PTCO_2$) remained within normal ranges (AJP 314: F985, 2018) but the mechanisms for this potential accelerator of GFR decline were not explored. We now examine if changes in urine net acid excretion (UNAE) or its components associated with changes in H^+ retention in longitudinally followed patients with CKD 2 (eGFR 60-89 ml/min/1.73 m²) without metabolic acidosis.

Methods: One hundred twenty macroalbuminuric, non-diabetic participants with CKD 2 (eGFR=73.4±6.1 ml/min/1.73 m²), 40 treated with 0.5 mEq/kg bw $NaHCO_3$, 40 with 0.5 mEq/kg bw NaCl, and 40 with usual care (UC) were evaluated annually for 5 years. We assessed H^+ retention by comparing observed to expected increase in plasma [HCO_3] in response to retained HCO_3 (dose-urine excretion) 2 hours after an oral $NaHCO_3$ bolus (0.5 mEq/Kg bw), assuming 50% body weight HCO_3 space of distribution. Specifically, H^+ retention = [(retained HCO_3/0.5 x body weight) – observed increase in plasma [HCO_3]] x (0.5 x body weight). We measured 8-hour urine NAE as the sum of ammonium (8h UNH_4^+V), titratable acidity (8h UTAV) and bicarbonate ($UHCO_3V$).

Results: Although 5-year vs. baseline H^+ retention was higher in UC (19.2±10.2 vs. 17.4±9.7 mmol, $p<0.05$) and NaCl (23.2±13.8 vs. 19.2±16.4 mmol, $p<0.05$) but was lower in $NaHCO_3$ (16.0±12.8 vs. 18.1±14.6 mmol, $p<0.05$), 5-year vs. baseline 8h UNAE was not different for any group and was not different among groups at baseline or at 5 years. Nevertheless, longitudinal change in 8h UNH_4^+V was inversely associated with change in H^+ retention for UC ($p<0.01$, $R^2=0.82$), NaCl ($p<0.01$, $R^2=0.71$), and $NaHCO_3$ ($p<0.01$, $R^2=0.20$). Combining all three groups, the change in 8h UNH_4^+V was also inversely associated with the change in H^+ retention ($p<0.01$, $R^2=0.48$) but the longitudinal change in 8h UTAV was directly associated with change in H^+ retention ($p<0.01$, $R^2=0.19$).

Conclusions: These longitudinal data support that less ability to maintain UNH_4^+V as eGFR declines contributes to worsening H^+ retention, despite maintenance of overall UNAE. Further studies will help determine reasons for individual variability in UNH_4^+V with progressive eGFR decline and the apparent greater importance of UNH_4^+V than greater UTAV in avoiding increasing H^+ retention.

Funding: Private Foundation Support

PO2519

Kidney Function and Renin-Angiotensin-Aldosterone System in Hypouricemia

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Background: Uric acid (UA), the end-product of human purine catabolism, is produced using xanthine dehydrogenase (XDH) and xanthine oxidase enzymes. Both enzymes are encoded by the *XDH* gene. Disruption of UA homeostasis has been implicated in chronic kidney disease for many years. However, the mechanisms behind the correlation remain unclear. Increased level of UA (hyperuricemia) has been shown to activate the intrarenal Renin-Angiotensin-Aldosterone system (RAAS) in many studies. RAAS in the decreased levels of UA (hypouricemia) has not been studied adequately.

Methods: We have created a new rat model with genetic ablation of the *Xdh* gene in the Dahl salt-sensitive rat background ($SS^{Xdh-/-}$) to study hypouricemia. RAAS components were quantified using liquid chromatography-tandem mass spectrometry. Rats were kept on a standard diet, and their plasma, urine, and kidneys were collected when they were 6 weeks old. Mean arterial blood pressure (MAP) was measured by using radio telemetry.

Results: The rat model is hypouricemic (UA in plasma 0.25± 0.03 mg/dl & not detectable for $SS^{Xdh+/+}$ & $SS^{Xdh-/-}$ respectively). Histology of $SS^{Xdh-/-}$ kidneys shows severe damage. The $SS^{Xdh-/-}$ rats show renal function decline with different parameters. They demonstrate significantly higher diuresis (2.7± 0.9 & 14.4± 5.1 ml; N=9 & 8 for $SS^{Xdh+/+}$ & $SS^{Xdh-/-}$) , lower creatinine clearance (0.51± 0.19 & 0.12± 0.04 ml/min; N=7 & for both $SS^{Xdh+/+}$ & $SS^{Xdh-/-}$) and Na^+ retention (136± 1.8 & 150± 3.7 mmol/l; N=10 & 9 for $SS^{Xdh+/+}$ & $SS^{Xdh-/-}$). The $SS^{Xdh-/-}$ rats have significantly lower levels of Angiotensin I/II and Renin and an increased level of Aldosterone compared to $SS^{Xdh+/+}$ rats (**Table 1**). The 10-week-old $SS^{Xdh-/-}$ compared to $SS^{Xdh+/+}$ rats did not have a difference in MAP on the standard diet. When they were challenged with a 4% NaCl diet, they failed to survive.

Conclusions: These results show that the Xdh enzyme is crucial for kidney function, and lack of the enzyme can lead to electrolyte imbalance and changes in RAAS.

Funding: Other NIH Support - NHLBI R35 HL135749

Table 1: RAAS in plasma

RAAS component	$SSXdh+/+$ (pmol/l) (N=5)	$SSXdh-/-$ (pmol/l) (N=4)
Angiotensin I (1-10)	650 ± 291	178 ± 80*
Angiotensin II (1-8)	583 ± 261	171 ± 77**
Renin (indirect measurement using Ang I + Ang II)	1233 ± 551	349 ± 156*
Aldosterone	870 ± 389	4106 ± 1836*

PO2520

Angiotensin II Type 2 Receptor Agonist C21 Acutely Prevents the Loss of Megalin in the Kidney Cortex and the Onset of Proteinuria in Obese Zucker Rats Fed with High-Sodium Diet

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Background: The appearance of protein in the urine (i.e. proteinuria) is a function of the glomerular filtration rate of protein and the reabsorption of protein from the post-glomerular filtrate by the endocytic receptors, megalin and cubilin, localized in the renal proximal tubules. We have shown that treatment with the angiotensin-II type 2 receptor (AT_2R) agonist C21 for 2 weeks reduces proteinuria in obese Zucker rats (OZR) fed HSD. The consumption of sodium-rich diet (HSD) can acutely precipitate proteinuria which is a risk factor and indicator of kidney injury. Therefore, the objective of this study was to identify the acute and chronic mechanism that may have been involved in proteinuria upon consumption of HSD and to identify the anti-proteinuric mechanism upon AT_2R activation in obesity.

Methods: Male OZR were treated acutely (2 days) or chronically (14 days) without or with AT_2R agonist C21 (1mg/kg/day) while fed with normal salt diet NSD (0.4%) or HSD (4%).

Results: The effects of HSD feeding on the expression of endocytic receptor megalin was biphasic. The HSD feeding for 2 days decreased, but for 14 days, increased megalin expression ($p<0.05$ vs. OZR). However, at 2- and 14-days, HSD feeding caused significant proteinuria ($p<0.05$ vs. OZR). The expression of cubilin remain unaffected. The AT_2R agonist treatment significantly prevented the HSD-associated changes in the expression of megalin at 2-days and 14-days, and prevented the onset of proteinuria. The expression of glomerular proteins, nephrin and podocin, which are part of the renal filtration apparatus, in the kidney cortex remains unaffected at 2-days, which suggest that glomerular filtration of protein due to the loss of these glomerular proteins, per se, is not affected by HSD intake and that altered tubular reabsorption is involved in the initiation of proteinuric injury.

Conclusions: Collectively, these data suggest that AT_2R activation protects against HSD induced proteinuria in obese rats by preventing the early loss of endocytic receptor megalin.

Funding: NIDDK Support

PO2521

Revealing the Antifibrotic Mechanism of Finerenone in the DOCA-Salt Nephropathy Rat Model Using Single Nuclei and Bulk Transcriptomics

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Background: Finerenone is a nonsteroidal mineralocorticoid receptor antagonist (MRA) which has been proposed to possess pronounced antifibrotic efficacy with a reduced risk to develop hyperkalemia in comparison to steroidal MRAs. However, the exact mechanism of this investigational medication has not been revealed. Single nuclei RNA-sequencing by determining the transcriptional signature at single cell level is an emerging method for elucidating the molecular mechanism of drug action.

Methods: Uninephrectomized, Sprague-Dawley rats were treated with DOCA and salt with an equivalent antihypertensive dose of finerenone (10mg/kg/d), spironolactone (50mg/kg/d), or vehicle. Kidney interstitial fibrosis was considered as outcome. Single nuclei RNA-seq using 10X Genomics Chromium platform in 11 and bulk RNA-seq in 14 specimens were generated.

Results: Interstitial fibrosis was significantly lower in the finerenone group than rats who received DOCA or spironolactone. Unbiased clustering was performed on 85′661 nuclei. All kidney cell types were represented in the final dataset. Comparison of cell type fractions in each group demonstrated that injured and proliferative proximal tubule (PT) cells as well as principal cells of the collecting duct and immune cells were significantly different. Side by side comparison of differential gene expression in PT cells demonstrates that finerenone normalizes genes involved in metabolic processes. Trajectory analysis on the PT cells indicates that PT cells in DOCA and spironolactone treated rats are more susceptible to the injury and transforming to injured PT cells. The results of bulk RNA-seq analysis is consistent with single nuclei transcriptomics indicating the normalization of the genes enriched in metabolic processes and immune responses by finerenone.

Conclusions: Overall, our results demonstrate that treatment with finerenone protects the kidney from interstitial fibrosis. Using single nuclei and bulk transcriptomics revealed that the protection of the PT cells via normalizing the expression of genes which are enriched in metabolic processes and immune response could be a putative further protective mechanism of finerenone in renal diseases.

PUB001

Regional Citrate and Systemic Heparin Are Adequate to Maintain Filter Half-Life for COVID-19 Patients on CRRT

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Background: The aim of our study is to compare clotting of CRRT filters in patients with COVID-19-associated AKI vs. septic shock-associated AKI.

Methods: Retrospective single center study of adult patients with COVID-19 infection compared to those with septic shock admitted to the ICU at a tertiary university hospital April-October 2020. We used independent t-test and chi square test to determine statistical significance of CRRT filter clotting and related factors in COVID-19 patients compared with septic shock patients in the ICU. Time to event data was analyzed with Kaplan-Meier curves. Analyses were performed on Microsoft Excel and MedCalc.

Results: A total of 27 ICU patients with AKI requiring CRRT were included in the study, 13 with COVID-19 infection and 14 with septic shock. The mean half-life of CRRT hemofilter was similar in COVID-19 patients compared to non-COVID-19 patients (27.4 hours vs 27.5 hours, p=0.79). The number of CRRT hemofilter changes per day were also similar in both groups (0.6 filter changes per day, p=0.84) (fig. 1). However, However, significantly more patients with COVID-19 were on systemic heparin compared to the non-COVID-19 patients (69% vs 13%, p= 0.02) (fig. 2).

Conclusions: We found that COVID-19 patients with AKI requiring CRRT had similar CRRT hemofilter half-life compared with sepsis-associated AKI patients with use of regional citrate anticoagulation and systemic heparin use. Further studies are needed to find which methods of anticoagulation is optimal in patients with COVID-19 infection with AKI requiring CRRT.

Figure 1. Details about CRRT in COVID-19 and non COVID-19 patients with AKI

Filter Changes Per Day (Median, 25-75 P)		
COVID-19 (N=13)	**Non-COVID-19 (N=14)**	**p-value**
0.6 (0.5 to .7)	0.6 (0.5 to 0.8)	**0.84**
Life of hemofilter (hours) with CRRT (Median, IQR)		
27.4 (16.8 to 25.9)	27.5 (19.5 to 32)	**0.79**

Mean filter changes per day per group; Mean life of the CRRT hemofilter in hours per group

Figure 2. Demographic and clinical data for COVID-19 and non-COVID-19 patients with AKI on CRRT

Demographic Data			
	COVID-19 N=13	**Non-COVID-19 N=14**	**p – value (95% C.I.)**
Age (years), mean (±SD)	55.1 (±12.3)	59.6 (±13.5)	0.37 (-5.6 to 14.61)
Male Sex, n (%)	10 (77)	9 (60)	0.84
BMI (kg/m²), mean (±SD)	40.7 (±15.9)	35.1 (±12.8)	0.31 (-16.7 to 5.6)
CKD, n (%)	2 (15)	5 (33)	
DM, n (%)	4 (31)	3 (20)	
HTN, n (%)	5 (39)	7 (47)	
CVD, n (%)	2 (15)	1 (7)	
Cirrhosis, n (%)	0	4 (27)	
Immunocompromised, n (%)	3 (23*)	2 (13**)	
Admission Data			
	COVID-19 N=13	**Non-COVID-19 N=14**	**p-value (95% C.I.)**
Days to CRRT from admission, mean (±SD)	5.9 (±6.1)	6.1 (±8.8)	0.94 (-6.2 to 5.7)
SOFA score, mean(±SD)	12.3 (±1.9)	14.3 (±2.8)	0.03 (-3.9 to -0.15)
Baseline serum creatinine mg/dL, mean (±SD)	1.0 (±0.3)	1.0 (±0.4)	0.61 (-0.2 to 0.3)
Admission creatinine mg/dL, mean(±SD)	1.8 (±1.4)	3.5 (±3.0)	0.07 (-0.2 to 3.5)
Admission BUN mg/dL, mean (±SD)	32(±19)	51 (±27)	0.03 (1.2 to 37.9)
Days on CRRT, mean (±SD)	8.4 (±5.9)	8.2 (±6.1)	0.94 (-4.5 to 4.9)
CRRT replacement fluid rate (mL/kg/hr), mean	28.5 (±8.8)	25 (±6.2)	0.22 (-9.4 to 2.3)
Citrate with CRRT, n (%)	8 (62)	8 (53)	0.73
Systemic heparin, n (%)	9 (69)	2 (13)	0.02
pRBC units transfused while on CRRT, mean (±SD)	1.9 (±2.3)	2.5 (±3.4)	0.59 (-1.7 to 2.9)
In-hospital HD requirement, n (%)	8 (62)	8 (53)	0.22
Mortality, n (%)	7 (53)	8 (53)	0.41

Hypertension, CVD: Cardiovascular disease, CRRT: continuous renal replacement therapy, SOFA: Sequential Organ Failure Assessment, BUN: blood urea nitrogen, TPA tissue plasminogen activator, HD: hemodialysis *asplenia, biologic therapy, kidney transplant; **both solid organ transplant other than kidney

PUB002

Elevation in Donor-Derived Cell-Free DNA Triggered by COVID-19 Vaccination

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Introduction: Donor derived cell free DNA (dd-cfDNA) is a biomarker that helps to predict acute rejection in kidney allografts. Baseline dd-cfDNA levels are <1% in 96% of kidney transplant recipients (KTRs) and a value ≥ 1% suggests allograft injury usually from acute rejection. Adjuvants used to amplify vaccine immunogenicity could elicit non-specific inflammatory responses and thus could potentially incite immune mediated allograft injury. Here we present a KTR who developed elevated dd-cfDNA within one week of SARS-Cov-2 vaccination.

Case Description: A 70-year old man who underwent pediatric en bloc deceased donor kidney transplantation 30 months earlier with peri-operative Thymoglobulin induction and tacrolimus/mycophenolic acid maintenance and excellent allograft function was found to have an elevation in surveillance dd-cfDNA (AlloSure, CareDx, Brisbane, CA) level at 3.0%. Patient had multiple negative dd-cfDNA values on all prior testing with a last level of 0.17% 3 months earlier. Serum creatinine was 0.8 mg/dl with no DSA and negative urinalysis. Serum BK virus and CMV PCR were negative. Patient did receive first dose of Pfizer/BioNTech Covid-19 vaccination (BNTb162b2) one week prior to the current dd-cfDNA measurement. Subsequent kidney allograft biopsy done due to elevated dd-cfDNA level did not show any evidence for rejection. Repeat dd-cfDNA 10 weeks later normalized to 0.15%.

Discussion: We believe that elevation in dd-cfDNA in our patient with stable renal allograft function was triggered by SARS-Cov-2 vaccination. Pfizer/BioNTech utilizes an mRNA platform in which mRNA is encapsulated in lipid nanoparticles which act as delivery devices and possess natural adjuvant activity. Even though the allograft biopsy did not show clear evidence for rejection, we feel that the adjuvant lipid nanoparticles caused immune stimulation in the host thus triggering dd-cfDNA elevation. Since more and more KTRs will be receiving SARS-Cov-2 vaccination, temporal relationship between vaccination and dd-cfDNA elevations should be entertained. Post-marketing surveillance will be essential to delineate any potential association between SARS-CoV-2 vaccine components and allograft rejection.

PUB003

Kidney Disease in the Aftermath of COVID-19 Infection

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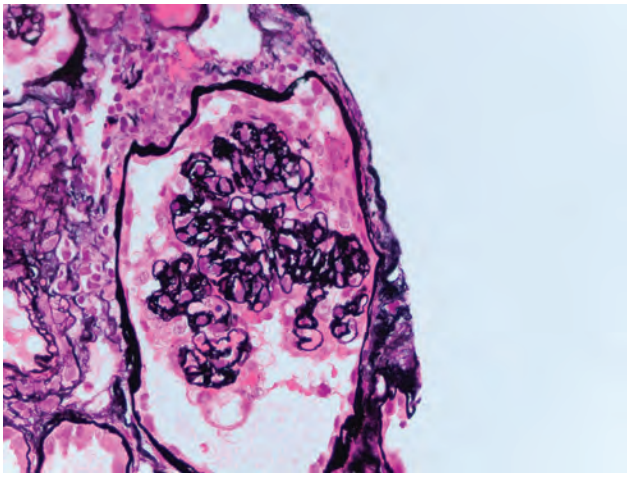
Introduction: COVID-19-associated nephropathy (COVAN) is a known, but potentially missed cause of AKI. We present a case of COVAN presenting with a severe AKI in a previously healthy patient.

Case Description: A 48-year-old African American male with no known past medical history and a recent COVID-19 infection presented with hypertension and lower extremity edema. Initial work-up showed BUN 60, Cr 4.8. Urinalysis was significant for proteinuria. Urine protein to Cr ratio was 1.4. Renal ultrasound did not show any hydronephrosis. Initial management included blood pressure control and intravenous hydration, and his Cr downtrended to 3.1. Of note, his Cr was 1.2 two weeks prior to admission. Given his acute renal failure and significant proteinuria, a renal biopsy was obtained which showed collapsing FSGS consistent with COVAN.

Discussion: Glomerular disease is a known complication of COVID-19. The most distinct presentation is the collapsing FSGS seen in this case (Image 1). This has primarily been reported in patients of African descent, specifically those with high-risk APOL1 genotypes. Patients may recover kidney function, but some may also develop CKD. One month after the hospitalization, this patient's Cr was 4.3 and we suspect he will likely have significant CKD. COVAN can be a difficult diagnosis to make. Proteinuria can often be attributed to common co-morbidities, therefore confounding its diagnosis. The timing also complicates the diagnosis, as in our patient who presented a week after his COVID-19 symptoms resolved. With COVID-19 vaccines, perhaps COVAN may become rarer, but the prevalence and incidence in the era of vaccines must be studied. The long-term repercussions of COVAN are unknown; COVAN should be considered in patients with recent COVID-19 infection presenting with proteinuria. We should make people aware of the possible renal consequences of COVID-19 and sharing this knowledge may help with vaccine hesitancy.



PUB004

Treatment Outcome of New-Onset Collapsing Focal Segmental Glomerulosclerosis in a Patient with COVID-19

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Introduction: COVID-19 has been shown to cause acute kidney injury (AKI) in as high as 46% of hospitalized patients. This case describes a patient who developed an AKI during her admission for COVID-19 pneumonia and was found to have collapsing focal segmental glomerulosclerosis (FSGS). Several cases of FSGS associated with COVID-19 have been described in the literature with varying outcomes. Unfortunately, the patient described in this case has not had significant recovery despite months of high-dose prednisone.

Case Description: A 57-year-old African-American female with a history of diabetes mellitus type 2, hypertension, and small cell lung cancer was admitted for intractable vomiting and found to be positive for COVID-19. Despite no history of kidney disease, patient developed an AKI over the first few days of hospitalization with creatinine 1.96mg/dL (which continued to rise) from baseline 0.7-0.8mg/dL. Urinalysis demonstrated new onset high urine protein/creatinine ratio greater than 12 g/g. Renal biopsy demonstrated collapse of the glomerular tufts and associated hypertrophic podocytes, consistent with collapsing FSGS. No significant immunofluorescence staining was seen. Other serologies were negative, including HIV. Following discharge, she was started on prednisone 60mg daily. Despite several months of prednisone, patient's creatinine remained elevated, mostly in the range of 2.5-3.5mg/dL, never returning to baseline. She continued to have nephrotic range proteinuria and no response to prednisone therapy was noted.

Discussion: As COVID-19 is a new and rapidly evolving disease, extrapulmonary disease is being newly identified, necessitating development of effective treatment strategies. Many of the cases that described collapsing FSGS in COVID-19 patients required initiation of dialysis. The patient in this case recovered from the respiratory symptoms of COVID-19, but continued to have impaired renal function despite several months of treatment. This case demonstrates prednisone failure for our patient, and further study is needed to determine more effective treatment regimens.

PUB005

Incidence and Prognosis of COVID-19 in People with CKD

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Background: Coronavirus-disease-2019 (COVID19) disproportionately affects people with chronic diseases such as chronic kidney disease (CKD). We assessed the incidence and outcomes of COVID19 in people with CKD.

Methods: We searched MEDLINE, EMBASE and PubMed through February 2021 for cohort and case-control studies measuring the incidence or outcomes of COVID19 in people with CKD. We extracted data on COVID19 incidence, death, respiratory failure, dyspnoea, COVID19 recovery, intensive care admission, acute dialysis, and acute kidney injury. Certainty evidence was adjudicated using GRADE.

Results: We included 348 studies (382407 participants with COVID19, 1139979 with CKD). In low-certainty evidence, the incidence of COVID19 was higher in people with dialysis-dependent CKD (105/10000-person-weeks [pw]; 95% confidence interval [CI] 91-120; 95% prediction interval [PrI] 25-235; 59 studies; 468233 participants) than pre-dialysis CKD (16/10000-pw; CI 4-33; PrI 0-92; 5 studies; 70683 participants) and kidney transplant recipients (KTRs) (23/10000-pw; CI 18-30; PrI 2-67; 29 studies; 120281 participants). In low-certainty evidence, the incidence of death in people with CKD and COVID19 may be higher than those without COVID19 (incidence rate ratio 10.26; CI 6.78-15.53; PrI 2.62-40.15; 4 studies; 18347 participants). In low/very low-certainty evidence, people with CKD may experience a high incidence of other outcomes (Table 1).

Conclusions: The incidence of COVID19 may be higher in people with dialysis-dependent CKD compared to pre-dialysis CKD or KTRs. People with CKD and COVID19 may have a higher incidence of death than those without COVID19.

Table 1. Summary of findings: the incidence of COVID19 and outcomes in people with CKD

Outcomes	Number of events	Number of individuals	Incidence (95% confidence interval) [95% prediction interval]	Number of studies	Evidence certainty
Incidence of COVID19 for people with CKD (pre-dialysis, dialysis-dependent or kidney transplant recipient)	14,972	740,452	66 per 10,000 person weeks (58-75) [10-169]	88 studies	Low
Death	19,938	70,922	32 per 1000 person weeks (30-35) [4-81]	229 studies	Low
Respiratory failure	14,635	68,840	31 per 1000 person weeks (27-35) [3-81]	101 studies	Low
Dyspnoea	2587	5767	80 per 1000 person weeks (66-95) [2-234]	75 studies	Low
COVID19 recovery	1473	3463	83 per 1000 person weeks (52-120) [0-304]	21 studies	Very low
Intensive care admission	17,590	76,532	27 per 1000 person weeks (24-30) [4-63]	109 studies	Low
Acute dialysis	1017	15,994	17 per 1000 person weeks (11-24) [0-82]	48 studies	Low
Acute kidney injury	3418	6900	73 per 1000 person weeks (60-87) [5-199]	59 studies	Low

PUB006

Safety and Efficacy of Bedside Insertion of Tunneled Hemodialysis Catheters in Critically Ill Patients with COVID-19

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Background: Critically ill patients with coronavirus disease-2019 (COVID-19) and kidney dysfunction often require tunneled hemodialysis catheter (TDC) placement for kidney replacement therapy (KRT), typically under fluoroscopic guidance to minimize catheter-related complications. This entails transportation of patients outside the intensive care unit (ICU) to a fluoroscopy suite, which may potentially expose many health care providers to COVID-19. One potential strategy to mitigate the risk of viral transmission is to insert TDCs at the bedside, using ultrasound (US) and anatomic landmarks only, without fluoroscopic guidance.

Methods: We reviewed all COVID-19 patients in the ICU who underwent right internal jugular (RIJ) TDC insertion at the bedside utilizing anatomic landmarks under US guidance between April-December 2020. Outcomes included procedural complications such as bleeding, arterial puncture, venous air embolism, arrhythmias, pneumothorax, hemothorax and catheter tip malposition. TDC insertion was considered successful if the catheter was able to achieve blood flow sufficient to perform a single hemodialysis treatment.

Results: We collected data on 25 patients with COVID-19 who had RIJ TDCs placed at the bedside, 10 of whom underwent simultaneous insertion of small-bore (5 Fr) RIJ tunneled central venous catheters (T-CVC). The median age and body mass index of the cohort were 62 years (interquartile range [IQR]:55-70) and 28.8 kg/m^2 (IQR:25.2-33.2) respectively; comorbid conditions included chronic kidney disease (n=14), diabetes mellitus (n=12) and hypertension (n=18). Continuous veno-venous hemodialysis was the KRT modality employed in all patients. A median catheter blood flow rate of 200 ml/min (IQR:200-200) was achieved in all patients without any deviation from the dialysis prescription. No catheter related complications were observed and none of the catheter tips were mal-positioned on post-insertion chest radiographs.

Conclusions: Bedside RIJ TDC placement in COVID-19 patients, using US and anatomic landmarks without fluoroscopic guidance, may potentially reduce the risk of COVID-19 transmission amongst health care workers without compromising patient safety or catheter function. Concomitant insertion of small-bore RIJ T-CVCs may also be safely accomplished and further help limit personnel exposure to COVID-19.

PUB007

Irreversible Damage from a Pandemic Outbreak: A Rarely Described Case Report

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Introduction: Renal cortical necrosis (RCN) is a rare cause of acute kidney injury (AKI) in developed countries with frequency of 1.9%-2% of all patients with AKI. Drugs especially non-steroidal anti-inflammatory drugs (NSAID's) are very rarely described to cause cortical necrosis. It happens due to a permanent occlusion of afferent arterioles and interlobular arteries in the cortical vasculature, either by prolonged vasospasm or primary vascular damage with thrombosis.

Case Description: We present the case of a 20 year-old black man who was admitted to the hospital due to abdominal pain and decreased urine output. He had been symptomatic with severe toothache due to a dental abscess. Since it happened during the pandemic outbreak of COVID-19 he was unable to contact any dentist and he was given regular oral paracetamol and ibuprofen in doses he could not quantify (ibuprofen exceeded 600 mg every 8 hours daily in a week). Initial laboratory tests revealed anemia (Hb 11 g/dL), slight increase in inflammatory parameters and acute renal failure (sCreatinine 12.7 mg/dL, sUrea 109 mg/dL) and a urine protein-to-creatinine ratio of 1.8 g/g. Renal ultrasound excluded obstruction. Viral serologies were negative, clonal gammopathies were excluded, autoimmune study and serum complement levels were normal. Blood and urinary cultures were also negative. He underwent tooth extraction and completed 10 days of amoxicillin-clavulanate and metronidazole with resolution of

infection. Despite proper fluid replacement the patient showed no clinical improvement and presented with anuria, so hemodialysis was started. Abdominal and pelvic CT scan showed no positive findings. A renal biopsy was obtained showing extensive cortical necrosis. At that moment we concluded renal cortical necrosis probably secondary to NSAIDs intoxication. Unfortunately, the patient did not recover and became dependent on renal replacement therapy.

Discussion: This case illustrates the need to be aware of the effect of NSAIDs. Despite being readily available, a subset of individual is susceptible to serious renal toxicity and caution should be exercised when these drugs are used. Our patient presented with bilateral renal cortical necrosis with irreversible renal failure secondary to prolonged use of over-the-counter NSAIDs in the setting of pandemic outbreak of COVID-19.

PUB008

Challenges in Conducting a Clinical Trial During the COVID-19 Pandemic

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Background: The COVID-19 pandemic has caused a global upheaval in daily life, economics, clinical care, and research. We report challenges faced and addressed based on our experiences conducting an NIH-funded randomized controlled clinical trial during the pandemic.

Methods: Combination of Novel Therapies for CKD Comorbid Depression (CONCORD) is an ongoing multi-center randomized trial comparing two novel 16-week treatment strategies for depression, *vs.* a placebo and attention control group, in 200 patients with stages 3b-5 non-dialysis CKD. One strategy is to deliver bupropion antidepressant drug for 8 weeks, with augmentation to combination bupropion and behavioral activation teletherapy (BAT) for an additional 8 weeks if depression did not remit. The second strategy is to deliver BAT for the first 8 weeks, with addition of bupropion for 8 more weeks for non-remitters.

Results: Since October 2020 to-date, 690 patients were screened at the University of Texas Southwestern, Dallas, and at the University of Washington, Seattle, of whom 151 (21%) met the screening cutoff for depression. Despite the ongoing pandemic, this percentage was similar to previously reported rates for CKD patients. Thirty-one (80%) of the 39 target to-date were randomized, and 22 (71%) have completed the trial. Only 2 exited before 16 weeks. The national shift away from in-person visits to telehealth slowed screening from outpatient clinics. A lower number of screening surveys were conducted due to unavailability of patients via telephone. Because CKD patients have a high burden of healthcare contact and barriers to accessing in-person care, CONCORD was designed prior to COVID-19 to use teletherapy instead of in-person visits to minimize burden. Telehealth intervention delivery has been especially beneficial in minimizing in-person contact during the pandemic. Blinded assessments of primary outcome were also conducted by computer-assisted telephone interview. Thus, the protocol allowed minimization of in-person visits, which were further decreased from every 4 to every 8 weeks only for phlebotomy and drug dispensation.

Conclusions: Despite challenges posed by COVID-19, CONCORD successfully upheld near-target recruitment, due to perseverance of staff, use of teletherapy to minimize in-person visits, and patients' willingness to participate.

PUB009

Mortality and Evolution Between Community and Hospital-Acquired COVID-AKI (CA-AKI and HA-AKI)

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Background: Differences between HA-AKI and CA-AKI are not well stablished

Methods: Retrospective cohort. We included 877 patients hospitalized with COVID at two hospitals in Mexico. Primary outcome was all-cause mortality at 28 days compared between COVID with CA-AKI and HA-AKI. Secondary outcomes included the need for KRT, and risk factors associated with the development of CA-AKI and HA-AKI.

Results: A total 33.7% developed AKI. CA-AKI occurred in 59.9% and HA-AKI occurred in 40.1%. Patients with CA-AKI had more comorbidities than those with HA-AKI. Patients' survival with CA-AKI it was 75.4%, and with HA-AKI 69.6%. Age > 60 years (OR 1.12), COVID severity (OR 1.09), mechanical ventilator (OR 1.67), and HA-AKI 3 (OR 1.16) increase mortality. The presence of CKD (OR 1.48), serum lymphocytes < 1000 μL (OR 1.03), the need for mechanical ventilator (OR 1.06), and CA-AKI stage 3 (OR 1.37) were the only variables associated with a KRT start.

Conclusions: We found that COVID complicated by CA-AKI have more comorbidities and worse biochemical parameters than HA-AKI patients, but despite these differences, their probability of dying is similar

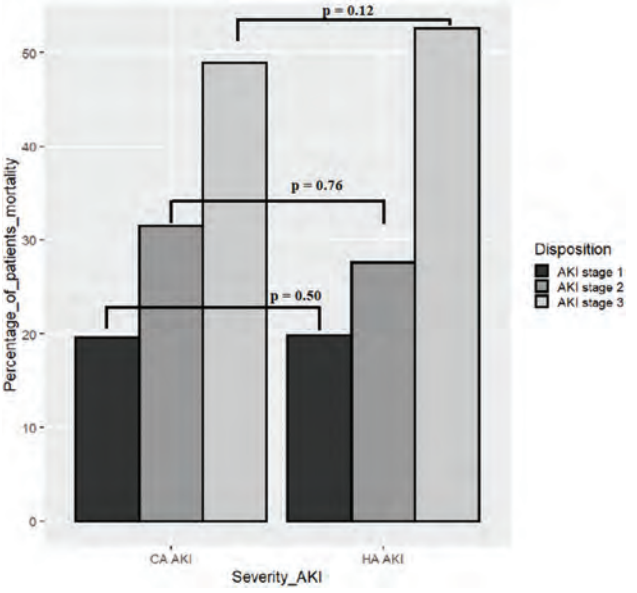

Table 7. SARS-AKI score as a tool for predicting death in SARS-CoV-2 patients

Predictors [a]	Points
Age > 60 [years]	
<=60 years	0
> 60 years	1
Severe SARS-CoV-2	1
Mechanical ventilator	2
AKI stage	
AKI 1	0
AKI 2-3	1
AKI acquisition	
Community-acquired AKI	0
Hospital-acquired AKI	1
Cut-off value	>= 3

PUB010

Predictors of Short- and Longer-Term Mortality After COVID-19 Presentation Among Dialysis Patients in the Americas

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Background: We aimed to build machine learning (ML) models to understand the predictors of short- and longer-term mortality among hemodialysis (HD) patients affected by COVID-19 in four countries in the Americas.

Methods: We used data from adult HD patients treated at regional institutions of a global provider in Latin (LATAM) & North America (NA) who had COVID-19. We used data on 96 variables from Jul-2019 through Dec-2020 to develop XGBoost models (60%:20%:20% random split for training, validation, & testing) to predict the likelihood of death in 0-14, 15-30, >30 days after COVID-19 presentation, and identify importance of predictors. Models were developed in a side-by-side manner and used same programing for datasets in LATAM (Argentina, Columbia, Ecuador) & NA (United States) countries.

Results: Among HD patients with COVID-19 in LATAM (n=12,121) and NA (n=21,624), 15.8% and 7.3% died within 0-14 days, 8.2% and 4.6% died within 15-30 days, and 4.8% and 8.6% died >30 days after presentation, respectively. Models in LATAM & NA had area under cure (AUC) in testing datasets of 0.64 & 0.70 for death within 0-14 days; top predictors at presentation were diabetes, lower interdialytic weight gain (IDWG) in LATAM, and higher age and longer vintage in NA. AUCs were similar across models. Top predictors of death 15-30 days were higher pre-HD weight and post-HD systolic blood pressure (SBP) in LATAM, and same as 0-14 days in NA. Top predictors after >30 days were diabetes and higher pre-HD SBP in LATAM, and higher age and lower dry weight in NA.

Conclusions: Profiles of mortality in HD patients after COVID-19 were distinct in LATAM & NA. Mortality more often occurred within 0-14 or 15-30 days after COVID-19 in LATAM versus NA. About 5% to 9% of COVID-19 patients died >30 days after presentation. Top two predictors of mortality differed in LATAM & NA during earlier and later periods after COVID-19, albeit when considering top 15 predictors similarities exist. Comorbidities, demographics, weight, and BP appear risk factors for death after presentation. Use of underexplored follow-up timeframes along with ML modeling techniques that account for collinearity and missingness provide novel insights related to mortality in COVID-19.

Funding: Commercial Support - Fresenius Medical Care

PUB011

SARS-CoV-2 Breakthrough Infection in a Fully Vaccinated Hemodialysis Patient

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Introduction: End-stage kidney disease (ESKD) is associated with immunosuppression manifesting as both increased infection rates & impaired vaccine immunoresponsiveness. Nonetheless, COVID-19 vaccines have proven highly effective in dialysis-dependent ESKD patients, with reported seroconversion rates as high as ~96%. Herein, we describe a case of breakthrough SARS-CoV-2 infection in a fully-vaccinated hemodialysis patient.

Case Description: A 69 year-old white male with dialysis-dependent ESKD presented for routine rural in-center hemodialysis with a new intermittent nonproductive cough following known COVID-19 exposure. He tested positive for COVID-19 via both rapid antigen testing & RT-PCR despite full mRNA-1273/Moderna SARS-CoV-2 vaccination ~2 mo prior, & was admitted for inpatient management pending availability of isolated outpatient dialysis. He was afebrile, normoxemic, & clinically stable at presentation & throughout his subsequent hospital course. Following 10 d of uneventful isolation, during which he received thrice-weekly hemodialysis but no COVID-19-specific therapies, he resumed maintenance outpatient dialysis. Of note, he was current on all recommended vaccinations for dialysis patients, but had required multiple courses of hepatitis B vaccination for a documented history of impaired serocoversion. The patient ultimately developed both anti-nucleocapsid IgM & anti-spike IgG antibodies directed against SARS-CoV-2, & viral genome sequencing revealed a novel SARS-CoV-2 variant of interest (B.1.526).

Discussion: While breakthrough COVID-19 is rare – reported in <0.001% of the fully vacciniated U.S. population as of 20 Apr 2021 – incidence rates may be higher in specific immunosuppressed subgroups such as ESKD patients. This case illustrates the potential for fully-vaccinated ESKD patients to contract COVID-19, particularly following known exposure(s) or in the setting of viral variants. It is also consistent with accumulating anecdotal clinical experience suggesting that breakthrough infections are generally milder phenotypically than primary infections in vaccine-naïve individuals. As such, high levels of suspicion may be required for identification & proper isolation. Constrained local resources in rural settings may also require different risk mitigation & management strategies for in-center hemodialysis patients with breakthrough COVID-19.

PUB012

Membranous Nephropathy in a Patient with Recent COVID-19 Infection

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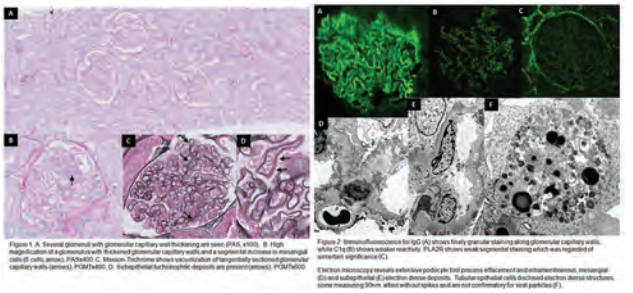
Introduction: Membranous nephropathy (MN) associated with COVID-19 infection is rare and most reported cases are anti-phospholipase A2 receptor(PLA2R) negative. We report a case of PLA2R seropositive MN with COVID-19 infection.

Case Description: A 29-year-old Asian male presented with fever, myalgia and lower limb swelling for 3 days. 4 weeks prior, he was treated symptomatically for COVID-19 infection. He was diagnosed with acute kidney injury and nephrotic syndrome. Immune markers, virology and imaging of kidneys were normal.(Table1) MN was diagnosed on renal biopsy (Figure1&2). PLA2R was negative in the glomeruli by immunofluorescence but serum PLA2R antibodies was positive at 139RU/ml. Workup for other causes of secondary MN was unrevealing. Due to increasing COVID-19 infections at that time, immunosuppression was deferred. ACE inhibitor was titrated to the highest tolerated dose. After 8 months, he remained nephrotic and Modified Ponticelli regimen was commenced with oral cyclophosphamide 2mg/kg and prednisolone 0.5mg/kg. 2 months after initiation of immunosuppression, patient has shown partial response.

Discussion: Seropositive but biopsy-negative PLA2R associated MN is uncommon, and occurs rarely in patients with possible secondary MN. PLA2R positivity on renal biopsy has been reported in viral hepatitis and some cases had circulating serum PLA2R antibodies. To our knowledge, there are no reported cases of circulating PLA2R antibodies with COVID-19 infection. Our case illustrates the diagnostic and management challenges of MN in the era of widespread COVID-19 infection. Clinical course and PLA2R antibody titres remain useful guides for consideration of immunosuppressive treatment.

Table 1; Laboratory Data

Laboratory test	Admission	3 months	6 months	8 months	10 months	Reference
Serum Biochemistry						
Sodium, mmol/L	142	142	140	142	140	136-146mmol/L
Potassium, mmol/L	3.7	4.3	4.0	4.2	4.7	3.5-5.1 mmol/L
Chloride, mmol/L	109	110	109	111	107	98-107 mmol/L
Bicarbonate, mmol/L	26.1	24.2	25.5	27.5	24.7	19-29 mmol/L
Urea, mmol/L	4.1	5.1	4.3	4.8	5.6	2.7-6.9 mmol/L
Creatinine umol/L	145	121	119	129	100	59-104umol/L
eGFR, ml/min/BSA	56	70	71	65	88	>60
Glucose, mmol/L	6.4	5.4	5.3	5.6	6.4	3.0-11.0
Total protein, g/L	45					66-85g/L
Albumin, g/L	22	31	29	23	29	40-51g/L
Urine protein/Cr ratio g/g	7.5	11.8	7.7	9.2	4.9	<0.2
Urine protein 24-hour g/day	8.71					<0.13g/day
Lipid						
Total cholesterol, mmol/L	7.66					<5.2 mmol/L
HDL, mmol/L	0.92					>1.6 mmol/L
LDL mmol/L	5.25					<2.6 mmol/L
Triglycerides, mmol/L	3.28					<1.7mmol/L
Serology						
HBs antigen	Negative					
HCV Ab screen	Negative					
HIV Ag	Negative					
Complement C3, G/L	1.58					0.9-1.8 G/L
Complement C4, G/L	0.51					0.1-0.4 G/L
Antinuclear antibody	Negative					
Anti dsDNA IU	0.83					<25IU
Anti MPO RU/ml	<2.0					<20 RU/ml
Anti PR3 RU/ml	<2.0					<20 RU/ml
Anti-phospholipase A2 receptor (ELISA), RU/mL	139.51	106.32				<14 RU/ml
Monoclonal gammopathy screen	Negative					



PUB013

IgA Nephropathy Post COVID-19 Infection

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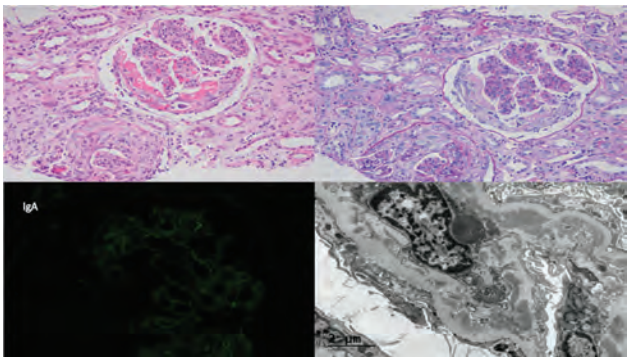
Introduction: Acute kidney injury (AKI) occurs in > 20% of hospitalized patients with SARS-CoV2 infection. Etiology of renal injury includes acute tubular injury, collapsing focal segmental glomerulosclerosis, and thrombotic microangiopathy. Rarely COVID-19 has been associated with antineutrophil cytoplasmic antibody associated vasculitis, anti-glomerular basement membrane antibody disease, and IgA nephropathy. We report a case of crescentic IgA nephropathy in a patient with recent COVID-19 infection.

Case Description: A 55-year-old man with prolonged hospitalization for COVID-19 complicated by pulmonary embolism presented with hemorrhage secondary to a spontaneous retroperitoneal bleed. On admission, he was hemodynamically stable but received large-volume blood product transfusion. Significant admission labs included serum creatinine 3.54 mg/dl (baseline 1.34mg/dl), urinalysis with large blood and protein, spot urine protein to creatinine ratio 6,697 mg/g. Renal function and hemoglobin continued to decline despite stabilization of his bleed. Hemolysis workup revealed haptoglobin <10, lactate dehydrogenase 714, occasional schistocytes on the peripheral blood smear, concerning for TMA secondary to COVID-19 infection. Renal biopsy revealed crescentic IgA nephropathy with moderate acute tubular injury. He was started on prednisone 80mg daily for crescentic IgA nephropathy. Unfortunately his kidney function continued to worsen, and renal replacement therapy was initiated. He continued to require dialysis while inpatient with no meaningful renal recovery.

Discussion: AKI is a common complication in COVID-19, however, this is not typically due to glomerular disease. Although viral infections such as COVID-19 can trigger IgA nephropathy, to the best of our knowledge, there is only one other case report of IgA nephropathy in a patient with a COVID-19 infection. COVID-19 associated glomerular disease, including IgA nephropathy, should be considered in patients with nephrotic range proteinuria, and hematuria in the setting of recent COVID-19 infection.



PUB014

Impact of COVID-19 on Kidney Transplantation

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Background: Detrimental impact of COVID-19 on renal function unraveled over time. Nephrology community was in a dilemma whether transplantation should continue under such circumstances. We investigated which States within the US continued to perform kidney transplantation despite such odds.

Methods: Retrospective data from Organ Procurement and Transplantation Network (OPTN) regions for kidney transplant alone (KTA) performed across the US from 2019 to 2020, reflecting the peak of the first wave of COVID -19 pandemic were analyzed. To address whether the COVID-19 had an impact on transplanted kidneys, we analyzed graft survival at 3- and 6-months post-transplant during that era. We further investigated the statewide variation of KTA in both deceased donor (DD) transplants and living donor (LD) transplants.

Results: There was a 3.1% decrease in KTA from 2019 to 2020 (22,429 to 21,731). There was an overall trend of a decrease in number of transplants across all states with a peak decline in March-April 2019 era and rebound in May 2019 onwards. Statewide regional decline or variation of DD KTA was most significant in region 9 (NY, Vermont) while regions 4 (Oklahoma and Texas) continued to perform transplants unabated. In 2019, 30.6% of KTA were from LD while in 2020 the rate decreased to 24.1%. The transplantations of DD increased from 15,562 to 16,497 in 2020. Overall, 3-month graft survival was significantly negatively impacted for DD KTA performed between February and May. The decrease in KTA in the southern regions was less compared to the north-eastern regions.

Conclusions: The COVID-19 pandemic had a major impact on kidney transplantation with a significant reduction within all OPTN regions. While LD transplantation could presumably be rescheduled, DD organs must be procured immediately, or they are lost. Therefore, the number of DD transplants decreased initially between March and May but recovered afterwards. Transplanted kidneys during COVID-19 first wave pandemic era performed reasonably well but with an increase rate of injury and rejection.

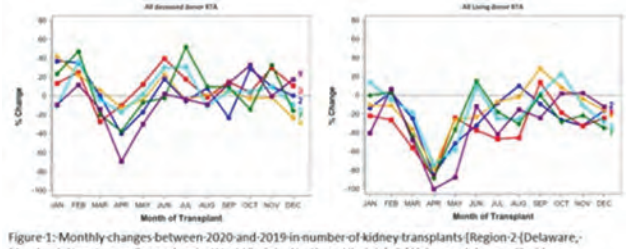

Figure-1: Monthly changes between 2020 and 2019 in number of kidney transplants [Region-2 (Delaware, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia), 3 (Alabama, Arkansas Florida, Mississippi, Puerto Rico), 4 (Oklahoma, Texas), 5 (Arizona, California, Nevada, New Mexico, Utah), 7 (Illinois, Minnesota, North Dakota, South Dakota, Wisconsin), 9 (New York, Western Vermont)]

PUB015

SARS-CoV-2 Antibody Dynamics in Chronic Hemodialysis Patients

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Background: Data on the persistence of COVID-19 antibodies against SARS-CoV-2 in maintenance hemodialysis (MHD) patients from the U.S. is still scarce and an association with race and ethnicity is unknown. We explore antibody dynamics in MHD patients from three U.S. states with a diverse racial and ethnic background.

Methods: We obtained consent from MHD patients with COVID-19, confirmed by RT-PCR, from 12 clinics. Phase 1 antibody testing was done between June and August 2020. Re-testing was done 6-8 months later. Antibodies were tested with an emergency use authorized assay (Diazyme DZ-LITE SARS-CoV-2 IgG CLIA kit). Linear mixed-effects models were employed to estimate the IgG half-life in patients with repeated IgG measurements. Patients were stratified by sex, race, ethnicity, obesity, and medians of age, dialysis vintage and body mass index.

Results: 104 patients (age 63.8±13 years, 67 (64.4%) males; 48 (46.2%) Africa-American, and 34 (32.7%) Hispanics) were studied. IgG was obtained 82 days (range 13 to 151) and 253 days (range 170 to 309) post-COVID-19. At initial testing, 101 (97.1%) patients were positive for IgG. 89 of them were available for repeated testing, where 74 (83.1%) showed persistent IgG. The luminescence signal was declined by 35.5 AU/mL (95% CI 28.7 to 42.4) from 47.8 ± 44.9 to 12.3 ± 21.1 AU/mL (P<0.0001; paired t-test; **Figure.1).** The estimated half-life of IgG was 62.8 days (95% CI 56.8 to 68.8). We observed no significant differences in the stratified analysis (**Table 1;** all p > 0.05).

Conclusions: The half-life of IgG against SARS-CoV-2 was approximately 63 days, corroborating reports from both the general and other MHD populations. Importantly, we found no association between IgG half-life, race and ethnicity.

Figure 1: Dynamics of IgG antibodies over time.

The x-axis indicates days since COVID-19 diagnosis. The y-axis indicates the natural log of IgG levels. The light lines indicate the patient-specific changes (N=89), the heavy line indicates the average change.

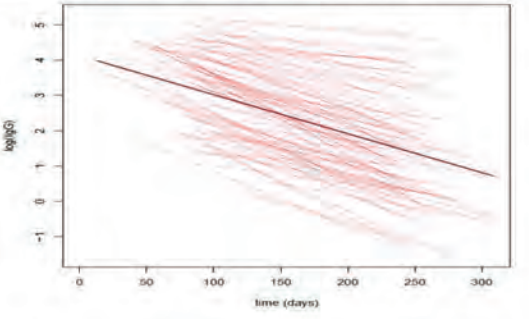

Table 1: IgG half-life ($t_{1/2}$) for the entire population and stratified by patient characteristics.

Group	IgG $t_{1/2}$ (95% CI), in days	P values
All (N=89)	62.8 (56.8 to 68.8)	n.a.
Gender		
Female (N=42)	59.4 (50.3 to 68.4)	0.3982
Male (N=47)	64.7 (56.7 to 72.7)	
Ethnicity		
Hispanic (N=21)	66.9 (58.8 to 74.9)	0.0619
Non-Hispanic (N=68)	55.4 (47.2 to 63.6)	
Race		
Black (N=38)	60.6 (53.0 to 68.3)	0.4244
Non-Black (N=51)	65.6 (55.9 to 75.3)	
Age (years)		
≥ 64.1 (N=45)	63.7 (54.8 to 72.6)	0.7754
< 64.1 (N=44)	61.9 (53.7 to 70.2)	
Vintage (years)		
≥ 4.1 (N=45)	60.4 (52.6 to 68.2)	0.4147
< 4.1 (N=44)	65.4 (56.1 to 74.7)	
Obesity		
Yes (N=34)	65.8 (57.5 to 74.2)	0.2333
No (N=54)	58.5 (50.1 to 66.9)	
BMI (kg/m^2)		
≥ 27.1 (N=44)	67.6 (57.7 to 77.6)	0.1523
< 27.1 (N=44)	58.7 (51.2 to 66.1)	

PUB016

Incidence and Risk Factors for SARS-CoV-2 Infection in Patients with Lupus Nephritis

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Background: Patients with lupus nephritis (LN) are known to be at higher risk for severe infections due to both an underlying immune dysfunction and as a consequence of immunosuppressive therapy (IS). We sought to investigate the impact of COVID-19 pandemic in patients with LN.

Methods: A total of 95 patients with LN actively monitored in our department between 26th February 2020, when the first case of COVID-19 was diagnosed in Romania, and 1st May 2021 were included in the study. Demographics, comorbidities, clinical and laboratory characteristics, current IS therapy, COVID-19 symptoms and outcome were collected. A COVID-19 diagnosis was made if clinical symptoms were accompanied by a positive SARS-CoV-2 PCR.

Results: Fifteen patients (15.8%) were diagnosed with COVID-19 at a median 279 days (IQR:218-341) since the first case was diagnosed in Romania. The majority of infections were mild (73.3%), moderate infections being encountered in the remaining patients (26.7%), while none has developed a severe infection. The most common

symptoms were fatigue (73.3% of patients), followed by loss of taste and/or smell (53.3%) and fever (46.7%). Overall, 40% of patients were hospitalized for a median of 11.5 days (IQR:3.75-14). Of these, 2 patients needed supplemental oxygen and 1 patient non-invasive ventilation. There were no COVID-19-related deaths during the study period. Of the clinical variables associated with infection development, fewer patients with COVID-19 were on hydroxychloroquine (66.7% vs. 89%, p=0.04) or were on clinical remission during the study period (40% vs. 67.5%, p=0.04), while the median maintenance oral corticosteroid dose was significantly higher in those with SARS-CoV-2 infection compared to those without [16 mg (IQR:7-21) vs. 6 mg (IQR:4-10), p=0.007]. In multivariate Cox regression analysis, use of hydroxychloroquine (HR, 0.23; 95%CI, 0.04-1.26) and oral corticosteroid dose (HR, 1.11; 95%CI, 1.01-1.22) remained the most important predictors of COVID-19.

Conclusions: The burden of SARS-CoV-2 infection in patients with LN seems to be low. Use of hydroxychloroquine seems to be associated with a lower risk for COVID-19, while from different immunosuppressive agents corticosteroid dose was identified as an independent risk factor for infection development.

PUB017

Long-Term Mortality Risk of Hemodialysis Patients Surviving Initial COVID-19: A Report from the Quebec Renal Network COVID-19 Study

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Background: Dialysis patients are at high-risk of morbidity and mortality early after SARS-CoV-2 infection. Long-term consequences of SARV-CoV-2 infection are however still not well described in this population. We aimed to compare long-term mortality between dialysis patients who survived 30-day after a SARS-CoV-2 infection and dialysis patients negative to SARS-CoV-2.

Methods: We included patients with SARS-CoV-2 PCR tests performed between March 1st 2020 and February 30th 2021 from 7 dialysis centers in Quebec. Patients alive at 30 days after SARS-CoV-2 diagnosis were matched by age, sex, center and PCR test date to patients negative for SARS-CoV-2 and followed for up to one year, starting at 30 days after initial infection (or negative test). We assessed mortality risk in unadjusted and adjusted multivariable Cox regressions.

Results: Ninety-eight patients with SARS-CoV-2 infection alive 30-day after diagnosis were matched to 166 SARS-CoV-2-negative patients. Baseline characteristics were similar between the two groups. Patients were followed for a median of 331 (301-347) days. Overall, 32 patients died during the study period (15 [15%] in the SARS-CoV-2-positive group and 17 [10%] in the SARS-CoV-2-negative group, p=0.22). There was no statistically significant association between mortality risk and previous SARS-CoV-2 infection (HR 1.5, 95% CI 0.8-3.1), even after adjustment for residual imbalance (aHR 1.4, 95% CI 0.7-3.1). Results remained similar after exclusion of 4 patients who died of SARS-CoV-2 infection > 30-day after diagnosis (**Table 1**).

Conclusions: One-year survival of dialysis patients surviving SARS-CoV-2 infection was similar to those never infected.

Funding: Government Support - Non-U.S.

Baseline Characteristics	SARS-CoV-2 positive (n=98)	SARS-CoV-2 negative (n=166)	p-value
Age, years	72 (62; 79)	71 (61; 78)	0.76
Sex male	58 (59)	149 (61)	0.71
Long-term care residency	19 (19)	26 (16)	0.44
Primary kidney disease			0.65
Diabetic nephropathy	43 (44)	83 (50)	
Hypertensive disease	21 (21)	27 (16)	
Glomerulonephritis	11 (11)	21 (13)	
Others	23 (23)	35 (21)	
Diabetes	58 (59)	103 (62)	0.65
Cardiovascular disease	62 (63)	102 (61)	0.77
Respiratory disease	14 (14)	32 (19)	0.30
Cancer (previous or active)	11 (11)	35 (21)	0.04
Previous kidney transplantation	7 (7)	6 (4)	0.20
Kidney replacement therapy duration, *in years*	2.6 (1.0;6.5)	2.7 (1.2;4.9)	0.88
Adjusted mortality predictors	**aHR**	**95% CI**	**p-value**
Positive SARS-CoV-2 infection	1.4	0.7-3.1	0.33
Long-term care housing	3.5	1.7-7.3	0.001
Kidney replacement therapy duration, *per year*	1.05	0.99-1.11	0.09
Diabetic kidney disease (vs. other)	1.9	0.9-3.9	0.09

PUB018

Impact of COVID-19 on Hemodialysis Patients: The Quebec Renal Network (QRN) COVID-19 Study

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Background: Hemodialysis patients had to face numerous challenges during the COVID-19 pandemic. They are at increased risk of severe complications of COVID-19 and continued to visit hospitals thrice weekly, increasing their risk of being infected. The objective of this study was to document the impact of the COVID-19 on patient's experience in hemodialysis in Quebec.

Methods: Between November 2020 and May 2021, we conducted semi-structured interviews with 20 patients who were undergoing dialysis treatments in six hemodialysis units in Montreal. Interviews were transcribed and analyzed using thematic content analysis.

Results: Patients were satisfied by the measures implemented within their units in order to prevent COVID-19 outbreaks, such as making masks mandatory, restricting access to the dialysis ward, and even limiting the number of accompanying persons allowed. Participants reported that following the public health guidelines (social distancing, wearing a mask and washing hands) was easy and important in order to ensure their own and their family members' safety. Because of this, participants were more likely to refuse to see their family resulting in feeling of isolation. This was particularly relevant for Indigenous patients who were having their hemodialysis treatment away from their home and family. This sub-group experienced particular issues due to the prolonged remoteness from their loved ones, change in their hemodialysis center and with the measures put in place by the hotel they were residing at. Even though their usual routine outside of dialysis might have changed due to the pandemic, hemodialysis treatments allowed patients to keep a certain normality in their lives. Positive consequences were mentioned such as frequent contact through telemedicine and the existing solidarity between patients during the pandemics.

Conclusions: Patients undergoing hemodialysis faced particular challenges due to the COVID-19 pandemic. Nonetheless, they showed great resilience in their capacity to adapt to the new reality of their hemodialysis treatments.

Funding: Government Support - Non-U.S.

PUB019

Financial Hardships in a Population of Inner-City Dialysis Patients During the COVID-19 Pandemic and Relationship to Attitudes About Dialysis

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Background: We studied inner-City hemodialysis pts who reported financial difficulties and how this affected their attitudes towards dialysis and other aspects of life during the height of the COVID-19 pandemic.

Methods: 21 randomly selected hemodialysis pts were interviewed by telephone during the summer of 2020 using the Stress and Social Support Survey, the Attitude Towards Dialysis survey and questions regarding food scarcity, financial stressors, and feelings about COVID-19.

Results: There were 12 (57%) female, 9 (42%) male, 20 (95%) Black, 1 Other, mean age 53.7±3.4 yrs, mean yrs on dialysis 5.0±1.1, 3(15%) employed, 7 (35%) on disability, 14% Medicaid only, 38% Medicaid/Medicare, 40% living alone. 55% (11) reported that finances affected how well they could control their medical condition (FIN+). FIN+ were more likely to agree that it was difficult to buy their medications because of expense (r=0.58, p+0.007), but that they made dialysis a priority (r=0.5, p=0.03), could discuss their financial concerns with their MD (r=0.75, p<0.001), and that their healthcare team was a source of support (r=0.65, p=0.002). There was no difference in age, insurance type, education or gender but FIN+ pts had much lower mean BMI (22.1±1.1 vs 32.0±1.1, p=0.001) due to lower weight (67.6±3.7 vs 88.8±4.9 kg, p<0.001). No pt was receiving SNAP benfits and there was no difference in albumin or creatinine. FIN+ were more likely to believe they knew how to protect themselves from COVID (r=0.98, P<0.001), and did not fear COVID-19 itself, but were more likely to report feeling things were out of control over the preceding several weeks (r=0.9, p<0.05).

Conclusions: In our population of Inner-City Dialysis pts: 1. Over half of pts surveyed reported financial stress and were more likely to report difficult affording medication, but were more reliant on the dialysis team for social support and made dialysis a priority. 2. Pts reporting financial stress weighed signficiantly less, although mean creatinine and albumin values did not differ. 4. These patients were not afriaid of COVID-19 and felt knowledgeable, but reported feeling out of control, possibly due to financial stressors affecting other aspects of their lives, including ability to pay for food.

PUB020

AKI-D in Ventilated Critical Patients with COVID-19

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Background: Acute Kidney Injury (AKI) is a frequent complication in critical patients with Coronavirus Disease 2019 (COVID-19) and has been associated with a poor prognosis, especially when it is necessary to implement renal replacement therapy (KTR). The mortality reported in COVID-19 patients with AKI and KTR (AKI-D) is variable according to studies published today.

Methods: In this retrospective cohort study, we analyzed the clinical characteristics, comorbidity and prognosis of 87 COVID-19 patients, older than 18 years, ventilated and AKI-D between March 2020 and February 2021. We divided our patients into two groups: Group 1: Patients who start KTR in the period of time between the onset of COVID-19 symptoms and day 21. Group 2: Patients who initiate KTR after day 21 of the onset of COVID-19 symptoms. The Charlson Comorbidity Index and SOFA Score were calculated on the day of admission to hemodialysis.

Results: Our cohort of 87 patients had a mortality 95%, Group 1: 98%, Group 2: 82%. We found no significant differences in age, SOFA before KTR, Charlson score, AKI at admission and survival after the start of KTR between the two groups. Of the total patients, 10 recovered kidney function; four patients were discharged from hospital without KTR (1 from group 1 and 3 from group 2), the other six died during hospitalization. 29 patients (33,3%) died within 48 hours of starting dialysis, with a median pre-KTR SOFA: 15 (IQR =13-16)

Conclusions: In this study, a high mortality is reported, particularly in ventilated patients with the need for KTR in the first 21 days from the onset of COVID-19 symptoms (Group 1). We observed an excess of mortality compared to Group 2. We assume that it may be due to the severity of the underlying viral condition during the initial days of infection, a matter that would become less relevant as time goes by.

Characteristic	Group 1 (n = 70)	Group 2 (n = 17)	TOTAL (n = 87)
Age *(median)*	69 (IQR = 60-73)	62 (IQR = 53.5-72)	68 (IQR = 57-63)
Gender: men *n (%)*	52 (74%)	15 (88%)	67 (77%)
Charlson Score			
less than or equal to 3 *n (%)*	31	11	42
greater than 3 *n (%)*	39	6	45
AKI during admission *n (%)*	28 (40%)	5 (29%)	33 (37%)
SOFA pre-dialysis *(median)*	13.5 (IQR = 12-15)	13 (IQR = 11.5-15)	13 (IQR = 12-15)
Use of potentially nephrotoxic antibiotics ***n (%)***	43 (61%)	15 (88%)	
Vancomycin *n*	40	10	50
Colistin *n*	40	15	55
Anfotericin *n*	3	2	5
Number of dialysis sessions *(median)*	3 (IQR = 2-7)	3 (IQR = 1-8)	3 (IQR = 2-7)
Recovered Kidney functions *n (%)*	6 (8%)	4 (23%)	10 (11%)
Deaths *n (%)*	69 (98%)	14 (82%)	83 (95%)
Survival days from HD until death *(median)*	4 (IQR = 2-11)	3 (IQR = 1-9)	4 (IQR = 2-11)
Discharge from hospital *n (%)*	1 (1%)	3 (17%)	4 (4%)
Hospitalization days *(median)*	15 (IQR = 11-23)	30 (IQR = 24.5-39.5)	17 (IQR = 12-30)

AKI = Acute Kidney Injury; IQR = Interquartile Range 25%-75%; HD = Hemodialysis

PUB021

Cardiac Troponin and AKI in COVID-19 Sepsis-Related Patients

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Background: The COVID-19 pandemic become the major reason of hospitalization of patients in ICU worldwide. AKI is a major disease and continue closely related with sepsis and COVID-19 infection. Cardiac injury is frequent in patients with septic schock and higher levels of cardiac troponin are expected in AKI patients however whether this is related with a poor outcome in the pandemic scenario still remain unknown. The objective of the study was evaluate the impact of the occurrence of AKI and cardiac troponin levels in patients with severe SARS-CoV-2 infection and their major outcomes

Methods: We conducted an observational study during COVID-19 pandemic in 2020 first wave outbreak in Brazil. The research was approved by IRB and patients of a Sao Paulo major public hospital. The main inclusion criteria were the occurrence of COVID-19 infection confirmed by oropharyngeal swab in the last 3 days of admission and the need of permanence of at least 3 days. Patients with a poorer expectancy of survival in the next 24 hours of inclusion were not considered elegible. Blood sample at admission was used to confirm sepsis and AKI and the patients were followed daily untill discharge of the unit or dead. AKI occurrence was seen as the rise of serum creatinine happened according KDIGO AKI guideline. Patients were divided in groups regarding the development of AKI and major outcome (mechanical ventilation or dead)

Results: A total of 86 patients with sepsis were included. Female patients represented 58.3% of the sample. About 96,51% of the patients had at admission a level of d-dimer above 500 ng and 77,91% of patients had a cardiac troponin I above 20 ng in AKI patients group with a p level 0f 0,003. About 44 patients had AKI due to COVID-19 sepsis related by admission in the ICU Median serum creatinine at admission was 2.44 mg/dL (1.64-4.02). There was a higher proportion of patients in mechanical ventilation with development of AKI after admission (14) than those without AKI during the whole hospitalization (11) with a p of 0,299 The mortality of patients with higher cardiac troponin were significantly higher in AKI patients than the non AKI patients.

Conclusions: IIn patients with COVID-19 sepsis related disease, there is a positive correlation between AKI and higher levels of cardiac troponin and higher days with mechanical ventilation.

Funding: Private Foundation Support

PUB022

Predicting Factors of Humoral Response to Pfizer BNT 162b2 in Hemodialysis Patients

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Background: Immunization against COVID19 has become the cornerstone in prevention of Sars-CoV-2. Maintenance Hemodialysis (HD) patients are at higher risk of both exposure and mortality. This study aims to describe humoral immunogenicity and suggest risk factors for low or absent response to Pfizer BNT162b2 in an HD cohort.

Methods: Observational prospective study including a group of HD patients followed in a Portuguese Nephrology Center who received BNT162b2. Anti-Spike IgG measured as arbitrary units per milliliter (AU/mL) was obtained on two separate occasions, corresponding to the first and second doses' humoral response. Absolute IgG value, rate of Non-Responders (NR), IgG<1AU/mL after each dose, and Weak-Responders (WR), under Percentile 25 after each dose, were evaluated for risk factors that included demographic and analytical variables.

Results: IgG anti-Spike levels showed a strong correlation with CCI and PTH after each inoculation (ρ=–0.64;–0.66/ ρ=0.56/0.65, respectively; p<0.01). Higher CCI and lower PTH was observed in NR subgroup after the 1st (p<0.01), whereas with the 2nd there was a lower albumin and PTH (p=0.01) and an association with female sex (p<0.01). Similarly, WR also showed higher CCI and lower PTH after the 1st (p=0.02) and 2nd doses (p<0.01), adding older age (p=0.03) and lower albumin (p=0.05) to the 2nd. After both inoculations, WR subgroup was associated with age over 75 yo (p=0.03); female sex (p=0.01), CCI over 8 (p=0.01), CVC over AVF/AVG (p<0.01), dialysis vintage under 24 mo (p=0.01) and PTH under 150 μg/L (p<0.01). A model combining CCI, sex (male) and vascular access (CVC) as a regression model associated those factors to WR after the 2nd dose with OR (95% CI): 1.81 (1.06-3.08); 0.05 (0.01-0.65); 13.55 (1.06-174.18), respectively (p=0.01).

Conclusions: Older age, high CCI, low PTH and albumin, CVC over AVF/AVG and recently started dialysis (less than 2 years) relate to lower response. High comorbidity burden is suggested as a more significant risk factor than age alone. THe role of PTH as a marker of low immunogenicity in the HD population should be target of further investigation. Signalization of HD patients at risk of low response may play a key role in policy making, namely the necessity for booster doses, follow-up measurements and isolation methods.

PUB023

COVID-19 and Kidney Disease: A Follow-Up Study

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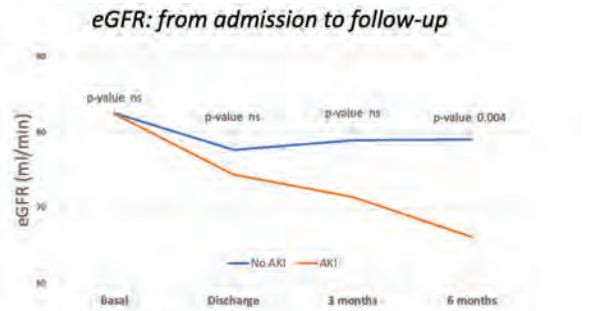
Background: It is well known that SARS-CoV-2 infection is associated with the development of acute kidney disease; however, not much is known about the long-term kidney effects of this pathology.

Methods: We analyzed kidney function data during hospitalization and subsequent follow-up (6 months) of 150 (of which 51 with CKD) patients hospitalized for COVID-19.

Results: 28% of subjects developed AKI during hospitalization; proteinuria and microhematuria were present in 53% and 40% of subjects respectively. At discharge, 61% of patients had already fully recovered their basal kidney function; the presence of proteinuria and microhematuria was reduced to 4% and 6% at subsequent follow-up. However, looking at the trend of the eGFR during the follow-up, an accelerated reduction in the glomerular filtration rate at 3 and 6 months was observed in subjects with AKI being admitted (73.30±17.08 ml/min vs 62.43±17.13 ml/min at six months; p=0.004). This result was confirmed even after exclusion from the analysis of those patients already known for CKD (eGFR < 60 ml/min) at the time of admission for COVID (eGFR 79.05±14.28 vs 66.17±16.99; p=0.004; figure 1).

Conclusions: Starting from these data, we can assume that COVID-19 patients, with intra-hospital AKI development, have an accelerated loss of renal function during follow-up. Further studies are needed to identify pathogenic mechanisms and the long-term evolution of kidney damage after Sars-Cov-2 infection.



eGFR (ml/min) at different times		All patients (150)		No CKD (99)	
		Mean	SD	Mean	D.S.
Basal eGFR	No AKI	79.01	18.08	82.67	15.45
	AKI	74.27	23.43	82.58	19.45
eGFR Discharge	No AKI	73.81	16.76	77.73	15.20
	AKI	64.91	21.29	74.48	18.81
eGFR 3 months	No AKI	74.27	17.12	78.96	15.30
	AKI	70.71	19.40	71.54	16.83
eGFR 6 months	No AKI	73.31	17.08	79.05	14.28
	AKI	62.43	17.13	66.17	16.99

PUB024

COVID-19 and Kidney Transplantation in a Colombian population

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Background: Patients with kidney transplants seem to be at particularly high risk for severe COVID19 disease due to their impaired immune responses and comorbidities

Methods: We performed an observational study of kidney transplant recipients with SARS-CoV2 infection admitted at Fundación Valle del Lili from June to December 2020. To be eligible for this study, patients have symptoms compatible, a positive RT-PCR and inpatient management. Asymptomatic patients were excluded

Results: We enrolled a total of 50 patients. 64% were male, and the median age was 53.5 years (range 46-60). The comorbidities were: 36(70%) hypertension, 16(32%) diabetes mellitus, 5(10%) obesity. The most common immunosuppressive regimen was tacrolimus 76% and prednisone 88%.The median time from symptoms onset to the positive RT-PCR was 7 days. The most common initial symptom was fever (64%), and fatigue (58%), cough (44%) and dyspnea (36%). Baseline levels of CRP was 6.43 mg/dL (3.25-11.22). The median lymphocyte count was 785 mm3/uL (550-1230). Baseline D-Dimer was 0.767 ug/ml (0.484-1153.5), ferritin median level was 1011ng/ml (670-2145). Clinical outcomes are shown in **Table**. Six of the patients died (12%), 4/6 were by sepsis-related multi-organ failure and 2/6 were by ARDS

Conclusions: Major complications such as acute kidney injury, acute respiratory distress syndrome and mortality related to COVID-19 infection observed in our study are lower than those reported in other countries

Clinical outcomes of the hospitalized patients

Outcomes	N(%)
ARDS	13 (26)
Sepsis	14 (28)
ICU admission	18 (36)
Invasive mechanical ventilation	11 (22)
Days of IMV, median (IQR)	17 (11-23)
Acute renal failure	13 (26)
Renal replacement therapy	11 (22)
Days of hospitalization, median (IQR)	11 (6-16)
Withdrawal immunosuppressor	20 (40)
Treatment	
Hydroxychloroquine	3 (6)
Azithromycin	3 (6)
Tocilizumab	1 (2)
Corticosteroids	39 (78)
Vasopressor	10 (20)
Inotropic	1 (2)

PUB025

Predictors of In-Hospital Mortality Among Hospitalized Patients with COVID-19 and AKI: A Single-Center Study

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Background: AKI and COVID-19 infection are both independently associated with high mortality rates and those with COVID-19 who develop AKI have higher mortality rates. We investigated the predictors of mortality in patients admitted to our hospital with COVID-19 who developed AKI during their hospital stay.

Methods: We conducted a retrospective analysis of all patients hospitalized at University of Virginia Medical Center for COVID-19 infection who developed AKI from March 2020 through April 2021. In-hospital mortality was defined as death during admission or within 7 days of discharge to hospice. Data on patients' demographics, comorbidities, AKI stage, dialysis requirement, admission to ICU, serum albumin, ferritin, d-dimer, fibrinogen, hemoglobin, as well as mortality at hospital discharge and 90 days were collected through chart review. Univariate analysis and a multivariate logistic regression model were used to identify factors associated with in-hospital mortality.

Results: 219 patients qualified for study inclusion criteria. The average age was 66.2 years and 56.6% of patients were men. The in-hospital mortality rate was 27.9%. An additional 1.37% died in the 90-day follow-up period. Age ($p = 0.001$), male sex ($p = 0.049$), AKI-D ($p < 0.001$), AKI stage ($p < 0.001$), serum albumin ($p < 0.001$), and ICU admission ($p < 0.001$) were associated with mortality in the univariate analysis (Table 1). After adjustments for covariates, age ($p < 0.001$), AKI-D ($p = 0.001$), and ICU admission ($p < 0.001$) were predictors of mortality in our multivariate analysis [AUC: 0.863, 95% CI (0.815-0.911)].

Conclusions: Age, dialysis requirement, severity of AKI, and ICU admission are predictors of mortality among patients with COVID-19 and AKI at our institution.

Table 1. Univariate and Multivariate Analysis of Predictors of Mortality

	Nonsurvivor (n = 61)	Survivor (n = 158)	P-value	Multivariate aOR (95% CI)	P-value
Age (years)	71.3 +/- 13.3	64.2 +/- 15.1	0.001	**1.08 (1.05-1.12)**	**<0.001**
Sex					
Female	20 (32.8%)	75 (47.5%)	0.049	**0.460 (0.207-1.02)**	**0.056**
Male	41 (67.2%)	83 (52.5%)		**[REF]**	
Race				—	—
African American	19 (31.1%)	68 (43.0%)	0.109		
White	34 (55.7%)	65 (41.1%)	0.053		
Asian	1 (1.64%)	1 (0.63%	0.499		
Other	5 (8.20%)	21 (13.3%)	0.301		
American Indian	0 (0%)	1 (0.63%)			
Ethnicity				—	—
Hispanic	9 (16.1%)	23 (14.6%)	0.798		
Non-Hispanic	47 (83.9%)	134 (85.4%)			
Baseline CKD	26 (42.6%)	65 (41.1%)	0.842	—	—
CKD stages					
CKD 3a	10 (38.5%)	31 (47.7%)	0.584		
CKD 3b	8 (30.8%)	24 (36.9%)	0.697		
CKD 4	8 (30.8%)	10 (15.4%)	0.108		
AKI-D	29 (47.5%)	22 (13.9%)	<0.001	**4.22 (1.75-10.2)**	**0.001**
Comorbidities				—	—
Diabetes	29 (47.5%)	73 (46.2%)	0.859		
Hypertension	46 (75.4%)	128 (81.0%)	0.358		
Obesity	10 (16.4%)	35 (22.2%)	0.344		
Morbid Obesity	18 (29.5%)	54 (34.2%)	0.510		
Congestive heart failure	16 (26.2%)	35 (22.2%)	0.522		
COPD	11 (18.0%)	26 (16.5%)	0.780		
Liver disease	5 (8.20%)	8 (5.06%)	0.383		
Immunosuppression	9 (14.8%)	30 (19.0%)	0.463		
AKI Stage				—	—
Stage 1	13 (21.3%)	82 (51.9%)	<0.001		
Stage 2	14 (23.0%)	37 (23.4%)	0.942		
Stage 3	34 (55.7%)	39 (24.7%)	<0.001		
Biomarkers					
Peak Ferritin (ng/mL)	2110 +/- 2310	1936 +/- 3621	0.750		
Peak D-dimer (ng/mL DDU)	2813 +/- 7035	1853 +/- 6537	0.418		
Minimum Fibrinogen (mg/dL)	534 +/- 170	513 +/- 186	0.583		
Minimum Albumin (g/dL)	2.43 +/- 0.64	2.82 +/- 0.62	<0.001	**0.928 (0.458-1.88)**	**0.836**
Minimum Hemoglobin (g/dL)	8.97 +/- 2.42	10.2 +/- 7.02	0.187		
Peak Proteinuria					
1+	19 (31.1%)	48 (30.4%)	0.857		
2+	17 (27.9%)	33 (20.9%)	0.383		
3+	11 (18.0%)	27 (17.1%)	0.974		
4+	1 (1.64%)	3 (1.90%)	0.853		
Trace	7 (11.5%)	14 (8.86%)	0.657		
Negative	1 (1.64%)	11 (6.96%)	0.136		
ICU admission	56 (91.8%)	72 (45.6%)	<0.001	**14.7 (4.55-47.8)**	**<0.001**

PUB026

Impact of COVID-19 in Quebec Hemodialysis Units: Health Care Providers' Experiences

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Background: Chronic kidney disease is a risk factor for the severe form of COVID-19 and the hemodialysis unit represents a high-risk setting for virus transmission. Healthcare providers (HCPs) have the duty to keep patients safe and healthy, and also to protect themselves from the virus. The objective of this study was to gather health care providers' experiences working in dialysis units.

Methods: We conducted semi-directed interviews by phone or video with 21 HCPs working in 6 hemodialysis units - nurses, nephrologists, pharmacists, social workers, security agent and housekeeping attendant - between November 2020 and May 2021. The content of the interviews was analyzed using thematic content analysis.

Results: Participants identified positive and negative impact of Covid-19 pandemic. In their professional life, HCPs declared developing more collaboration, creativity and mutual support. However, due to the pandemic restrictive measures and lack of resources, HCPs felt a lot of distress not being able to provide adequate care for patients' needs. Participants also reported disruption in communication between HCPs and patients because of physical distancing and wearing a mask. They also described problems associated with patient transportation leading to delays or even absence of patients to their treatment. In their personal life, some HCPs declared being concerned by these new challenges at work and reported difficulties balancing work and family life. Also, most of them feared to contaminate their family and adopted certain routine cleaning to alleviate this fear.

Conclusions: HCPs working in hemodialysis unit faced multiple challenges during the Covid-19 pandemic that impacted their wellbeing. However, they have shown high level of resilience and dedication to ensure health care delivery and to support hemodialysis patients.

Funding: Government Support - Non-U.S.

PUB027

In-Hospital Mortality in Patients with ESRD Undergoing Hemodialysis Admitted with COVID-19 Compared to Those Without COVID-19

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Background: Patients with end-stage renal disease (ESRD) undergoing chronic hemodialysis (HD) have higher cardiovascular and infection-related death compared to the general population. ESRD patients have many of the comorbidities associated with COVID-19-related death, are at increased risk for severe COVID-19, and have higher COVID-19-related mortality. Whether patients with ESRD and COVID-19 have higher in-patient mortality than patients with ESRD without COVID-19 is unknown.

Methods: Retrospective chart review of hospital admissions due to COVID-19 infection or those with ESRD admitted for any other reason between March to June 2020. We collected data on demographics, comorbidities, hospital length of stay, ICU utilization, and mortality. We categorized patients in three groups: ESRD with COVID-19, ESRD without COVID-19, and COVID-19 without ESRD. Mortality analysis was performed using Pearson's Chi-Square and logistic regression analysis.

Results: A total of 494 patients with a mean age of 64 years were included, of which 55% were males, 33% were African American, 55% were Hispanic, 49% had hypertension, and 49% had diabetes. 20 patients had ESRD with COVID-19, 195 had ESRD without COVID-19, and 279 had COVID-19 without ESRD. The crude in-hospital mortality rate was 25% in patients with ESRD and COVID-19, 18% in patients with ESRD without COVID19, and 15% in those with COVID-19 without ESRD (p=0.465 for all comparisons). In multivariable logistic regression analyses, the adjusted odds ratio [OR] for in-hospital mortality in patients with ESRD with COVID-19 was 1.46 [95% confidence interval (CI), 0.77-2.80], the OR in patients with ESRD without COVID19 was 1.02 [95% CI, 0.73-1.42], as compared to patients with COVID-19 without ESRD.

Conclusions: In-hospital mortality in patients with ESRD with COVID-19 is higher but not significantly different than in patients with ESRD without COVID-19 or than in those with COVID19 without ESRD. Further studies should evaluate the long-term COVID-19-related mortality in patients with ESRD.

PUB028

Gross Hematuria Following Moderna SARS-CoV-2 Vaccination

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Introduction: While knowledge about coronavirus disease of 2019 (COVID-19) has been rapidly growing, healthcare systems are still challenged by uncertainties surrounding currently available preventive measures. The mRNA-1273 vaccine (Moderna Inc., Cambridge, Massachusetts, USA) encodes the spike glycoprotein of the coronavirus. Whereas pain at the site of injection and headache are among the most recognized adverse events, little is known about the vaccine's less frequent side effects in the setting of rapid deployment.

Case Description: 1) A 71-year-old man noted frank blood in his urine the day after he received his second dose of Moderna COVID-19 vaccination. He also experienced two episodes of epistaxis. The patient's past medical history was significant for a non-ST elevation myocardial infarction about 2 months prior to presentation, after which he had been on aspirin 81 mg daily and clopidogrel 75 mg daily. Lab results were significant for blood in the urine. Both hematuria and epistaxis resolved without intervention, and he has not had any further bleeding episodes to-date. 2) A 72-year-old man noted "wine-colored" urine the day after he received his second dose of Moderna COVID-19 vaccination. His past medical history was significant for a remote history of nephrolithiasis (22 years ago) and atrial flutter. His medications included aspirin 75 mg daily and rivaroxaban 20 mg daily. Urine dipstick confirmed large blood. Hematuria resolved completely after cystoscopy with bladder irrigation and has not recurred to-date.

Discussion: COVID-19 Moderna post-vaccination bleeding events (e.g. epistaxis and vaginal bleeding) have been recorded as infrequent adverse events. While actual COVID-19 infection has been associated with hematuria, development of gross hematuria following the second dose of the Moderna vaccine has also been reported in patients with IgA nephropathy. However, to our knowledge, these are the first two reported cases of gross hematuria associated with COVID-19 Moderna vaccine in men without a history of kidney disease. Raising the awareness of clinicians is important in that entering these events into the vaccine adverse events reporting system can clarify their true incidence. Whether these patients need to be followed to determine if they will develop signs of a previously undiagnosed nephrologic disease in the future remains to be elucidated.

PUB029

Renal Manifestations and Their Association with Mortality in COVID-19 Patients at a Safety-Net Hospital

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Background: Renal involvement in COVID-19 leads to severe disease and higher mortality. We study additional previously not studied renal parameters in COVID-19 patients and their association with mortality.

Methods: A retrospective study (n=340) of confirmed COVID-19 patients with renal involvement determined by the presence of acute kidney injury. Multivariate analyses of logistic regression for mortality and linear regression for length of stay (LOS) adjusted for relevant demographic, comorbidity, disease severity, and treatment covariates.

Results: Mortality was 54.4% and mean LOS was 12.9 days. For mortality, creatinine peak (OR:35.27, 95% CI:2.81, 442.06, p<0.01) and persistent renal involvement at discharge (OR:4.47, 95% CI:1.99,10.06, p<0.001) were each significantly associated with increased odds for mortality. Increased blood urea nitrogen peak (OR:0.98, 95%CI:0.97,0.996, p<0.05) was significantly associated with decreased odds for mortality. For LOS, increased blood urea nitrogen peak (B:0.001, SE:<0.001, p<0.01), renal replacement therapy (B:0.19, SE:0.06, p<0.01), and increased days to acute kidney injury (B:0.19, SE:0.05, p<0.001) were each significantly associated with increased length of stay.

Conclusions: As persistent renal involvement at discharge is associated with increased odds for mortality, this suggests that early identification of renal involvement characteristics in COVID-19 patients is useful for treatment management. Clinicians should focus on renal parameters of blood urea nitrogen peak, renal replacement therapy, and days to acute kidney injury for predicting patient length of stay.

PUB030

COVID-19 and Vitamin D in an Urban US Hemodialysis Population

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Background: Due to logistical constraints of in-center hemodialysis (HD) ESKD patients have endured increased risk during the COVID-19 pandemic. Minorities are overrepresented in EKSD, making this group more susceptible to poor outcomes given existing racial disparities. Studies have emerged spotlighting vitamin D's effects on autocrine regulation of immune function and the relevance of extra-renal one alpha hydroxylase. Many studies describe links between vitamin D deficiency and severity of SARS-CoV-2 infection in high-risk patients, but there is a paucity of data specific to ESKD patients. This study explored the association between vitamin D status and COVID-19 infection in a primarily black HD population.

Methods: Emory Dialysis patients' vitamin D levels [25(OH) D] were collected November 2020 as part of a quality improvement project. All SARS-CoV-2 positive HD patients were identified (October 2020 to April 2021). Retrospective chart review including baseline data and labs were collected. An unpaired t-test was used to compare vitamin D levels between COVID-19 positive and negative patients.

Results: 620 patients were included. All patients enrolled in-center HD three times per week. Patient identified race makeup included black (n=570) and non-black n= 50. Average age was 59 years. Gender: males (n=324) and females (n=296). 73 patients developed COVID-19 and 68 patients identified as black race. Average vitamin D levels for COVID-19 positive patients 27.33 and COVID-19 negative patients 26.2 (p=0.55).

Average PTH in COVID-19 positive patients 507.3±371 and COVID-19 negative patients 557.57±458 (p=0.25). Average calcium level in COVID-19 positive patients 8.74±0.66 and COVID-19 negative patients 8.73±0.72 (p=0.48). Relative risk of developing COVID-19 in black HD patients was 1.14 compared to others (p=0.75).

Conclusions: Our study showed no statistically significant correlation between Vitamin D level and COVID-19 acquisition. The role of vitamin D deficiency as a risk factor and the role of Vitamin D supplementation for prevention or treatment COVID-19 in this population is unclear. Further studies investigating the relation between Vitamin D levels and severity of COVID-19 infection in this population should be explored.

PUB031

Antibody Response Following Vaccination to SARS-CoV-2 in Dialysis-Dependent Patients

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Background: SARS-CoV-2 is a novel virus resulting in the loss of lives globally. Recently it is recognised that dialysis dependence and end stage renal disease are risk factors for severe COVID-19 infection. In addition, those receiving renal replacement therapy are thought to be immunosuppressed as a result of persistent uraemia and chronic inflammation. The effects of immune dysfunction including T and B cell suppression have caused concerns that haemodialysis (HD) patients may have a reduced immunological response to the vaccine. Recent studies looking at SARS-CoV-2 antibodies demonstrated different outcomes, with some showing diminished antibody responses following vaccination in HD patients whilst others suggest good efficacy and persistence of antibodies.

Methods: In January 2021 Royal Preston Hospital, UK commenced a COVID-19 vaccination programme for all HD patients in accordance with the UK government advice and guidelines. In May 2021 a prospective study including 546 patients receiving incentre and home HD started. SARS-CoV-2 antibodies are being collected during routine dialysis visits and serum samples for spike and nucleocapsid proteins are being measured as markers of immune response. Antibodies are measured monthly alongside secondary outcomes including hospital admissions, mortality and subsequent COVID-19 infection. This study has been approved by the Health Research Authority and the Research and Development team at Lancashire Teaching Hospitals NHS Foundation Trust.

Results: Data collection is ongoing. Sixteen patients (2.9%) declined the vaccine and the majority (85.1%) received the Oxford-AstraZeneca vaccine. The median age is 63.34 years (IQR 54-75 years) and there is a 59.9% male predominance (n=327). 48 patients (10.5%) are receiving home haemodialysis and the remaining 498 patients receive in centre haemodialysis on a twice or thrice weekly basis. Initial results are due in June 2021 and 6 month data will be available in November 2021.

Conclusions: We aim to quantify antibody response to the COVID-19 vaccine in HD patients. This will potentially allow us to identify those patients who may still be vulnerable to COVID-19 despite vaccination and guide further management options in the future. Ongoing research and data analysis is required to investigate both the initial and chronic immune mediated response.

PUB032

Mortality Among ESKD Patients with COVID-19: Comparison Between Kidney Transplant and Hemodialysis

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Background: The COVID-19 pandemic has had an impact on almost every aspect of human life. With more than 170 million cases and more than 3.5 million deaths worldwide (as of May 30, 2021), new facets of the fallout are being uncovered day after day. We analyzed the effects of COVID-19 on end stage kidney disease (ESKD) patients and compared the demographic profile and mortality in patients on hemodialysis (HD) to those who received kidney transplant (KT) in a large multicenter cohort.

Methods: We performed a retrospective multi-center cohort study using TriNetX Research Network database, a federated electronic medical records network, to identify 3601 ESKD patients ≥ 18 years who had either received a kidney transplant (KT) (n=1849 from 34 healthcare organizations [HCOs]) or had been started on hemodialysis (HD) before 12/31/2019 (n=1752 from 31 HCOs) and who had been diagnosed with COVID-19 infection between 1/1/2020-12/31/2020. We used the KT group as the reference and calculated the comparative risk of 6-month mortality after COVID-19 infection for the HD group, reported as the odds ratio (OR) and 95% confidence interval (CI).

Results: Compared with KT patients, HD patients were more likely to be older at the time of COVID-19 infection (57.4±14.5 vs. 53.3±13.8 years; p<0.0001), more likely to be African-American (<0.0001), diabetic (p<0.0001), hypertensive (p=0.0002), and with a history of coronary artery bypass graft (CABG) (0.0021). A total of 366 patients died within 6 months of diagnosis of COVID infection. After propensity matching, COVID-19 positive patients on HD had a higher odds of mortality (OR: 1.48; CI: 1.14, 1.90) compared with COVID-positive patients with a KT.

Conclusions: Among ESKD patients who contracted COVID-19 infection during 2020, the patients on HD were more likely than patients who had received a KT to be African-American, to have a history of diabetes, hypertension and CABG. HD patients were more likely to die within 6 months of COVID diagnosis compared to patients who received a KT.

PUB033

Outcomes in Critically Ill COVID-19 Patients with AKI Requiring Renal Replacement Therapy

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Background: In the past year acute kidney injury(AKI) has been shown to be a common complication of COVID19[1]. with 61-78% of all patients who had COVID developing AKI and needing renal replacement therapy (RRT) [2]. There are still many facets of the novel coronavirus' effect on the kidneys and our approach has changed over time. We report on our experience with AKI requiring RRT early on in the pandemic.

Methods: We performed a retrospective chart review between the months of April to July 2020 at Coney Island Hospital, a public hospital in New York City. Upon identifying those with COVID-19 and AKI requiring RRT, we collected data regarding medications administered, inflammatory markers, demographic data and outcomes.

Results: 62 patients had AKI requiring RRT. 22.6% were female, 77.4 % were males with the mean eGFR on admission being 57.34 with SD OF 29.4. Average age of our cohort was 63 years old. In our cohort the average max values of the following were: ferritin 3495, IL-6 284 and D-dimer 12,460. Average BMI of our cohort was 31 with SD OF 7 (table 1). On average there was 16.5 days between initiation of dialysis and death. After initiation of RRT 30 day mortality and 90 day mortality was found to be 80.6% (50/62) and 87.1% (54/62) respectively. Overall 98.4 % of the cohort died. Using Cox regression analysis no treatments were associated with survival, including thrombolytic administration, full dose anticoagulation, IL-6 administration, plasma, steroids and hydroxychloroquine. Of all the variables collected, only age was associated with mortality.

Conclusions: Acute Kidney injury requiring renal replacement therapy carried significant mortality in the early stages of the pandemic. Our numbers are similar to, but worse than other reports from other New York area hospital systems which had a mortality rate of 79%[3]. Our initial numbers may be partially explained by the population served by the New York City public hospital system. As our experience with this disease expands, hopefully our management of AKI in these patients will improve.

Table 1

	N	maximum	Mean	SD
eGFR on admission	59	148	57.3	29.4
Days from Dialysis to outcome (death or discharge)	62	83	16.45	20.1
age on admission	62	86	63	14.5
D-dimer	53	61416	12,460.79	15,594.10
IL-6	39	1994	284.35	386.4
Ferritin	58	25345	3495.02	4,213.60
BMI	62	60.5	31.15	7

PUB034

Impact of Different COVID-19 Vaccines on Platelet Count Changes in a Dialysis Cohort

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Background: Mortality rates from COVID-19 are significantly higher in patients requiring renal replacement therapy (20-30%) than the overall estimated mortality of 1-4% worldwide. COVID-19 vaccines offer a strategy to protect this vulnerable cohort. Patients on hemodialysis are at higher risk of exposure to COVID-19 due to an inability to self-isolate, and were prioritised for vaccination in the UK. The Oxford Astra-Zeneca (Ox/AZ) vaccine allows administration on the dialysis unit, due to ease of storage and transportation. During the time period between the 1st and 2nd dose in the vaccination schedule, a rare clinical syndrome of thrombocytopenia and thrombosis was observed in patients after receiving the Ox/AZ vaccine.

Methods: We undertook a retrospective analysis of routine dialysis bloods, examining any significant changes in platelet count pre and post vaccine in our dialysis cohort, prior to offering 2nd doses.

Results: Data for 780 hemodialysis patients with platelet count pre and post first dose Covid-19 vaccine were analysed. Of these, 471 patients received the Ox/AZ vaccine, 145 received Pfizer, and the remainder were vaccinated elsewhere, therefore data on vaccine type not available. Mean platelet count for the whole cohort pre-vaccine was $215x10^9$/L, and post was $218x10^9$/L. 126 patients had a platelet count below $150x10^9$/L pre-vaccine, and this number was the same post vaccination. No difference was observed based on vaccine type (see table).

Conclusions: No signal of vaccine-induced thrombocytopaenia was detected in this cohort, though the numbers were small to detect such a rare event. The benefits of completing the vaccine schedule outweigh any small risk of vaccine-associated thrombocytopaenia and thrombosis in this clinically extremely vulnerable cohort.

Results of platelet count changes pre post COVID-19 vaccination by Vaccine type

	Oxford AZ	Pfizer	p
Baseline Platelet count	211 (173-257)	204 (263-248)	0.13
Post vaccine platelets	212 (170-264)	202 (164-247)	0.1
Change in platelet count pre/post vaccine	-2 (-26-16)	-4 (-29-18)	0.99

Platelet count values given as 10^9/L

PUB035

The Tale of Two Collapsing Glomerulopathies Associated with COVID-19 in Stamford Hospital

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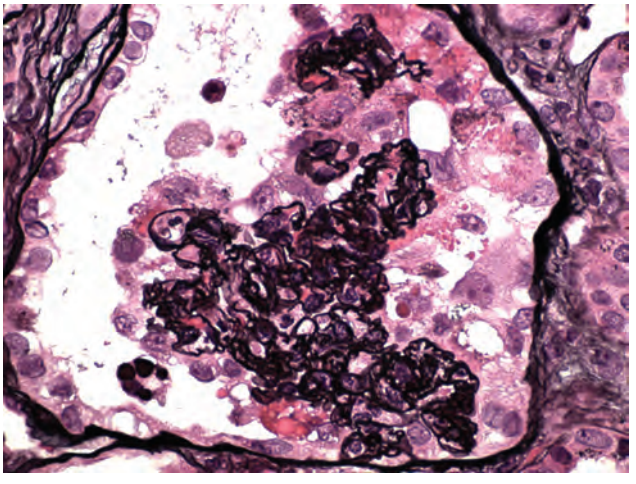
Introduction: One pattern of kidney injury seen in COVID 19 is collapsing glomerulopathy (CG), a type of Focal Segmental Glomerulosclerosis (FSGS). It has been hypothesized that direct viral effect or increased circulating cytokines from the inflammatory response of the virus, or both, can lead to CG especially in patients with high-risk alleles of APOL1 gene.

Case Description: Patient 1: 63-year-old man, COVID-19 positive, who received only supportive care while hospitalized (Results in table 1). **Patient 2:** 62-year-old man, COVID-19 positive, who required brief treatment with dialysis and received high-dose steroids (Results in table 1).

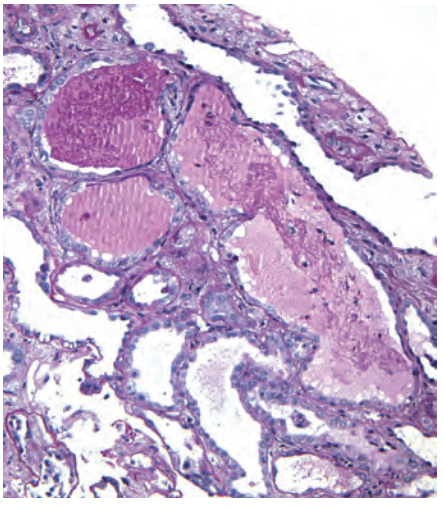
Discussion: We present 2 cases who achieved partial renal recovery despite different treatments, raising the question of the role of steroids in patients with COVID associated CG.

Table 1

Laboratory & Pathology	Patient 1	Patient 2
Baseline Cr	2 mg/dL	1 mg/dL
Admission Cr	10.7 mg/dL	11.6 mg/dL
UA	>600 mg/dL protein	>600mg/dL protein
24-hr urine protein	12 gr	13 gr
Renal Biopsy	Collapsing FSGS, tubular atrophy and moderate interstitial fibrosis	Collapsing FSGS, tubular atrophy and moderate interstitial fibrosis
APOL1 Genetic testing	Positive	Positive
Discharge Cr	9 mg/dL	4.8 mg/dL
Cr 8 months after	3 mg/dL	2.3 mg/dL



Renal biopsy (Patient 1) showing glomerular collapse



Renal biopsy (Patient 1 & 2): Tubular microcyst formation; also seen in HIV-associated nephroptahy

PUB036

Impact of First vs. Second COVID-19 Surge in Dialysis Patients in San Antonio

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Background: San Antonio, Texas witnessed a COVID-19 surge during July and December 2020. COVID-19 had disproportionately severe impact on dialysis population during first surge; however, experiences from second surge is not known. The aim of our study is to compare the effect of two surges on prevalence and outcomes of COVID-19 infections in dialysis patients within University Health System

Methods: First surge was from April 20 to Sept 20; second was from Oct 20 to Mar 21. Over12-month period, we recorded COVID-19 infections and outcomes for adult patients receiving dialysis at three centers (1st surge n=359 including 25 home and 2nd surge n=362 including 37 home). Demographic, clinical, laboratory, treatment and outcomes data were analyzed

Results: COVID-19 infection were similar during surges (36 [10%] vs.43 [12%]). There was no difference in age, sex, ethnicity, smoking, co-morbidities, cause of ESKD, access and medications. However, patients during second surge were more obese (28 ±4.5 vs 30.4±7.5 kg/m^2 p=0.015), less dialysis vintage (6.2±4.5 vs. 5.7±3.1 yr, p=0.006), higher WBC (6.5±2.2 vs. 7.3±3.6 x 10^3/ml, p=0.016), ferritin (939±719 vs. 12273±1621 µg/L, p=0.048), and D-dimer (2285±2120 vs. 5670±12410 IU ng/ml, p=0.02). No infection occurred in home dialysis patients during first surge compared to 6 (14%) during second surge (p=0.02). Table shows outcomes

Conclusions: Incidence of COVID-19 infections in our dialysis population were similar in the two surges. Hospitalization rates were similar, but more patients required ICU admission, ventilation and longer stay during second surge, although non-significantly. Death was significantly higher during second surge. Home dialysis patients more frequently affected than first surge suggesting change in health behaviors

Table 1

Outcome	1st Surge (N=36)	2nd Surge (N=43)	P Value
Hospitalization n (%)	20 (56)	17 (40)	NS
Missing Information	4 (20)	4 (23.5)	
N for hospitalized Data	16	13	NS
ICU	3 (19)	5 (38)	NS
Ventilation	1 (6)	3 (23)	NS
Vassopressors	2 (12.5)	2 (15)	NS
Length of stay (d)	8.2±5.7	10.4±7.8	NS
Dexamethasone	8 (50)	7 (54)	NS
Remdesivir	0	0	
Death n(%)	1 (3)	7 (16)	0.048
Long term care facility n(%)	0	1 (2)	NS

PUB037

A Single-Center Experience: SARS-Cov-2 in ESKD and Kidney Transplant Patients

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Background: A new strain of coronavirus was first recognized in late 2019 resulting in a worldwide pandemic by early 2020. This pandemic challenged health care systems worldwide. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in a spectrum of illnesses ranging from asymptomatic, mild, and self-limiting to severe disease. To this date, there are no clear treatment guidelines or protocols for the management of patients in general and for hemodialysis and transplant patients in particular. The Centers for Disease Control and Prevention (CDC) lists patients with chronic kidney disease and immunocompromised patients as high risk for severe disease from SARS-CoV-2.

Methods: Our study is a single-center retrospective study. We conducted an observational, retrospective study in ESKD and Kidney transplant recipients hospitalized and diagnosed with COVID-19 disease at Advocate Christ Medical Center admitted between March 1 to May 31, 2020, a 3-month period. We describe our experience in patients with ESKD and kidney transplants during the COVID 19 pandemic. With particular attention to the treatments used, prognosis, and kidney outcomes in these patients.

Results: From the aggregate total of patients diagnosed with SARS-COV 2 between March 1 to May 31, 2020, there were 34 patients with ESKD on KRT and 3 kidney transplants. The median age of our ESKD cohort was 63.5 years while the KT cohort was 69 years. For both patient populations were predominantly male with 52.9% for ESKD and 66.7% for KT. With 64.7% of ESKD being composed of African Americans, while our KT patients were predominantly Caucasian at 66.7%. The average length of hospital stay was longer for KT patients at an average of 22 days. The incidence of in-hospital death was significantly higher in ESKD patients at 27.8% while we had no mortality for KT pts. For in-patient mortality serum Na, K and BUN were not statistically significant from those who survived. D-dimer peak was significantly higher in mortality.

Conclusions: COVID-19 infection is associated with a high rate of mortality amongst patient's with pre-existing End Stage Kidney Disease. This study redemonstrates this high mortality rate at a single center institution. More research is needed in understanding and managing these patients.

PUB038

D-Dimer Levels as a Prognostic Marker for Developing AKI in Those Hospitalized with COVID-19

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Background: Severe COVID-19 is associated with higher levels of inflammatory markers than mild disease. D-dimer levels correlate with disease severity and are a prognostic marker for in-hospital mortality. Tracking these markers may allow prediction of disease progression. Data on role of D -Dimer levels in AKI are scant.

Methods: We retrospectively analyzed the clinical and laboratory characteristics of 3,212 consecutive cases of COVID-19 in the Bronx, between March 01, 2020 and July 16th and again between October 15th 2020 and February 28th 2021. D dimer levels were separated by increments of 1000/2000 when over the normal value. Bivariate and generalized estimating equation (GEE) methods were used to explore risk factors associated with in-hospital AKI. Correlations of D-dimer and developing AKI during admission was analyzed.

Results: Results: The first surge data showed that, after adjusting for and controlling for age, race/ethnicity, peak CRP, Diabetes, Chronic Kidney Disease and Hypertension, patients with a peak D-Dimer greater than normal had significantly higher odds of having AKI during admission with highest risk for levels over 3000. The second surge data showed that a peak D-Dimer greater than 2000 was associated with highest odds of AKI. Both surges indicated an increase in D-Dimer was correlated with increased odds of AKI.

Conclusions: Monitoring D- Dimer levels may serve as warning for development of AKI. This may facilitate categorization of patients into risk groups, and help in the identification of those who might potentially benefit from continuous vigilance and prompt intervention. Evidence is still lacking as to the causal mechanisms and whether the associations are specific effects of SARS-CoV-2 infection or are consequences of an intense systemic inflammatory response. Dysregulation of coagulation/anti-coagulation cascades is also a known phenomenon in COVID-19. This finding may help us better understand the pathogenesis of AKI in Covid 19. Significantly elevated D Dimer levels in COVID-19 may serve as an early warning for AKI and help ensure optimal resource allocation.

PUB039

ICU Admission During the COVID-19 Pandemic in Overwhelmed Institutions: Is CKD a Significant Risk Factor for Consideration in ICU Admission?

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Background: The SARS-CoV-2 pandemic has strained healthcare systems worldwide. Increasing age and comorbidities, as CKD are associated with worse outcomes. Information is needed to assist the decision-making process for ICU admission. The aim of this study was to evaluate mortality rates of COVID-19 CKD patients, percentage of patients admitted to ICU and the role of CKD as a risk factor (RF) for mortality.

Methods: Prospective cohort study from a referral center for COVID-19 in Mexico City. All patients hospitalized between March 2020 and March 2021 with complete follow up were included. Subjects were segregated into 4 groups: 1) CKD stages 3-4 (CKD3-4, n=109), 2) renal replacement therapy (RRT, n=103), 3) kidney transplant (KT, n=31), and 4) patients without CKD (no CKD, n=2520). We registered if ICU admission was requested and if patients were admitted or rejected. RF associated with mortality were evaluated by Cox-regression analysis.

Results: Mean age of the population was 56 years (IQR 46-67), 1697 (61%) were male, 837 (30%) had diabetes, and 1105 (40%) were obese. The group of CKD3-4 patients was older (median 62 years, IQR 38-86), diabetic (58%), and had higher incidence of acute kidney injury (76%). ICU admission was requested for 52 (48%), 32 (31%), 10 (32%), and 1043 (41%) patients in the CKD3-4, RRT, KT, and no CKD groups, respectively ($p<0.001$). Of these, 17/52 (33%), 12/32 (38%), 4/10 (40%), and 576/1043 (55%) were admitted ($p<0.001$). Mortality in each group and in patients admitted in ICU is shown in Figure 1. The adjusted multivariate analysis for mortality showed that CKD was not associated with increased mortality.

Conclusions: CKD patients during the COVID-19 pandemic, conditioning high mortality rates. However, adjusted analysis suggests that CKD should not be considered as a single criterion for the decision of admission to ICU.

Funding: NIDDK Support

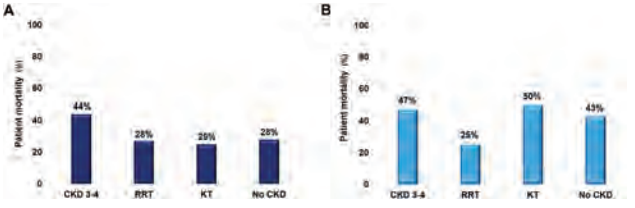

Figure 1. Mortality rates by group (A) and for patients admitted in ICU(B).

PUB040

Rate of Developing Hyponatremia and Outcomes in Kidney Transplant Recipients During COVID-19 Hospitalization

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Background: Hyponatremia is one of the surrogate markers of poor clinical outcomes especially in hospitalized patients. Outcomes related to hyponatremia particularly rate of developing hyponatremia in kidney transplant recipients (KTR) with COVID-19 is unknown. We aim to examine association between the degree of hyponatremia and outcomes in hospitalized KTR with COVID-19.

Methods: This is a single-center retrospective cohort study including consecutive KTR admitted for COVID-19. Association of delta serum sodium (ΔSNa) defined by percent drop of admission serum Na (SNa) from a 3-month pre-admission SNa with outcomes including acute kidney injury (AKI) defined by rising serum creatinine (SCr) 0.3 mg/dL from the baseline SCr 3-month prior, death, and length of stay (LOS) is examined by multiple logistic and linear regression as appropriate.

Results: Of 125 KTR, mean age±SD was 47.03±15.19 years old and 53% were male. The majority were White 87 patients (70%) followed by others 27 (22%), Asian 9 (7%), and Black 2 (1%) patients. Mean SNa was 133±6 mmol/L and ΔSNa were -4±5 mmol/L. Mean ΔSNa were -3.02±4.09%. Seven patients (6%) died, and 24 (19%) patients developed AKI. Every one percent increase in ΔSNa was associated 2% decrease the odds of death and developing AKI (OR_{death} 0.98, p 0.81, 95%CI 0.81, 1.18 and OR_{AKI} 0.98, p 0.74, 95%CI 0.86, 1.11). Mean LOS was 12.6±15.4 days (range 1 to 70). Every one percent increase in ΔSNa was associated 0.33 day increase in the LOS (β_{LOS} 0.33, p 0.547, 95% CI -.76, 1.41). After adjusted by age, gender, race, presence or absence of diabetes or hypertension, the magnitude and direction of the association were similar in those all three outcomes.

Conclusions: Hyponatremia appears to be protective for mortality and AKI in KTR hospitalized for COVID-19 but associated with increased LOS; although the statistical significance was limited by small sample size. Future studies are required to elucidate the association of hyponatremia particularly degree of worsening SNa in immunocompromized patients such KTRs who are generally at risk for poor clinical outcomes.

PUB041

The Relevance of Urinalysis in the Hospitalization of Patients with COVID-19 and Nephrology Early Intervention

Lilia M. Rizo Topete,[1,2] Giovanna Y. Arteaga Muller,[1] Elisa M. Guerrero Gonzalez,[1] Adrian Camacho-Ortiz,[1] Luis C. Mata,[1] Luis F. Rangel,[1] Gabriela E. Aguilar Díaz.[1] Hospital Universitario de Monterrey "José Eleuterio González", UANL *[1]Hospital Universitario "José Eleuterio Gonzalez", UANL, Monterrey, Mexico; [2]Hospital Christus Muguerza Alta Especialidad, Monterrey, Mexico*.

Background: Multidisciplinary management of the COVID's patients is essential for their evolution, and the early detection ok AKI is a important role to avoid morbi-mortality. In March 2020, the pandemic by COVID-19 appeared in Mexico, and it led all the health system to change the intrahospital management.

Methods: In a retrospective, observational analysis of all the patients >18 Y that were hospitalized at the Hospital Universitario de Monterrey, in the COVID area, from March to August 2020, we notice how the urinary sedimentation evaluation from the beginning could detect patients who could develop AKI or the need of RRT. All data were analyzed using SPSS statistical software (version 25; IBM Corporation, Armonk, New York).

Results: A total of 344 patients hospitalized from March to August 2020. 220 patients with EGO since the beginning (obtained when our nephrology team take place on the presential participation on AEMA) 102 did not have proteinuria, and, on the other hand, the rest (61 or 37%) reported it. 95 patients (41.7%) had hematuria. Hematuria were more likely to be treated with KRT. Patients with hematuria demonstrated an increased tendency to require RRT: 38.2% of patients with hematuria versus 11.6% without hematuria, the greater chance that needs RRT (P<.001).

Conclusions: The presence of active sedimentary urinary on COVID patients is frequent. The patients who present the combination of hematuria and proteinuria develop severe AKI (KDIGO 3 without RRT) or the need for RRT. Factors in patients such as to be on their upper edge of 40 years old, the presence of hyperkalemia, metabolic acidosis, also the hematuria and proteinuria, suggest the AKI risk that required RRT.

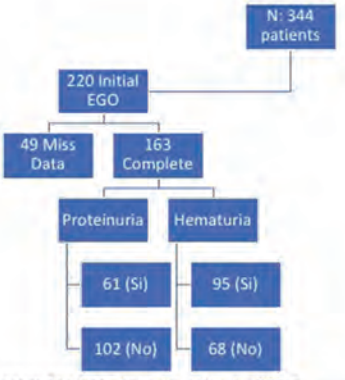

Table 1. Description from the hospital admission by RRT a

Variable	Global	RRT	Without RRT
	n=344	n=51	n=293
Edge, Average (DE)	50.77(16.14)	54.58(14.25)	50.1(16.37)
Gender, Male n(%)	204(59.3)	35(68.6)	169(57.7)
Protenuria, n(%)	102(62.6)	32(86.5)**	70(55.6)
Hematuria, n(%)	68(41.7)	26(70.3)***	42(33.3)
Mortality, n(%)	32(64)	32(65.3)	0(0)
Hypoalbuminemia, n(%)	222(68.7)	40(80)	182(66.7)

Pearson's chi-square, T-test
*p<0.05
**p<0.01
***p<0.001

PUB042

Thrombotic Microangiopathy Following COVID-19 Infection

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Introduction: The relationship between COVID-19 infection and the activation of a wide spectrum of pro-inflammatory and pro-thrombotic mechanisms such as antiphospholipid syndrome (APS) and Thrombotic Microangiopathy (TMA) is not yet well understood. However, there is emerging evidence on the link between COVID-19 and TMA. Here, we report a case of a biopsy-proven chronic TMA following COVID-19 infection.

Case Description: A 48-year-old Hispanic female with a past medical history of diabetes, and hypothyroidism, who was recently discharged from the hospital following a COVID-19 infection (complicated by ICU admission requiring intubation about a month ago), presented with severe abdominal pain. No prior history of miscarriage in the past; the patient has two kids with uneventful pregnancies. Denies any family history of autoimmune disease. Initial workups indicated that splenic and renal infarcts concerning primary antiphospholipid syndrome were further supported by positive serological testing confirming the presence of positive Antineutrophil antibody, Cardiolipin antibody, B2glycoprotein, and Lupus anticoagulant. In addition, the urinalysis showed active urinary sediment with dysmorphic RBCs and nephrotic range proteinuria. The patient had a kidney biopsy which was consistent with chronic TMA and was initiated on anticoagulation therapy with warfarin for antiphospholipid antibody syndrome.

Discussion: The possibility of occurrence of TMA following COVID-19 infection and the possible association between markers of endothelial activation, intravascular hemolysis, coagulation and organ damage in infection should be considered. This understanding is clinically relevant as it may necessitate the need for early APS antibody and TMA panel testing and initiation of anticoagulation in the amplified hypercoagulable state in COVID-19, especially in preventing life-threatening thrombosis.

PUB043

Algorithm for Predicting AKI

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Background: Current detection of AKI relies on acute rise in serum creatinine (sCr) and/or a decline in urine output over given time interval. However, biomarkers for AKI have been shown to be elevated prior to change in sCr, suggesting that the time to intervene and prevent AKI is before the change in sCr occurs, when irreversible damage has already occurred. The purpose of the present study was to identify variables that would predict patients at risk for developing AKI without relying on sCr or urine output.

Methods: Retrospective chart review was conducted on all patients admitted from Jan. 2019 to Jul. of 2019. Comparison was made between those that developed AKI defined as change in sCr >1.5mg/dL and those that did not develop AKI, a change of sCr <0.3mg/dL. After exclusion criteria, the final data set consisted of a total of 547 patients and was basis to detect variables that are readily available.

Results: Data showed the higher the rise in sCr the worse the renal injury requiring renal replacement therapy and worse the patient outcome. sCr ≥ 1.5 x baseline correlated with prerenal or mild AKI, while contrast induced nephropathy correlated with ≥ 2x baseline sCr and acute tubular injury and need for renal replacement therapy correlated with ≥ 3x baseline sCr. 20 specific variables were identified in differentiating those that will develop AKI and those that did not develop AKI. Individually some variables weighed more than others in differentiating between AKI and no AKI, however same variables were present across any severity of AKI. Using the 20 variables a specific algorithm was developed to identify any patient admitted and their risk to develop AKI in any inpatient clinical setting. To confirm the accuracy of the data, the same variables were extracted via computer (instead of manually) on a new pool of 769 patients with retrospective admissions yielding same result as the clinician with 81% sensitivity, 80% specificity and 80% accuracy in detecting AKI.

Conclusions: The variables are readily available without need to change patient management or increasing cost. Further study is being conducted to answer the following: How early and accurately will this algorithm predict AKI? Will this prevent AKI by altering management of clinicians when alerted? This could potentially be integrated into hospitals' electronic health records for real time patient monitoring and detection of early AKI and modify patient care and outcomes.

PUB044

Not Everything Is About COVID-19: An Unusual Case of Rhabdomyolysis and AKI After Physical Activity

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Introduction: Rhabdomyolysis is the breakdown of striated muscle, leading to systemic manifestations that typically include myoglobinuria, being responsible for 5 to 7% of non-traumatic acute kidney injury(AKI). It can be caused by trauma, status epilepticus, metabolic myopathies, drugs, infections, thryroid disease and hemoglobinopathies

Case Description: We report a case of 31 year old woman who was admitted with muscle pain and choluria 12 hours after physical exercise for a public contest, having mild SARSCoV2 infection 3 weeks before. She was previously healthy, without regular use of any medication, in training for a physical test, with no family history of blood or muscle diseases. At admission she was dehydrated. Exams are shown in table 1. During hospitalization she was conducted with vigorous hydration, diuretics when necessary and urine alkalinization, without hemodialysis. After 12 days, she was discharged. In outpatient follow-up, although the history fits as rhabdomyolysis after extenuating physical activity in a post-covid patient, additional tests were performed:TSH 2,41 mU/L, negative serology for HIV, normal CRP and ESR. Despite negative family history of hemoglobinopathy, hemoglobin electrophoresis was compatible with sickle cell trait (HbA1 57.8%, HbA2 3.1%,HbF 0.3%, HbS 38.8%)

Discussion: Sickle cell disorder(SCD) is a genetic disease where hemoglobin (Hb) S mutation is present on at least one beta chain. When both β chains of HbA carry HbS mutation, the patient exhibits phenotypic features of SCD. If a mutation affects only one β globin chain and the other is normal, the patient is said to have sickle cell trait(SCT), which is a relatively benign carrier state and does not have the classic phenotypic features of SCD. It is estimated that affects 1 million to 3 million americans, and 8 to 10 percent of African Americans, configuring a serious public health problem. SCT does not appear to be associated with increased overall mortality, but studies demonstrate that it is associated with a significantly higher risk of severe exertional rhabdomyolysis, and this case is a reminder to perform this assessment

Laboratory

Exams	23/12	25/12	29/12	04/01 (discharged)	14/01	17/03
BUN (mg/dL)	54	75	140	131	43	30
Creatimne (mg/dL)	2,4	4,7	8,5	5,5	1,4	1,0
CPK (U/L)	120.053	94.832	49.137	988	325	86,1

PUB045

Kidney Involvement in Hantavirus Infection: The Importance of Kidney Biopsy

Gabriela Lupusoru,[1,2] Ioana Ailincai,[1] Georgiana Fratila,[1] Mircea Lupusoru,[2] Andreea G. Andronesi,[1,2] Achim Camelia Adriana,[1,2] Mihaela A. Banu,[2] Gener Ismail.[1,2] *[1]Institutul Clinic Fundeni, Bucuresti, Romania; [2]Universitatea de Medicina si Farmacie Carol Davila, Bucuresti, Romania.*

Introduction: Hantavirus infection, a rare zoonosis, associates two major syndromes: hemorrhagic fever with renal syndrome (HFRS) and cardiopulmonary syndrome (CPS). We present two cases of HFRS in which kidney biopsy (KB) was the key in guiding diagnosis

Case Description: Case 1: 26-year-old female (no medical history) presented with acute kidney injury (AKI), nephrotic syndrome (NS), hematuria, high blood pressure (HBP), hepatic cytolysis, severe thrombocytopenia, anemia, leukocytosis, elevated LDH, normal haptoglobin, positive Coombs test, negative immunological and viral tests (C3/C4, ANA, ANCA, antiGBM, hepatitis B/C, HIV, Epstein-Barr, Cytomegalovirus), normal ADAMTS13 activity KB showed macroscopic features of hemorrhage in the renal medulla, light microscopy with normal glomeruli, proximal tubules with intratubular erythrocytes and important interstitial hemorrhage in the medulla, electron microscopy with endotheliosis and interstitial inflammation, features suggesting Hantavirus infection. Serological testing of IgM/IgG antibodies (Ab) for Hantaan serotype (HTNV) established the final diagnosis of HTNV hemorrhagic interstitial nephritis Therapy included steroids and Ramipril. Serum creatinine and liver enzymes returned to normal **Case 2:** 30 year-old male (no medical history) presented with AKI, macroscopic hematuria, NS, HBP, the same laboratory modifications as the previous case and low complement level KB showed the same macroscopic and histological features of massive interstitial hemorrhage in the medulla and arterial endothelial swelling. Serological testing revealed IgM/IgG Ab for Dobrava Hantavirus. The final diagnosis was Dobrava Hantavirus Hemorrhagic Interstitial Nephritis Therapy included steroids and 3 hemodialysis sessions with good evolution and correction of laboratory abnormalities

Discussion: HFRS is most often caused by Dobrava and Puumala serotypes in Balkan Peninsula. Both presented cases live in the same rural area. Case 1 had positive serology for HTNV, usually found in China and Russia, but our patient didn't travel abroad before she got ill. This emphasizes that HTNV nephritis remains an underdiagnosed disease and the need to re-evaluate geographic distribution of different strains. Both cases presented as thrombotic microangiopathies and KB had a decisive role in guiding diagnosis

PUB046

Electronic AKI Alert at the Brandenburg Medical School: Implementation and Follow-Up

Daniel Patschan. *Medical School of Brandenburg, Brandenburg, Germany.*

Background: Acute kidey injury (AKI) substantially worsens the prognosis of hospitalized patients worldwide. In order to optimize early AKI recognition and therapeutic intervention, so-called AKI alert systems have been implemented and evaluated in the past. Herein, we aimed to analyze outcome variables of AKI subjects under the conditions of a de-novo established AKI alert system at the Brandenburg Hospital of the Brandenburg Medical School.

Methods: Based on an electronic algorithm, an automated e-mail message was generated and sent to the nephrologist in responsibility. The message was exclusively generated if one of the two first KDIGO criteria was fulfilled. During period 1, all alerts were ignored. During the second period, every alert was followed-up, coupled with therapeutic management of respective individuals according to an AKI care bundle. Endpoints were in-hospital death, need for dialysis, and renal recovery.

Results: In period 1 and 2 n=200 and n=112 patients were included. In period 1, n=150 out of 200 AKI alerts were identified as correct (75%), in the second period, n=93 out of 112 AKI alerts were accepted as correct (83%) (p=0.16). Renal replacement therapy (RRT) was initiated in n=21 (14%) of all period 1 subjects and in n=32 (34.4%) of the period 2 patients (p=0.001). In-hospital mortality of affected subjects was n=24 (16%) in period 1 and n=21 (22,6%) (p=0.19). Restoration of kidney function was exclusively evaluated in surviving patients. It was n=62 (49.2%) in period 1 and n=40 (55.5%) in period 2. In both periods, higher age was not associated with differences in the endpoints death and renal recovery.

Conclusions: We finally conclude that an AKI alert system as implemented and followed-up in our study did not significantly improve clinical relevant endpoints in AKI subjects. Potential weaknesses were: (I) the lack of documentation of the time between receiving the alert and patient contact, (II) physicians in responsibility were not particularly informed about the alert system, (III) it is questionable whether serum creatinine is suitable for AKI alert systems in general.

PUB047

Precipitous AKI due to Acute Renal Artery Thrombosis in a Patient with Protein S Deficiency

Tyler Reed, Mujahed Abualfoul, Roberto L. Collazo-Maldonado. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Renal arterial thrombosis and infarction is an under-recognized condition due to its rarity and ability to mimic other disease processes. It can lead to secondary hypertension, acute kidney injury, and chronic kidney disease. Clinical manifestations include nausea, vomiting, flank pain, and sudden elevations in blood pressure. Here, we present a case of a patient with previous normal kidney function presenting with a severe AKI due to an acute renal arterial thrombus.

Case Description: A 58-year-old woman with previously normal kidney function (baseline Cr of 0.8 mg/dL) presented with complaints of nausea and vomiting and was found to have a stage 3 AKI with a creatinine of 4.65 mg/dL. Her creatinine level continued to rise, peaking at 8.5 mg/dL, despite volume expansion. Her urinalysis showed moderate blood and moderate protein. Her FeNa was calculated to be 6.5% and the P/creatinine was found to be 4.56 grams. Renal ultrasound revealed right renal atrophy and a normal appearing left kidney. She remained non-oliguric with good urine output and initially did not meet requirements for renal replacement therapy. Due to the unknown etiology of her AKI, a left kidney biopsy was performed which revealed fulminant acute cortical necrosis. Subsequently, an MRA revealed complete occlusion of the left renal artery. No angioplasty or stent placement was performed, and she eventually required renal replacement therapy. Hypercoagulable testing revealed protein S deficiency. Other serologic work up was negative. She was tested multiple times for COVID19 infection during her hospital stay and each test was negative.

Discussion: The majority of renal thromboembolisms originate as emboli from the heart. Much less commonly, thrombi may form in the renal arteries themselves, especially in those with a hypercoagulable state such as this patient. In light of the recent global COVID19 pandemic, renal artery thromboembolism has gained increased recognition and prevalence. As such, our patient tested negative multiple times for COVID19 as a potential explanation for her hypercoagulable state. Acute renal artery thrombosis should be considered as an explanation for AKI of unknown etiology, especially in those who have underlying risk factors. In the appropriate context, imaging studies should be obtained promptly to prevent permanent kidney injury.

PUB048

Serum Cystatin C as an Early Marker for AKI for Coronary Angiography Patients in a Mexican Population

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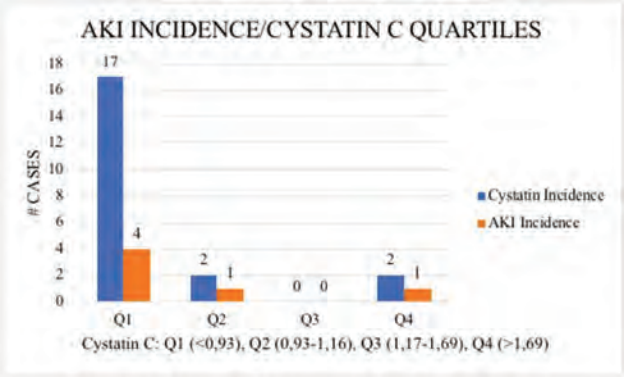
Background: Cystatin C is only filtered and metabolized in the kidney, which makes it the ideal marker of kidney function. High sensitivity and specificity for early detection of acute kidney injury (AKI) and contrast induced kidney injury (C-AKI). Early identification of C-AKI after percutaneous coronary intervention may help to change the prognosis of this patients.

Methods: Prospective, observational study, 21 patients, Feb-2020 to Jan-2021. Capillary serum samples prior to contrast administration. Cystatin C was quantified by quantitative immunofluorescence analysis (GETEIN1100). AKI was defined by the KDIGO-AKI criteria. Follow up with creatinine every 24 H for up to 72 H. Primary outcome was to determine the incidence of AKI, secondary outcome was to determine comorbidities and epidemiological risk factors.

Results: From the 21 patients, 14 men (67%), the average age was 63 years. 28.5% had DM, 74.5% HTA, 38.1% ischemic heart disease, and 4.6% had a history of cancer. GFR rate by MDRD was 76.27 ml/min in the group without AKI and 68.7 ml / min in the group with AKI, without statistically significant differences (p= 0.56). There was statistically significant difference between both groups in the serum tests: Cystatin C 1.11 vs 1.20 (p= 0.047), Creatinine at 48h 0.91 vs 1.64 (p= <0.001), Phosphorus 3.81 vs 4.8 (p= 0.024), Glucose 105.86 vs 134.6 (p= 0.021), Cholesterol 178.7 vs 117.7 (p= 0.046), Iron 77.8 vs 45.7 (p= 0.027). It was divided into interquartile groups of cystatin C; Q1 (<0.93 mg / dl), Q2 (0.93-1.16 mg / dl), Q3 (1.17-1.69 mg / dl), Q4 (> 1.69 mg / dl) where the incidence is 23.5%, 50%, in Q3 no data, and 50% respectively.

Conclusions: We founded higher incidence of C-AKI than previously reported. Major risk factors were hyperglycemia, iron deficiency and low cholesterol levels. Cystatin C use must continue to grow, it can be efficiently used as a screening tool in the Cath lab.



PUB049

AKI in Newborns with Infection, Including Sepsis, Detected by Novel Biomarkers

Joycilene d. Barbosa,[1] Luan R. Castelo,[1] Geraldo B. Silva Junior,[2] Gdayllon C. Meneses,[1] Alice Maria C. Martins,[1] Elizabeth D. Daher,[1] Tiago L. Sampaio,[1] Amanda d. Gomes,[1] Paula Roberta de Lima,[1] Nicole C. Lopes,[1] Rosangela P. Machado,[2] Romelia P. Lemes.[1] *[1]Universidade Federal do Ceara, Fortaleza, Brazil; [2]Universidade de Fortaleza, Fortaleza, Brazil.*

Background: Acute kidney injury (AKI) is still poor understood in newborns and hard to detect by traditional means. The aim of this study was to evaluate novel biomarkers in the early diagnosis of AKI in premature newborns (NBs) with infection, including sepsis.

Methods: This is a prospective observational study with 62 NBs admitted to a tertiary hospital in Fortaleza, northeast Brazil, between August 2019 and September 2020. Using serum samples and urine, the biomarkers were measured by ELISA and compared to the determination of AKI by neonatal *Kidney Disease: Improving Global Outcomes* (KDIGO), by urinary output.

Results: No AKI was found by using the traditional biomarkers. CysC levels were 4.78 (1.9 – 25.63) ng/mg-Cr, uCysC 0.64 (0.2 – 2.29) ng/ml; NGAL 27.81 (14.29 – 58.98) ng/mg-Cr; sNGAL 0.85 (0.4 – 1.39) ng/ml; and uNGAL 3.14 (1.74 – 5.51) ng/ml. In the group of sick NBs, the levels of uCysC and uNGAL were associated with a longer period of hospitalization. As a consequence, after combining the two biomarkers, it was possible to observe a poor prognosis in NBs with neonatal infection or sepsis (AUC: 0.783; p = 0.016), Figure 1.

Conclusions: Our study evidenced that uCysC, uNGAL and sNGAL were associated with kidney injury in premature NBs with neonatal infection or early sepsis. Also, there was an association of uCysC and uNGAL with hospital stay time longer than 30 days and the prognosis of NBs.

Funding: Government Support - Non-U.S.

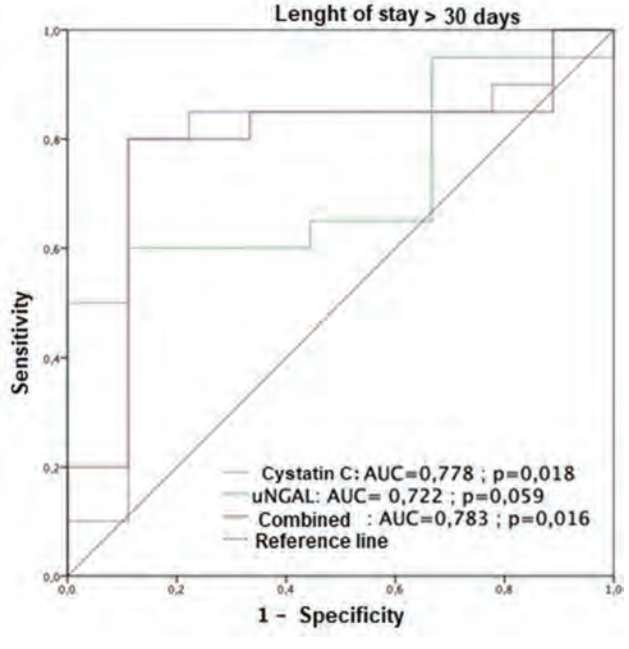


Figure 1. Urinary cystatin C and NGAL sensitivity and specificity for better prognosis for hospital stay time longer than 30 days. uCysC: urinary; uNGAL: urinary lipocalin associated with neutrophilic gelatinase; AUC: area under the curve.

PUB050

Risk of Clinical Outcomes Following AKI After Major Surgery

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Background: Risk of acute kidney injury (AKI) is high among patients undergoing major surgery. Limited evidence suggests that AKI episodes increase the risk of subsequent chronic kidney disease, regardless of the AKI cause. Aim of this study was to investigate clinical outcomes in patients with AKI following major surgery as seen in routine clinical care.

Methods: A retrospective cohort study was conducted in a US claims database (Optum Clinformatics Data Mart) using data from Jan 1st, 2009 to Jul 31st, 2020. Adults with an inpatient AKI diagnosis (index date) and a major surgery during the 30 days prior to the AKI were included and followed-up for a maximum of three years until end of enrolment, death or end of study period. Individuals with CKD stage ≥ 3, end-stage kidney disease (ESKD), dialysis or kidney transplant prior to the index AKI were excluded. The primary outcome was CKD stage ≥ 3. Further kidney and cardiovascular outcomes were investigated. The period of 90 days after index AKI was not used for outcomes identification to allow for kidney function recovery. Outcomes were assessed by time-to-first-event analysis.

Results: In total, 41,134 patients were included in the cohort, mean age was 71.3 years (standard deviation: 11.4); 60.9% were male. Coronary artery bypass graft, open heart surgery with extracorporeal blood circulation and hip replacement were most frequent major surgeries prior to AKI. End of follow-up during the 90-day post-AKI period happened in 9,882 (23.0%) patients with death being the main reason (7,518; 76.1%). 31,252 patients were available for time to event analysis. The 3-year cumulative risk of CKD stage ≥ 3 was 41.2% with the majority of events seen in the first 3 months of outcomes assessment period. The 3-year cumulative risk of all-cause hospitalization, myocardial infarction, stroke, ESKD, dialysis and kidney transplant was 64.2%, 14.4%, 17.7%, 6.6%, 6.2% and 0.2%, respectively.

Conclusions: This study demonstrates that patients experienced AKI are at high risk of subsequent serious clinical outcomes, including CKD stage ≥ 3. The study underlines the high unmet medical need in patients with AKI to prevent CKD, its progression and consequences.

Funding: Commercial Support - Bayer AG

PUB051

A Case of Neurotoxicity in a Patient with Cefepime-Induced Nephrotoxicity

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Introduction: Cefepime-induced neurotoxicity is a phenomenon which may occur due to its ability to cross the blood brain barrier and act as a GABA antagonist. There is an increased risk of neurotoxicity in patients with renal dysfunction. Additionally, there are well documented instances of cefepime-induced nephrotoxicity. We describe an unusual case of a patient with acute toxic encephalopathy with cefepime in the setting of cefepime-induced acute interstitial nephritis.

Case Description: A 79-year-old man was brought in by family with new onset expressive aphasia and confusion which had progressively worsened over the past two days prior to admission. His past medical history was significant for chronic left skull base osteomyelitis currently on the sixth week of an eight-week course treatment of cefepime. His laboratory results were significant for oliguric acute kidney injury (AKI) without significant uremia. On early admission, he was observed to develop truncal and upper extremity choreiform movements with mutism. Then, he progressed to a catatonic like state with upper and lower extremity rigidity and immobility. A lumbar puncture was performed. The analysis of the cerebrospinal fluid was unrevealing and no infectious etiology was identified. Continuous electroencephalogram (EEG) showed nonspecific slowing without epileptiform activity. Microscopic urinalysis showed muddy brown casts suggestive of possible acute tubular necrosis (ATN). A follow-up Gallium-67 radionuclide imaging study confirmed increased bilateral renal uptake suggesting intermediate probability for AIN. Cefepime was discontinued and patient was started on hemodialysis. There was rapid improvement of neurologic symptoms with return to baseline mental status after three rounds of hemodialysis, as well as eventual recovery of renal function.

Discussion: This case illustrates the linked multi-organ adverse effects that may result from cefepime including reversible neurologic and nephrotoxic effects. Early hemodialysis can be considered for rapid symptomatic improvement in instances where neurotoxicity is directly secondary to nephrotoxicity.

PUB052

Interaction of Acute Respiratory Failure and AKI on In-Hospital Mortality of Patients with Acute Exacerbation COPD

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Background: Both acute respiratory failure (ARF) and acute kidney injury (AKI) are two common complications in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Moreover, both ARF and AKI are reported as increasing the risk of mortality of patients with AECOPD. However, the interaction of ARF and AKI

on the mortality of patients with AECOPD remains unknown. Therefore, the aim of this study is to investigate the joint effect of ARF and AKI on mortality in AECOPD patients.

Methods: We performed a retrospective, observational cohort study of data from Nanjing First Hospital. The effect of AKI and ARF on in-hospital mortality was assessed using a multivariate logistic regression model. Additive interaction was assessed with the relative excess risk due to interaction.

Results: 1647 participants were enrolled for analysis. Most (77%) patients were male, and the median age of the overall cohort was 78 years (IQR: 71 - 84). ARF and AKI occurred in 515 (31.3%) and 357 (21.7%) patients, respectively. Overall, in-hospital mortality was 5.7% (94/1647). The in-hospital mortality of the neither ARF nor AKI group, the ARF only group, the AKI only group, and the both ARF and AKI group were 0.8%, 7.0%, 7.5%, and 29.9%, respectively. After multivariate logistic regression analysis, the independent risk factors for in-hospital death included: albumin (OR 0.88, 95% CI 0.83-0.93, $P < 0.001$), ARF only (OR 8.53, 95% CI 3.64-19.99, $P < 0.001$), AKI only (OR 8.99, 95% CI 3.58-22.55, $P < 0.001$), and both ARF and AKI (OR 39.13, 95% CI 17.02-89.97, $P < 0.001$). The relative excess risk due to interaction was 22.62 (95% CI, 0.31 to 44.93), the attributable proportion due to interaction was 0.59 (95% CI, 0.36 to 0.79), and the synergy index was 2.46 (95% CI, 1.44 to 4.20), indicating ARF and AKI had a significant synergic effect on in-hospital mortality.

Conclusions: ARF and AKI were independent risk factors for in-hospital mortality in AECOPD patients. Moreover, those two complications had a synergistic effect on in-hospital mortality.

PUB053

Vanquishing Vancomycin-Associated Acute Interstitial Nephritis

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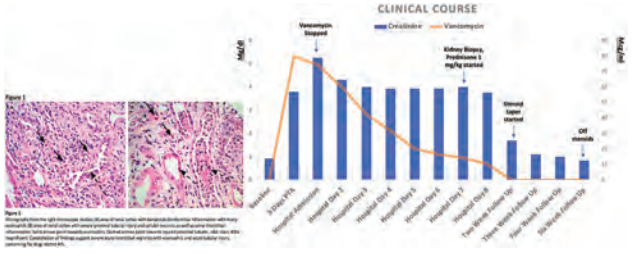
Introduction: Intravenous (IV) vancomycin is a ubiquitously used antibiotic for a variety of infections that can cause nephrotoxicity. We present a remarkable biopsy-proven case of acute interstitial nephritis (AIN) attributed to supratherapeutic vancomycin levels successfully treated with corticosteroids.

Case Description: A 44-year-old woman monitored by an outpatient parenteral antibiotic therapy (OPAT) program presented with a morbilliform rash 2 weeks after starting postoperative IV vancomycin (goal trough 15-20 mcg/mL) for mastoiditis. Baseline serum creatinine (SCr) was 0.92 mg/dL, which had increased to 3.8 mg/dL on labs through the OPAT program 3 days prior. Her vancomycin trough was notably >80 mcg/mL. Repeated values on admission were 5.27 mg/dL and 74.3 mcg/mL, respectively. Last vancomycin dose was 1 day prior. Urine microscopy showed 1+ protein, 104 white cells and 36 non-dysmorphic red cells. Urine culture and eosinophils were negative, but peripheral eosinophilia was present. SCr nadired to 3.93 mg/dL after IV hydration. A subsequent kidney biopsy showed severe acute interstitial nephritis with eosinophils, concerning for drug-induced AIN. She was started on prednisone 1 mg/kg with eventual taper leading to improved SCr (0.85 mg/dl) after 6 weeks.

Discussion: Acute kidney injury (AKI) in this case was attributed to vancomycin. Interestingly, only 12 biopsy-proven cases of vancomycin-induced AIN have been reported prior to this case. To help mitigate AKI from vancomycin, a vital strategy is monitoring plasma drug levels during therapy because there is a linear relationship between risk of AKI and higher plasma trough concentrations. In this case, OPAT monitoring was imperative in helping to promptly identify kidney injury. The role for steroid therapy remains controversial in AIN, especially drug-induced AIN, with no prospective trials and conflicting evidence from retrospective series. Nevertheless, our case demonstrates how prompt steroid use can improve AKI from vancomycin-associated AIN and may mitigate development of chronic kidney disease and need for kidney replacement therapy.



Patient's kidney biopsy (left), clinical course (right)

PUB054

N-acetylcysteine and Contrast-Induced AKI: An Umbrella Review of Systematic Reviews

William He, Emma Ruzicka, Edward G. Clark, Jennifer Kong, Swapnil Hiremath. *University of Ottawa, Ottawa, ON, Canada.*

Background: There have been numerous trials and metaanalyses of n-acetylcysteine (NAC) in contrast-induced acute kidney injury (CI-AKI). The large trials do demonstrate the futility of NAC. In this umbrella review, we synthesize the evidence as collated from the systematic reviews and metanalyses.

Methods: A literature search was done to identify all systematic reviews on NAC and CI-AKI using databases from inception to end 2020. Two independent reviewers screened the studies and extracted data on including assessment of heterogeneity, publication bias and we used the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) to appraise the included studies.

Results: The literature search retrieved 273 citations, of which 42 systematic reviews were eligible. The quality assessment using the AMSTAR-2 was variable (see table) with high quality noted for certain domains (eg explicit question, explanation of study designs), low for others (funding, reasons and list of excluded studies). All studies reported high heterogeneity; 39/42 (93%) performed a meta-analysis, all with an overall benefit with NAC (pooled relative risks range 0.38 - 0.84). 26/42 (62%) reported on the presence of publication bias, and 31/42 (74%) reported the risk of bias. Only 2/42 studies (5%) reported on efforts to resolve heterogeneity did not report a summary effect size as a result.

Conclusions: Systematic reviews can provide misleading results if heterogeneity and publication bias are not taken into account.

AMSTAR Checklist

Critical domain question	N (%) of studies judged as yes
Did the research questions and inclusion criteria for the review include the components of PICO?	42 (100%)
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	5 (12%)
Did the review authors explain their selection of the study designs for inclusion in the review?	42 (100%)
Did the review authors use a comprehensive literature search strategy?	37 (88%)
Did the review authors perform study selection in duplicate?	27 (64%)
Did the review authors perform data extraction in duplicate?	29 (69%)
Did the review authors provide a list of excluded studies and justify the exclusions?	3 (7%)
Did the review authors describe the included studies in adequate detail?	42 (100%)
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	31 (74%)
Did the review authors report on the sources of funding for the studies included in the review?	3 (7%)
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	37 (100%)
Did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	26 (70%)
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	25 (69%)
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	39 (93%)
Did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	26 (62%)
	27 (64%)

PUB055

Nephrologist Interventions to Avoid Kidney Replacement Therapy in AKI

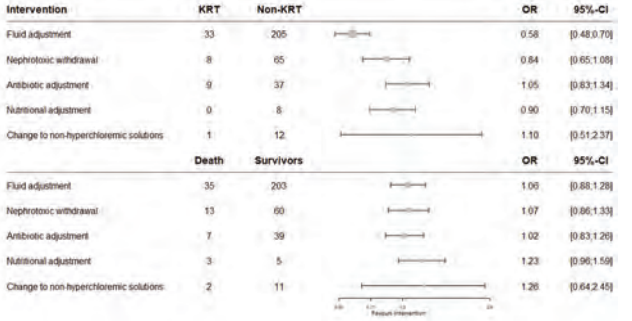
Jonathan Chavez,[1,2] Jorge I. Michel González,[1,2] Andres E. De la torre quiroga,[1,2] Andres Aranda,[1,2] Alexia C. Romero,[1,2] Bladimir Diaz Villavicencio,[1,2] Guillermo Garcia-Garcia.[1,2] *[1]Universidad de Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico.*

Background: We investigated the impact of 5 early nephrology interventions on starting kidney replacement therapy (KRT), AKI progression and death in AKI patients

Methods: In a prospective cohort, we followed-up for 10 days AKI patients. We analyzed 5 interventions of the nephrology team (fluid adjustment, nephrotoxic withdrawal, antibiotic dose adjustment, nutritional adjustment and removal of hyperchloremic solutions) and multivariate analysis for the risk of starting KRT (primary objective), AKI progression to stage 3 and death (secondary objectives).

Results: We analyzed 288 AKI patients. The mean age was 55.3 years, 60.7% were male, AKI KDIGO stage 3 was present in 50.5% of them, sepsis was the main etiology 50.3%, and 72 (25%) patients started KRT. The overall survival was 84.4%. Fluid adjustment was the only intervention associated with a decreased risk for starting KRT (OR 0.58, 95% CI 0.48-0.70, p = <0.001) and AKI progression to stage 3 (OR 0.59, 95% CI 0.49-0.71, p = <0.001). Receiving vasopressors and KRT were associated with mortality. None of the interventions studied was associated with reducing the risk of death.

Conclusions: In this prospective cohort study of AKI patients, early nephrologist intervention and fluid prescription adjustment was associated with lower the risk of starting KRT and progression to AKI stage 3.



KRT, kidney replacement therapy; OR, odd ratio; CI, confidence interval

Table 2. Univariable-Multivariable logistic regression model to determine the variables associated with start KRT in AKI patients before propensity score analysis.

	Univariate (95% CI)	p	Multivariate (95% CI)	p
Age	0.99 (0.99-1.00)	0.64	0.99 (0.99-1.00)	0.06
Female	0.98 (0.83-1.16)	0.86	1.09 (0.88-1.33)	0.40
Type 2 Diabetes Mellitus	0.97 (0.87-1.07)	0.58	1.07 (0.97-1.19)	0.14
Hypertension	1.01 (0.85-1.20)	0.86	1.02 (0.82-1.26)	0.85
Smoker	0.95 (0.76-1.18)	0.65	0.99 (0.79-1.24)	0.95
Hypothyroidism	1.03 (0.79-1.35)	0.78	1.11 (0.85-1.46)	0.43
Chronic kidney disease grade 1-4	1.01 (0.84-1.21)	0.85	0.91 (0.75-1.11)	0.37
Cerebrovascular disease	1.10 (0.70-1.73)	0.65	1.25 (0.78-2.02)	0.34
Ischemic heart disease	0.84 (0.47-1.49)	0.56	0.75 (0.40-1.41)	0.38
Body Mass Index	0.99 (0.98-1.01)	0.90	0.99 (0.98-1.01)	0.59
Sepsis	1.10 (0.93-1.30)	0.24	1.03 (0.86-1.24)	0.69
Hypovolemia	1.01 (0.85-1.20)	0.86	0.97 (0.80-1.17)	0.77
Cardiorenal syndrome	0.77 (0.60-0.99)	0.04	0.83 (0.61-1.13)	0.24
Nephrotoxic drugs	1.00 (0.80-1.23)	1.00	1.02 (0.81-1.29)	0.81
Shock	1.13 (1.02-1.26)	0.01	1.03 (0.92-1.15)	0.58
Vasoactive drugs	1.07 (0.90-1.27)	0.39	1.14 (0.94-1.38)	0.16
AKI KDIGO 1	0.76 (0.61-0.95)	0.02	1.01 (0.74-1.37)	0.94
AKI KDIGO 2	0.96 (0.74-1.24)	0.79	1.00	1.00
AKI KDIGO 3	1.21 (1.01-1.45)	0.03	1.28 (0.99-1.66)	0.053
NSAIDs	1.04 (0.88-1.23)	0.61	1.06 (0.88-1.27)	0.51
Antibiotics	1.06 (0.87-1.29)	0.54	1.01 (0.80-1.27)	0.90
Antihypertensive	0.98 (0.81-1.18)	0.85	1.04 (0.85-1.28)	0.67
Diuretics	1.07 (0.79-0.96)	0.01	1.23 (1.00-1.50)	0.04
Fluid adjustment	0.61 (0.52-0.71)	<0.001	0.58 (0.48-0.70)	<0.001
Nephrotoxic withdrawal	0.83 (0.66-1.04)	0.11	0.84 (0.65-1.08)	0.19
Antibiotic adjustment	0.89 (0.71-1.12)	0.35	1.05 (0.83-1.34)	0.64
Nutritional adjustment	0.77 (0.57-1.04)	0.09	0.90 (0.70-1.15)	0.41
Remove hyperchloremic solutions	1.00 (0.49-2.01)	1.00	1.10 (0.51-2.37)	0.80

AKI, acute kidney injury; KDIGO; kidney disease initiative global outcomes; NSAIDs, non steroidal analgesic anti-inflammatory drugs.

PUB056

Acute Interstitial Nephritis (AIN): Current Presentation and Therapy Beyond Corticosteroids (CS)

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Background: AIN is most often caused by drugs (DI-AIN) and autoimmune disease (AI-AIN). Many patients (PTS) are treated with CS. There are sparse data on management of relapsing disease.

Methods: 53 PTS with AIN followed at our center between 2010-2020. Median (IQR) are reported. T-Test, Fisher's exact were used as appropriate.

Results: Median age was 55 years (31-64) at diagnosis and 28 (53%) were female. The cohort included 26 (49%) DI-AIN, 20 (38%) AI-AIN, 1 (2%) infection, and 6 (11%) unknown etiology. Antibiotics were the most common drug; Sjogren's predominated AI-AIN. **Table 1** summarizes the clinical course. Serum Creatinine (SCR) at biopsy was higher in DI-AIN. 4 (15%) DI-AIN were dialysis dependent at diagnosis vs. 0 AI-AIN PTS (p=0.12). 44 (83%) PTS received CS as initial therapy, and DI-AIN PTS received shorter courses. 2 (8%) DI-AIN and 6 (30%) AI-AIN reached ESKD (p=0.06) after 66.5 months (mo) (33-97). Among the CUIMC-AIN cohort not reaching ESKD, the follow up SCR was 1.7 mg/dl (0.9-2.1) after 51 mo (20-83). More AI-AIN PTS than DI-AIN PTS received steroid sparing therapy (SST) for relapsing disease. 19 (95%) SST PTS received MMF, and 8 (41%) received more than one SST. 30% of SST PTS reached ESKD after 111.5 mo (44.8-151.25). Among SST patients not reaching ESKD, the follow up SCR 1.8 mg/dl (1.2-2.2) after 60 mo (38-114).

Conclusions: DI-AIN and AI-AIN continue to be the most common forms of AIN. DI-AIN PTS presented with worse renal function but were CS responsive. AI-AIN PTS were more likely to receive SST due to relapsing disease. 70% of SST PTS were with stable CKD after 60 mo. Further study in the role of SST in relapsing AIN is warranted.

CUIMC AIN Cohort: Treatment Response and Outcomes

Characteristic	All Cases (53)	DI-AIN (26)	AI-AIN (20)	p-value
Baseline SCR (mg/dl)	1.1 (0.8-1.4)	1.1 (0.8-1.3)	1.1 (0.8-1.6)	0.2
Presentation SCR (mg/dl)	2.5 (1.9-3.8)	3.0 (2-4.8)	1.9 (1.6-2.6)	0.02
Duration of Corticosteroid (month)	3 (2-6)	3 (2-3)	6 (4.5-12)	0.01
Reached ESKD during Follow Up	9/53 (17%)	2/26 (8%)	6/14 (30%)	0.06
SCR Last Follow Up Among non ESKD (mg/dl)	1.7 (0.9-2.1)	1.7 (0.9-1.9)	1.9 (1.3-2.1)	0.28
Median Follow Up Overall Cohort (month)	51 (20-86)	52 (20-73.5)	41 (18-79)	0.38
Received SST	20/53 (38%)	3/26 (12%)	14/20 (70%)	0.0001
SCR before SST (mg/dl)	2.2 (1.4-3.1)	2.6 (1-3)	2.1 (1.4-3.2)	NA
Received SST and reached ESKD	6/20 (30%)	0/3 (0%)	6/14 (43%)	NA
SCR last follow up among SST non ESKD (mg/dl)	1.8 (1.2-2.2)	2.0 (1-2.3)	1.7 (1.2-1.9)	NA
Median Follow up for SST cohort (month)	60 (38-114)	61 (42-94)	46 (33-127)	NA

PUB057

The Impact of Elective Withdrawal of Long-Term Concurrent RAAS Blockade in CKD Patients Presenting with Progressive AKI: A Prospective 40-Months' Single-Unit Analysis

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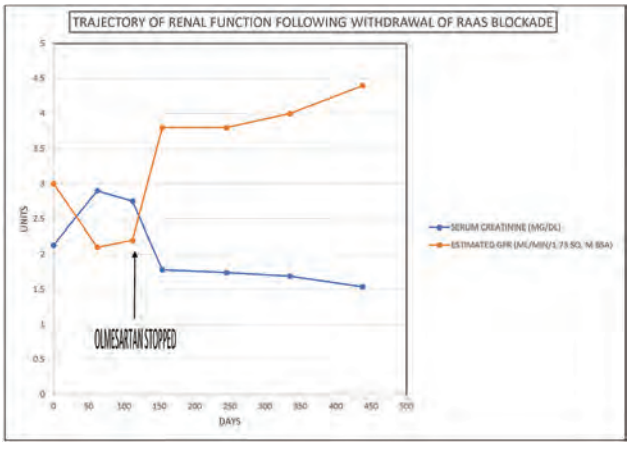
Background: There is consensus that RAAS blockade is renoprotective for both diabetic and non-diabetic proteinuric CKD. Nevertheless, there remains considerable debate and controversy regarding renal and cardiovascular (CV) outcomes with discontinuation of concurrent RAAS blockade in advanced CKD. Recent studies demonstrated discordant renal and CV outcomes.

Methods: In a Nephrology Office at the University of Vermont Medical Center, in Burlington, VT, USA, over 40 months, February 2018 – May 2021, concurrent RAAS blockade was electively discontinued in all patients who presented with progressive and >25% increase in baseline serum creatinine. Kidney function of this cohort was followed prospectively.

Results: 71 patients, 69 Caucasians, 1 African American and 1 Hispanic, 42:29 (M:F), mean age 69.4 (37-95) years were treated. Medical co-morbidities included diabetes mellitus (37) and hypertension (66). They were mostly asymptomatic. Lisinopril was commonest agent in 40 (56%) patients. Mean duration of RAAS blockade before discontinuation was 2057 (112-4043) days. Baseline creatinine was 1.38 ± 0.49 (0.66 - 2.7) mg/dL, n=70. Peak creatinine was 2.31 ± 1.09 (1.1 – 8.3) mg/dL, n=67, P<0.0001, t=6.4872, df=135. Nadir creatinine after drug discontinuation was 1.49 ± 0.45 (0.84 – 3.3) mg/dL, n=54, p<0.0001, t=5.1805, df=119. There were 5 (7%) deaths from nonrenal causes. Hyperkalemia in 34 (48%) and hyperphosphatemia in 13 (18%) resolved with improved kidney function.

Conclusions: The elective withdrawal of concurrent RAAS blockade in CKD patients who present with progressive worsening AKI generally demonstrate clearly improved renal outcomes. We posit that in selected CKD patients with progressive AKI such as in our study, RAAS blockade discontinuation indeed is the correct next step in their management for both improved renal and CV outcomes.



Kidney function trajectory after stopping Olmesartan

PUB058

A Case of Acyclovir Neurotoxicity Masquerading as Progression of Zoster Encephalitis

Jonathan Vincent M. Reyes, Arpita Joshi, Dawn Maldonado, Aaron S. Stern, Maritza Brown. *Mount Sinai Health System, New York, NY.*

Introduction: We present a case of varicella zoster virus (VZV) central nervous system infection complicated by acyclovir neurotoxicity.

Case Description: A 53-year-old male with ESRD on hemodialysis presented with acute encephalopathy. He had been diagnosed with VZV labyrinthitis 10 days prior to presentation, and was discharged on oral valacyclovir. He now presents with altered mental status. As the CSF was positive for VZV IgM and his symptoms persisted, this raised concern that his VZV infection was progressing to encephalitis. He was therefore transitioned to intravenous acyclovir for better coverage. However, the patient's encephalopathy did not improve. Acyclovir level was found to be elevated at 4.9 mcg/mL (normal <2 mcg/mL). Acyclovir was then held and he improved – demonstrating that his encephalopathy was most likely due to acyclovir.

Discussion: Valacyclovir is a renally-cleared prodrug of acyclovir. Acyclovir neurotoxicity has been rarely described in literature, and was only first recognized in the 1980s. Symptoms include lethargy, confusion, visual hallucinations, dysarthria, myoclonus and death delusions. The diagnosis is clinical. Studies suggest a temporal association between symptoms and acyclovir administration as patients typically present within 24 to 72 hours; while VZV encephalitis patients present 1 week after the onset of skin eruptions. MRI findings for VZV encephalitis include clustered subcortical plaque-like lesions with rapid demyelination. CSF demonstrates pleocytosis with mononuclear predominance and high protein. The pathophysiology for acyclovir neurotoxicity remains

under investigation. Currently the presumed mechanism is via high concentrations of 9-carboxymethoxymethylguanine (CMMG), a metabolite of acyclovir. Large doses of CMMG may inhibit mitochondrial DNA polymerase and alter mitochondrial function. Hemodialysis serves as the only treatment as the half-life of acyclovir in patients with ESRD can reach up to 20 hours, as compared to 3 hours in patients with normal kidney function. Acyclovir neurotoxicity poses a diagnostic dilemma since VZV encephalitis carries a mortality rate of up to 20%. Recognizing the risk factors and the temporal relationship between acyclovir administration and symptoms will lead clinicians to a timely diagnosis.

PUB059

Severe AKI Leads to Worse Patient-Centered Outcomes in Survivors of Critical Illness

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Background: Acute kidney injury (AKI) is a detrimental condition that occurs in about half of critically ill patients. Survivors of critical illness are at high risk of persistent impairments in physical, cognitive, and emotional health, which may be worse in patients who suffered from AKI. The main objective of this study was to evaluate patient-centered outcomes of critical illness survivors who did and did not have severe AKI.

Methods: Retrospective observational study of adult patients surviving an ICU admission due to critical illness who attended outpatient follow-up in the ICU Recovery Clinic at the University of Kentucky. Patients with end-stage kidney disease were excluded. Patients were also excluded if they had an acute neurologic, traumatic, or orthopedic injury that prevented participation in outcomes testing at their follow-up visit. The primary outcomes were distance patient ambulated on the six-minute walk test (6-MWD) and self-reported health-related quality of life (HrQoL) in a visual analog scale ranging from 0 to100 with higher scores indicating better quality of life at 3-month follow-up.

Results: A total of 105 patients were studied. Mean age (SD) was 54.6 (13) years, 53% were male, and 73% white. Sixty-eight (65%) patients had AKI, 46 of them severe AKI (KDIGO stage ≥2). ICU survivors that suffered from AKI stage ≥2 had lower HrQoL scores than those with AKI stage 1 or no AKI (69.1 ± 20.6 vs. 77.8 ± 14, p=0.015) and ambulated shorter distances on 6WMD (195.0 [153.8-285.0] vs. 300.0 [180.0-408.0]293 ± 153 meters, p=0.059). In multivariable regression analyses, older age, longer ICU length of stay, and AKI severity were associated with lower HrQoL scores; while older age and need for tracheostomy were associated with shorter distances achieved on 6-MWD.

Conclusions: Survivors of critical illness who suffered from severe AKI during their ICU stay had increased physical disability and worse quality of life compared to ICU survivors without severe AKI. Critical illness/AKI survivors may benefit from specialized post-ICU care and rehabilitation treatments. Future studies should focus on testing interventions that could ameliorate patient-centered outcomes in this special patient population.

Funding: NIDDK Support

PUB060

High Symptom Burden in Medical ICU Patients with Any Degree of AKI

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Background: We know little about patients' physical symptoms during acute kidney injury (AKI). Here we provide one of the first descriptions of symptoms in medical intensive care unit (MICU) patients with varying degrees of AKI.

Methods: This is a cross-sectional study from the MICU of an urban teaching hospital conducted 07/2016-01/2019. Study staff obtained informed consent from patients able to provide it or from a proxy (family member / friend) present at the bedside. Study staff then asked the patient or proxy if 12 specific symptoms had bothered the patient in the past 2 days. A nephrologist ascertained the presence and KDIGO stage of AKI at the time of study participation. This analysis excluded patients with end-stage kidney disease or a kidney transplant.

Results: Patient characteristics and symptom prevalence are shown in the table. In a linear regression model adjusting for AKI category, age, sex, race, ethnicity, reporter type, MICU length of stay, mechanical ventilation, and receipt of pressors / inotropes, only patient (rather than proxy) as symptom reporter was significantly associated with total number of symptoms (β=1.6, P<0.01).

Conclusions: MICU patients with any degree of AKI have a high symptom burden. The inability of most MICU patients to report their own symptoms might lead to underestimation of this burden.

Funding: Other NIH Support - NIA T32 AG049666 (SJR), NCI R35 CA197730 (HGP)

	Overall (n=165)	No AKI (n=68)	Stage 1 AKI (n=37)	Stage 2 and 3 AKI (w/o RRT) (n=35)	Stage 3 AKI (w/ RRT) (n=25)	P
Age, years	68 (53-78)	66 (49-78.5)	75 (63-83)	70 (55-77)	61 (47-69)	0.02
Female	64 (39)	27 (40)	16 (43)	10 (29)	11 (44)	0.54
Non-white race	52 (32)	19 (28)	13 (35)	8 (23)	12 (48)	0.04
Hispanic ethnicity	24 (15)	10 (15)	5 (14)	5 (14)	4 (16)	0.99
Mechanically ventilated	112 (69)	43 (65)	12 (32)	26 (77)	18 (72)	0.69
Receiving vasopressors / inotropes	49 (30)	12 (18)	11 (30)	17 (49)	9 (36)	0.01
Patient rather than proxy reporting symptoms	25 (15)	14 (22)	5 (15)	3 (9)	3 (13)	0.37
Physical symptoms bothering patient in past 2 days						
Pain*	89 (59)	38 (60)	19 (59)	18 (58)	14 (58)	1.00
Tiredness*	120 (82)	48 (79)	27 (87)	25 (81)	20 (87)	0.70
Weakness*	132 (87)	54 (87)	27 (82)	30 (91)	21 (88)	0.75
Trouble sleeping*	63 (47)	26 (43)	15 (58)	12 (46)	10 (45)	0.67
Shortness of breath*	105 (71)	45 (73)	20 (67)	22 (69)	18 (75)	0.89
Swelling*	86 (59)	31 (49)	18 (62)	18 (60)	19 (79)	0.08
Total number of symptoms**	5 (4-7)	5 (4-7)	5 (4-6)	5 (3-6)	6 (5-8)	0.47

Continuous variables as median (interquartile range); categorical variables as n (%).

*Some missing responses, so cell n may be less than column n.

**The 6 least-reported symptoms (vomiting, nausea, constipation, diarrhea, sweating, lack of appetite) not shown; P>0.10 for all.

PUB061

Expanded Hemodialysis (HDx) May Improve Inflammation in AKI due to COVID-19 Disease Requiring Renal Replacement Therapy

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Background: A baseline hyperinflammatory state afflict COVID-19 positive patients (pts). AKI as a final common pathway of systemic inflammation and increased immunologic response leading to uncontrolled circulating levels of pro-inflammatory mediators and direct cytokine-induced organ damage. HemoDialysis expanded (HDx) represents an innovative strategy to remove uremic toxins up to 50 Kda, thanks to the medium cut-off membrane (MCO) and internal convection. Transcription of pro-inflammatory cytokines in peripheral leukocytes is markedly reduced and removal of soluble mediators of inflammation is enhanced by HDx. In vitro studies confirm that HDx limit neutrophil activation by decrease of ROS, TNF-alpha and IL6 and increase of apoptosis. Aim of this study is to evaluate the response to treatment with HDx and HF-HD in AKI due to COVID-19 disease.

Methods: Six pts were enrolled in a retrospective observational study: 3 pts were treated with HF-HD (FX80-Fresenius) and 3 with HDx (Theranova 400-Baxter) during COVID-19 infection. 2 pts treated with HDx and 1 with HF-HD showed hemodynamic instability and need for vasopressors. They were daily assessed using the following: urea, creatinine, C-reactive protein (CRP), procalcitonin (PCT), D-Dimer and Albumin. The values have been reported as mean±SD.

Results: HDx (Qb=218±48 ml/m) discovered in every patient a significant reduction for CRP (-59.7% average) and PCT (-11,2% average), whereas HF-HD (Qb=205±27 ml/m) showed an opposite trend (+69,1% and +39,1% average). Moreover HDx induce a greater reduction of D-Dimer (51.4% vs 19.8% average), Urea and serum Creatinine in comparison to HF-HD (average), (Tab.1) and better hemodynamic stability (Pam 75 vs 67 mm/Hg).

Conclusions: HDx effectively impact on inflammation and renal markers, compared to HF-HD, in COVID-19 positive. HDx, due to the increased clearance of cytokines, has recently been confirmed as a support for COVID-19 positive treatment in some Italian dialysis centers. Our preliminary results has to be confirmed by enlarged studies but in the meantime could help to build a new scientific evidence.

Tab. 1

		HDx				HF-HD			
	n. patients	1	2	3	mean	4	5	6	mean
Urea	Baseline	376,0	391,0	183,0	316,7	84,0	129,0	76,0	96,3
	After	190,0	163,0	261,0	204,7	111,0	116,0	81,0	102,7
Creat	Baseline	6,2	6,9	7,9	7,0	5,0	5,5	3,5	4,7
	After	3,8	3,5	6,7	4,7	5,4	4,3	2,5	4,1
PCT ng/ml	Baseline	19,5	0,6	1,3	7,1	2,2	2,2	0,4	1,6
	After	18,0	0,2	0,8	6,3	2,0	4,2	0,5	2,2
CRP mg/l	Baseline	188,0	16,9	153,0	119,3	74,0	97,4	4,4	58,6
	After	64,1	7,4	72,7	48,1	78,1	210,0	9,1	99,1
D-Dimer ng/ml	Baseline	7893	3104	1872	4289,7	1593	599	2748	1646,7
	After	2062	1982	2198	2080,7	1284	1648	1026	1319,3

PUB062

Enhanced Recovery After Surgery (ERAS) Protocol and the Risk of AKI

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Background: Two of the components of ERAS protocol are the maintenance of euvolemia and the use of multimodal analgesia, which includes NSAIDs. Given the restrictive fluid therapy strategy and the potential use of nephrotoxic analgesics, it's pertinent to assess the risk and potential consequences of acute kidney injury (AKI). The objectives of this study are to assess the incidence of AKI and its outcomes.

Methods: Descriptive and single-center retrospective study. It included the first two hundred adult patients consecutively enrolled for colorectal surgery according to the ERAS protocol. AKI was defined according to KDIGO criteria.

Results: The median age was 71 years (IQ 62-78) and 64.5% of patients were male. The clinical follow-up time was 39 months (IQ 33.8-44.2). Compliance with the ERAS protocol was 81.5% (IQ 71.4-66.5). The median length of stay was 7 days (IQ 5-11). AKI occurred in 23% (46), mostly KDIGO 1 (71.7%). There was a need for renal replacement technique (RTFR) in 8.7%. Patients who developed AKI had a higher median age (76 vs. 70, p<0.001), incidence of diabetes (32.6% vs. 15.6%, p=0.011), hypertension (84.8% vs. 57.8%, p<0.001) and chronic kidney disease (65% vs. 48%, p=0.041). Weight loss in the first 24h was higher in patients who developed AKI (-1.9kg vs. -0.5kg, p=0.010). There was no statistical difference in the administration of NSAIDs. Patients who developed AKI had a greater need for postoperative aminergic support (13% vs. 1.9%, p=0.001) and mechanical ventilation (13% vs. 0.65%, p<0.001). They were more often submitted to laparotomy (41% vs. 25.3%, p=0.036) and exposed to intravenous iodinated contrast (34.8% vs. 17.5%, p=0.012). Patients with AKI had greater need for admission to intensive care (23.9% vs. 9.7%, p=0.019) and lower survival at follow-up (log rank 19.030, p<0.001). None of the patients were dependent of dialysis at discharge. In the first 2 years of follow-up, patients who developed AKI had a more pronounced decline in eGFR (6.3mL/min/1.73m2/year vs. 3.48mL/min/1.73m2/year, p=0.030).

Conclusions: AKI was associated with a worse clinical prognosis with reduced survival. Additionally, the development of AKI negatively influenced the reduction of glomerular filtrate in the first 2 years. Some clinical factors were identified, as age and comorbidities, that may help us to identify patients at higher risk.

PUB063

Renal Surgery and Postoperative AKI Risk in Normal Renal Function Patients: A Hidden Threat

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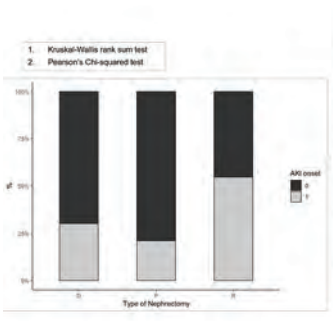
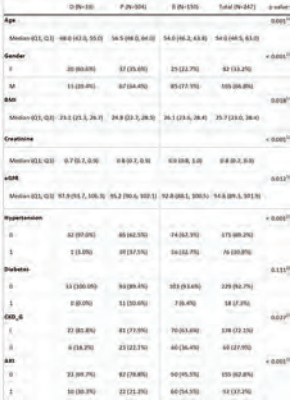
Background: Acute kidney injury(AKI) is a major postoperative complication in renal surgery, both in radical(RN) than in partial nephrectomy(PN). One of the most intriguing arguments is to understand if normal renal function patients(pts) can develop post-operative AKI after renal surgery, both in the oncological and in the living donors' assets. Aim of our study was to compare the AKI incidence in the two major renal surgeries approaches in a selected cohort of pts with normal renal function

Methods: We enrolled a cohort-study of 214 pts who underwent RN or PN due to the presence of a kidney mass suspected of malignancy in a tertiary Institution. A control group of 33 kidney living donors was also enrolled to measure the impact of RN in non-oncological pts. Serum creatinine (s-Cr) values were collected before surgery (t_0), at 48 hours after surgery and at dismissal to detect renal function fluctuations and the subsequent risk of AKI. GFR was estimated at each time point using CKD-EPI 2012 formula. Comparisons between groups were performed using Kruskal-Wallis ranks sum test for numerical variables and Pearson's Chi square test for categorical variables

Results: Descriptive analysis is reported in table1. AKI onset showed a significantly different distribution(p<0.001) between the three groups. In the oncological RN asset the AKI developed in the 55% of pts, whereas in the PN group occurred in 21% of pts. In RN for living donation AKI happened in 30% of pts(Figure1). AKI onset was not significantly correlated with any other variables(Age, Gender, BMI, basal eGFR, Hypertension, Diabetes)

Conclusions: Our study highlights that both radical(55%- 30%) than partial(21%) nephrectomies harbor a non negligible risk of post-operative AKI even in normal renal function patients without renal abnormalities





PUB064

Mind the Gut: Gastric Complications of Immunosuppressive Therapy in a Patient with ANCA Vasculitis

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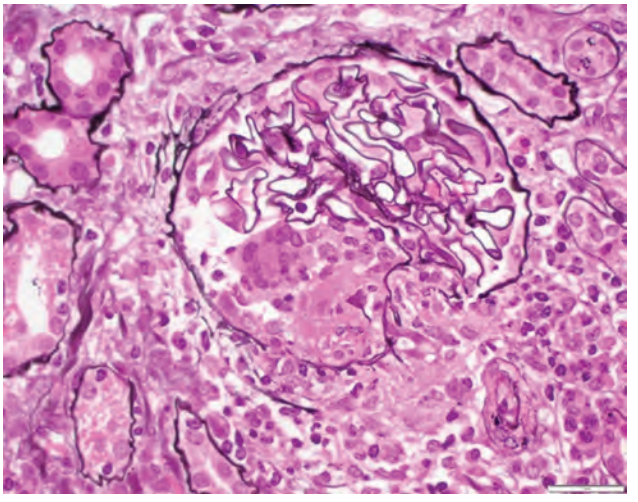
Introduction: Granulomatosis with polyangiitis (GPA) is one of three ANCA-associated vasculitidies which frequently affects the small vasculature of the pulmonary and renal systems. Management has evolved due to several pivotal trials, and recent data from PEXIVAS trial suggests lower prednisone doses maybe just as effective as the higher doses, with fewer complications.

Case Description: A 76-year-old - previously healthy woman presented with shortness of breath and cough. She was treated as an outpatient for presumed atypical bacterial pneumonia without improvement. On admission, she had a RR of 24 and oxygen saturation of 87% on room air and examination revealed crackles in bilateral lung bases. Labs were remarkable for Hgb 7.1 mg/dL and Cr 4.2 mg/dL from a baseline of 1mg/dl. UA showed moderate blood and 100mg/dl protein. On day 2, she developed new-onset hemoptysis. Kidney function deteriorated over the next several days requiring temporary dialysis. She was started on empiric pulse dose steroids and kidney biopsy confirmed severe diffuse crescentic, necrotizing pauci-immune glomerulonephritis with anti-MPO antibody/P-ANCA sero-positivity. She was treated with steroids and rituximab. She continued to have hemoptysis, prompting initiation of plasmapheresis as well as discharge on a 6-month course of prednisone. She was also discharged with GI prophylaxis, which unfortunately she was not taking and she was readmitted 1-month later for gastric ulcer perforation likely as a complication of steroid use, and unfortunately expired.

Discussion: This case outlines the severity and high risk for mortality in patients with GPA. Not only can the associated inflammation itself be fatal but immunosuppression is not without risk; such as the risk for peptic ulcer disease with steroid use as highlighted in this case. Data from trials such as PEXIVAS should be considered.



Renal Biopsy (Jones stain) showing cresecentic glomerulonephritis.

PUB065

Magnetic Resonance Imaging Contrast Leads to Acute Tubular Damage and Accumulation of Gadolinium-Rich Nanoparticles in Renal Cortex

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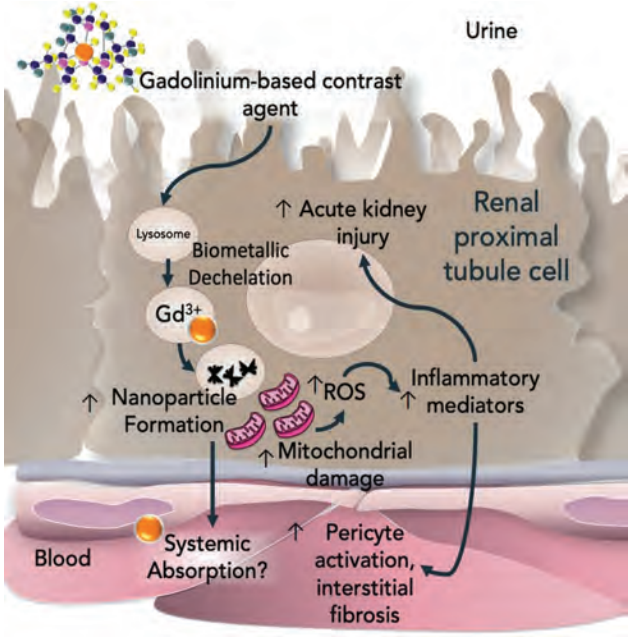
Background: Intravenous administration of gadolinium-based contrast agents leads to long-term gadolinium retention in every vital organ, including the kidney and the brain, regardless of brand. The *safety profile of gadolinium-chelate agents remains the subject of debate.*

Methods: Male and female C57/BL6 mice were randomized by age and weight to GBCA-treatment (Omniscan, 2.5 mmol/kg, intraperitoneally, 20 doses over 4 weeks) or control (n = 20 each). Kidneys were isolated, fixed, sectioned at 200 nm, and supported with carbon holey grids. Scanning electron microscopy and multiple elemental analyses by energy-dispersive x-ray spectroscopy (EDS) were performed using JEOL 2010F FEGSTEM (200kV) microscope and the FEI Tecnai G(2) F30 S-Twin (300kV) transmission electron microscope.

Results: Renal proximal tubule cells of GBCA-treated animals exhibited lipid-laden vacuoles and extensive mitochondrial damage. Spiculated, electron-dense nanoparticles self-assembled in the tubular epithelia of gadolinium-treated animals. The electron densities were rich in gadolinium, phosphorous, and calcium. Gadolinium and phosphorous co-localized within the electron densities.

Conclusions: Systemic magnetic resonance imaging contrast treatment leads to the self-assembly of gadolinium-rich nanostructures in kidney tubular cells. These *in vivo* findings demonstrate that transmetallation is occurring (and this may be a mechanism for the resultant fibrosis) (**Figure**). Speciating the gadolinium-rich precipitates may aid in prophylactic strategies and therapies for gadolinium-induced diseases (including acute kidney injury, gadolinium deposition disease, gadolinium-associated plaques, 'nephrogenic' systemic fibrosis, and gadolinium-induced encephalopathy).

Funding: NIDDK Support, Veterans Affairs Support, Commercial Support - Dialysis Clinic, Inc.



PUB066

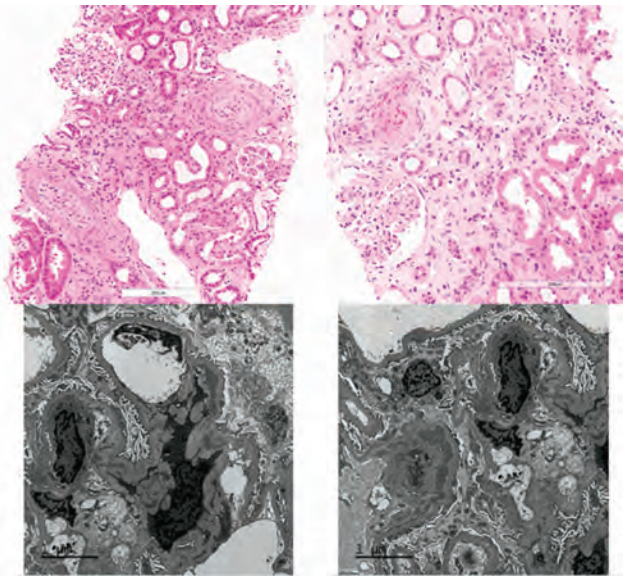
Scleroderma Renal Crisis Sans Scleroderma

Zachary Drury,[1] Adhish Agarwal,[1] Martin C. Gregory,[1] Niraj K. Yadav,[1] Monica P. Revelo Penafiel,[1] Isaac Lloyd,[2] Josephine Abraham.[1] *[1]University of Utah Hospital, Salt Lake City, UT; [2]Intermountain Healthcare, Salt Lake City, UT.*

Introduction: Scleroderma renal crisis (SRC) is an uncommon autoimmune disease that can present with hypertension, acute kidney injury (AKI), proteinuria, hematuria. Rarely is SRC the initial manifestation of scleroderma (scleroderma renal crisis sans scleroderma). We report a case of a patient presenting with SRC complicated by malignant hypertension, thrombotic microangiopathy, and acute kidney injury (AKI).

Case Description: A 47 year old female with four months of headache, blurry vision, and chest palpitations who presented to an outside hospital in hypertensive crisis. Serum Creatinine (Scr) was 1.1 mg/dl initially, however steadily increased to a peak level of 4.46 mg/dl. Urinalysis showed small blood and protein, and spot urine protein to creatinine ratio was 1,412 mg/g. SSA antibody was positive, while SLC 70 antibody and centromere antibody were negative. Serum aldosterone was 60.3 ng/dl and plasma renin activity 43.4ng/ml/hr with aldosterone/renin ratio 1.4. Evaluation for renal artery stenosis was negative. A kidney biopsy showed thrombotic microangiopathy with scattered subendothelial immune complex deposits. The patient was transferred to our facility where her SCr continued to worsen. She was started on lisinopril 2.5mg when her creatinine level was 3.89 mg/dl. SCr stabilized after three days of ACE inhibition.

Discussion: SRC is a medical emergency requiring prompt diagnosis and treatment. Diagnosis can be challenging when this is the initial presentation of scleroderma. SRC should be considered in the differential diagnosis for patients presenting with AKI, new-onset microscopic hematuria, proteinuria, malignant hypertension and thrombotic microangiopathy. ACE inhibition is crucial for patient survival and can lead to renal recovery, which could take as long as 24 months after a renal crisis.



PUB067

Fenofibrate-Induced AKI: An Underrecognized Adverse Effect

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Introduction: Fenofibrate is widely used as a second-line agent for hyperlipidemia refractory to statin therapy, especially in the setting of nephrotic syndrome and severe hypertriglyceridemia. There is growing evidence that fenofibrate can cause acute kidney injury (AKI) and that this might be occurring more often than previously thought.

Case Description: 42-year-old male patient with a history of hypertension and hyperlipidemia (predominantly hypertriglyceridemia in the 500-600 mg/dL range) had been on fenofibrate and angiotensin-II receptor blocker (ARB) for 18 months (no recent dose changes) and had a serum creatinine (S Cr) 1.0 mg/dL at baseline. He developed sub-acute kidney injury with S Cr peaking at 2.2 mg/dL over 6 months. He underwent kidney biopsy that showed tubular injury. Possibility of fenofibrate-induced AKI was entertained, as he was not on any other potential nephrotoxic medications. The drug was stopped and renal function returned to his prior baseline within a month. It remains normal and unchanged 9 months after stopping the drug.

Discussion: It is known that fenofibrate can cause fully reversible isolated elevations in serum creatinine by inducing increased metabolic secretion of creatinine. It causes a true AKI by means of rhabdomyolysis, often when used with a statin, and in patients who have other risk factors like chronic kidney disease (CKD). However, there are recent studies showing fenofibrate causing true AKIs evidenced by rise in cystatin C, an independent marker for kidney function, with subsequent decline in glomerular filtration rate (GFR). The exact mechanism of fenofibrate-induced AKI is still not fully understood but one hypothesis is that it impairs the production of renal vasodilatory prostaglandins, leading to renal vasoconstriction, and subsequently causing reduced renal plasma flow and glomerular pressure. Fenofibrate-induced AKI remains an under-recognized adverse effect of the drug. Although there is growing evidence and reports of these incidences, the exact mechanism remains unclear. Further studies showing the effects of fenofibrate on renal tissues at the molecular level are needed to better understand the pathophysiology of renal injury.

Serum creatinine (SCr) trend

Date	5/2019	11/2019	5/2020	7/2020	5/2021
SCr (mg/dL)	1.0	1.3	1.5	2.2	1.0

PUB068

Granulomatous Interstitial Nephritis Unrelated to Drug Exposure in a Patient with Ulcerative Colitis

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Introduction: Granulomatous interstitial nephritis (GIN) has been reported in patients with inflammatory bowel disease (IBD) treated with mesalamine but rarely as inherent manifestation of IBD. Herein, we report a rare case of a young adult with a non-bloody diarrhea and acute kidney injury (AKI) caused by GIN and subsequently newly diagnosed with ulcerative colitis (UC).

Case Description: A 24-year-old man presented to an outside hospital with non-bloody watery diarrhea for 4 months, abdominal pain and unintentional weight loss. No report of voiding disturbance. He was taking no medications. Upon arrival, his vital signs and physical exam were normal. Laboratory data were pertinent for a serum creatinine of 8.0 mg/dL (baseline 0.6 mg/dL), and severe anemia. Urine studies were only relevant for sterile pyuria, no proteinuria. A kidney ultrasound showed no abnormalities. A kidney

biopsy was performed on the 9th day of hospitalization. He was discharged the next day. He presented to clinic 6 days post-discharge with persistent diarrhea. His vital signs and physical examination remained normal. Serum creatinine was still elevated at 7.2 mg/dL. Microscopic examination of the urinary sediment only revealed coarse granular casts. The kidney biopsy specimen revealed a diffuse cellular infiltrate involving 80% of the interstitium**,** 70% interstitial fibrosis with atrophy, acute tubular injury and tubulitis. No glomeruli was present for immunofluorescence. Electron microscopy showed no deposits. Treatment of GIN with prednisone 60 mg qd was begun. After 3 weeks, his serum creatinine improved to 4.8 mg/dL. A colonoscopy showed severe pancolitis consistent with UC and adalimumab and azathioprine were added. Six months later, his serum creatinine value remains at 4.8 mg/dL (eGFR 16 ml/min).

Discussion: GIN is a rare histologic diagnosis that may be the first manifestation of a systemic disease or caused by drugs. GIN causing AKI has been rarely described in therapy-naïve patients with IBD, primarily in Crohn disease. Given the profound inflammation and young age and despite the severe chronicity in the biopsy specimen, the patient was treated with immunosuppressive therapy (IST). IST was later escalated to treat the UC lesion. Drug-naïve IBD should be listed as potential cause of GIN.

PUB069

Post Coronary Angiography Cholesterol Embolization Syndrome Resulting in Atheroembolic Renal Disease

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Introduction: Cholesterol embolization syndrome (CES) has been characterized as being a multi-system disease resulting from embolization of cholesterol crystal from atherosclerotic plaque of large arteries to small class arteries resulting in organ insult. A poorly recognized subgroup of CES is atheroembolic renal disease (AERD) or renal CES which accounts for a considerable subgroup. We present a case of a 69-year-old female who developed renal CES after undergoing coronary angiography.

Case Description: Our patient was a 69-year-old female with past medical history of chronic kidney disease stage 3, diabetes mellitus, hypertension, and heart failure with ejection fraction 40-45%, coronary artery disease, and chronic obstructive pulmonary disease who presented with progressive dyspnea and lower extremity edema for several months. Two months prior to this admission she had undergone coronary angiography. Her initial creatinine was 1.28 mg/dL. Over the next two months her creatinine up trended to 2.93 mg/dL. The inciting factor was initially attributed to acute kidney injury secondary to over diuresis. On examination the patient looked euvolemic but continued to have dyspnea despite diuresis. Right heart catheterization was performed to better assess volume status which demonstrated normal filling pressures. Laboratory results were notable for persistent eosinophilia. In the context of recent contrast, rising eosinophilia, and normal filling pressures a renal biopsy was performed which demonstrated acute tubular injury, arterionephrosclerosis, and cholesterol emboli. Despite medical management, the patient's renal function did not recover.

Discussion: Our patient's initial presentation was concerning for decompensated heart failure with a possible cardiorenal insult. Post-diuresis instead of having improvement in her dyspnea and acute kidney injury, she continued to decompensate. Further complicating her presentation was recent contrast exposure for coronary angiography and rising eosinophilia. Biopsy ultimately showed cholesterol emboli that most likely dislodged post catheterization and caused acute tubular injury. The teaching point of our case is to consider atheroembolic renal injury irrespective of coronary angiography timing in patients with preexisting cardiac and kidney disease non-responsive to medical therapy.

PUB070

Checkmate? A Rare Case of Immune Checkpoint Inhibitor-Related AKI

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Introduction: With the advent of Immune checkpoint inhibitors (ICPIs) used in cancer therapy, there has been improved prognosis in various malignancies; however, with the use of these novel class of drugs, there has been a rise in associated immune-related adverse events reported, including acute kidney injury (AKI). ICPI-associated AKI is an emerging entity and in this case we highlight one such ICPI, Nivolumab, an antibody directed against programmed death-1, causing renal dysfunction.

Case Description: An 80-year-old man with renal cell carcinoma with baseline creatine of .58 mg/dl (RCC) was referred to Nephrology services to evaluate AKI, with serum creatinine 2.3mg/dl, found in routine labs. The patient received immunotherapy with Nivolumab every four weeks. Urinalysis revealed no active sediment and renal ultrasound remarkable for solid mass in the left kidney, consistent with previous imaging of his RCC. The patient was diagnosed with Nivolumab-induced immune tubulointerstitial nephritis. At the time of presentation, the immunosuppression was placed on hold, and he was started on steroids. His kidney function gradually improved to serum creatinine of 1.3 mg/dl, with the withdrawal of Nivolumab and initiation of steroid therapy.

Discussion: In this case, we highlight an instance of Nivolumab-induced AKI, which poses a unique diagnostic and management challenge to clinicians due to lack of clinical awareness in the account of the rarity of such immune-related side effects. With the rise in the use of new novel biologic agents, a multidisciplinary approach is essential so that clinicians can make a timely diagnosis when there is a high suspicion. Prompt discontinuation and early steroid therapy institution is crucial in management and can prevent further kidney injury or potential chronic kidney disease.

PUB071

Severe ESA Resistance Reversed by Cinacalcet in a Hemodialysis Patient with Sickle Cell Anemia

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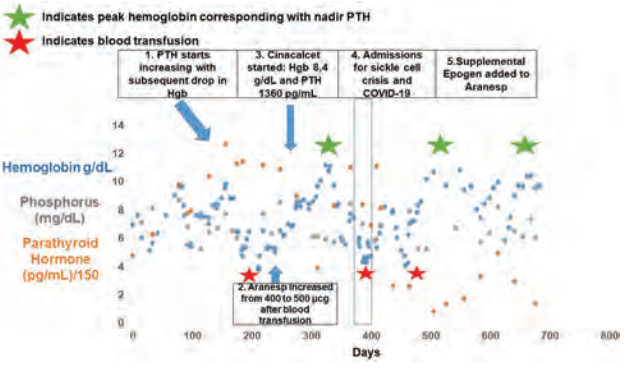
Introduction: Hematologic diseases such as sickle cell disease (SCD) complicate anemia of end-stage renal disease (ESRD). Hyperparathyroidism is another etiology of ESA resistance that can cause irreversible bone marrow fibrosis. We present a case of severe anema in a SCD patient on hemodialysis (HD) that dramatically improved with cinacalcet.

Case Description: The patient is a 28 year old Black man with SCD and ESRD from FSGS on thrice weekly HD. His anemia had been treated with hydroxyurea and high dose subcutaneous Aranesp (400 µg every 2 weeks) with a mean hemoglobin (Hgb) of 6.4 (1.4) mg/dL over several years. He developed worsening hyperparathyroidism on phosphate binders and vitamin D. Despite stable Aranesp doses, Hgb decreased until a blood transfusion was needed. Aranesp was increased to 500 µg every 2 weeks with some increase in Hgb. After starting cinacalcet, parathyroid hormone (PTH) decreased (1390 to 593 pg/mL), and Hgb further increased (8.2 to 11.2 mg/dL). Intermittent nonadherence to cinacalcet led to PTH variability until hospital admissions for sickle cell crisis and then COVID-19. Afterwards, PTH was more consistently suppressed. Following day 500, supplemental Epogen was given in addition to Aranesp, but Hgb increased only when PTH was most suppressed. During the first year on cinacalcet, there was a strong inverse correlaton between Hgb and PTH (r=-0.6, p=.001). Figure 1 shows the Hgb, phosphorus, and PTH (divided by 150 to simplify y-axis) where Hgb peaks correspond to PTH nadirs.

Discussion: We demonstrate a case of severe anemia from both ESRD and SCD where Hgb dramatically improved with cinacalcet. We acknowledge that Aranesp increases preceded the initial Hgb rise, but Hgb peaks following PTH suppression exceeded any prior levels. These Hgb peaks were reproducible and sustained whenever PTH suppression was achieved. This case demonstrates that some hyperparathyroidism-related ESA resistance may be reversible and supports how important control of bone mineral disease is in specific populations of HD patients that are susceptible to severe anemia.



PUB072

Addition of Roxadustat to Erythropoiesis-Stimulating Agent (ESA) Effectively Corrects ESA-Hyporesponsive Anemia in Peritoneal Dialysis Patients

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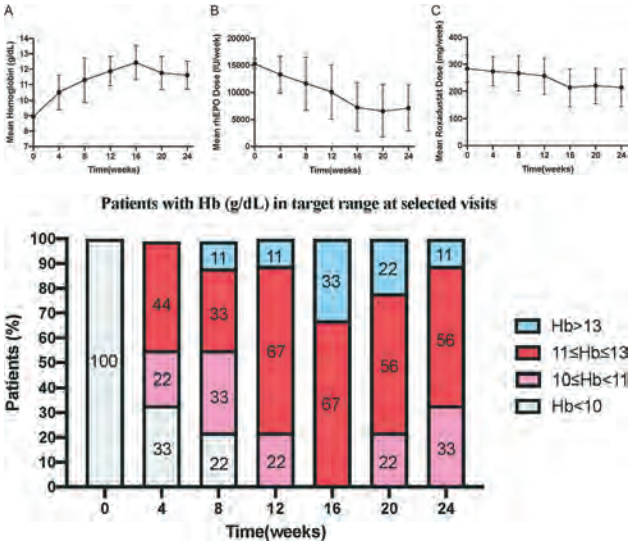
Background: Erythropoiesis-stimulating agent (ESA) hyporesponsiveness is an important cause for the undertreatment of anemia. This study aimed to investigate the effectiveness and safety of adding HIF-PHI (roxadustat) to ESA for the treatment of ESA-hyporesponsive anemia in Peritoneal Dialysis (PD) patients.

Methods: This was a single-center prospective-designed study in PD patients of Huashan Hospital, Fudan University. Patients with ESA-hyporesponsive anemia were enrolled from January 2020 to April 2020 with a 24-week follow-up period. Patients were added with roxadustat at a starting dose of 50 or 100 mg thrice weekly without changing the ESA dose. Roxadustat and ESA dose adjustments were made as needed to maintain Hb levels within 11.0–13.0 g/dL. Efficacy outcomes and safety were assessed.

Results: A total of nine patients were recruited in the study. Both the cumulative responsive rate and the maintenance rate of patients with Hb>11g/dL were 100%. Six out of nine patients had ESA dose reduced from 15,000 UI/week or more to 7000 IU/week or less at week 24. No drug-related severe adverse event was reported in this study.

Conclusions: The present study showed that the addition of roxadustat not only effectively corrected anemia in patients who were resistant to ESA, but also reduced the dose of ESA.



PUB073

Hypercalcemia Secondary to Silicon Injections (Granulomatous Disease): Case Report

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Introduction: Hypercalcemia is a relatively common clinical problem. Among all the causes of hypercalcemia, primary hyperparathyroidism and malignancy are most common. Other less common causes include granulomatous diseases (tuberculosis and sarcoidosis), milk alkali syndrome, immobility, medications and familial hypocalciuric hypercalcemia. We Have seen a case of hypercalcemia secondary to silicone injections leading to granulomatous inflammation.

Case Description: 39 y/o F with a history of Sjogren's disease (+ ANA 1:80 cytoplasmic, 1: 2,560 speckled, +SSA/SSB + sicca symptoms), recurrent hypercalcemia, malnutrition, history of silicone injections (gluteal), at age 19, who presented to the hospital with facial swelling and found to have hypercalcemia (calcium 17, ionized calcium 1.89, serum albumin 2.3). On examination she had severe soft tissue changes in her bilateral legs, ankles, buttocks and hips. Initial differential was malignancy, primary hyperparathyroidism and soft tissue tumor. Work up consistent with elevated 1,25-Vit D(280), ACE (77; nml 9-67), PTHrP (11.3; nml 0.0-3.4) and PTH was found to be appropriately suppressed (<6.3; nml 18.5-88). CT Scan reveal marked edema gluteal region bilaterally, pelvic wall, perineum and proximal thighs due to foreign body granulomatous/silicone injections. There was no evidence of malignancy on CT scans. She had no clinical signs of sarcoidosis. She has been treated with IVF, pamidronate, and calcitonin, with minimal improvement of her calcium levels. She continues to have recurrent hypercalcemia requiring steroids and repeat treatment with pamidronate, despite extensive excisional debridement of silicone implants.

Discussion: Our patient diagnosed with the granulomatous disorder secondary to silicon injections as the etiology of hypercalcemia. This is supported by her low parathyroid hormone (PTH) level and high (1,25) dihydroxy vitamin D level. Her Skin and soft tissue fragments from debridement/excision showed foreign body (silicone) granulomas, associated scarring and dystrophic calcification. Cosmetic filler injections are known to cause several acute and chronic effects, including local inflammation, nodule formation, and granulomatous reaction. Treatment includes steroids, bisphosphonates, and the removal of implants. Hypercalcemia may persist, and long-standing low dose steroid recommended to maintain calcium and kidney function.

PUB074

Lack of Testing, Urgency to Treat, Consensus, and Concrete Guidelines All Contribute to Subpar Management of Secondary Hyperparathyroidism and Vitamin D Insufficiency for Non-Dialysis Patients with CKD

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Background: During October and November 2020, we conducted an independent, retrospective patient chart audit of 1,030 non-dialysis patients with CKD (eGFR<60) who were most recently seen by their nephrologist (n=183). The purpose of this study was to understand the real world patient presentation and treatment priorities for non-dialysis CKD patients as it pertains to the management of CKD MBD.

Methods: Using a HIPAA-compliant, online chart review tool, nephrologists submitted de-identified clinical and non-clinical demographic information beginning at the time of patient referral and concluding with details from the most recent visit. These data were then merged with the physician demographic profile and attitudinal responses. The full data set was analyzed in SPSS.

Results: When asked about their top interest in nephrology, only 6% selected bone and mineral metabolism/SHPT; respondents were most interested in glomerular diseases, AKI, and diabetic kidney disease. At the time of first referral, 38% of patients had a 25,D level in their chart and 36% had an iPTH level. At the most recent visit, only slightly more than half of the patients had at least one measure for 25,D and iPTH. Among patients treated with active vitamin D (AVD), more than half (57%) had increases in the serum calcium level and 7% had a level of at least 10.0mg/dL at last measure. Importantly, among patients currently prescribed AVD, 31% did not have a iPTH test in the past 12 months. Among treated patients with a iPTH test, 19% had a level >300pg/dL. Unlike the use of AVD, which increases as renal function declines, treatment with nutritional vitamin D (NVD) is more consistent across stages, with 46% of patients being treated; at referral, more than one-in-five are already on NVD (vs. just 2% for AVD). Similar to AVD testing patterns, there are gaps in follow-up testing. Furthermore, treatment patterns reveal that AVD is often added to the NVD regimen instead of a switch, resulting in about half of the AVD-treated patients also on NVD. Less than 10% of NVD-treated patients achieve a 25,D level of 50ng/mL, despite that, 28% have iPTH levels >100.

Conclusions: Improved monitoring of 25,D and iPTH among CKD-ND patients could lead to better outcomes.

PUB075

Use of Alkaline Phosphatase as a Bone Marker in Patients on Hemodialysis

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Background: Some patients on hemodialysis may suffer from high turnover bone disease despite having levels of parathormone (PTH) within the targets set by KDIGO. Recent international guidelines suggest the use of other bone markers, such as serum total and bone-specific alkaline phosphatase (TALP and BALP respectively). The caveat of using TALP to assess bone turnover status is that other conditions, such as hepatic cholestasis, also cause increases in TALP. We can, however, use it as an alternative to BALP as long as gamma-glutamyl-transferase (GGT) is normal. Though it would generally be expected that PTH and TALP move in the same direction with changes in bone turnover, these two markers can sometimes evolve in opposite directions. Our study aimed to evaluate the correlation between PTH, TALP and BALP.

Methods: Cross sectional study including all patients on hemodialysis at the Hôpital Maisonneuve-Rosemont from May 9, 2019 to June 7, 2019 (N=264 patients). We measured PTH, TALP and BALP in these patients and correlation coefficients were calculated. Regression analyses were performed for multiple potential confounding factors.

Results: The correlation between PTH and TALP was found to be positive and moderate (Rho 0.36; p-value < 0.0001). It was not statistically significant in patients having high GGT levels (above 60 IU/L) and was stronger in patients with normal GGT (Rho 0.40; p-value < 0.0001). The correlation between PTH and BALP was also positive and moderate, but stronger than with TALP (Rho 0.43; p-value <0.0001) and statistically significant even in patients having high GGT levels. The correlation between TALP and BALP was positive, strong and statistically significant (Rho 0.86 ; p-value <0.0001) ; it was stronger when GGT levels were normal compared to patients with high GGT levels (Rho 0.94 and Rho 0.71 respectively).

Conclusions: There is a positive correlation between PTH and TALP but it is only moderate. It is thus important to take into consideration TALP in patients with normal GGT levels when evaluating the bone status of patients on hemodialysis.

Correlation coefficients for all patients and stratified by GGT level

		All patients (N=264)		Patients with normal GGT levels (≤60 IU/L) (N=237)		Patients with high GGT levels (>60 IU/L) (N=27)	
		Rho	p-value	Rho	p-value	Rho	p-value
PTH	TALP	0.36	<.0001	0.40	<.0001	0.31	0.1156
PTH	BALP	0.43	<.0001	0.42	<.0001	0.48	0.0116
TALP	BALP	0.86	<.0001	0.94	<.0001	0.71	0.0003

PUB076

Intravenous Paricalcitol Treatment in Chinese Hemodialysis Patients: A Real-World Database Analysis

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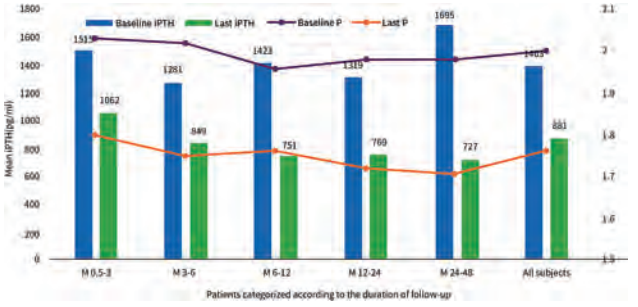
Background: The aim of this analysis based on the real-world database was to observe the effect of paricalcitol on blood calcium and phosphorus and the safety profile in Chinese hemodialysis patients with secondary hyperparathyroidism under routine clinical practice.

Methods: A total of 668 Chinese hemodialysis patients from 104 dialysis centers between 2015 and 2019 were included. Intact parathyroid hormone (iPTH), total serum calcium (Ca), phosphate (P), dosage of paricalcitol (Zemplar®) were analyzed via retrospective analysis of the database during the treatment.

Results: Patients were divided into five groups according to the duration of follow-up. Median iPTH levels decreased from 1183 pg/ml at baseline to 676 pg/ml at the final visit, or 30.88% (p < 0.0001). Serum Ca levels shown significantly increased just in the group of Month 12–24 (P=0.0479). The incidence of hypercalcemia for three consecutive laboratory draws was significantly lower than the incidence of hypercalcemia for two consecutive laboratory draws in all groups (0.5-3 months 0.49% vs 2.96%, respectively,

3-6 months 0.49% vs 4.88%, 6-12 months 4.00% vs 8.00%, 12-24 months 4.00% vs 20.00% and 24-48 months 2.10% vs 5.99%, respectively). Subgroup analyses of patients with hyperphosphatemia showed a rapid phosphate reduction, within the first few weeks, along with the reduction in the iPTH level.

Conclusions: This is the first national retrospective real-world observational study since intravenous paricalcitol is available in China since 2014. This study adds valuable information to real-world data investigating the use of paricalcitol in Chinese hemodialysis patients and demonstrated the use of paricalcitol as an effective and well-tolerated treatment for the control of PTH during its use in routine practice. The occurrence of hypercalcemia is mostly transient, followed by continuous treatment, the blood calcium level tends to be stabilized, and the blood phosphorus level will be improved with the control of PTH.



PUB077

Paricalcitol in Hemodialysis Patients with Secondary Hyperparathyroidism: A Long-Term Case Report

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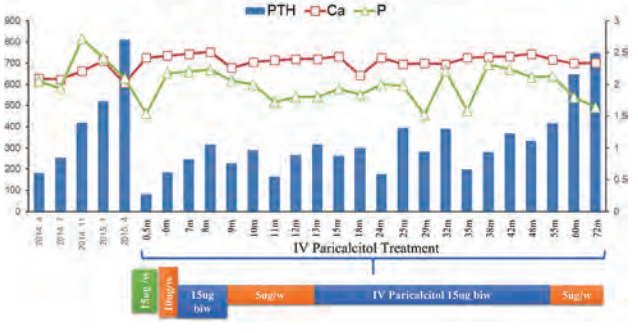
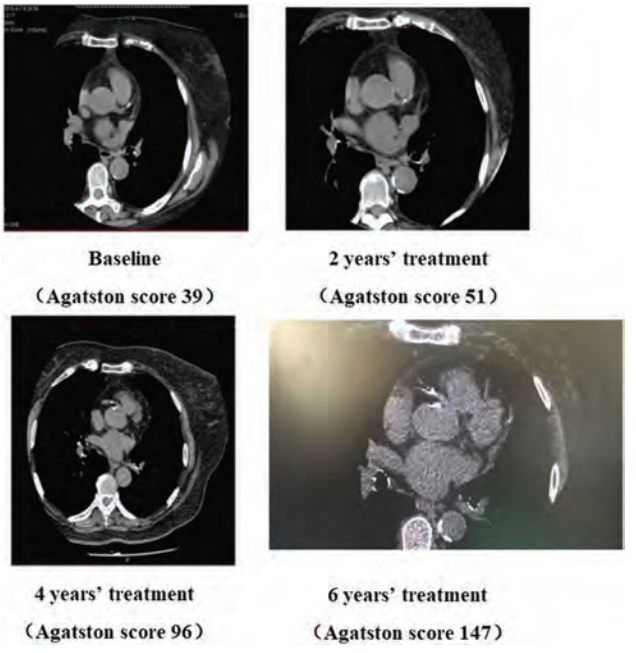
Introduction: A case analysis of a HD patient with SHPT was performed, who was in paricalcitol treatment for 72 months, to provide a reference for SHPT management.

Case Description: A 67-year-old female HD patient had calcitriol 0.25 ug qd since 2014. On April 2015, biochemical indexes were Ca 2.02 mmol/L, P 2.1 mmol/L, iPTH 810.1 pg/ml, ALP 88 U/L, without significant abnormality in Parathyroid ultrasonograpy. While Coronary CT showed high-density calcified plaque in the left anterior descending branch, with a calcium score of 39. Then, she discontinued calcitriol and initiated Paricalcitol (Zemplar®) treatment (Detailed treatment regimen and indexes variations in Figure 1). On Month 24, iPTH level decreased to 176 pg/ml (78%), and the left anterior descending artery calcium Agatston score was 51. During Month 24-48, iPTH were 150-500 pg/mL, with stable Ca and P levels in normal range. On Month 72, the left anterior descending calcium Agatston score was 115 and a total calcium score of 147 (CT Images in Figure 2).

Discussion: Paricalcitol can selectively activate VDR especially in parathyroid, to correct the CKD-MBD and prevent cardiovascular events. In this long-term case, we have seen its efficacy and safety in SHPT treatment, especially in controlling the risk of vascular calcification. There is still a lack of data on the clinical application of paricalcitol for long-term use in China, Further studies are needed to confirm its benefit, and to explore best dosage for preventing vascular calcification in dialysis patients.

Figure 1 Variations in Biochemical Indexes





PUB078

A Missing Key or Faulty Lock: Use of an Alternative Vitamin D Analog Opens the Door to Success

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Introduction: Secondary hyperparathyroidism is a complication of chronic kidney disease and characterized by high FGF-23 with low levels of 1,25-$(OH)_2$-vitamin D due to low renal 1α-hydroxylase activity. Doxercalciferol requires 25-hydroxylation by the liver, a step preserved in end-stage kidney disease (ESKD), but may be subject to genetic polymorphisms that determine responsiveness. We present a case of secondary hyperparathyroidism resistant to high dose doxercalciferol but responsive to calcitriol.

Case Description: A 76-year-old man with ESKD due to diabetes on thrice-weekly hemodialysis with uncontrolled secondary hyperparathyroidism (intact parathyroid hormone (iPTH) 1348 pg/mL) was started on a calcium-based phosphate binder and doxercalciferol 1 mcg IV three times a week. Doxercalciferol was titrated to 20 mcg three times a week, an equivalent calcitriol dose of 19 mcg/week, but his secondary hyperparathyroidism remained poorly controlled (iPTH 732 pg/mL, corrected calcium (cCa) 8.0 mg/dL, phosphorus (P) 5.1 mg/dl). He had normal liver function and did not take CYP3A4 inhibitors. He was changed to calcitriol 0.5 mcg daily with dramatic improvement over three months (iPTH 247 pg/mL, cCa 9.2 mg/dL, P 3.3 mg/dL).

Discussion: We highlight the use of an unusually high dose of doxercalciferol (60 mcg per week) resulting in suboptimal iPTH and calcium response. This dose is significantly higher than the annual mean IV doxercalciferol dose of 112 mcg per patient (~2 mcg per week). Our patient had a rapid reduction in iPTH and normalization of cCa using a relatively low dose of calcitriol. Unlike calcitriol, doxercalciferol lacks a 25-OH group requiring activation by hepatic 25-hydroxylase. A deficiency, or loss of function in this key enzyme, is a rare polymorphism seen in vitamin D dependent rickets type 1B, usually treated with 25-OH-vitamin D, but needs 1α,25-$(OH)_2$-vitamin D in ESKD. Alternatively, genetic variation of the vitamin D receptor-ligand binding domain may reduce its affinity for some vitamin D analogs. Clinicians should suspect potential polymorphisms at fault when high doses of vitamin D analog are used with inappropriate response. We recommend switching vitamin D analogs and consider genetic testing. Characterizing vitamin D receptor protein polymorphisms may influence prescribing practices of vitamin D analogs in the future.

PUB079

Persistent Severe Hyperparathyroidism After Parathyroidectomy

Tammy Yu, Jie Tang. *Brown University Warren Alpert Medical School, Providence, RI.*

Introduction: Parathyroidectomy is the definitive treatment for secondary hyperparathyroidism (SHPT) refractory to medical management. We report a case of persistent severe hyperparathyroidism after subtotal parathyroidectomy in a hemodialysis patient.

Case Description: A 35-year-old male with ESRD on HD due to idiopathic membranous nephropathy presented with progressive fatigue and bone pain. PTH was 3709 pg/ml, Phos 9.7 mg/dl, Ca 10 mg/dl, and ALKP 919 IU/L in the setting of noncompliance with his medications, including cinacalcet, calcitriol, and sevelamer. He was transitioned to IV etelcalcetide given at HD, but had poor response, with PTH levels between 2000-4000. After discussion, he opted for parathyroidectomy. Preoperative

sestamibi scan demonstrated a focus of increased uptake in the lower right thyroid lobe without evidence of ectopic uptake. Intraoperatively, the bilateral inferior parathyroids appeared nodular and were removed. Surgical pathology confirmed nodular hyperplasia. The normal-appearing left superior gland was autotransplanted to a subcutaneous pocket. Despite extensive exploration of the retroesophageal space and carotid sheath, the right superior gland could not be located, so a right thyroid lobectomy was performed. Intraoperative PTH (ioPTH) levels were 2612 pg/ml before resection, 519 pg/ml 10 minutes post-resection, and 560 pg/ml at 20 minutes. The patient had severe postoperative hypocalcemia which responded well to calcium supplementation. However, by post-operative day 8, his PTH had rebounded to 2524 pg/ml.

Discussion: Persistent hyperparathyroidism has been defined as PTH elevation developing within 6 months of surgery despite adequate ioPTH drop. Prior case series have attributed this to the presence of missed ectopic or supernumerary glands, although the unmasking of ectopic PTH secretion is a process that typically takes weeks to months. Despite an initial >75% reduction in ioPTH after 10 minutes, our patient's rapid return to preoperative PTH levels is atypical, and is concerning for the concurrent development of tertiary HPT in his residual parathyroid tissue. These observations suggest that a history of longstanding secondary HPT may lead to poorer outcomes after parathyroidectomy.

PUB080

Hospitalization Is Related to Osteoporosis in CKD Patients: Data from the Brazilian Registry of Bone Biopsy (REBRABO)

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Background: Mineral and bone disorder (MBD) is related with chronic kidney disease (CKD) and associated with significant morbidity and mortality. REBRABO database contains clinical, laboratorial and histological information about Brazilian CKD patients with MBD. The relationship between the type of renal osteodystrophy (RO) and clinical outcomes is unclear.

Methods: This is a national, observational and prospective clinical study. Clinical, demographics, laboratorial and bone histology data were collected from CKD patients between Aug/15-Dec/18. Patients were followed by five years and clinical outcomes such as bone fractures, hospitalization and death were registered.

Results: Data from 179 patients who were submitted to bone biopsy were analyzed. Patients aged 52±12 years, 93 (52%) men and 80 (45%) white; 133 (85%) patients were under hemodialysis treatment. Serum intact parathormone, alkaline phosphatase, calcium, and phosphate levels were 456 (63-514) pg/mL, 174 (73-205) IU/L, 9.2±1 mg/dL and 5.0±1.7 mg/dL, respectively. Osteitis fibrosa, mixed uremic osteodystrophy, adynamic bone disease, osteomalácia and osteoporosis occurred in 69 (39%), 39 (22%), 59 (33%), 7 (4%) and 82 (47%), respectively. The average follow-up time was 1,318 days; during follow-up 19 bone fractures, 61 hospitalizations and 47 deaths were detected. However, diagnosis of osteoporosis was related with hospitalization (p=0.03).

Conclusions: Osteitis fibrosa was the most prevalent type of RO in our sample. A high prevalence of osteoporosis was detected and related with increased hospitalization. Type of RO apparently is not related with outcomes.

PUB081

A Case of Tumor-Induced Osteomalacia (TIO) with Paradoxical Fibroblast Growth Factor 23 (FGF-23) Response After Surgical Excision

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Introduction: FGF-23's role in TIO and renal phosphate wasting in mesenchymal & certain other tumors is increasingly being identified. We present a case of TIO in a patient with End Stage Renal Disease (ESRD) & on hemodialysis (HD) whose FGF-23 remained elevated despite normalization of phosphorus (Phos) levels after surgical excision of tumor, raising a question if there are other yet unidentified tumor associated factors affecting phosphorous levels in these patients.

Case Description: A 59 year old male with ESRD status post renal transplant followed by allograft failure after 3 years, gradually progressing to Chronic Kidney Disease stage V, presented with oliguria & was restarted on hemodialysis. Hospital course was complicated by episodes of severe hypophosphatemia (Phos < 1.5) despite aggressive repletion. Pertinent lab work included: corrected calcium 9.5-10.5 mg/dl, ionized calcium 1.1-1.2 mmol/L & PTH 268 pg/ml. He developed blurry vision & was found to have a fourth ventricle mass in brain. FGF-23 came back elevated at 2303 (measured via manual enzyme-linked immunosorbent assay by Quidel Corporation) & TIO was suspected. After surgical excision of the tumor, serum Phos normalized. Over the course of next 2 to 3 days, patient developed hyperphosphatemia, as expected in patients with ESRD. However, interestingly FGF-23 level, in contrast to returning to normal as would be expected with the tumor excision, increased 5 times. 10 days later, FGF-23 was found to have increased to 11,120. At this time, serum Phos ranged between 3.6-4.5 as patient was receiving HD 3 times a week. Repeat CT head showed some residual calcification within the resection cavity raising the possibility of residual tumor however minimal only. MRI brain could not be done as patient clinically deteriorated in the setting of septic shock & died. Pathology of the tumor mass was consistent with both ependymoma & subependymoma.

Discussion: TIO is thought to be caused by FGF-23 released by tumor cells that cause phosphate wasting. Our case is unique as serum Phos normalized post tumor excision but FGF-23 continued to rise raising the possibility of yet unidentified tumor associated factors that might be involved in Phos homeostasis. Based on the FGF-23 response in our patient, we also hypothesize that FGF-23 might not be a useful tumor marker in ESRD patients.

PUB082

Normocalcemic Hyperparathyroidism in Calcium Kidney Stone Formers

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Introduction: Primary hyperparathyroidism is a strong risk factor for calcium kidney stone (CKS) formation. However, the kidney stone effect from normocalcemic hyperparathyroidism have not been described. Here we present a case series of six recurrent CKS formers who had elevated plasma parathyroid hormone levels with normal serum calcium.concentration. All of them underwent nuclear imaging of the parathyroid gland showing features consistent with parathyroid adenoma and underwent subsequent resections of the adenoma. We compared pre- and post-operative 24-hour urine calcium (UC) and phosphorus (UP) standardized by urine creatinine, as well as changes in kidney stone burden assessed 2-12 months after the surgery. All patients included in this report were instructed to maintain their diet before and after the surgery.

Case Description: Of these six stone formers, three were men, and the mean age was 60 years. All had vitamin D deficiency with normal serum 1,25-$(OH)_2$-vitamin D. Two had hypertension. Two others had dyslipidemia. Of the three who had DEXA scan performed, all had osteopenia. Mean serum calcium was 9.8 mg/dl, mean serum phosphorus was 3.0 mg/dl. Five had baseline 24-hour UC >240 mg (median 309 mg), one had normal 24-hour UC (186 mg). 24-hour UP ranged from 663 mg to 1672 mg. None of them were prescribed with thiazide diuretics, calcium containing supplements or medications that could affect phosphorus absorption during the study period. After partial parathyroidectomy, mean serum calcium reduced by 0.75 mg/dl, mean serum phosphorus increased by 0.1 mg/dl, and neither serum 25-(OH)-vitamin D nor 1,25-(OH)2-vitamin D changed significantly (mean, -0.8 ng/ml, +0.7 pg/ml, respectively). For the urine studies, two had increases in UC (mean 61 mg, 18%), four had reductions in UC (mean -23mg, -9%). One had an increase in UP (349 mg, 53%), five had reductions in UP (mean -244 mg, -19%). Of the five patients who had kidney ultrasound performed before and 2-12 months after the surgery, four had increases in the post-operative stone burden (mean +43%), one had a 100% reduction.

Discussion: In this small case series, normocalcemic hyperparathyroidism did not appear to have a consistent effect on the risk of calcium kidney stone formation.

PUB083

Misregulation of Interstitial Matrix Fiber Patterning in a Model of Stromal Cell Abnormalities

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Background: Murine kidney interstitial extracellular matrix (ECM) is a network of proteins and glycosaminoglycans outside cells. The ECM forms intricately patterned fibers in the developing kidney capsule, vertically aligned in the cortex, and surrounding the medullary rays. Forkhead box D1, $(Foxd1)^+$ cells synthesize interstitial matrix and are required for kidney stromal cell patterning of the nephron; however, the role of *Foxd1* in interstitial ECM fiber patterning has not been investigated.

Methods: Murine embryonic day (E)18.5 *Foxd1* knockout ($Foxd1^{-/-}$) and phenotypically normal littermate controls ($Foxd1^{+/-}$) kidneys were decellularized with sodium dodecyl sulfate, fixed and stained for ECM proteins, and rendered in 3D.

Results: Vertical fibers were abnormally, perpendicularly aligned relative to the branching nephron in $Foxd1^{-/-}$ kidneys (open arrow), suggesting *Foxd1* is important for stromal cell orientation of interstitial ECM (Figure 1). However, the organization of capsule and fibers around the medullary ray sheath was maintained when compared to $Foxd1^{+/-}$ controls.

Conclusions: Kidney interstitial ECM dramatically changes with development. Abnormalities in the vertical fibers in the $Foxd1^{-/-}$ mouse correlate with the loss of the nephrogenic zone, suggesting the fibers are involved in nephron morphology development.

Funding: Other NIH Support - 1DP2AT009833-01 to SC

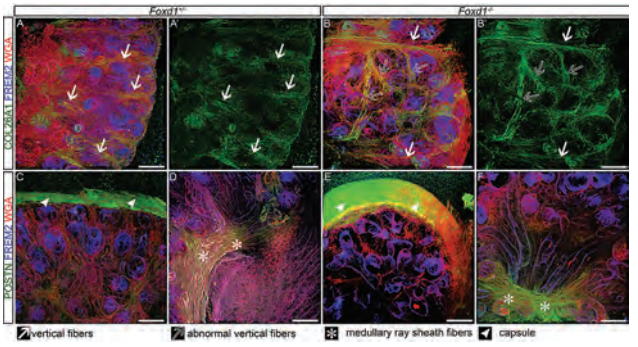

Figure 1: *Foxd1* knockout alters vertical fiber orientation, but capsular and medullary ray sheath fibers were maintained. (A-A′) Control kidneys showed vertical fibers (closed arrow) (green = COL26A1) aligned parallel to the developing nephron (FREM2 = blue, WGA = red). **(B-B′)** In the *Foxd1*$^{-/-}$ kidney, the vertical fibers (closed arrow) were present, but some vertical fibers were abnormally perpendicular to the nephron (open arrow). **(C-F)** POSTN^{+} (green) capsular fibers (arrowhead, C-D) and medullary ray sheath fibers (*, E-F) appear retained in the *Foxd1*$^{-/-}$ kidney. Scale bar = 100 μm. 25× confocal z-stacks 590 × 590 × 171 μm (A-B′), 57 μm (C-F).

PUB084

Adipose-Derived Regenerative Cells Treatment of Injured Kidney Organoids

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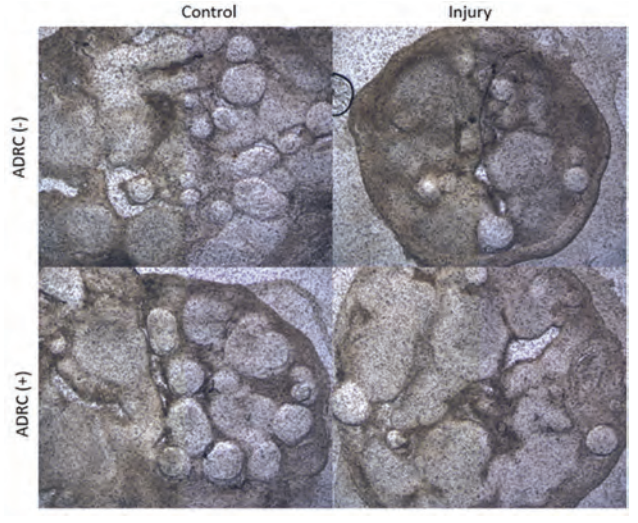
Background: Adipose derived regenerative cells are a heterogeneous cell population that include mesenchymal stem cells (ADRCs) and are derived from adipose tissue. Previous studies showed that ADRCs have beneficial effects of an anti-oxidative activity, an anti-inflammatory activity, and an anti-apoptotic activity. Reactive oxygen species (ROS), inflammation, and apoptosis play a deleterious role in injured kidney repair. Therefore, we hypothesis that ADRCs will aid in the repair of the injured kidney.

Methods: Kidney organoids were assigned into four groups including non-injury (control), injury, ADRCs-treated in non-injury and ADRCs-treated in injury groups. Injured kidney organoids were induced by exposure to 10 μM hydrogen peroxide for 60 minutes.

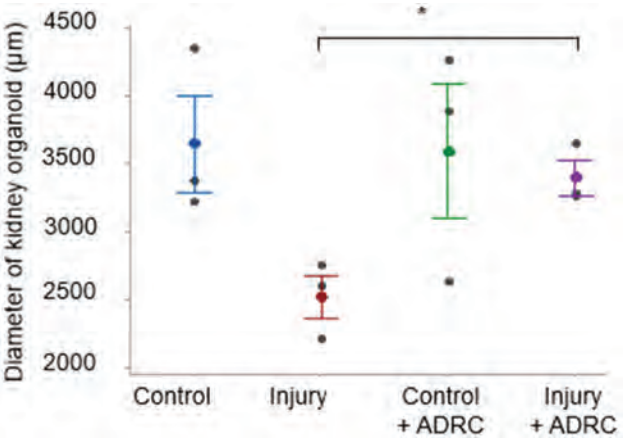
Results: Kidney organoids in this study, ADRCs-treated injured kidney organoids had significantly larger diameter than injured kidney organoids (p=0.014).

Conclusions: ADRCs showed a positive effect by increasing or maintaining the diameter size of organoids. ADRCs show promise as a therapy of injured kidney organoids.

Funding: Government Support - Non-U.S.



Light microscope: images of control and injury rat kidney organoids after non-treating and treating with ADRCs (40x magnification).



Qualification (diameter) of control and injury rat kidney organoids after non-treating and treating with ADRCs (n=3).

PUB085

Urine-Derived Stem Cells Attenuate Renal Inflammation and Fibrosis After Renal Ischemia Reperfusion

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Background: After renal IRI, regeneration and recovery of the renal tubular cell occurs. However, if the renal repair process is maladaptive, it progresses to renal fibrosis. The role of stem cells in kidney regeneration or fibrosis has not been fully elucidated. we evaluated the urine drived stem cells(UDSC) for renal inflammation and fibrosis after renal ischemia reperfusion(IR).

Methods: 10 week old balb/c nude male mice were used. sham, sham with UDSC, sham with adipose drived stem cell(ADSC), IR, IR with UDSC, IR with ADSC. UDSC and ADSC were infused 1 times via tail vain 7 day After renal IR. Urine NGAL/creatinine(Cr) were checked. The kidneys were harvested at day 14 day. for. *in vitro* fibrosis model, HK2 cell were treated with TGF beta. Co-culture of UDSC and ADSC were performed. Molecular and histologic study were performed.

Results: Urinary NGAL/Cr were significantly increased in IR mice after 14 day IR, compared to sham mice. Urinary NGAL/Cr significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. we confirmed UDSC migrate into renal tubular area after 2 weeks renal IRI. In H&E and PAS stain, renal tubulo interstitial injury were significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. In masson trichrom stain, renal fibrosis area were were significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. The renal expression of MCP-1, ostemopontine, TGF beta, alpha SMA, collagne IV, and F4/80 positive cellswere significantly decreased in UDSC treated IR mice, compared to IR and ADSC treated IR mice. in vitro, alpha SMA, collagen IV, smad 2/3 were significantly increased in TGF beta treated HK2 cells. co-culture of UDSC decreased the alpha SMA, collagen IV, smad 2/3 in TGF beta treated HK2 cells. however, co-culture of ADSC did not decreased the alpha SMA, collagen IV, smad 2/3 in TGF beta treated HK2 cells.

Conclusions: UDSC ameliorate renal inflammation and fibrosis after renal IR.

PUB086

Effects of Açai on the Inflammatory Response of NLRP3 in Experimental Diabetes Mellitus

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Background: Inflammatory factors associated with innate immunity, such as Nod-like receptors, constituents of the NLRP3 inflammasome complex has been linked to the development and progression of diabetic nephropathy. Recent research in our Laboratory showed that açai extract (EA, *Euterpe oleracea*), a tropical fruit from Amazon with high antioxidant capacity, rich in polyphenols, exhibited also an anti-inflammatory activity, through the modulation of NF-kB/Nrf-2 system in a diabetes mellitus (DM) model, in cultured cells. The aim of the present study was to analyze the effects of EA on the inflammatory response of NLRP3 in experimental DM.

Methods: Human immortalized mesangial cells (HiMC) were grown in DMEM 10% FBS according to the groups: normal glucose (NG, 6.7 mmol/L), high glucose (HG, 30 mmol/L) or mannitol (osmotic control). HiMC in HG medium were treated with EA (500, 100 or 50 μg/mL). Cell viability and proliferation were determined by MTT after 72 hours and protein content of NLRP3 by Western Blot. In male adult Wistar rats DM was induced by streptozotocin (60mg/ kg, i.v.); control rats (CTL) received the drug vehicle. Both groups were treated with EA 200mg/kg BW, diluted in water, via gavage

for 8 weeks. The rats were euthanized and the kidneys stored at -80°C. We analyzed the metabolic profile, nitric oxide (NO, for nitrosative stress), TBARS (an indirect measure of oxidative stress, OS) and renal function in plasma and urine. The results were described as mean ± SE, $p < 0.05$.

Results: Viability was 100% in all HiMC groups; there was a significant increase in cell proliferation and in NLRP3 expression in HG group, which were reduced with EA. In DM rats EA reduced glycemia and normalized other metabolic parameters, in addition to improving renal function and OS analyzed after 3 days, 4 and 8 weeks of treatment, being the more prolonged treatment, more effective. The histology analysis showed that EA reduced structural lesions of the renal cortex such as diffuse sclerosis and glycosidic degeneration, in DM animals.

Conclusions: The consumption of EA could contribute to a better control of OS associated with the reduction of inflammatory factors, suggesting the importance of these bioactive compounds as non-pharmacological adjuvants, to delay the complications in diabetic patients.

Funding: Government Support - Non-U.S.

PUB087

Pentoxifylline in Diabetic Kidney Disease (VA PTXRx): Protocol for a Pragmatic Randomized Controlled Trial

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Background: Diabetic kidney disease (DKD) is the most frequent cause of end-stage renal disease (ESRD) in the U.S. and worldwide. Recent experimental and clinical data suggest that the non-specific phosphodiesterase inhibitor pentoxifylline (PTX) may decrease progression of kidney disease. However, a large-scale randomized clinical trial is needed to determine whether this agent can reduce ESRD and death in patients with DKD.

Methods: VA PTXRx is a pragmatic, randomized, placebo-controlled multicenter Veterans Affairs (VA) Cooperative Study to test the hypothesis that PTX, when added to usual care, leads to a reduction in the time to ESRD or death in type 2 diabetic patients with DKD when compared to usual care plus placebo. The study aims to enroll 2510 patients over a 4-year period with an additional up to 5-year follow-up to generate a total of 646 primary events. The primary objective of this study is to compare the time until ESRD or death (all-cause mortality) between participants randomized to PTX or placebo. Secondary endpoints will be: (1) Health-related quality of life, (2) Time to doubling of serum creatinine, (3) Incidence of hospitalizations for congestive heart failure (CHF), (4) Incidence of a three-point major adverse cardiovascular events (MACE) composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), (5) Incidence of peripheral vascular disease (PVD), (6) Change in urinary albumin-to-creatinine ratio (UACR) from baseline to 6 months, (7) Rate of annual change in estimated glomerular filtration rate (eGFR) during the study period. **Ethics and Dissemination:** This study was approved by the VA Central Institutional Review Board (cIRB) (ID: 1382143) and will be conducted in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The Hines Cooperative Studies Program (CSP) will finalize the study results, which will be published in accordance with the CONSORT statement in a peer-reviewed scientific journal. **Trial Registration:** This study is registered with clinicaltrials.gov (Identifier: NCT03625648)

Results: Study enrollment began in November 2019. Through April 2021, 146 patients have been randomized during the ramp-up phase of the study.

Conclusions: PTX is a readily available, safe, and inexpensive medication which might be effectively repurposed to treat DKD.

Funding: Veterans Affairs Support

PUB088

Perceptions of Care Coordination During and After Hospitalization Among Patients Receiving In-Center Hemodialysis

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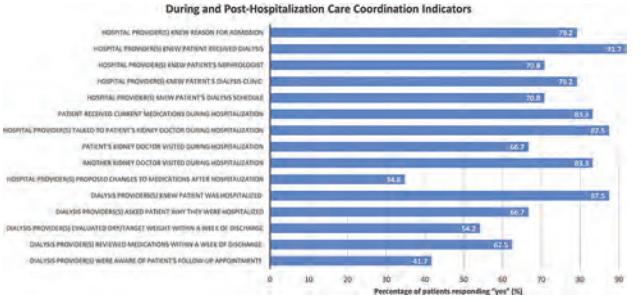
Background: In the United States, 34% of hospital discharges among patients receiving dialysis are followed by a 30-day unplanned readmission. As part of an ongoing pilot study (DialysisConnect), we examined the perceptions of patients receiving hemodialysis (HD) regarding care coordination between providers at the hospital and dialysis clinic.

Methods: Our study targeted all 113 patients receiving in-center HD who were being treated at one of four dialysis clinics and had been hospitalized at a single hospital in Atlanta, Georgia, in the prior 6 months. We administered a one-time survey about their care coordination during their hospitalization episode and used descriptive statistics to summarize the results.

Results: Respondents (n=24, 21% response rate) had an average age of 62 years, 100% were Black, 46% were male, and on average patients had been receiving HD for 4 years; non-respondents were similar in terms of demographics. The percentages of patients who reported that their hospital and dialysis providers knew key information or performed care coordination tasks during and after hospitalization were generally high (Figure). Most patients reported that hospital providers asked about their reason for hospital stay (79%), dialysis schedule (75%), symptoms (75%), current medications (71%), vascular access (67%), nephrologist name (67%), dialysis facility name (54%), and/or dry weight (50%). Only half (48%) brought discharge instructions to the next outpatient HD session.

Conclusions: Most patients (62-91%) perceived that both hospital and dialysis providers were aware of the patient's clinical situation and had exchanged necessary clinical information, which might discourage patients from actively engaging in their own care coordination. Future efforts to improve coordination of care between dialysis clinics and hospitals should target not only providers in both settings but also patients and their healthcare surrogates.

Funding: NIDDK Support



PUB089

Leptin Levels and Appetite Score in Patients on Hemodialysis Using High Flux or Medium Cut-Off Membranes

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Background: Chronic kidney disease (CKD) patients on hemodialysis may have a modified appetite due to several factors including a lack of uremic toxins elimination. The use of new dialysis membranes, such as medium cut off (MCO) has been suggested as an alternative to improve the removal of toxins, especially those of medium and high molecular weight. This study aimed to evaluate if the use of the MCO membrane would decrease toxin levels, particularly leptin and improve the appetite of CKD patients on hemodialysis program.

Methods: This is a pre-defined exploratory analysis of a randomized, open study, with a crossover design of 28 weeks of follow-up, which compared the effects of MCO and high flux membranes in 32 CKD patients on hemodialysis. Appetite assessments were performed using the Appetite and Food Satisfaction Questionnaire (AFSQ).

Results: The high-flux group had an appetite score of 3.25 ± 3.62 and 2.80 ± 3.14 at the beginning and at the end of treatment period, respectively, and the MCO group 3.62 ± 3.21 and 3.26 ± 3.28. There were no effects of treatment ($p = 0.573$), time ($p = 0.376$) and interaction ($p = 0.770$) between the high-flux and MCO groups. Leptin levels, at the beginning and at the end of the treatment period, were 2.47 ± 1.57 and 2712,72 ± 1.54 ug/L in the high-flux group and 2.45± 1.65 and 2.78 ± 1.62 ug/L in the MCO group, respectively. There was a time effect ($p = 0.014$), showing an increase in leptin levels in both Groups, while treatment ($p = 0.771$) or interaction ($p = 0.218$) effects were not observed.

Conclusions: There is no difference between the effects of MCO or high flux membranes on leptin levels or appetite of CKD patients in hemodialysis during the study.

Funding: Private Foundation Support

PUB090

Can Restoration of Heart Rate in ESRD Lower Brain Natriuretic Peptide?

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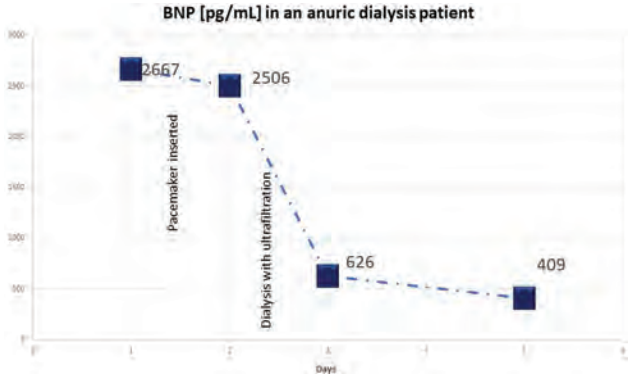
Introduction: Brain Natriuretic Peptide (BNP), is predominantly produced by the left ventricular (LV) myocytes. BNP's production is triggered in response to stretch of the left ventricular myocytes by either increased volume or pressure within the LV cavity. Elevation of BNP is induced by bradyarrhythmia and high degree atrioventricular blocks. We describe a case of a dialysis-dependent patient presenting with complete heart block with an elevated BNP from his baseline and review whether correcting the rhythm problem resulted in correction of his BNP.

Case Description: 98 yr old male with ESRD receiving maintenance hemodialysis presented with shortness of breath and decreased heart rate. He reported shortness of breath on ambulation but denied chest pain, increased swelling, or any other symptoms. Heart rate (HR) was 40 bpm and blood pressure 138/52 mm Hg. Electrocardiogram (ECG) revealed a complete heart block. the chest x-ray did not reveal any acute cardiopulmonary abnormalities. BNP was 2667 pg/ml. Cardiac pacing pads were placed in the Intensive Care Unit while planning for permanent pacemaker placement. He remained hemodynamically stable with HR in the 30s-40s bpm and a dual-chamber pacemaker was placed 24 hr later. Symptoms of dyspnea improved after the procedure with a paced rhythm of 60 bpm. BNP repeated 90 min after the procedure remained

elevated, 2506 pg/ml. The patient underwent a hemodialysis session with ultrafiltration to his usual estimated dry weight and BNP decreased to 626 pg/ml. Repeat BNP after two more dialysis sessions was 409 pg/ml.

Discussion: Our patient provided a unique opportunity to differentiate between the effects on BNP of an improved cardiac output with restored cardiac rhythm versus changes in intravascular volume. This case demonstrates that this anuric patient's rhythm restoration was not sufficient to lower BNP values, while ultrafiltration did. Thus, we seem to be able to confirm that, it is solely the volume status that affects BNP value, not the cardiac rhythm or cardiac output.



PUB091

Temporal Changes in Physiology During Inpatient Hemodialysis Sessions

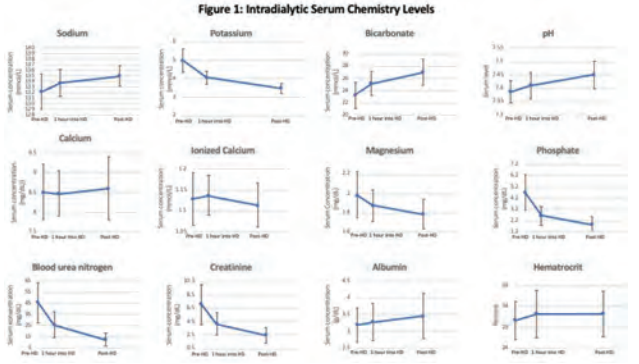
Katherine M. Scovner,[1,2] Caroline Espersen,[1,2] Katherine Curtis,[1,2] Elke Platz,[1,2] Finnian R. McCausland.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: Patients receiving maintenance hemodialysis (HD) in the United States have an average of 1.6 admissions per year (>700,000 inpatient HD sessions). Little is known about the temporal changes in laboratory values, ECGs, and volume status during HD sessions in these vulnerable patients.

Methods: We performed a prospective cohort study (n=30) of hospitalized HD patients to measure serum laboratory concentrations (electrolytes, blood gases, and ionized calcium levels), ECGs, and ultrasonographic measures of volume status (8-zone lung images for the number of B-lines and internal jugular vein diameter) pre-, one hour into, and post-HD during one inpatient HD session. Ultrasound images were analyzed offline by a core imaging laboratory blinded to clinical information and imaging time point.

Results: The mean age of participants was 62 years. 53% were male and 43% were Black. Serum chemistry levels were dynamic, with the most rapid changes occurring within the first hour for all biomarkers (Figure 1). The median increase in QTc duration on ECG (post-HD QTc minus pre-HD QTc) was 7.5 [-5-19] msec. Though the sum of pulmonary B-lines decreased from pre- to post-HD (median decrease: 5 [1-6.5], p=0.02), internal jugular vein diameter did not change (p=0.73).

Conclusions: Among hospitalized patients undergoing HD, there are dynamic changes in serum chemistry parameters, QTc durations, and volume status during their HD sessions. Further research is required to assess how variations in these changes during HD are associated with clinical outcomes and whether HD prescriptions can be tailored to optimize patient care.



PUB092

Predictors of Mortality in Hemodialysis Patients in a Large Dialysis Network in India

Suresh Sankarasubbaiyan, Venkatraman Ganapathi Subraman, Mallikarjuna Gowda B. Gowda, Vikram A. Sonawane, Kamal D. Shah, Kaparaboina K. Kumar, Satyanarayana R. Puvvada, Mohammad S. Husain. *Nephroplus, Hyderabad, India.*

Background: Mortality of HD pts is influenced by age, cormorbidity, dialysis, facility and socioeconomic factors. With much unknown regarding MHD mortality in India, we aimed to study the incidence and factors predicting mortality in a large dialysis network in India

Methods: Consecutive deaths, Jan 1 to March 31, 2021 in a HD network were reviewed for age, gender, HD freq, vascular access, Hb, comorbidity, MHD duration, payer type, eductional status, and BMI. An age stratified matched control was used to comparefactors using t test and Chi sqaured test. Bianry logistic (uni & multi) was used to identfy risk factors associated with death. Significance: 5%. SPSS ver 26 was used

Results: 797(4.8%) deaths occured among 16516 patients. Table 1 shows pt characteristics. Simple logistic regression: Tier III city, ↓ education, <6 mon HD, public Insurance, ↓ Hb, temporary access, Kt/v <1.2, Alb <3.5, DM, h/o MI and hospiltalization <3 mon had significant OR (not shown). Multiple logistic regression showed OR for illiteracy: 2.7 (1.7-4.4), secondary school: 1.7 (1.1-2.5), public insurance 2 .3 (1.3-3.8), <1 mon on HD: 2.3 (1.3-4.4), temporary catheter:1.7 (1.3-2.7), Alb <3.5 g%: 2 (1.3-3.8), ↓ Hb 2.9 (1.5 -5.9), DKD: 1.5 (1.1-2), HD in PPP centre: 2.1 (1.3-3.2) and hospitalizations <3 mon: 4.7(3.3-6.6) were significant.

Conclusions: Mortaltiy is high in MHD pts in India and is associated with temp access, ↓ alb, ↓ Hb, recent hospitlization, DM, ↓ education & public Insurance status.

Table 1: Characteristics of patients who died Jan 1 to March 31, 2021 (n=797)

Zone (%) N/E/W/S	16.4/15.4/11.2/15.7
Age	54.9 ± 13.8
Gender (M:F %)	70.5:29.5
Educational status (%) Illiterate High school Hfgher secondary College	38.3 30.7 15.1 15.9
BMI	22.4 ± 4.5
Payer type (%) Cash/Pvt Insurance/Public	26.7/21.2/50.3
Hemoglobin (G%)	8.6 ± 1.5
Kt/V	1.3 ± .2
Albumin (G%)	3.4 ± 0.7
Frequency of HD per week (%) 1/2/3	3.3/54.1/41
Diabetic CKD (%)	39.1
Htn (%)	78.5%
H/o Ischemic heart disease (%)	9.2
H/o Hospitalisation in the previous month (%)	36.9

PUB093

A Multicenter, Retrospective, Observational Study of Dialysis Facility-Level Hyperkalemia Burden in China: Rationale and Design of the Visualize-HD Study

Xinju Zhao, Li Zuo. *Peking University People's Hospital, Beijing, China.*

Background: Hyperkalemia (HK) is a deadly complication in patients (pts) undergoing hemodialysis (HD), accounting for about 1/4th of emergent dialysis treatment. Excess mortality and hospitalization have been associated with HK, especially after the long (2-day) interdialytic interval (LIDI) in thrice-weekly HD pts compared with the short (1-day) intervals. Research on disease burden, risk factors and association of HK and mortality in Chinese pts is scanty.

Methods: This multicenter (300 HD centers), observational study will involve Chinese patients with chronic HD from eastern, central and western parts of China (except Hong Kong, Macao and Taiwan) (**Figure 1**). HD centers having >100 chronic pts (≥3 months on HD) within 3 years before study initiation, participation willingness, having routine blood collection post LIDI and death records will be included. Pooled data (at HD facility-level) about pts characteristics, sK levels, dialysis prescriptions on facility practice patterns, and death records will be collected retrospectively.

Results: The primary and secondary endpoints will be to examine the association between suspected risk factors and HK-proportions and to describe HK burden respectively. Suspected risk factors include dialysis and sK testing frequency; patient characteristics and medication usage. The constitution ratio of different sK levels after LIDI will be collected [(0-3.5), (3.5-5), (5-5.5), (5.5-6), (6-6.5), (6.5-7), (>7.0) mmol/L] to calculate the HK (≥5 or 5.5 mmol/L) burden. Meanwhile, we propose to explore crude mortality rates association with HK-proportions. Final results are planned to be released in 2022.

Conclusions: The results of Visualize-HD will generate contemporary evidence to fill epidemiological research gaps of HK in Chinese HD pts and explore risk factors associated with HK disease burden.

PUB094

Predicted Rebalancing of Sodium in a Sorbent Dialysis System

Tzu Tung Chen, Brandon D. Borrillo, Osman Khawar, Clayton Poppe. *Diality Inc, Irvine, CA.*

Background: The Diality Hemodialysis Machine will provide a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One modality uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: To test sodium ion rebalancing in a 125L circulating volume over 270 minutes using a predicted alkali infusion to maintain a Na concentration of approx. 140 mEq/L.

Methods: A 125 L volume of dialysate was circulated at approx. 400 mL / min & 37 C through a sorbent filter. It is expected that with each pass through the filter the dialysate will be depleted of electrolytes and sodium [Na] and pH will lower. Dialysate is refurbished with an additional infusion of Ca, Mg and K salts. Based upon the predicted [Na] profile another pump will infuse an alkali solution at a varying rate to maintain the final [Na] at approx. 140 mEq/L. The experiment is continued until breakthrough occurs or the infusate outlet reaches 10 ppm of NH_4.

Results: The [Na] over 270 mins are depicted in table 1. TP1, the [Na] of the dialysate taken prior to passing through the sorbent filter after leaving a stirring tank containing 150L of dialysate was 137.9 – 143.4 mEq/L. TP2, the [Na] in the fluid upon leaving the filter was an average of 129.5 mEq/L ranging from 119.1 – 136.0 mEq/L. TP3, the [Na] in the dialysate after refurbishing with an alkali solution prior to reentering the stirring tank was an average of 139.3 mEq/L ranging from 138.1 – 143.4 mEq/L.

Conclusions: The results validate the ability to maintain dialysate sodium balance over the dialysis period using a sorbent filter while refurbishing dialysate with a predicted alkali infusion.

Funding: Commercial Support - Diality Inc

Table 1.

Time (min)	TP1 [mEq/L]	TP2 [mEq/L]	TP3 [mEq/L]
0	140.0		
10	141.4	137.8	143.4
30		135.8	139.4
45		132.5	138.1
60	140.9	128.2	138.4
90		124.1	140.1
120	141.2	121.8	142.0
150		120.0	139.6
180	140.9	119.6	138.9
210		119.1	139.1
240	140.8	121.7	140.8
255	140.2	123.5	142.5
265	140.1	124.1	140.7

PUB095

Bicarbonate and pH Maintenance in a Sorbent Dialysis System

Brandon D. Borrillo, Tzu Tung Chen, Osman Khawar, Clayton Poppe. *Diality Inc, Irvine, CA.*

Background: The Diality Hemodialysis Machine is designed for a range of hemodialysis modalities to expand the population of patients that may benefit from hemodialysis. One of the modalities uses a sorbent filter that will accommodate the decentralization of dialysis delivery. Specific Aims: Demonstrate bicarbonate and pH can be balanced with an alkali infusion.

Methods: Dialysate volumes of 125 L were circulated at approx. 414 mL/min & 37 C through a sorbent filter. The starting dialysate concentrations for electrolytes, pH and Urea are provided in table 1. The dialysate will be regenerated by an infusate solution containing Ca, Mg and K salts. In the first experiment a predicted [Na] profile pump will infuse an alkali solution at a varying rate to control the final [Na] at approx. 135mM. A second experiment a constant infusion of the same alkali was used as a reference. The total bicarbonate buffer was measured by titration. The pH was measured by a laboratory grade probe.

Results: The total bicarbonate buffer as alkalinity for an experiment with a constant infusion of alkali is compared to an experiment with varied infusion of alkali (controlling outlet sodium) in Figure 1. The same two experiments also show pH data in Figure 2.

Conclusions: The results show that the alkali infusion can simultaneously balance alkalinity and pH in a sorbent system using this infusion to maintain sodium at a set point.

Funding: Commercial Support - Diality Inc

Table 1:

Starting Dialysate(125L)	
Chemical	Conc (mM)
NaCl	100
KCl	3
CaCl2	1
MgCl2	0.5
NaHCO3	35
Urea	14
pH	7.04

Figure 1

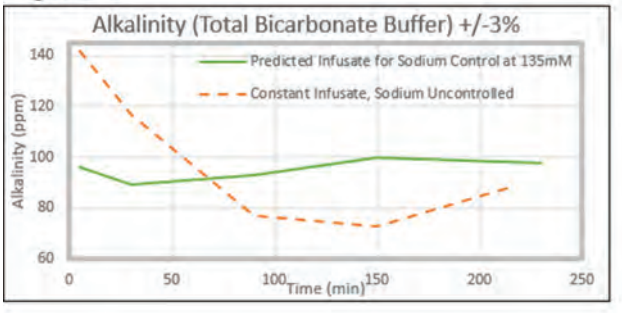
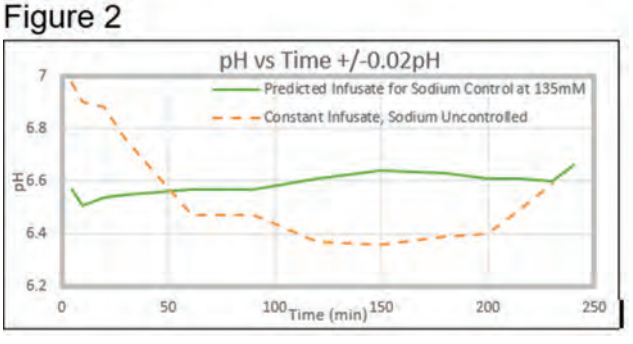


Figure 2



PUB096

Effect of Hemodialysis Rounding Report Availability on Hospitalized ESRD Patient Parameters

Khalid Elharrif,[1,2] Nidal Alhosainat,[2] Petersen Greti,[1] Ratha V. Kulasingam,[1] Omar S. Al-Taweel,[2] Hania Kassem.[2] *[1]Kern Medical Center, Bakersfield, CA; [2]The University of Texas Medical Branch at Galveston, Galveston, TX.*

Background: Each ESRD patient has a rounding outpatient HD report which is established by the outpatient dialysis unit and contains pertinent information including dry weight (EDW), dialysis prescription, and current medications. In this study, we compared inpatient dialysis-related parameters between 2 groups of patients, those for whom rounding reports were made available and those whose reports were not able to obtain.

Methods: The outpatient hemodialysis facility list was available for all healthcare providers. The facilities were contacted to obtain the hemodialysis report for the hospitalized patients with ESRD. The relevant parameters were obtained from these reports, which included hemoglobin, phosphorus, and EDW. The aforementioned identical parameters were monitored during the course of the hospitalization on all ESRD patients. Patients with available outpatient dialysis reports were restarted on the same outpatient doses of Epogen, phosphate binders, and EDW was adjuted to the same outpatient HD EDW. For those who do not have HD report available, their regimen was adjusted based on their clinical parameters. The dry weight was adjusted based on their volume status during the hospitalization.

Results: Sixteen ESRD patients admitted to the hospital were included. Upon discharge, those who had outpatient dialysis reports (10 out of 16) had significant improvement of phosphorus levels, better control of the volume status, and no significant changes in hemoglobin. Three out of ten patients developed intradialytic hypotension. The average length of hospitalization was 9 days. Those who didn't have the outpatient dialysis reports available during their hospitalization (6 out of 16) had no significant changes in phosphorus levels, post-dialysis weights, or hemoglobin. Five out of six patients developed intradialytic hypotension. The average length of stay was 10 days. **Table 1.**

Conclusions: Patients who have dialysis rounding reports available to guide their treatment while hospitalized have better dialysis-related parameters than those who don't.

	Dialysis report available			Dialysis report not available		
	On admission	On discharge	P Value	On admission	On discharge	P Value
phosphorus	6.08 ± 0.4 mg/dl	4.9 ± 0.5 mg/dl	0.004	5.8 ± 0.4 mg/dl	5.6 ± 0.6 mg/dl	0.3
Hemoglobin	9.6 ± 0.5 g/dl	9.34 ± 0.37 g/dl	0.2	10.1 ± 1.16 g/dl	9.15 ± 1.2 g/dl	0.07
Weight	77.9 ± 7.8 kg	74.5 ± 6.8 kg	0.008	90.5 ± 7.5 kg	89.9 ± 6.8 kg	0.4

PUB097

Caustic Injury After Ingestion of Naturalyte®

Gaoyuan Huang, Carly Bowser, Chibuzo C. Okoye, Elena Frolova, Winston Lee. *New York City Health and Hospitals Coney Island, Brooklyn, NY.*

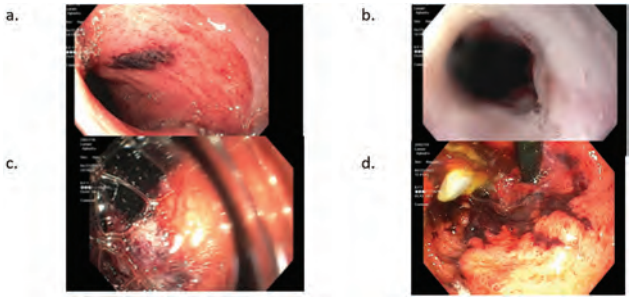
Introduction: Naturalyte® is a liquid acetic acid solution--a common dialysate concentrate in the United States.

Case Description: A 43-year-old man with ESRD on hemodialysis (HD) and depression presented with suicidal ideation. Vital signs: BP 235/142, P 99. He was agitated, but otherwise, his exam was unremarkable. Labs showed potassium (K) of 3.7 mmol/L and bicarbonate (CO2) of 25 mmol/L. He was admitted to intensive care and scheduled for dialysis. While HD was being set up, he ingested 100ml of the Naturalyte® dialysate concentrate in attempted self-harm. He vomited immediately. After ingestion labs showed K 4.1 mmol/L, CO2 20 mmol/L and venous pH 7.4. The patient received HD and underwent endoscopy (EGD) which revealed grade 2 esophagitis and stomach ulceration. He was treated with intravenous pantoprazole. Follow-up EGD showed healing lesions (fig 1) and the patient did well.

Discussion: To our knowledge, suicide attempt by ingesting dialysate concentrate has not been reported. Naturalyte® has a composition with a pH of 2.4-2.7 and various electrolytes (1) (table 1). Acetic acid ingestion can cause life-threatening toxicity and multiorgan failure (2). In our case ingestion of Naturalyte® did not have any systemic effects; this was due to several factors. Acidic solutions often cause an immediate reaction with emesis, which limits absorption (3). Our patient was also treated with early hemodialysis. In summary, ingestion of Naturalyte® can cause severe mucous membrane injury and potentially life-threatening complications.

Composition of Naturalyte®

Component	Weight %
Acetic Acid	0.8
NaCl	20.4
KCl	0.5
CaCl	0.4
MgCl	0.2
Dextrose	3.8



PUB098

Use of Electronic Consent and Navigating the Ethical and Governance Issues: Experience from the NightLife study

Niamh A. Quann,[1] Victoria Cluley,[1] Katherine L. Hull,[1,2] James Burton.[1,3] NightLife Study *[1]University of Leicester, Leicester, United Kingdom; [2]Leicester General Hospital, Leicester, United Kingdom; [3]Loughborough University, Loughborough, United Kingdom.*

Background: UK Government COVID-19 restrictions have necessitated rethinking the conduct of healthcare research. Obtaining informed, written consent remains a necessity that requires adaptation to accommodate the virtual environment. Here we report the experience of implementing electronic consent as part of the NightLife study. NightLife is a randomised controlled trial assessing the effectiveness of thrice weekly, extended, in-centre nocturnal haemodialysis. Continuation of the qualitative workstream during the COVID-19 pandemic resulted in the implementation of electronic consent where face-to-face consent was unfeasible.

Methods: As electronic consent was not part of the original study design, the proposal to use DocuSign to obtain electronic consent was discussed with the Trial Management Group (TMG), patient representatives and study Sponsor; a substantial protocol amendment was submitted. The study team liaised with the University's Information Governance (IG) and IT Risk and Continuity departments to mitigate potential data protection issues. A data protection impact assessment was completed to outline the data handling, management and storage arrangements. The functionality and practicality of the DocuSign portal was trialled and the Database Development team confirmed it integrated well with the clinical study database.

Results: The substantial protocol amendment was reviewed by the Research Ethics Committee, Health Research Authority and Confidentiality Advisory Group and received regulatory approvals less than three weeks after submission. As part of capacity and capability assessments at participating centres, approval was sought from local Privacy and Data Protection Officers with no issues identified.

Conclusions: Implementation of DocuSign as an electronic consent platform highlighted the importance of early and effective dialogue with the TMG, patient representatives, Sponsor, IG and Data Protection departments. While advantageous in the COVID-19 climate, face-to-face consent is still favoured and will recommence once restrictions are lifted. Integrating electronic consent is feasible from an ethical and governance perspective and represents an alternative for other studies that now require virtual engagement.

Funding: Other NIH Support - NIHR Health Technology Assessment (HTA) Programme (ref: NIHR127440)

PUB099

Delivering Patient and Public Involvement During the COVID-19 Pandemic: Experience from the NightLife Study

Victoria Cluley, Katherine L. Hull, Niamh A. Quann, James Burton. NightLife Study *University of Leicester, Leicester, United Kingdom.*

Background: Patient and Public Involvement is essential for research as it provides a supportive environment for patients to share their opinions. Traditionally, involvement events are held in person. National lockdowns due to the COVID-19 pandemic limit such meetings. Alternative approaches to enable continuation have been undertaken by the NightLife study team.

Methods: Patient and Public Involvement opportunities were advertised through: leaflets, social media and the Kidney Patient Involvement Network (KPIN). Patients expressed their interest by completing and returning leaflets using a pre-paid envelope, direct message on social media, or emailing the dedicated email address. A virtual introductory event was held.

Results: Over the course of a two month period, 16 expressions of interest were received via social media (n = 3), KPIN (n = 2) and leaflets (n = 11) from 10 men and 6 women. The patients were of a variety of ethnic backgrounds and renal replacement therapy modalities. An introductory, virtual meeting was completed. The main reasons for patients' inability to attend were conflict with healthcare appointments or work. One patient expressed nervousness about attending the meeting due to unfamiliarity with virtual platforms. Communication and engagement methods were discussed with patients at the meeting: Flexible meeting times due to commitments (dialysis schedules, work and personal responsibilities) Virtual calls during dialysis treatment may be preferable All forms of communication (e.g. letters, email, social media, phone) and meeting options (e.g. virtual, face-to-face, phone) Offer follow-up interviews after group discussions so patients feel they can effectively express personal experiences Advertise in all formats possible including patient organisations Use different languages and interpreters

Conclusions: Patients are enthusiastic to engage in Patient and Public Involvement events for research making it is achievable despite social restrictions. Flexibility of approach and delivery is essential, especially for individuals on haemodialysis where there are already significant healthcare commitments. Using multiple formats for engagement will enhance inclusivity and ensure the panel is representative.

Funding: Other NIH Support - National Institute for Health Research (UK)

PUB100

Prevalence and Severity of Pruritus in Patients on Maintenance Hemodialysis

Huei Hsun Wen, Kinsuk Chauhan, Wonsuk Oh, Steven G. Coca, Girish N. Nadkarni, Lili Chan. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Chronic kidney disease associated pruritus (CKD-aP) is a common symptom in patients on in center-hemodialysis (HD), reported in approximately 40% of patients. Recent clinical trials have identified novel agents for treatment of CKD-aP. Understanding the prevalence of uremic pruritus and its association with other symptoms can aid in identifying patients who would most benefit from this treatment.

Methods: We surveyed patient's ≥18 years old who had been on iHD for ≥30 days, and were receiving HD three times a week at the Mount Sinai Kidney Center. Patients completed surveys asking about the presence of absence of 21 different symptoms during the final 15 minutes of their HD treatments for 4 weeks. We performed multiple correspondence analysis (MCA) to identify associations between symptoms and group individuals with similar symptom profiles.

Results: Of the 97 HD patients who completed the study, 40 (41%) of them reported itching at least once during the study period. There were no significant differences in patient characteristics between patients who did and did not report itching **(Figure 1A)**. Of the patients who reported itching, on average they reported itching on 30±24% of their treatments **(Figure 1B)**. On MCA analyses, symptoms most correlated with itching was dry skin and fatigue (**Figure 1C**), Spearman correlation coefficient 0.63, P<0.001 for dry skin and 0.37, P<0.001 for fatigue **(Figure 1D)**. Using symptom data only, there was no obvious patient groupings.

Conclusions: CKD-aP affects a large proportion of patients on HD, occurs repeatedly, and clusters with dry skin and fatigue.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

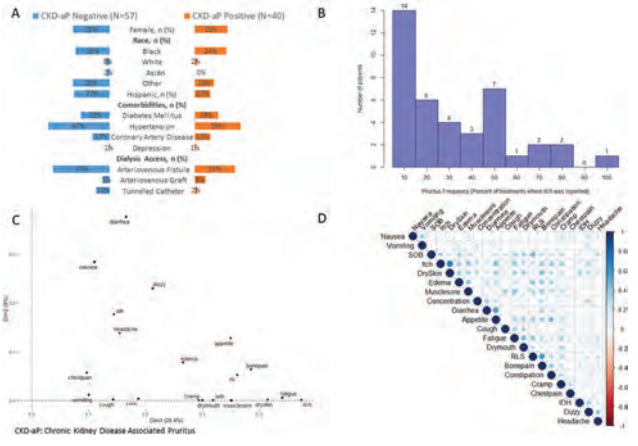


Figure 1: A) Demographics of patients by those who did and did not have CKD-aP, B) Patient distribution of symptom frequency, where 100 indicates itch was experienced at every treatment, C) Visualization of symptoms and MCA principal dimension, symptoms that are closer indicate higher correlation, D) Correlation plot, size and color of circle indicate Spearman Correlation Coefficient.

PUB101

Hyperkalaemia Prevalence, Recurrence, and Treatment in Haemodialysis: A Prospective Multicentre Cohort Study (PRECEDE-K Trial)

Zhaohui Ni,[1] Haijiao Jin,[1] Renhua Lu,[1] Li Zuo,[2] Weimin Yu,[3] Junsheng Wang,[4] Rong Wang,[5] Yuqing Ren,[6] Qiongqiong Yang,[7] Jie Xiao,[8] Qinghong Zhang,[9] Lihong Zhang,[10] Xinzhou Zhang,[11] Qinkai Chen,[12] Chaosheng Chen,[13] Guojian Shao,[14] Qun Luo,[15] Li Yao,[16] Shuguang Qin,[17] Hui Peng,[18] Qing Zhao,[19] Hongyan Shang.[19] The PRECEDE-K study group *[1]Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; [2]Peking University People's Hospital, Beijing, China; [3]Shanxi Bethune Hospital, Taiyuan, China; [4]Suqian People's Hospital of Nanjing Drum-Tower Hospital Group, Suqian, China; [5]Shandong Provincial Hospital, Jinan, China; [6]Yangquan Coal Industry (Group) General Hospital, Yangquan, China; [7]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; [8]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; [9]Taihe Hospital of Shiyan City, Shiyan, China; [10]The First Hospital of Hebei Medical University, Shijiazhuang, China; [11]Shenzhen People's Hospital, Shenzhen, China; [12]The First Affiliated Hospital of Nanchang University, Nanchang, China; [13]The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; [14]Wenzhou Central Hospital, Wenzhou, China; [15]Ningbo No.2 Hospital, Ningbo, China; [16]The First Hospital of China Medical University, Shenyang, China; [17]Guangzhou First People's Hospital, Guangzhou, China; [18]The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [19]AstraZeneca Investment China Co Ltd, Shanghai, China.*

Background: Hyperkalaemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes and is common in patients with kidney failure. However, there is no evidence on the occurrence, recurrence, and treatment of HK in patients on haemodialysis (HD) in China.

Methods: The HK Prevalence, Recurrence, and Treatment in Haemodialysis Trial (PRECEDE-K; NCT04799067) is a prospective, multicentre, observational cohort study being conducted across 18 sites in China. Approximately 600 patients with end-stage kidney disease on HD are anticipated to be enrolled and will be followed up with for 24 weeks. Patients will be in the long interdialytic interval (LIDI) at enrolment and will receive follow-up care every four weeks in LIDI for pre-dialysis and post-dialysis (at enrolment only) serum potassium measurements. To obtain pre-dialysis serum potassium levels in the short interdialytic interval (SIDI), a follow-up visit in SIDI in Week 1 will be performed. Concomitant medications, blood gas analysis, and biochemistry measurements will be obtained at enrolment and at each follow-up visit.

Results: The primary endpoint is the proportion of patients experiencing any HK (defined as serum potassium > 5.0 mmol/L) at the study enrolment or during a 24-week follow-up. The key secondary endpoint is the proportion of patients experiencing HK recurrence (defined as any HK event after the first HK event) within 1–6 months (if applicable) during a 24-week follow-up, including enrolment assessment.

Conclusions: PRECEDE-K will generate high-quality evidence on the occurrence, recurrence, and treatment pattern of HK in patients on HD in China, and is expected to help inform practice guidance for HK management.

Funding: Commercial Support - AstraZeneca

PUB102

Dialysis in New Old Patients. Ten Years of Experience

Tatiana Tanasiychuk, Daniel Kushnir, Alon Antebi, Oleg Sura, Amnon Gil, Jerom Marcuson, Yasir Sanalla, Yosef Shihada, Victoria Svistunov, Muhammad Abd Elhalim, Victor Frajewicki. *Department of Nephrology and Hypertension, Carmel Medical Center, Haifa, Israel.*

Background: The most fast growing dialysis population during the last decades is old- age people. Mortality on dialysis patients is still high, especially among old patients. The two-year mortality rate for patients who initiate chronic dialysis over the age of 75 may exceed 50%. The risk of Acute Kidney Injury (AKI) also rises with age, while mortality risk increases dramatically in old patients with AKI. The prognosis and benefit of dialysis treatment are still unclear in very old patients. We performed a retrospective analysis of outcomes in all cases of first dialysis performed to very old patients (75 and more years old) during a 10 years period in our center.

Methods: The analysis included all ≥75 years aged patients started hemodialysis in our hospital for every indication (AKI, Acute on Chronic Renal Failure (CRF), End Stage Renal Disease (ESRD)) during the period January 1, 2009 - November 31, 2019. Patients were followed for one year from the first dialysis. The study main end point was one year all-cause mortality.

Results: In this period, 951 patients had their first hemodialysis treatment. Mean age was 82.4±5 years, 58.5% were male, 55.3% diabetics. Mean Charlson Comorbidity index was 8.3±2.2, Dementia was diagnosed in 11.4% of patients and 34.6% were nursing care dependent. Indications for dialysis were AKI in 16%, Acute on CRF in 64 % and ESRD in 20% of cases. One year mortality was 72.4%, 60% and 26.6% in AKI, Acute on CRF and ESRD respectively. Age, Nursing State, Dementia, AKI, Acute on CRF, and dialysis in a Intensive Care Unit (ICU) were associated with worse prognosis. Multivariate Cox regression models stratified by age, nursing state, AKI, Acute on CRF and ICU showed an OR of 1.3, 1.4, 3.2, 2.5, 2.0 respectively. Neither Charlson Score nor Diabetes mellitus (DM) were not associated with worse prognosis. DM, in opposite, was associated with a trend of better survival although the difference was not statistically significant.

Conclusions: The outcome of very old patients started with elective maintenance dialysis was much better than in acute unscheduled hemodialysis. The baseline general condition and severity of acute illness seems to be the main prognostic factors for one year mortality. Charlson Score and Diabetes Mellitus did not influence the outcomes in this age group.

PUB103

Vaccination Rates Among Hemodialysis Patients in Nueva Ecija and Aurora Provinces

Rommel P. Bataclan. *University of the East Ramon Magsaysay Memorial Medical Center Inc, Quezon City, Philippines.*

Background: Infections is one of the most common causes of morbidity and mortality in dialysis patients. Vaccinations have been proven to give seroprotection & reduce incidences of infection. This study investigates vaccination rates among out-patient hemodialysis patients in two provinces in the Philippines.

Methods: A cross-sectional study based on hemodialysis records among patients in 12 hemodialysis centers. Vaccination records from 2018 were checked & verified in all individuals. Descriptive statistics & chi-square analysis among selective clinical characteristics were performed.

Results: A total of 550 hemodialysis patients were included in this study. 67.5% have completed their Hepatitis B vaccination. 59.1% of patients had Tetanus Toxoid 59.1% but only 46.2% had pneumococcal vaccine. Influenza vaccinations were low (2018, 11.1%; 2019, 8.4% and 2020, 8.9%). On further analysis, there are significantly more females who received Tetanus Toxoid (66.0% vs. 50.2%, p<0.01).

Conclusions: There is still a significant percentage of patients who did not receive the recommended vaccinations. Lack of access even prior to last year, financial constraints and misconceptions on vaccines may have played important roles. These have to be addressed in order to increase vaccine confidence among hemodialysis patients.

	Number (n=550)	Hepatitis B (371, 67.5%)	p-value	Pneumo. (254, 46.2%)	p-value	Tetanus (325, 59.1%)	p-value
Age			0.39		0.15		0.35
18-39	106	72		41		66	
40-64	295	192		137		166	
65 & above	149	102		76		93	
Sex			0.19		0.15		<0.01
Female	309	166		151		204	
Male	241	143		103		121	
ESRD Duration			0.84		0.17		0.79
<1 year	65	41		26		41	
1-2 years	116	79		48		67	
3-4 years	212	146		97		128	
>4 years	157	105		83		89	
CKD Cause			0.36		0.40		0.19
DM	301	211		140		182	
HTN	143	96		59		78	
GN	71	45		36		40	
Others	35	20		19		25	

Table 1. Vaccination Rates of Hepatitis B, Pneumococcal and Tetanus Toxoid

	Number (n=550)	2018 (61, 11.1%)	p-value	2019 (46, 8.4%)	p-value	2020 (49, 8.9%)	p-value
Age			0.67		0.63		0.18
18-39	106	10		11		16	
40-64	295	23		26		30	
65 & above	149	13		12		15	
Sex			0.73		0.41		0.89
Female	309	27		28		34	
Male	241	19		21		27	
ESRD Duration			0.85		0.68		0.23
<1 year	65	6		6		10	
1-2 years	116	11		12		14	
3-4 years	212	15		15		26	
>4 years	157	14		16		11	
CKD Cause			0.12		0.07		0.99
DM	301	24		25		33	
HTN	143	9		10		16	
GN	71	11		12		8	
Others	35	2		2		4	

Table 2. Vaccination rates of Influenza among Hemodialysis from 2018-2020

PUB104

Impact of Menaquinone 7 Intake on Mortality in Hemodialysis Patients

Mabel Aoun,[1,2] Dania Chelala,[1,3] Serge S. Finianos,[1,3] Hiba Azar.[1,3] *[1]Universite Saint-Joseph, Beirut, Lebanon; [2]Saint-George Hospital, Ajaltoun, Lebanon; [3]Hotel Dieu de France Hospital, Beirut, Lebanon.*

Background: Vitamin K deficiency was shown to be associated with vascular calcifications in hemodialysis patients. Studies evaluating the impact of vitamin K2 therapy on long-term outcomes are still scarce. This study aims to assess whether treatment with Menaquinone 7 (MK7) reduces mortality in hemodialysis patients.

Methods: This is a two-center longitudinal retrospective study that included all patients on hemodialysis during August 2016 and followed until August 2020. Some patients were treated with MK7. Data collection included vascular calcification score and dp-ucMGP at baseline, mean serum calcium, phosphate, PTH and albumin of the last year of follow-up and mortality at 1, 2, 3, 4 years. Kaplan Meier analysis was used to compare survival between the MK7 group and the control.

Results: A total of 143 patients were included. Table 1 summarizes the main differences between the two groups. Mortality was not significantly different between the two groups (Figure 1), even after adjustment to risk factors such as age, phosphate and coronary artery disease.

Conclusions: This study showed no significant difference in mortality at 4 years in hemodialysis patients treated or not by Menaquinone 7.

Table 1

	On Vitamin K2 (n=31)	No Vitamin K2 (n=112)	P
Age in years	73 [59,80]	68 [58,76.7]	0.175
Sex (M/F)	58/42	63/37	0.588
Diabetes	38.7	37.5	0.902
HTN	83.9	89.3	0.410
Coronary Artery Disease	54.8	34.8	0.047
Death at 1 year at 2 years at 3 years at 4 years	16.1 25.8 35.5 45.2	8.9 14.3 24.1 34.8	0.249 0.130 0.206 0.291
Time to death in months	24 [9,28]	26 [15.7,35.7]	0.116
Albumin g/L	39 [37,41]	38.3 [35.2,40.1]	0.375
Phosphate mg/dL	3.9 [3.1,4.5]	4.2 [3.6,4.9]	0.056
Calcium mg/dL	8.9 [8.8,9.3]	9.1 [8.9,9.4]	0.135
PTH pg/mL	187 [77,236]	219 [125,410]	0.097
AC-24 score	8.5 [3.2,15.7]	10 [2,17]	0.766
Dp-ucMGP level	3110 [2065,4383]	2724 [1498,3794]	0.171

Continuous variables are presented as medians and categorical variables as percentages

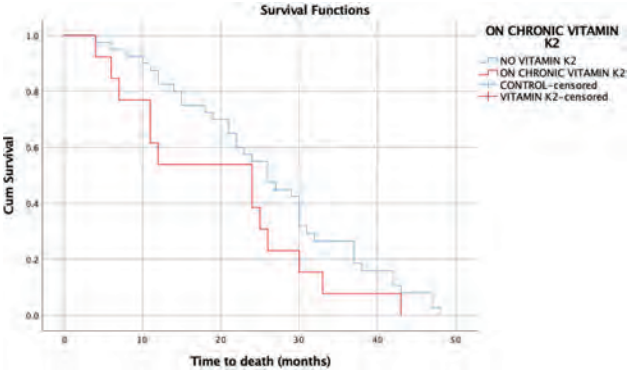


Figure 1. Survival of the two groups

PUB105

Outcome of Migrant Patients Starting Maintenance Hemodialysis in Switzerland

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Background: ESRD migrants without permanent resident status is a particularly vulnerable population in regards of chronic renal replacement therapy or kidney transplantation access. Healthcare policies greatly vary between different countries which influence their clinical outcomes. Switzerland grants medical healthcare including renal care to anyone living in the country for more than 3 months.

Methods: In this report, we retrospectively analyzed the characteristics and the outcome of migrants starting dialysis at the University Hospital of Geneva (Switzerland) between January 2000 and December 2019.

Results: 775 patients started hemodialysis during this period. 38 patients (4.9%) were non-permanent residents being either asylum-seekers or undocumented. Compared to resident patients, they were significantly younger (42 and 63 years old, respectively) with less male gender (50% and 66%, respectively). The cause of ESRD was more frequently unknown with no difference for diabetes prevalence. Their modified Charlson

comorbidity index was overall lower. Emergency hemodialysis initiation was more frequent and mean eGFR at dialysis start was significantly lower (5 vs 7 ml/min/1.73m2). Most of the migrant patients eventually obtained a stable resident status (24/38, 63 %). Seven were sent back to their home country (7/38, 18 %) and 3 were lost of follow-up (3/38, 8%). Among the 28 migrant patients who stayed in Switzerland, 6 patients died during the follow-up period and 17 (61%) obtained a kidney transplantation. To account for their characteristic differences, propensity score matching was performed. Time to transplantation after dialysis initiation was significantly delayed for migrants with a median time to transplantation of 60 (43-99) and 25 (12-49) months for eligible migrants and propensity-score matched residents, respectively. Survival censored for kidney transplantation was overall significantly much higher in migrants compared to resident patients with a 5-year survival rate of 85% and 55%, respectively. When censored for kidney transplantation, survival remained better among migrants compared to matched resident patients (85% and 65% at 5 years, respectively).

Conclusions: In conclusion, ESRD clinical outcomes are excellent when standard care is provided. Aside the ethical issue, previous data from the US suggested that it is economically sustainable.

PUB106

The Cost of the Quanta SC+ Hemodialysis System for Sustained Low-Efficiency Dialysis in the Intensive Care Unit

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Background: Over 20% of patients in the intensive care unit (ICU) experience acute kidney injury requiring treatment with dialysis. There are several modalities available to provide dialysis in the ICU, including conventional hemodialysis, continuous renal replacement therapy (CRRT) and sustained low-efficiency dialysis (SLED). Recent meta-analyses have found that there is no definitive advantage of either of these modalities with respect to patient outcomes; however, they are associated with different cost and resource requirements. The SC+ Hemodialysis System is a commercially available, portable hemodialysis system that can be operated with minimal training by ICU nurses.

Methods: We described the incremental costs of CRRT, regular 4-hour conventional dialysis provided by specialized hemodialysis nurses, and SLED with the SC+ Hemodialysis System in the ICU. The analysis was performed from the perspective of the US health payer with results presented in 2020 US dollars. We considered costs with respect to the dialysis console, dialysis-related supplies (cartridges, tubing, dialyzers, dialysate, bags, and saline), and nursing-related human resources modeled from a large US based hemodialysis program.

Results: The cost of CRRT assumed that ICU nursing staff would provide the therapy, with consumables costs ranging between $320 and $380 per ICU-day. Dialysis provided with conventional 4-hour therapy in the HD unit ranged between $205 and $245 per day including both incremental nursing and renal technician expenses and consumables. Dialysis provided with the SC+ as 8-hour SLED treatments was estimated to cost between $59 and $85 for consumables and operated by the ICU nursing staff.

Conclusions: SLED treatment with the Quanta SC+ operated by ICU nurses offers significant cost advantages over CRRT and conventional HD treatments with no demonstrable disadvantage to patient outcomes.

Funding: Commercial Support - Quanta Dialysis Technologies

PUB107

Incident Dialysis Patients in Latin America (LA): An Unpaid Debt

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Background: Predialysis care in LA is conditioned by uneven accesibility to adequate treatment and odds healthcare systems. Timely initiation, vascular access (VA) creation and anemia and bone disease management are still barriers to overcome. The aim of this study was to compare incident (INC) and prevalent (PRV) dialysis patients outcomes from Fresenius Medical Care LA (FME LA) and possible correlations with survival

Methods: Patients from FME LA (Argentina, Brazil, Chile, Colombia, Ecuador, Perú) on hemodialysis between Jan 1 and Dec 31, 2020 were included. INC were defined with <90 days since first treatment in life and PRV >90 days. INC accounted during first 90 days, then they became PRV. Thus, results and time collected during first 90 days accounted to INC and after that to PRV. Values are expressed as mean ± SD. Means were compared using Student t-test. Kaplan-Meier (KM) and Cox regression models (CM) were created to evaluate survival

Results: 43,390 patients were included (7,969 INC / 35,421 PRV). Main differences between INC and PRV are shown in table 1. KM showed mean survival time INC 322.4 vs PRV 338.7 days (LogRank p<0.0001). Cox Model showed RR for Diabetes 1.30 / Age 1.03 / Male 1.08 / Hb 0.96 / Ca 1.06 / Alb 0.44 / Creat 0.98 / Graft 1.31 / Cuffed cath 1.31 / Uncuffed cath 1.48 (vs fistula), all p<0.0001, but INC vs PRV showed no statistical difference after covariables were included

Conclusions: Alb, Hb, Ca and P were lower in INC than PRV while catheter prevalence was considerable higher suggesting late referral, poor clinical management and dificulties in VA creation before dialysis initiation. Survival in INC was markedly inferior than PRV, but this effect vanished when the model was adjusted, suggesting non modifiable (diabetes, age, gender) and modifiable factors (Hb, Ca, P, Alb, Creat and VA) may be driving survival. Efforts to improve the latest should be done in order to ameliorate INC survival in our region

	Age (yrs)	Gender (male, %)	Diabetes (%)	Hemoglobin (Hb, g/dl)	Albumin (Alb, g/dl)	Serum Calcium (Ca, mg/dl)	Serum Phosphorus (P, mg/dl)	AV fistula (%)	AV graft (%)	Cuffed cath (%)	Uncuffed cath (%)
Incident patients (INC) N=7,969	60.01 ± 15.6	60.8	33.2	9.16 ± 1.8	3.49 ± 0.58	8.42 ± 0.87	4.59 ± 2.03	13.6	0.9	34.7	50.9
Prevalent patients (PRV) N=35,421	59.6 ± 15.4	59.3	30.3	10.9 ± 1.7	3.92 ± 0.42	8.74 ± 0.79	4.75 ± 1.55	70.3	6.2	18.2	5.2
p	0.012	0.012	0.017	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Table 1: Incident / Prevalent patients characteristics

PUB108

Ultrafiltration Accuracy in a Modified Batch Dialysis System

Clayton Poppe, Nicholas Hyun, Sean C. Nash, Melany Yeung, Osman Khawar. *Diality Inc, Irvine, CA.*

Background: Ultrafiltration accuracy is an important way of improving mortality and morbidity on dialysis. The Diality Hemodialysis Machine will provide tight control of ultrafiltration during treatment. Specific Aims: To assess ultrafiltration accuracy during simulated dialysis utilizing a novel modified batch process. In this setup, ultrafiltration was conducted by alternating collection into two-liter reservoirs that contain both dialysate and ultrafiltrate.

Methods: Two simulated dialysis sessions were conducted utilizing blood flowrates of 300 ml/min, dialysate flowrates of 300 ml/min and ultrafiltration flowrates of 2500 ml/hr. (Table 1) Dialysis and ultrafiltration occur off of a two-liter batch of dialysate. Once two liters of dialysate has been circulated through the dialyzer, the collected ultrafiltrate and spent dialysate are discarded and dialysis switches to a separate two-liter reservoir of dialysate while the first reservoir is drained and filled with fresh dialysate.

Results: The results are provided in Table 1. The average ultrafiltration accuracy was measured by comparing the machine-calculated ultrafiltration volume with the weight of the simulated patient. The mean error represents the average difference between machine and patient during the simulated treatments, while the total error represents the total error after the simulated run was completed.

Conclusions: The initial experiments using a modified batch system show promising ultrafiltration accuracy. Future tests will demonstrate accuracy over a larger range of flowrates, volumes and times.

Funding: Commercial Support - Diality Inc

Table 1

Test Number	Q_B (ml/min)	Q_D (ml/min)	Ultrafiltration Rate (ml/hr)	Mean Error (ml)	Standard Deviation (ml)	Total Error (ml)
Run 1	300	300	2500	6.156	7.752	7.69
Run 2	300	300	2500	1.949	6.813	3.62

PUB109

Recruitment Experience for a Year-Long Prospective Observational Study Using a Commercially Available Wearable Device

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Background: Wearable activity trackers can allow healthcare providers to access patients' health parameters remotely. These commercially available devices may provide valuable insights at low cost. Research of the use and acceptance of this technology is necessary to scale the use of trackers and integrate them into clinical care. We aim to share our experience of recruiting hemodialysis (HD) patients to a research study using a wearable activity tracker.

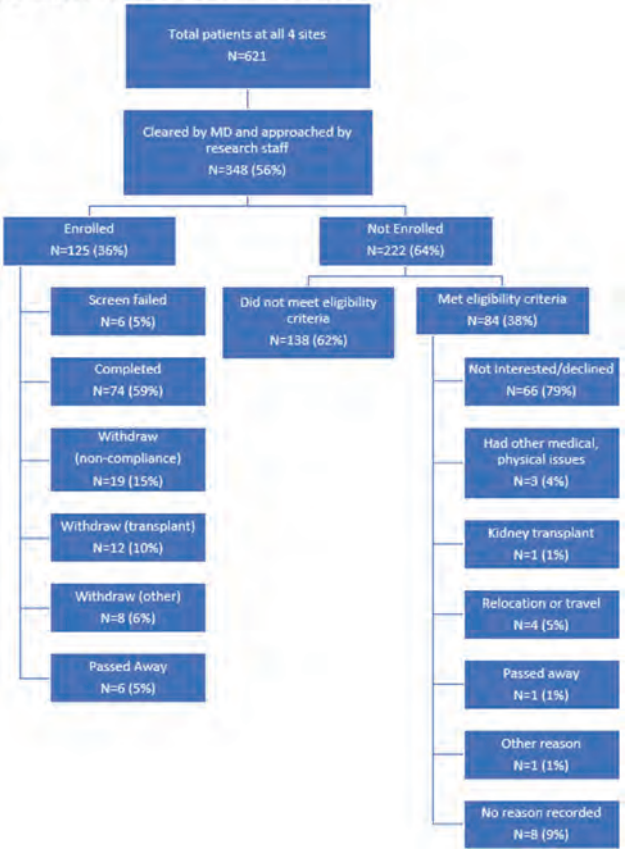
Methods: Patients were recruited in 4 dialysis clinics in Manhattan, NYC. Patients who received their attending nephrologist's approval to participate in the study were approached for recruitment. Patients ≥18 years on maintenance HD, able to walk, owning smartphone, tablet or PC were included in the study. Patients were observed for up to 1 year and were asked to wear a Fitbit Charge 2™. Questionnaires were administered to capture subjective physical and emotional wellness. Subjects who inconsistently synced their Fitbits were withdrawn. We enrolled continuously from May 2018 to November 2019.

Results: Only a third of patients who were approached consented to participate in our study. 79% of patients who were eligible choose not to participate in the clinical study. Details of the recruitment and enrollment process are shown in the flowchart in **Figure 1**.

Conclusions: With most eligible patients choosing to not participate, the value of patients' contributions to research needs to be emphasized. We encourage healthcare providers take the time to educate patients on the importance of clinical research.

Funding: Commercial Support - Fresenius Medical Care

Figure 1. Recruitment and enrollment flowchart



PUB110

Anemia Status and Root Cause Analysis of Maintenance Hemodialysis (MHD) Patients in Shaanxi Province

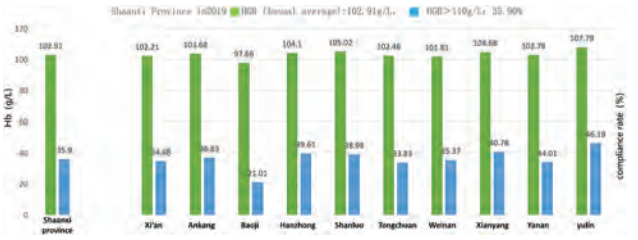
Hua Liu. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*.

Background: According to the national nephrology professional medical quality control index (2020 version) and the related quality control index of renal anemia in hemodialysis patients, combined with the Chinese National Renal Data System (CNRDS) system feedback data in 2019, the anemia control rate of MHD patients in Shaanxi Province was analyzed and the root cause analysis was carried out to promote the continuous improvement of the anemia.

Methods: Based on CNRDS feedback data, the data of the routine timing test rate, anemia control rate, serum ferritin and transferrin saturation timing test completion rate of MHD patients in Shaanxi Province were analyzed and compared with the national situation. Meanwhile, the anemia compliance rate of different regional in Shaanxi Province was compared.

Results: According to the CNRDS statistics in 2019, 54.4% of the patients registered for hemoglobin at least once in 2019, while 79.7% in Shaanxi Provincial website. However, the monitoring of iron indicators was lower than the national average (9.5% vs 16.2%). We can also find that the compliance rate of renal anemia in MHD patients in Shaanxi Province is only 35%, which is lower than the national compliance rate of 39.3%. There are differences in the compliance rate and average value among different regions of Shaanxi Province, but 75.2% of the total patients have hemoglobin>90g/L. There are many reasons for the low control rate of MHD renal anemia in Shaanxi Province, including lack of process and homogeneous training and implementation of anemia management in various cities, lack of grass-roots training by local quality control centers, some test items, such as iron index test, can not be generally achieved in district and county hospitals, there are regional differences in economic level and reimbursement ratio of medical insurance.

Conclusions: We need to continue to focus on the standard operating procedure (SOP) of blood purification, strengthen the grass-roots training, strengthen the promotion of the integrated mode of medical care Strengthen the task implementation of quality control centers in various cities, strengthen the supervision and rectification of CNRDS network report.



PUB111

Serratia liquefaciens Bacteremia in Two Dialysis Patients

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Introduction: *Serratia* are an unusual cause of bacteremia but can present a risk for patients receiving maintenance hemodialysis.

Case Description: Two patients who were sitting proximately receiving maintenance dialysis via central catheters developed chills and fever. Cultures grew *E. cloacae;* vancomycin and gentamicin were administered. They were hospitalized; cultures grew *S liquefaciens*. Both recovered with antibiotics and returned without sequelae. An experienced RN with excellent catheter technique cared for both patients. The only common medication was a multi-dose heparin vial with clear solution. The patients had no relationship outside the facility and neither had evidence of catheter or exit site infection. No other patients had signs of infection.

Discussion: *Serratia* are water dwelling bacteria which infect humans via environmental sources. Five cases of transfusion-related septic shock were reported between 1992 and 1999; no source was identified[1]. Ten cases of *S. liquefaciens* blood stream infection and six pyrogenic reactions at a hemodialysis center in 2001 were found to be related to multiple punctures of single-use vials with pooling of preservative-free Epogen®[2]. In 2017, two cases of bacteremia were reported among nine patients who underwent myocardial perfusion scanning. Bacteria were found in the saline used to reconstitute the radiopharmaceutical[3]. The treatment area including handwashing sinks and water boxes were in good order; no bacteria were identified. Dialysate water cultures were without significant growth. In addition to reviewing catheter care and hand hygiene, we are reviewing proper storage and handling of multidose heparin vials. Water-borne bacteria are a threat to patients receiving maintenance dialysis. Vigilance must be paid to reduce the risk of infection. The differential diagnosis for bacteremia must be broad and treatment must cover relatively unusual etiologies.

PUB112

Adjusting Dialysate Bicarbonate for Chronic Respiratory Failure

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Introduction: Lung disease has been noted to be an independent predictor of mortality in patients with chronic kidney disease. With increased prevalence of obesity, coexistence of chronic lung and kidney disease in the same patient is expected to rise. We report a case of a patient with restrictive lung disease on maintenance hemodialysis who presented with acute hypoxic and hypercapnic respiratory failure, and her CO_2 retention during and after assisted ventilation was managed by adjusting dialysate bicarbonate.

Case Description: A 48 year old African American female with history of restrictive lung disease secondary to severe kyphoscoliosis on home oxygen therapy and end stage kidney disease on hemodialysis secondary to horseshoe kidney disease was brought to ED for decreased responsiveness. In ED, she was unresponsive with O_2 saturation of 60%. On initial ABG, pH was 7.02 and pCO_2 was 101 mmHg. Her baseline pCO_2 was 50-60 mmHg. She was intubated for acute hypoxic and hypercapnic respiratory failure and admitted to ICU. While she was intubated, she was dialyzed with the dialysate bicarbonate of 35 mEq/L. Her pCO_2 level was maintained within the range of 45-50 mmHg. Following extubation, dialysate bicarbonate was reduced to 30 mEq/L, and she was able to remain stable without worsening hypercapnia.

Discussion: In a person with normal renal function, the response to hypercapnic respiratory failure is to increase extracellular concentration of bicarbonate by renal compensation. In a person on maintenance hemodialysis, extracellular bicarbonate concentrations are dictated by nephrologist who can set plasma bicarbonate concentration by adjusting dialysate alkali concentration. In principle, the lower the bicarbonate concentration, the greater the respiratory drive. As uremia per se depresses respiratory drive, the higher extracellular bicarbonate concentration is expected to further suppress the respiratory drive, resulting in respiratory failure. In our patient, maintenance of a lower than usual extracellular bicarbonate concentration by reducing dialysate bicarbonate concentration was successful in achieving stable ventilation. One additional maneuver to prevent precipitation of respiratory failure would be avoiding aggressive home oxygen therapy by maintaining PaO_2 between 50 and 60 mmHg, since a higher PaO_2 is likely to suppress respiratory drive.

PUB113

Vitamin D Independently Related to Right Ventricular Dysfunction in ESRD Patients on Maintenance Hemodialysis

Firoozeh Farahmand. *Saint Louis University, Saint Louis, MO.*

Background: Right ventricular (RV) dysfunction is a major cause of death in patients undergoing maintenance hemodialysis (HD) and a major determinant of mortality in pulmonary hypertension that is common in HD patients. There is tremendous amount of data on the changes in left ventricular function in HD patients, but data on RV dysfunction and its mechanisms in HD patients are scarce. It has been suggested that vitamin D could be involved in the development or progression of heart failure by modulating oxidative stress. We investigated changes in RV function in HD patient and its correlation with vitamin D level.

Methods: In a university affiliated dialysis center, a retrospective cohort of ESRD patients treated with HD for at least 1 month followed in a dialysis unit. Patients without vitamin D assessment, prior myocardial infarctions, heart failure, or prevalent valvular disease were excluded. Subject characteristics were recorded, including age, gender and race. Echocardiography including tissue Doppler imaging (TDI) of the RV was evaluated. PH was defined as an estimated systolic pulmonary artery pressure (PAP) higher than 25 mm Hg using echocardiograms performed by cardiologist.

Results: A total of 77 HD patients were included in the study. The mean age of the patients was 53±7.4 years. The mean dilaysis vintage was 27± 14 months. The mean ejection fraction was 45±7%. The prevalence of PHT was 53%. 59% of patients with PH were female that was statisticaly ($p<0.05$). 30% of patients had RV dysfunction on echo. 72% of patients with RV dysfunction had a 25(OH)D level <30ng/ml ($p<0.05$).

Conclusions: Our findings demonstrate high incidence of RV dysfunction among ESRD patients under maintenance HD and it is strong association with suboptimal vitamin D. Further investigations are required to evaluate the beneficial effects of cholecalciferol in ESRD patients with RV dysfunction.

PUB114

Mortality and Associated Factors in Patients Under Hemodialysis in a Latin American Tertiary Center

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Background: Risk factors are associated with the prognostic and early diagnosis of chronic renal disease. We evaluated modifiable and non-modifiable factors related to mortality in patients who receive hemodialysis therapy.

Methods: Retrospective cohort study.

Results: A total of 347 patients were included. The mean age was 56.29, 71.13% were female, and 55.6% had more than two comorbidities. Diabetes and hypertension were the most common causes of chronic renal disease. Male participants were more likely to die than females. The Charlson index was higher [6 (5 – 7)] in deceased patients than those who did not die [5 (3 - 7)]. Patients with lower hemoglobin and albumin levels were more likely to die. Also, calcium levels [9.05 (8.5 – 9.4)] were higher in deceased patients. 69.23% of patients who died used central venous catheter

Conclusions: The use of central venous catheters is an important risk of mortality in patients who receive hemodialysis therapy. Other factors associated with mortality in these patients are an elevated Charlson index, low hemoglobin, albumin, and high calcium levels. These results show the importance of an early assessment of the patient and the factors mentioned above.

PUB115

Case Report of Hemodialysis-Associated Thrombocytopenia

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Introduction: Thrombocytopenia associated with hemodialysis is a rare complication that can be witnessed occasionally. Studies, however, showed that dialysis membranes could result in significant thrombocytopenia due to the role they play in activating the complement system. Herein, We present to you a case of polysulfone-dialyzer-induced thrombocytopenia in a patient with a previously normal platelet count.

Case Description: Our patient is a 44-year-old male with a past medical history of decompensated liver cirrhosis, who presented with hematemesis. Initial blood workup was remarkable for blood urea nitrogen of 25 mg/dL, Creatinine of 2.08 mg/dL. The patient was started on Ceftriaxone and Flagyl for the concern of spontaneous bacterial peritonitis in addition to pantoprazole drip, Octreotide drip, Norepinephrine, and vasopressin for hepatorenal syndrome. Due to worsening kidney function hemodialysis was initiated on day 18 of hospital admission using the Fresenius Optiflux 180 dialyzer with a synthetic polymer (electron-beam sterilized) membrane. The patient tolerated the first hemodialysis session without complications. However, on the next day, his platelet count decreased from 120,000 to 25,000. Workup was negative for other causes of thrombocytopenia. On the fourth hemodialysis session, the dialyzer was switched from the F180NR to Purema-Polyethersulfone dialyzer (gamma sterilized), after which the patient's platelet levels began to recover without any regression.

Discussion: Thrombocytopenia is a well-known complication of hemodialysis treatment, which results in platelet adhesion, aggregation, and activation. A post-dialysis platelet count decrease of more than 15% compared with predialysis values could identify dialysis-related thrombocytopenia. Verbeelen et al. showed that cellulose acetate dialyzer membranes could cause transient thrombocytopenia and platelet activation. In our patient's case, electron beam sterilization was used initially with the Optiflux 180 Polysulfone dialyzer, and the thrombocytopenia resolved when he was switched to the Purema-Polyethersulfone dialyzer that was gamma sterilized. This case of hemodialysis-associated thrombocytopenia in a new dialysis patient demonstrates that polysulfone dialysis membranes can variably affect platelet levels, despite previous evidence indicating that polysulfone membranes do not affect platelet counts.

PUB116

Frailty in Kidney Transplant Candidate Patients

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Background: Frailty increase the risk of falls, cognitive impairment, hospitalization and mortality in patients both in dialysis and with kidney transplant. Incidence is more than 35% in dialysis patients.

Methods: We perform a single center and transversal study(2021) with patients in haemodialysis(HD) and peritoneal dialysis(PD) in kidney transplant waiting list. We analyze clinical and analytical characteristics. We used Frail scale, validated in patients with chronic kidney disease, for frailty.

Results: We include a total of 81 patients, 62 in HD and 19 in PD, 65.4% males, with a median age of 59 years. Median time in dialysis was 3 years(2-5), significantly lower in PD patients($p<0.001$). There was a 27.2% with a previous kidney transplant. Median time in waiting list was 21 months (9.5,3.4) significantly higher in HD($p=0.023$). We observe an acceptable control of calcium-phosphorus metabolism, anemia and nutritional state with low levels of inflammation markers. HD patients had significantly lower levels of prealbumin and higher levels of RCP. PD patients had more eritropoyetin and phosphorus chelators requirements. Frailty tase was 3.7%(2 women, 1 man), all in HD group. The 39.5% of patients were on prefrail status, 37.7% men and 22% with an age under 50. PD group had higher tase of fatigability 42.1%($p=0.005$) and prefraility 57.9%($p=0.004$).

Conclusions: Our group has low prevalence of fraility because there was selected patients for the kidney transplant, with relative low time in dialysis and waiting list. There was not fraility in PD because of a better nutritional state with lower inflamation. There higher tase of fatigability and prefraility can be explained by increased daily activity. HD tends to have more comorbility and inflamation. We should maintain follow up and control of the potentially frail patients, to optimice his functional reserve and pretransplantation status.

	HAEMODIALISIS (n=62)	PERITONEAL (n=19)	TOTAL (n=81)	p (significance)
BASAL				
Age (years)	58.5 [47.25, 70]	59 [50, 66)	59 [48,69]	0.62
Male sex %(n)	69.4% (43)	52.6% (10)	65.4% (53)	0.5
COMORBID FACTORS				
Smokers % (n)	38.7% (24)	10.5% (2)	32.1% (26)	0.02
Obese %(n)	22.6% (14)	15.8% (3)	21% (17)	0.5
Hypertension % (n)	85.5% (53)	100% (19)	88.9% (72)	0.07
DM[1] % (n)	34.4% (21)	26.3% (5)	32.5% (26)	0.5
Number of drugs % (n)	8.2+/- 0.9	10 +/- 3.8	8.6+/- 3.3	0.06
NUTRITION				
Albumina (mg/dl)	4.2 [4, 4.3]	3.9 [3.7, 4.1]	4.1 [3.9,4.3]	0.15
Prealbúmina	29 [25,33]	36 [32, 39.5]	30 [27,34]	0.004
LTI[2] (kg/m²)	13,1 +/- 2,8	14.3 +/- 2.1	13.3 +/- 2.75	0.04
Triglycerides	122 [77.7, 171,7]	118 [80, 160]	122 [59, 169]	0.9
Cholesterol	140 [118, 165.7]	159 [147,179]	148 [127.5, 172]	0.05
INFLAMMATION				
PCR[3] (mg/dl)	1.85 [1.06, 3.37]	0.12 [0.07, 0.32]	1.4 [0.39, 2.9]	0.00
Ferritine	337 [158, 464]	259 [187, 342]	303[165.5, 458.5]	0.7
Leukocytes	5700 [4950, 6725]	6200 [5700, 7300]	5800 [5050, 6900]	0.22
ANEMIA				
Hemoglobine (g/dl)	11.5 [10.8, 11.97]	11.1 [10.7, 12.2]	11.5 [10.8, 12.1)	0.52
Transferrin saturation(%)	25.3 [19.6, 29.6]	28 [20.9, 38.6]	25.6 [20.2, 30.1)	0.4
Erythropoietin dose (U)	12000 [0,32000]	10000 [4000,24000]	12000 [4000,3200]	0.02
Bicarbonate	22 [21, 24)	23 [20,25)	22 [21, 24]	0.46
BONE/MINERAL METABOLISM				
Calcium	8.6+/-0.5	9.1+/-0.4	8.8+/-0.5	0.01
Phosphorus	4.4+/-1.1	5 +/-0.9	4.5+/-1.1	0.02
PTH	326.5 [221,449]	410 [297,528]	329 [233,456]	0.08

1 DM: Diabetes 2: lean tissue index 3: C reactive protein 4: parathyruid hormone

PUB117

Atraumatic Splenic Rupture in a Patient on Apixaban and Clopidogrel

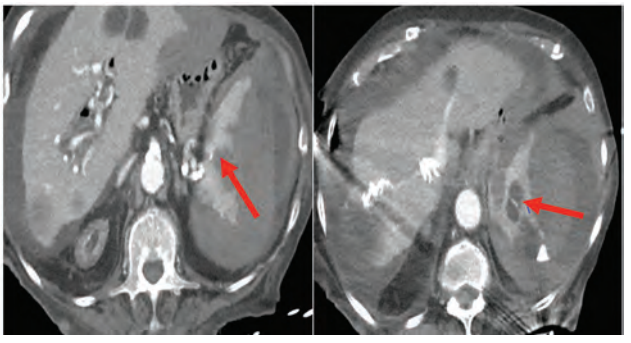
Pooja Patnaik, Pranav Sharma, Steve I. Khalil, Jonathan Lebowitz. *RWJBarnabas Health, New Brunswick, NJ.*

Introduction: Atraumatic splenic rupture (ASR) has an estimated overall mortality rate of 12.2% with 2.4% of cases occurring in patients on anticoagulation. Recently, more cases of ASR have been reported with the use of direct oral anticoagulants (DOACs). This is the first case of ASR in a patient on apixaban and clopidogrel.

Case Description: An 82-year-old woman with atrial fibrillation on apixaban, prior TIA on clopidogrel, and ESRD on hemodialysis presented with new, left-sided abdominal pain that radiated to her chest. There was no known prior abdominal trauma. Her abdomen was distended and diffusely tender with guarding. Hemoglobin was 8.7g/dL, platelets 240,000/μL, INR of 1.26, and lactate 8.8mmol/L. Her hypotension was not responsive to midodrine or NSS boluses, so she was initiated on IV norepinephrine. Over the next 12 hours, her hemoglobin dropped to 6.3g/dL, her lactate increased to 12.6mmol/L, and

her INR increased to 1.62. An urgent abdominal CT scan revealed splenic rupture and significant hemoperitoneum (Figure 1). An emergent exploratory laparotomy revealed splenic rupture and she underwent splenectomy. On pathologic examination, the spleen measured 12 x 6.5 x 1.9 cm with evidence of an organized splenic hemangioma.

Discussion: DOACs significantly reduce mortality from embolic complications in patients with atrial fibrillation but increase the risk of gastrointestinal bleeding. Additionally, patients on a DOAC with an add-on antiplatelet agent are 1.42 times more likely to have a major bleeding event than patients who do not receive add-on antiplatelet therapy. Furthermore, pharmacokinetic studies suggest that use of apixaban, even at recommended doses, may lead to supratherapeutic inhibition of factor Xa in patients with ESRD. Therefore, ASR should be suspected in any patient maintained on anticoagulation who presents with abdominal pain and shock, especially those who are taking both a DOAC and antiplatelet therapy. Bedside ultrasound showing free peritoneal fluid can aid in early diagnosis of these patients.



CT Abdomen showing splenic hematoma

PUB118

Adequacy of 4-Hour Sustained Low-Efficiency Dialysis Among Hospitalized Patients: A Retrospective Data Review

Mostafa Najim, Alaa Rahhal, Ahmed Mahfouz, Mhd Baraa Habib, Sara S. Hassen, Isra'a S. AlSheikh, Ashraf O. Ahmed, Haneen A. Toba, Mawahib A. Elhassan, Sumaya M. Alyafei, Amr M. Badr, Khaled M. Mahmoud. *Hamad Medical Corporation, Doha, Qatar*.

Background: Sustained low-efficiency dialysis (SLED) is a dialysis modality performed over 6-12 hours among hemodynamically unstable patients as it is characterized by a slower blood flow rate than intermittent hemodialysis. Conduction of 4-hour SLED may spare time and manpower for procedures needed in critical care units. However, the appropriateness of 4-hour SLED has not yet been evaluated.

Methods: We conducted a single-center retrospective observational study to explore the appropriateness of 4-hour SLED among critically ill patients admitted to Heart Hospital in Qatar from 1/06/2016 to 1/06/2020. Renal parameters, including blood urea nitrogen, serum creatinine, serum potassium, and serum bicarbonate were determined before and after each SLED session for all the patients who did up to ten SLED sessions during the index admission. The Wilcoxon signed-rank test was used to compare the variables before and after SLED sessions.

Results: Of the 297 patients included, 70% were male with a mean age of 64 years. The majority of patients were from the Middle East (65%), followed by 29% from Asia. Cardiogenic shock was the reason for hemodynamic instability in 45% of the study population, while mixed cardiogenic/septic shock was present in 10%. 4-Hour SLED resulted in a significant improvement in all evaluated renal parameters, as shown in Table 1.

Conclusions: The use of 4-hour SLED significantly improved renal parameters among critically ill patients, which warrants utilizing SLED shorter than 6 hours to preserve time for essential procedures in critical care units.

Table 1. Comparison of the renal parameters before and after 4-hour SLED (N= 297)

Variable	Pre-SLED*	Post-SLED*	P-value
BUN (mmol/L)	21 (15)	17 (10)	p <0.001
Serum creatinine (µmol/L)	383 (217)	299 (191)	p <0.001
Potassium (mmol/L)	4.5 (0.9)	4.1 (0.65)	p <0.001
Bicarbonate (mmol/L)	22 (6)	25 (5)	p <0.001

*Presented as median (interquartile range); BUN: blood urea nitrogen

PUB119

A Sliding PD Catheter: Caution on Repair of Pericatheter Hernias

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Introduction: Catheter migration is a common cause of catheter malfunction in peritoneal dialysis. Abdominal radiography is considered the standard of care to diagnose catheter migration. We are presenting a case where abdominal radiography failed to detect a migrated PD catheter. The catheter likely migrated due to a recurrence of repaired pericatheter hernia.

Case Description: A 56-year-old female with ESKD presented to the outpatient PD clinic with inflow and outflow failure. Four months after laparoscopic catheter insertion, she presented with PD catheter insertion site swelling. She underwent revision of the catheter where a pericatheter hernia at the peritoneal insertion site was found. The sac was sewn to incorporate the cuff, the old catheter was cut and tunneled to a new site. 6 months later, the patient presented with outflow failure and bulge at the catheter insertion site. Abdominal radiograph showed appropriate positioning of the catheter tip in the right lower quadrant. Laparoscopic surgery showed an incisional hernia at the previous peritoneal entrance site and no catheter in the peritoneal cavity. Incision of the bulge revealed a loculated subcutaneous fluid collection and the coils of the catheter. It appears that the hernia had pulled the catheter out of the abdominal cavity, and the peritoneum had sealed behind it, causing this loculated collection. The catheter was removed, the sac was resected, and the fascial defect was repaired. A new PD catheter was inserted on the other side.

Discussion: Pericatheter hernia can cause malposition of PD catheters. In this case, we believe the catheter suffered malposition due to the surgical technique employed in the initial surgery where the hernia sac had been sewn to the cuff. A plain posterior-anterior abdomen radiograph may be a useful tool in evaluating PD catheter position. However, in this case, despite the radiograph showing the tip in "appropriate position", the PD catheter migrated into the subcutaneous tissue. Other methods of identification for catheter placement like lateral abdominal x-rays, CT scan, or surgical exploration should be considered if catheter mispositioning is suspected

PUB120

Healthcare Perspective on Home Hemodialysis Use: Barriers and Interventions

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Background: Home hemodialysis (HHD) has been available for several decades with known benefits, yet <2% of dialysis patients in the US use this modality. In 2019, an executive order directed the US Department of Health and Human Services to develop policies to target a goal of 80% of ESKD patients to either dialyze at home or be transplanted. Few studies are published to identify barriers and suggest solutions for more use of the HHD modality. Most published studies focused on surveying patients and nephrology trainees.

Methods: We surveyed the Nephrology team at the University of Virginia (UVA) about their experience with HHD. UVA has approximately 950 dialysis patients among all modalities, with 12 dialysis units located in central Virginia.

Results: Of 274 individuals receiving the survey, 139 responded (50.7%) including dialysis nurses (56.1%), dialysis technicians (15.1%), dieticians (7.9%), social workers (7.2%), nephrologists (10.1%) and nephrology fellows (3.6%). Both physicians and staff expressed extreme (36.8% and 40.0%) and somewhat comfort (52.1% and 40.8%) with HHD care. Physicians suggested the main barriers to HHD are patients-related (social barrier, lack of support, fear and lack of interest), inadequate electronic medical record, and insufficient patient/staff education. The staff further added inadequate home space for HHD, more frequent HHD (4-5 session/week) vs in-center HD (3 session/week), lack of patients' confidence to perform HHD and worrying about care partners burn. To help increase using HHD, faculty suggested better education of patients and trainees and early introduction of HHD to patients with pre-dialysis advanced CKD. The staff suggested policy changes to allow more catheter use, solo HHD, more involvement of the HHD nurse in the in-center HD unit and hospital setting, more physician education, and referral of eligible patients to the HHD unit or a transitional care unit. All forms of education were recommended by both physicians and staff including webinars, lectures, printed materials, hands-on education, short videos and fliers.

Conclusions: Improving access to HHD is possible. Overall, surveying physicians and staff provided more insight into modifiable barriers that could increase use of HHD. We would recommend all centers to survey physicians and staff to find better ways to meet the goals of this new executive order.

PUB121

CardioMEMS and Peritoneal Dialysis: Synchronizing Data to Provide Patient-Centered Care at Home: A Road to the Future

Julie A. Minser, Max Liebo, Kavitha Vellanki. *Loyola University Health System, Maywood, IL.*

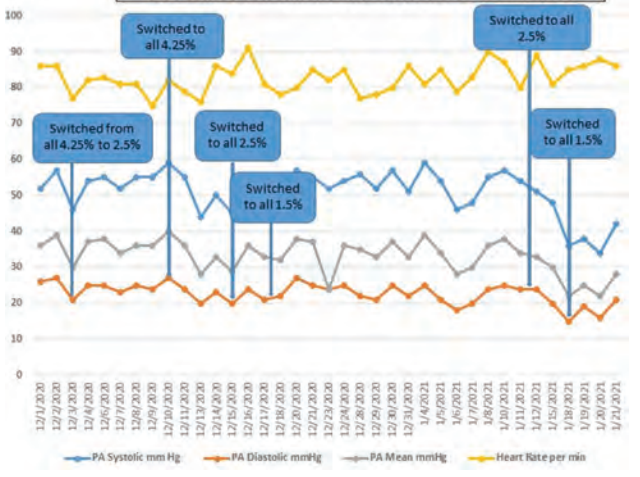
Introduction: End stage renal disease patients are the highest risk populations for heart failure (HF), an estimated 36% with congestive heart failure at dialysis initiation. CardioMEMS is an FDA approved wireless pulmonary artery (PA) pressure monitoring device in New Yor Heart Association (NYHA)class III HF patients hospitalized during the previous year. Here, we present our experience with assessing ultrafiltration (UF) needs in peritoneal dialysis (PD) using CardioMEMS data. There are very few published reports of CardioMEMS in dialysis patients. We believe this is the first to report adjusting PD prescription using CardioMEMS recordings.

Case Description: A 61 yr old female with failing kidney transplant was initially referred to general nephrology clinic for impending dialysis needs. She had extensive cardiac history with ischemic cardiomyopathy, HF with ejection fraction of 25% and NYHA Class IIIB symptoms, CardioMEMS implantation a year prior and being evaluated for combined heart-kidney transplant. She also had symptomatic orthostatic hypotension at baseline. With a coordinated effort between surgery, cardiology and nephrology, she had a laparoscopic PD catheter placement and initiated on PD in-hospital. Her clinical course was complicated with pancytopenia, CMV viremia, acute decompensated heart failure and severe symptomatic gastroparesis raising concerns on whether she can continue PD. She was successfully discharged home on PD and home PD regimen adjusted to attain a

goal PA diastolic pressure of 18-20 mm Hg (Figure 1). Rehospitalizations were prevented and she eventually received a combined heart-kidney transplant 3 months later.

Discussion: Assessment of UF needs in dialysis patients with HF is fraught with multiple limitations leading to frequent rehospitalizations. In our patient, PA diastolic pressure readings from CARDIOMEMS were used as a guide in assessing UF needs and adjusting PD regimen. Our case illustrates that a coordinated multidisciplinary approach can provide patient centered care at home and improve outcomes.

FIGURE 1: SNAPSHOT OF CHANGES MADE TO PD REGIMEN BASED ON PULMONARY ARTERY DIASTOLIC PRESSURE READINGS



PUB122

Development of a Registry for Peritoneal Dialysis at Yokohama City University and Affiliated Hospitals (Yokohama Bay-Shonan PD Registry)

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Background: Patient registry has become increasingly important as a strategy to promote clinical research and to improve the patient care. Yokohama City University Hospital is one of the leading hospitals in Kanagawa Prefecture, a representative and well-known urban area in Japan.

Methods: We started to construct a registry of peritoneal dialysis (PD) at Yokohama City University Hospital and 15 affiliated hospitals (Yokohama Bay-Shonan PD Registry) from the beginning of 2020. The categories of Yokohama Bay-Shonan PD Registry include an information including the age, sex, duration of PD, method of PD (continuous ambulatory PD, intermittent PD, or continuous cyclic PD), cause of end stage of kidney disease, prescription of renin-angiotensin system inhibitors (+/-), past history of heart disease (+/-), results of peritoneal function test, onset of new heart disease (+/-), onset of PD-related infection (+/-), and combination of hemodialysis (+/-).

Results: We collect data from each facility once a year. Only data of Yokohama City University Hospital were available for analysis this time, and total of 28 patients were registered at Yokohama City University Hospital. Mean age was 66.7 years old. Eleven patients were affected with PD-related infection, and 3 pateints discontinued PD (1 death, 1 pancreas cancer, and 1 PD-related infection).

Conclusions: We continue to collect data from each affiliated hospital and will expand the information recorded in the Yokohama Bay-Shonan PD Registry to find the persistence rate of PD and frequency of cardiovascular events for further analysis.

PUB123

Unusual Pathogen Causing Peritonitis in a Peritoneal Dialysis (PD) Patient

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Introduction: Pantoea species causes infection in humans and are pathogenic to plants. Pantoea agglomerans are mostly isolated from human and was reported to cause peritonitis. We are describing a case of peritonitis in a PD patient, caused by Pantoea Calida (PC) and Pantoea Gaviniae (PG). There are few case reports about it causing bacteremia, meningitis infection in human but not peritonitis.

Case Description: 44 years old man on continuous cycling PD, has history of cardiomyopathy, was found to have cloudy effluent and was complaining of abdominal pain, nausea and diarrhea. Vitals signs: temperature 38 C, BP 126/80, PR 91. on exam: generalized abdominal tenderness. Effluent fluid analysis cell counts of 3408/µl. With 80% polymorph neutrophils. patient was prescribed intravenous antibiotics vancomycin and cefepime, then started on continuous cefepime intraperitoneal the next day, while effluent culture was pending. On day 5 patient was feeling better and the cell count dropped to 1996/µl, so was discharged home, Cefipime was continued intraperitoneally. 2 days after discharge, effluent was noted to be cloudy again and the cell count was 2948/µl. At this time decision was made to remove PD catheter for persistent peritonitis. Efflent Culture was consistent with PC & PG, susceptible to cefepime. Fungal culture remain negative. PD catheter was removed & Patient was started on hemodialysis. patient was treated with ceftazidime for 2 weeks. infection was treated. patinet chose to remain on hemodialysis.

Discussion: Peritonitis is a common and serious complication of PD. It is the major cause of death in around 16% of PD patients.it is reported that Pantoea agglomerans can cause peritonitis. Our patient had peritonitis caused by PC, PG which is a very rare finding. Despite treatment with appropriate antibiotic the symptoms persist and eventually PD catheter was removed, the patient was started on hemodialysis. Pantoea species have been isolated from soil, water, plant, seeds, fruits, and human body fluids. PG, and PC were isolated from infant formula. PC was isolated from dialysate of PD patients and from urine, although pathogenicity remain unknown. In our case the patient had sever peritonitis caused by Pantoea species, the way of transmission is unclear. We recommend further research and examining the dialysate fluid in certain population, aiming that such an infection can be prevented in future.

PUB124

The Effects of Location of Peritoneal Dialysis Training, In-Home vs. In-Center, on Peritoneal Dialysis Patients

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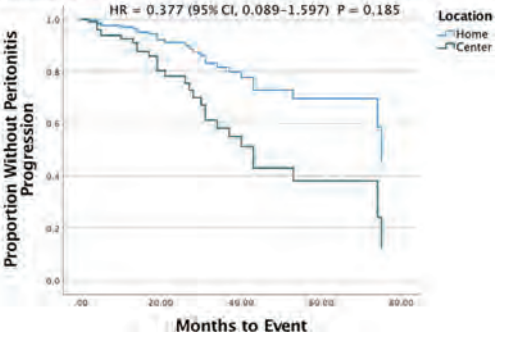
Background: The objective of this study is to investigate the relationship between peritonitis rates and whether peritoneal dialysis (PD) was taught in-center (n_1=104) or in-home (n_2=16) for 120 patients in a single center located in Southern Georgia. Preceding studies have assessed the link between peritonitis rates and demographic factors among PD patients. However, there is very limited research that examines the effects of peritoneal dialysis training location on a patient's chance of developing peritonitis.

Methods: This study is a retrospective analysis for data accumulated over a period of seven years. Subjects were categorized into two groups: one group's dialysis administrator received peritoneal dialysis training in their homes and the other group's dialysis administrator was trained in-center. The data collected includes gender, age, peritonitis occurrence, presence of family support to patient, and severity of comorbidities. The initial analysis was conducted by using a Fischer's test and Welch's t-test. Further investigation was done through a Cox hazards model to compare the influence of in-home and in-center training on peritonitis occurrence over time during PD.

Results: A hazard ratio (HR = 0.377) was utilized to compare the home trained group to the center trained group. The HR indicates that at any time during PD, patients who were home-trained had a 62.3% lower risk of peritonitis. The confidence interval includes one. Therefore, this result is not significant, and this finding is further verified by its p-value being over 0.05. Additionally, significance between peritonitis rate and location of training (P=0.352) could not be established and all models used to analyze each variable resulted in insufficient p-values and binary r-squared values.

Conclusions: Considering the use of unbalanced sample sizes and limited data, the results can be deemed misrepresentative of the general peritoneal dialysis patient population, this study finds that location of training, in-home versus in-center, may not be an accurate gauge of peritonitis risk in certain populations.

Figure 1. Time to Peritonitis for Home Trained Patients and Center Trained Patients



PUB125

Curious Rash

Parth Worah, Jingyin Yan, Sehrish Ali. *Baylor College of Medicine, Houston, TX.*

Introduction: Peritoneal dialysis (PD) involves infusing a solution into the peritoneal cavity via a catheter. PD provides removal of solute/fluids by using the peritoneal membrane as an exchange surface. Primary PD solutions are glucose containing. Glucose is not an ideal osmotic agent as it's easily absorbed; thereby attenuating the osmotic gradient driving ultrafiltration (UF). Icodextrin (ID) is an alternative to hyperosmolar glucose containing solutions. ID is an iso-osmolar solution consisting of a mixture of high molecular weight water-soluble polymers of glucose, isolated by the fractionation of hydrolyzed cornstarch. It's added when more UF is indicated and/or when patients are at an increased risk of hyperglycemia. Icodextren is generally well-tolerated; however, there have been reports documenting exfoliative rash from it. Our case describes biopsy proven spongiotic dermatitis on a patient who recently had ID added to her PD prescription.

Case Description: A 38-year-old female with past medical history of DM, HTN, and ESKD on PD for 1 year, presents with diffuse dry skin, pruritic rash and excoriations. This occured 4 days after changing her PD solution to ID. It worsened despite a 3 day course of steroids. Physical exam notable for diffuse superficial desquamation and excoriations. Labs showed mild leukocytosis with a neutrophil predominance. Upon removal of ID from the PD prescription, her symptoms improved and a slow resolution of the skin rash occured. Biopsy showed spongiotic dermatitis, consistent with eczematous/contact dermatitis.

Discussion: ID provides a continuous and longer osmotic gradient because it is absorbed through the peritoneal cavity slower than standard PD solutions. Therefore, ID is used to increase UF. A few case reports and studies documented rare hypersensitivity reactions and exfoliative rashes to ID in dialysis patients. The exact pathophysiologic mechanism is not fully understood, ID is slowly absorbed via the lymphatic system from the peritoneal cavity, and is rapidly hydrolyzed by amylase in maltose, which may cause pruritis. Hypersensitivity reactions may be caused by immune complex formation on the skin. Our case shows a case of spongiotic dermatitis caused by edema and exocytosis of lymphocytes. ID induced skin rashes typically resolves with discontinuation of ID, yet clinicians should remain attentive and consider these potential side effects in patients that develop skin rashes after being initiated on ID solution.

PUB126

Novel Combined Test for Osmotic Conductance to Glucose and Small Solute Diffusion Capacity in Peritoneal Dialysis

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Background: Peritoneal membrane small solute diffusion capacities and osmotic conductance to glucose (OCG) are key determinants of peritoneal dialysis treatment efficiency and patient outcomes. However, current peritoneal function tests for measuring these parameters are cumbersome, inaccurate, and time-consuming. Recently we developed an easy method to determine OCG on the basis of a single 1-h 4.25% glucose dwell (Fig. 1A). Here, we retrospectively assess the ability of the single dwell method to accurately determine also the diffusion capacity (PS) for creatinine.

Methods: Using a recently developed isocratic method, creatinine PS values were firstly determined on the basis of a single 1-h 4.25% dwell, and then validated against (reference) Three-pore model creatinine PS in a Bland-Altman analysis (n=28). Also, a simple equation was developed to convert between PS assessed using 1-hour dwells of 1.5% and 4.25% glucose fluid.

Results: Isocratic PS estimations based on the single 1-h 4.25% dwell correlated closely with the reference method (Fig. 1B) (r^2= 0.98), and had a mean difference of -0.6 ± 1.0 (1.96 SD) mL/min (Fig. 1C). The 1.5% glucose data showed higher variation, having a mean difference of -0.6 ± 3.9 mL/min and r= 0.81 (P <0.001).

Conclusions: The combined single dwell peritoneal function test shows promising estimation accuracy for both creatinine PS and OCG. The present retrospective findings need to be confirmed in a prospective clinical study.

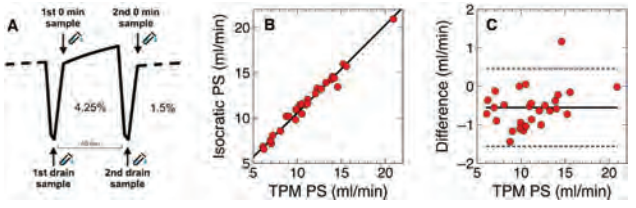

Figure 1. **A.** Single dwell peritoneal function test procedure. **B.** Linear regression of 4.25% glucose isocratic and Three-pore model PS (mL/min). **C.** Bland-Altman analysis of isocratic and Three-pore model PS (mL/min).

PUB127

Troubleshooting Drain Pain: When Imaging Is Nondiagnostic

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Introduction: Catheter problems account for 17% of cases of PD failure forcing transition to HD. Drain pain is common when starting PD, and is typically attributed to catheter malposition, or the catheter abutting sensitive visceral tissue. We present 2 patients who experienced drain pain with a newly placed PD catheter and discuss our strategies to resolve it.

Case Description: Case 1: A 34 yo woman on PD had an uneventful US guided Tenckhoff catheter placement. She started experiencing significant pain with drains during weekly flushes. The effluent was clear and free of fibrin. An abdominal film showed the catheter in good position. Her pain persisted despite a regular bowel regimen. Ultimately, the patient was taken to the OR for revision. Laparoscopy revealed an adhesion of omentum ensnaring the catheter. The catheter was freed from the adhesion and sutured to the abdominal wall. The patient's pain resolved. **Case 2:** A 24 yo man on PD had uncomplicated laparoscopic placement of a Tenckhoff catheter. He experienced abdominal pain post-operatively, and significant pain with drain during his first flush. Cloudy fluid was noted but cell counts were not concerning for peritonitis. A CT peritoneogram showed the catheter in good position in the pelvis overlying the bladder. Laparoscopic exploration was pursued. This showed no significant adhesions or omentum. The catheter was manipulated away from bowel and secured to the abdominal wall. This resolved the patient's pain.

Discussion: Pain with dialysate drain is often due to catheter obstruction by omentum, bowel, bladder or the peritoneal membrane. Treatment of constipation or use of tidal fill volumes are initial strategies used to address this. When noninvasive methods fail to correct the issue, imaging can help identify tip migration or any adhesions. In the presented cases, we highlight how laparoscopy can be an important tool to salvage a PD catheter, and correct any mechanical obstacles complicating PD therapy.

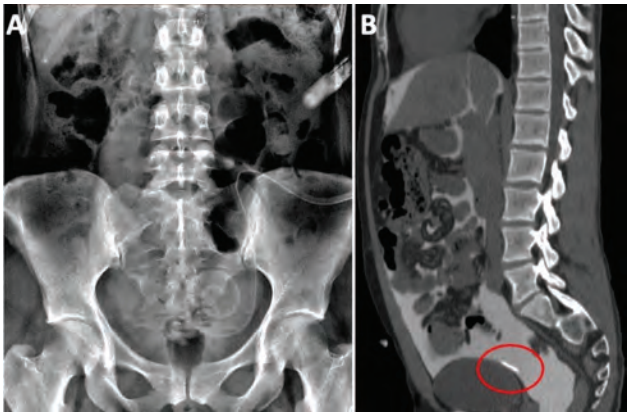


Figure 1. (A) X-Ray from Case 1, (B) CT from Case 2

PUB128

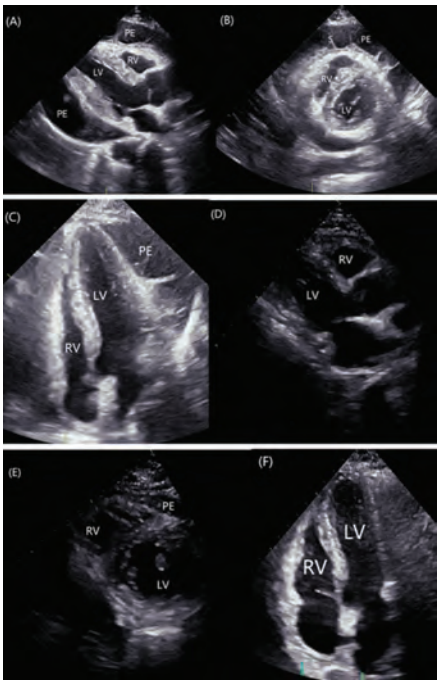
Hemorrhagic Pericardial Tamponade in a Peritoneal Dialysis Patient

Yihsin Chou, Chih-Ching Lin. *Taipei Veterans General Hospital, Taipei, Taiwan.*

Introduction: We report a case of hemorrhagic pericardial tamponade who was non-adherent to peritoneal dialysis with initial presentation of hypotension and syncope.

Case Description: A 46-year-old patient under peritoneal dialysis was hospitalized due to syncope, dyspnea on excertion and hypotension. He had high levels of BUN(~90 mg/dL) and creatinine(~20 mg/dL) in the past year. Low hemoglobin(7.9 g/dL) was found. Furthermore, chest radiograph revealed a round-head boot shape heart. Echocardiography revealed massive septated pericardial effusion with fibrinoid materials(Figure 1, A-C), which was difficult for echo-guided pericardiocentesis. He received pericardial window construction. More than 600 mL bloody effusion was drained. The pathology of pericardium revealed chronic fibrinoid pericarditis. After the operation, the patient's blood pressure increased from 90/60 mmHg to 130/100 mmHg. Follow-up transthoracic echocardiography revealed significant resolution of pericardial effusion and improvement of right ventricle compression(Figure 1,D-F).

Discussion: The traditional uremic pericarditis occurs within 8 weeks of renal replacement therapy. However, it can also develop in non-adherent and under-dialyzed patients with higher level of toxic nitrogenous metabolic end products, free radicals and increased endothelial permeability. Bleeding tendency due to platelet dysfunction can be caused by uremic toxin, anemia and von Willebrand factor dysfunction. Our patient presented with acute bleeding in a chronic inflammatory pericardial space, resulting in a rapid impedance to cardiac filling and decrease in cardiac output. Uremic pericarditis used to be a sign for initiation of dialysis in patient's with chronic kidney disease. It can also remind the clinician of reevaluating the patient's dialysis adequacy before any catastrophic complication such as cardiac tamponade.



PUB129

Abdominal Cocoon Syndrome in Peritoneal Dialysis

Julie G. van Baardwijk, Carlos Kuria, Joe N. Austin. *Christ Hospital, Cincinnati, OH.*

Introduction: Abdominal cocoon syndrome, also known as sclerosing encapsulating peritonitis (SEP), is a rare form of small bowel obstruction (SBO) resulting from peritoneal inflammation inducing formation of a fibrocollagenous membrane. Secondary (non-idiopathic) SEP is seen in patients on peritoneal dialysis, peritonitis, previous abdominal surgery, sarcoidosis, or tuberculosis. We present an interesting case of secondary SEP.

Case Description: A 54-year-old African American male with history of end-stage renal disease on hemodialysis (HD), sclerosing encapsulating peritonitis, recurrent SBO presented with weakness, failure to thrive and fecal drainage through his incision site. Because of his weakness, he had missed two HD sessions. Two and half weeks prior to presentation he was admitted for SBO and underwent ex-lap with lysis of adhesions, umbilectomy, small bowel enterotomy and drain placement to left lower quadrant abscess. He had been on peritoneal dialysis (PD) for about 20 years which was converted to HD due to interval development of intraperitoneal calcification consistent with SEP three years prior to presentation. On admission, potassium was 6.9. He was placed on empiric antibiotics and underwent emergent HD. CT scan of his abdomen demonstrated enterocutaneous fistula and extensive coarse intraperitoneal calcifications consistent with abdominal cocoon syndrome. There was also a left pelvic region abscess with tip of JP drain within the collection. He was evaluated by surgery with recommendations to treat with antibiotics and permanent cessation of oral intake. Abdominal wound cultures grew Escherichia coli. He was discharged with intravenous antibiotics and total parenteral nutrition (TPN).

Discussion: The exact etiology of SEP is unclear due to the rarity of this condition. Abdominal cocoon syndrome is an uncommon complication of chronic ambulatory peritoneal dialysis. It has an incidence of about 2% among patients undergoing PD. The incidence increases with PD duration and can be as high as 5-8% after 3 years. Mortality rates range as high as 50%. Patients can develop SEP while on peritoneal dialysis, but may also present later after renal transplantation or conversion to hemodialysis. The initial management includes removal of the PD catheter, bowel rest and TPN support. Additional treatment strategies include surgical management, steroids, immunosuppressive therapy and tamoxifen.

PUB130

Estimating Caloric Absorption on Peritoneal Dialysis: When Calories Matter!

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Background: Most formulas that estimate calories absorbed from dialysate do not consider peritoneal dialysis (PD) modality and transport characteristics. We wanted to determine more accurately how many grams of carbohydrate and calories our patients were absorbing from dialysate based on the modality and transport characteristics of patients' peritoneal membrane.

Methods: Nursing staff entered patients' PET information into Baxter Sharesource to determine the membrane type. RDN reviewed patients' monthly dialysis logs to determine what percent dextrose solution was used, obtained patients' dialysis prescriptions from nursing staff, and entered different combinations into PD ADEQUEST software (Baxter Healthcare) to determine the grams of carbohydrates and calories absorbed. This is based on the kinetic formula ($1\text{-}D/D_0$ for dwell time) x initial glucose instilled = grams glucose absorbed. Patient education was provided to reduce fluid intake when using high dextrose solution along with education on minimizing the overall use of high dextrose solution to prolong the longevity of the peritoneal membrane. Grams of carbohydrate and calories were added to the chart to improve communication between departments.

Results: 23 adult patients on peritoneal dialysis were reviewed. Baseline characteristics included 12 females age 25-76, 11 males 32-87; 9 diabetics; 3 on CAPD, 20 on CCPD. Peritoneal membrane transport type included 1 low, 9 low average, 11 high average, and 2 high. PD prescriptions accounted for 37-217 grams of carbohydrates and 128-868 calories based on individual prescriptions (% dialysate used, transport properties, modality).

Conclusions: Quantifying the calories and grams of carbohydrates from the dialysate in peritoneal dialysis is easily accessible through PD ADEQUEST software and is extremely valuable to improve the care of diabetics with ESRD. This information can help optimize blood sugars and improve eligibility for transplant. Estimating caloric absorption on peritoneal dialysis is important for patients needing nutrition support to avoid over/underfeeding and should be considered in patients who struggle with obesity.

PUB131

A Central Venous Catheter That Cannot Be Dislodged Easily by a Confused Patient

Shuqin Mei. *Shanghai Changzheng Hospital, Shanghai, China.*

Introduction: The optional type of permanent access for hemodialysis among the elder is controversial. Reliable vascular access which can provide adequate blood flow is a prerequisite for hemodialysis. Exhausted vasculature, patient comorbidities, and life expectancy should be taken into consideration for whether it is worth to place an arteriovenous fistula (AVF)/arteriovenous graft (AVG). So the tunneled central venous hemodialysis catheter are both preferred choices for end-stage renal disease patients who have an urgent need for hemodialysis. But sometimes patients dislodged or pulled out central venous catheters by mistake or confused.

Case Description: A 75-year-old hemodialysis man with a history of multiple arteriovenous fistula operations was admitted to our clinic for the poor blood flow of 150ml/min. Although the AVF was historically known to be the ideal option for vascular access, the aging old man had no chance because of the poor vessel quality on both arms, and the tunneled hemodialysis catheter was optioned to be chosen. In view of the cerebral infarction induced intelligence obstacles of the patient, atypical tunnel of the catheter should be considered in case of the catheter pulled out by the patient unconscious. During the procedure without fluoroscopy, the guidewire entered the vessel smoothly after successful puncture into the right external jugular vein with the left lateral position of the patient. The exit of the tunnel was 5cm right to the middle of the spine at the level of the third thoracic which was out of reach of the patient and a cuffed hemodialysis catheter was eventually inserted through the peel-away sheath, and finally the catheter entered the vessel with satisfactory venous blood return. Hemodialysis was initiated with blood 200ml/min without any complication.

Discussion: To find a solution for confused or uncooperative patients, we conducted a different method. On the basis of our experience, we recommend clinicians consider using these techniques when placing a central venous catheter in a patient who is confused or uncooperative to prevents the patient from dislodging it. Although the back exit at the level of the third thoracic is better to avoid dislodging the central venous cathete comparing with the normal exit, it may uncomfortable when the patinet lying on bed or receiving hemodialysis treatment. Anyway, the best method is the right and suitable for the patient.

PUB132

Hemodialysis Catheters: the Good, the Bad and the Ugly

Jafar Alsaid. *Ochsner Medical Center - New Orleans, New Orleans, LA.*

Background: Over the past decades with all the efforts spent for fistula first, hemodialysis catheters are still used in more than 80% of patients for hemodialysis initiation. Moreover, up to 18 months after starting dialysis around 20% of the patient still have catheters as the main vascular access. Catheters are a vital component of our ESRD renal replacement care, and we need to learn more about them. This review covers all the evidence based data on HD catheters. "Knowing your enemy would give a leading step in winning the battle" *Art of War.*

Methods: Review of the current evidenced based and research including the CDC and NKF recommendation for utilization and care of HD catheters. This will be discussed to answer the following specific questions: What is the relation of Hemodialysis catheters with blood stream infection? What is the optimal practice in utilizing HD catheters? When, Where, How and Why? to use a dialysis catheter?

Results: Upon reviewing the evidence including the NKF and the CDC latest recommendation, the following answers were obtained for the above questions: There was a higher association between hemodialysis blood stream infection and catheters. The studies were retrospective with association. There was no prospective randomized controlled trail which showed a difference in the type of the access and the risk of hemodialysis blood stream infection. Tight infection control policy with full PPE for the staff and patients showed reduced risk of infection. This is needed during insertion or when using the catheter for hemodialysis. No randomized controlled trials were found. The hemodialysis catheters might be recommended in certain cases; elderly or short life expectancy and those with sever heart failure. Rt. IJ is the preferable insertion site. Ultrasound guided insertion is required with fluoroscopy for cuffed tunneled catheters.

Conclusions: With all the efforts spent to make the AV fistula as the first and main vascular hemodialysis access, we still have significant number of patients, specifically upon initiation of hemodialysis, using catheters as the main hemodialysis access. Taking care of the catheter utilization using high infection control protocols might be able to reduce the negative impact the catheters has on the blood stream infection rates. We need these catheter to save patient lives and we need to improve the way we are handling them.

PUB133

Vascular Access: A Screening Medical Device to Identify Patients at Risk for Access Dysfunction and Thrombectomy

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Introduction: USRC Oakbrook has 13 dialysis stations for patients with end-stage kidney disease. The Medical Director wanted to improve patient outcomes by improving vascular access management. Vasc-Alert, an FDA-approved medical device, was used to screen for vascular access stenosis and provided reports with historical results upon initial staff training. Vasc-Alert was effective in identifying patients at risk for access dysfunction, which if left undetected can increase the risk for thrombosis.

Case Description: Initially, Vasc-Alert identified 9 patients on alert. 6 were deemed high risk. 4 patients were successfully referred for an angioplasty, but 2 patients thrombosed before referral. The remaining 3 alert patients were considered low risk. This report discusses 2 specific patients Vasc-Alert identified and proved intervention was needed. WA presented in March 2019 with no significant problems and met Kt/V. The patient was routinely on alert and later had longer post-bleeding time and plateauing lab data. Referred in April 2021 after Vasc-Alert training. The Kt/V and post-bleeding time significantly dropped. The patient has had no alerts and has been achieving adequacy. BP presented to USRC in January 2019 and had an angioplasty with minimal problems. Prior to thrombectomy in March 2021, BP was consistently on alert with no other clinical indicators of dysfunction. Clinical training for Vasc-Alert occurred two days prior to her clotting. There was insufficient lead time to refer based on Vasc-Alert data, but it is sufficient to deduce that Vasc-Alert successfully predicted future clotting.

Discussion: While USRC had an active vascular access management program, these 6 patients were not previously identified. The introduction of the Vasc-Alert surveillance helped focus on the patients at the greatest risk. While the recent 2019 KDOQI guidelines for vascular access discounted the use of surveillance devices from the prior 2006 guidelines, this case study indicates that surveillance devices can still be useful in helping busy staff focus on patients at high risk of complications. Vasc-Alert has successfully alluded to future problems and thus has the potential to improve diagnosis and treatment plans for patients with access dysfunction.

PUB134

Ambulatory Surgery for Vascular Access of Hemodialysis Patients: A Retrospective Observational Study

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Background: To demonstrate the clinical efficacy and safety of ambulatory surgery for vascular access of hemodialysis patients.

Methods: A total of 1845 hemodialysis patients receiving ambulatory surgery for vascular access from September 2017 through December 2020 were enrolled. The clinical characteristics, surgery procedures, safety, efficacy and cost were analyzed.

Results: The mean age was 57.1 years, 53.4% were male, and medium dialysis vintage was 61.9 months. The percentages of the existing vascular accesses of arteriovenous fistula (AVF), arteriovenous graft (AVG), tunnel-cuffed catheter (TCC) and non-cuffed catheter were 58.6%, 30.9%, 3.3% and 3.9%, respectively. The operation methods of ambulatory surgery was interventional surgery (82.3%), hybrid surgery (11.4%), TCC (4.1%) and digital subtraction angioplasty (1.3%). All of the surgery was successfully completed, and the primary patency rate was 100% at 30 days after the surgery. The average operation time was 68.3±10.6 minutes. The average duration of hospitalization was 17.7±6.3 hours. The average total cost of each hospitalization was 9121.3±2818.3 RMB including the operation fee of 2211.7±843.2 RMB and disposable medical material cost of 4587.6±2073.2 RMB.

Conclusions: Ambulatory surgery for vascular access of hemodialysis patients may help improve the efficiency of vascular access surgery.

Funding: Government Support - Non-U.S.

PUB135

The Patency of Percutaneous Intervention-Treated Vascular Access for Hemodialysis Patients and Risk Factors for Recurrent Vascular Stenosis

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Background: Stenosis is one of the main causes of dysfunction of vascular access for hemodialysis. Percutaneous transluminal angioplasty (PTA) has become a promising treatment. This study aimed to demonstrate the patency of percutaneous intervention-treated vascular access for hemodialysis patients in our dialysis center and to explore the risk factors for recurrent of vascular stenosis after PTA.

Methods: The general demographic information, complications, anthropometric parameters, ultrasonographic characteristics of internal fistula before operation, balloon diameter and stenosis opening pressure during operation, and corresponding vascular characteristics by ultrasound after operation were recorded. The patients were followed-up at 1, 3 and 6 months after operation, and follow-up every 6 months thereafter. The recurrent of stenosis and other fistula related complications were registered. Potential risk factors affecting the primary patency and postinterventional stenosis were analyzed.

Results: Among the 135 patients, 70 patients had arteriovenous fistula (AVF), the rests had arteriovenous graft (AVG). PTA was successfully operated in 90.37% of thr patients. Hematoma occurs in 5 patients during the operation. The primary patency rates at 1, 3, 6 and 12 months after operation were 97.78%, 84.4%, 62.96% and 45.93%, respectively. The larger peak systolic flow velocity ratio (PSVR) after PTA, smaller stenosis venous diameter before PTA, and older in age are risk factors for early recurrent of stenosis after PTA. Multivariate regression analysis showed that diastolic blood pressure > 88 mmHg and balloon diameter > 6mm were risk factors for recurrent of stenosis after PTA in patients with AVF. As for patients with AVG, the risk of recurrent of stenosis in patients taking antiplatelet medicine was 2.652 times than those without taking antiplatelet medicine (95% CI 1.393-5.047, P=0.003), suggesting that patients at hypercoagulable state may have a high risk of recurrent of stenosis.

Conclusions: The safety and efficacy of PTA for treatment of stenosis of vascular access is confirmed in this study. High diastolic blood pressure, balloon with larger diameter, elderly and antiplatelet medication are risk factors for recurrent of stenosis after PTA.

Funding: Government Support - Non-U.S.

PUB136

Successful Catheter Lock with Recombinant Tissue Plasminogen Activator as a Rescue Therapy in Hemodialysis Catheter Dysfunction in a Patient with Exhausted Vascular Access

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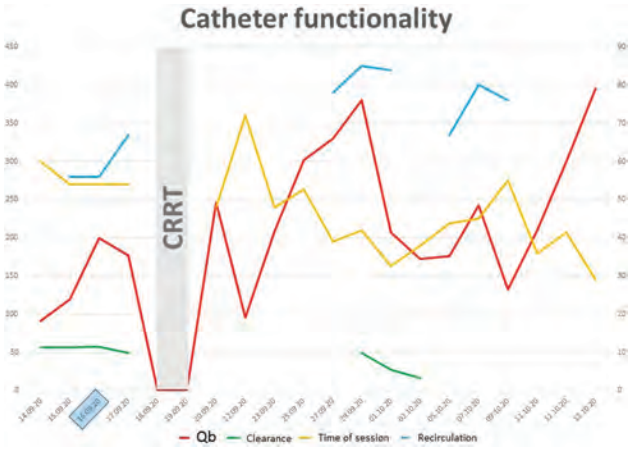
Introduction: Hemodialysis (HD) catheter complications are infection and occlusion. A catheter locking solution after HD sessions try to prevent them. Heparin and citrate has been used and the efficacy is successful in general population, but in patients with thrombophilia and exhausted vascular access could not have same effectiveness. Recombinant tissue plasminogen activator (rt-PA) has been used as an option.

Case Description: A 45 year-old women with ESRD due to collapsing glomerulophathy was taken to transplantation in 2 occasions with recurrence of glomerulopathy. She was maintained in peritoneal dialysis for 15 months, migrated to HDF due to refractory bacterial peritonitis. During next years she suffered from several catheter changes because of dysfunction and infections. Also, 2 arteriovenous fistulae did not work because of thrombosis, documenting elevated factor VIII, receiving anticoagulation. Then, central venous stenosis was documented and several femoral catheters were collocated, with infradialysis, increasing session time (240 to 270 min), using citrate locks, but blood flow pupm (Qb) diminished to 80 cc/min and she was hospitalized to perform an arteriovenous axilo-atrial graft placement presenting thrombosis. Finally, we use rt-PA to lock lumens, achieving an incremented Qb from 152.21 with citrate to 251.5 cc/min with rt-PA and substitution volume from 11.2 L to 33.56 L, respectively, but without improvement in recirculation rate (Figure 1). She was discharged, but after 2 days she died due to mesenteric ischemia.

Discussion: The options to treat a dysfunctional catheter in the setting of exhausted vascular access are limited with conventional lumen locks, the utility of rt-PA to prevent them in recently placement catheters has been demonstrated, but there is no description of the utility in cases like ours, to try to rescue an access to continue the therapy. We can improve the functionality of the vascular access, but the impact in substance clearance probably will not.



PUB137

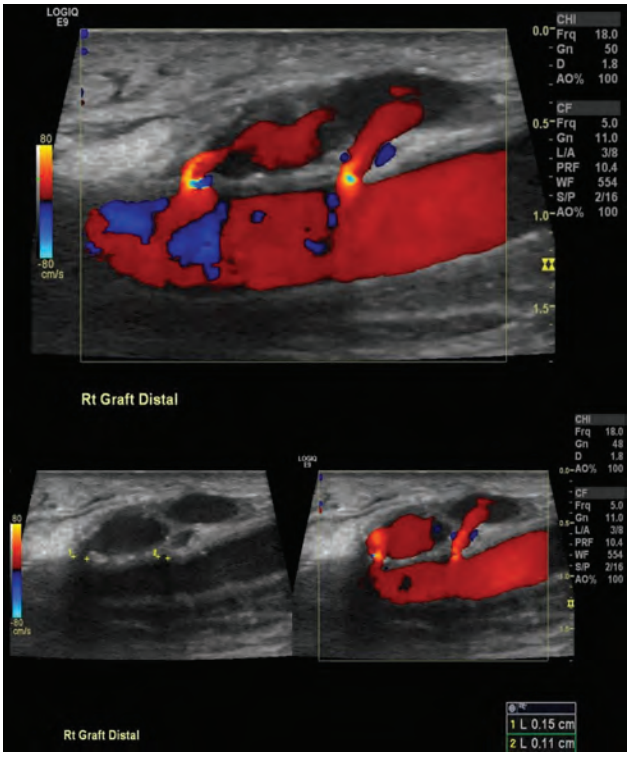
Unusual Ultrasound Graft Finding

Christy Gossett, Wisit Cheungpasitporn, Andrea G. Kattah, Fawad Qureshi. *Mayo Clinic Minnesota, Rochester, MN.*

Introduction: 42-year-old female with ESKD, dialysis dependent for 5 years, presented to ER feeling unwell and hyperkalemic to 6.8 mmol/L. Due for dialysis that morning but no missed dialysis sessions recently. Access is a right brachial artery to brachial vein loop graft created about 4 months ago. Graft had been difficult to cannulate with elevated pressures and pain requiring a decrease in blood flow rate or early treatment termination.

Case Description: Bruit, thrill and subcutaneous edema of the right arm overlying the graft noted. US revealed patent graft but unexpected findings of three adjacent fistulous communications between the distal loop graft and a superficially overlying subcutaneous branch of the right cephalic vein (figure 1). No surgical intervention recommended by Vascular Surgery. Repeat US done to mark patient's arm with cannulation sites resulted in successful cannulation and patient discharge. 1 month later, patient readmitted with similar presentation as markings not been preserved and cannulation challenges recurred. More extensive markings were created, identifying the overlying vein as well as cannulation sites. Patient refused further use of the graft and required central venous catheter placement.

Discussion: We describe an unusual case of difficult AV graft cannulation due to overlying cephalic vein. Cannulation improved with skin marking to guide cannulation, though due to impermanence of the markings, rehospitalization occurred and central catheter placement was required due to patient refusal to allow further graft cannulation. Early assessment of cannulation challenges with diagnostic US in patent dialysis fistulas or grafts may identify unexpected causes of cannulation. US and skin marking is a potential means of improving cannulation difficulties and avoid central catheter placement in unusual cases, such as described.



PUB138

Livestreaming in Instagram for the Kidney Health Promotion During Covid-19 Pandemic: Report of an Experience in Brazil

Juliana G. de Oliveira, Luisa Falcão Silva, Julia d. Barroso, Victor F. Costa, Lucas A. Mendes, Mirella N. Matos, Raul Victor L. Torres, Thaís A. Fontenele, Marcella Z. Martins, Geraldo B. Silva Junior. *Universidade de Fortaleza, Fortaleza, Brazil.*

Background: Chronic kidney disease (CKD) awareness is an important strategy to decrease its advance. The aim of this study was to describe livestreaming in Instagram during the World Kidney Day (WKD) 2021 in Brazil.

Methods: During the WKD 2021, the Renal Health project in Brazil carried out a week of health promotion online. Due to COVID-19 pandemic, which severely affected Brazil, all the activities were conducted online. From 1st to 11th March 2021, livestreaming sessions were carried out through the Instagram (@renal_health), with healthcare specialists and patients, discussing different aspects of CKD, with focus on the patients and the general audience. The followers could ask questions during the sessions and it was recorded to be accessed later (https://www.instagram.com/renal_health/channel/).

Results: A total of 3479 views were registered. The most viewed was the session about "resignifying life after dialysis", with 827 views, followed by "conservative treatment and lifestyle", with 549 views, and "kidney transplant and quality of life", with 537 views. There were 38 spontaneous feedbacks, most of them of compliments regarding the sessions. All sessions obtained a positive result from spectators, who posted compliments, such as "I loved the live, enlightening" and "congratulations on the subject, clear and highly enlightening language". Feelings about the impact of CKD were expressed: "these conversations with the interviewees are clearing my mind, as I also have kidney problems". Experiences that improved CKD knowledge could be shared: "I liked that the doctor said that it would be even better to have a transplant even before undergoing hemodialysis".

Conclusions: This experience evidence the importance of connecting with patients, using simple language, and the importance of digital means, including the Instagram, as a way of reliable health education. The true impact of COVID-19 on patients with CKD is yet to be known, but the nephrology community and health professionals as a whole should already be aware that patients are getting increasingly connected, and that is possibly the direction for the future.

Funding: Government Support - Non-U.S.

PUB139

Online CME Improves Clinician Understanding of Emerging Treatments for CKD-Anemia

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape Education, New York, NY.*

Background: We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists (nephs) and primary care physicians (PCPs) related to emerging Hypoxia-Inducible Factor Prolyl Hyproxylase Inhibitors (HIF-PHIs).

Methods: The effect of an online, 30-minute, CME-certified 2-expert discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and a paired samples t-test for overall and McNemar's test at the question level (5% significance level, P <.05) assessed educational effect. The activity launched January 5, 2021 and data were collected through March 25, 2021.

Results: In total, 354 nephs and 334 PCPs answered all pre-/post-assessment questions and were included in the study. Overall, 54% of nephs and 38% of PCPs improved their knowledge (P<.01 for both groups) 37% of nephs and 23% of PCPs demonstrated improvements at identifying dose requirement comparisons for inflamed vs noninflammed patients (P<.01 for both groups) 17% of nephs and 15% of PCPs demonstrated improvements at recognizing clinical trial data related to safety for emerging HIF PHIs (P=NS for both groups) 13% of nephs and 12% of PCPs demonstrated improvements at recognizing clinical trial data related to iron status for emerging HIF PHIs (P=NS for both groups) (P=NS for both groups) 54% of nephs and 46% of PCPs reported increased confidence in knowledge of HIF-PHIs in the treatment of anemia in patients with CKD who are iron replete or nonreplete Continued gaps: 35% of nephs and 54% of PCPs need additional education related to identifying dose requirement comparisons for inflamed vs noninflammed patients 56% of nephs and 70% of PCPs need additional education related to recognizing clinical trial data for emerging HIF PHIs 23% of nephs and 50% of PCPs need additional education related to recognizing clinical trial data related to iron status for emerging HIF PHIs

Conclusions: This study demonstrates the success of online, video-based 2-expert discussion on improving knowledge of nephs and PCPs related to HIF-PHIs for the treatment of anemia associated with CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - AstraZeneca ad Fibrogen

PUB140

Success of Online CME at Improving Nephrologist Understanding of Strategies to Reduce Progression of CKD

Amy Larkin, Kelly L. Hanley, Rita Moreira da Silva. *Medscape Education, New York, NY.*

Background: Clinicians need good clinical understanding of new strategies for reducing progression of CKD. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists and primary care physicians (PCPs) related to use of SGLT2 inhibitors to reduce the progression of CKD.

Methods: The effect of an online, 30-minute, CME-certified 3 faculty roundtable discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design was used and a McNemar's test was conducted to assess significance at the question level (5% significance level, P <.05) assessed educational effect. The activity launched November 30, 2020 and data were collected through February 22, 2021.

Results: In total, 307 nephrologists and 224 PCPs answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation in both CME activities: 16% of nephrologists and 21% of PCPs demonstrated improvements at identifying clinical trial data for SGLT2 inhibitors in the reduction of CKD progression (P<.05 for both groups) 9% of nephrologists and 11% of PCPs demonstrated improvements at adjusting therapy in a patient needing enhanced renal protection (P<.01 for nephrologists, P=.05 for PCPs) 40% of nephrologists and 39% of PCPs had a measurable increase in confidence in knowledge of renal benefits of SGLT2 inhibitors Continued educational gaps: 27% of nephrologists and 41% of PCPs need additional education related to clinical trial data for SGLT2 inhibitors in the reduction of CKD progression

Conclusions: This study demonstrates the success of online, video-based roundtable panel discussion on improving knowledge of nephrologists and PCPs related to use of SGLT2 inhibitors to reduce the progression of CKD. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - AstraZeneca

PUB141

Online Video-Based CME Successful at Improving Knowledge of Nephrologists Related to Mineralocorticoid Receptor Antagonists for CKD in Type 2 Diabetes

Amy Larkin, Kelly L. Hanley, Anne Le. *Medscape Education, New York, NY.*

Background: One goal of continuing medical education (CME) is improving knowledge related to mechanisms of action for new therapeutic options. We sought to determine if a video-based CME activity could improve the knowledge of nephrologists related to the mechanism of action of nonsteroidal mineralocorticoid receptor antagonists (MRAs) in the management of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D).

Methods: The online CME activity consisted of a 30-minute, video-based presentation by 1 expert faculty using green screen technology to enhance the visual presentation related to mechanism of action. To measure outcomes, a repeated pairs pre-/post-assessment study design was used and a paired samples t-test for overall and McNemar's test at the question level (P <.05 is considered significant) assessed statistical significance. The activity launched in December 2020 and data were collected through March 2021.

Results: In total, 233 nephrologists answered all pre-/post-assessment questions and were included in the study. Improvements were seen after participation in the CME activity: Overall, 36% of learners improved their knowledge (P<.01) 19% of nephrologists demonstrated improvements at identifying mechanism of action of MR blockade in treating CKD in T2D (P<.01) 24% of nephrologists demonstrated improvements recognizing clinical differences in steroidal MRAs and nonsteroidal MRAs (P<.01) 30% had a measurable increase in confidence in managing CKD in T2D (P<.01) Continued educational gaps: 22% need additional education related to mechanism of action of MR blockade in treating CKD in T2D 33% need additional education related to clinical differences in steroidal MRAs and nonsteroidal MRAs

Conclusions: This study demonstrates the success of online, video-based presentation using green screen technology on improving knowledge of nephrologists related to mechanism of action of nonsteroidal MRAs in managing CKD in T2D. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Bayer

PUB142

Success of Online CME Improving Nephrologists' Knowledge Related to Emerging Agents for Hepatorenal Syndrome

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape Education, New York, NY.*

Background: Clinicians need to understand clinical profiles of emerging agents in order to use safely and effectively when available to improve their patient management of HRS. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists related to emerging treatments for HRS.

Methods: The effect of an online, 30-minute, CME-certified summary of a satellite symposium presented at the American Association for the Study of Liver Diseases (AASLD) 2020 annual meeting was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design, paired samples t-test for overall and McNemar's test at the question level (5% significance level, P <.05) assessed educational effect. The activity launched January 5, 2021 and data were collected through April 12, 2021.

Results: In total, 324 nephrologists answered all pre-/post-assessment questions and were included in the study. Matched learner data indicate that overall, 35% of responses improved from pre-to-post (P<.001) On a question-level: 12% of nephrologists improved at recognizing clinical trial data for an emerging treatment options for HRS 27% of nephrologists improved at acute kidney injury (AKI) in a patient with cirrhosis 5% of nephrologists improved at selecting the next step in treatment for a patient with HRS Overall, 58% of nephrologists had a measurable improvement in confidence in your knowledge of emerging treatment options for patients diagnosed with HRS-AKI, for an average confidence shift of +70%. Continued educational gaps: 35% of nephrologists did not recognize clinical trial data for an emerging HRS treatment option 16% of nephrologists did not recognize AKI in a patient with cirrhosis

Conclusions: This study demonstrates the success of an online summary from a satellite symposium on improving management of HRS by nephrologists. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Mallinckrodt

PUB143

Online CME Is Successful in Prompting Performance Improvements Related to Hyperkalemia Management

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape Education, New York, NY.*

Background: We studied the effect of online education designed to improve the clinical performance of nephrologists, cardiologists, and NPs/PAs related to hyperkalemia management to enable/optimize RAAS inhibitor use.

Methods: The CME activity was a 30-minute online video roundtable panel discussion between 3 experts. Faculty discussion was reinforced with synchronized slides presenting supportive data. The impact of the education on performance outcomes was measured with a survey immediately post-education to assess planned changes in clinician practice as a result of participation in CME activity. Survey participants were contacted 8 weeks later to assess self-reported actual changes in practice. The activity launched October 6, 2020 and data were collected through April 30, 2021.

Results: A total of 275 clinicians completed the survey immediately post-education (91 nephrologists, 75 cardiologists, 109 NPs/PAs) 19% of nephrologists, 8% of cardiologists, and 4% of NPs/PAs treat >100 patients per month taking RAAS inhibitors 63% of nephrologists, 40% of cardiologists, and 42% of NPs/PAs are in private practice 44% of nephrologists, 64% of cardiologists, and 36% of NPs/PAs reported being in a suburban location 91% of respondents indicated an average of 3.2 planned practice changes each 28 cliniciansw completed the follow-up survey (12 nephrologists, 6 cardiologists, 10 NPs/PAs) Of those, 86% reported making an average of 3.9 changes in practice as a result of this activity. Changes in practice include: Consider a loop diuretic to increase potassium clearance and enhance volume management (67% nephrologists, 83% cardiologists, 50% NPs/PAs) Reviewing medications and diet to identify factors contributing to hyperkalemia (58% nephrologists, 83% cardiologists, 70% NPs/PAs) Controlling hyperkalemia with a novel potassium binder to optimize dose of RAASi (58% nephrologists, 33% cardiologists, 50% NPs/PAs) Using patiromer in patients on spironolactone to maintain normokalemia and allow for spironolactone continuation and dose uptitration, per the PEARL-HF Study (58% nephrologists, 33% cardiologists, 40% NPs/PAs).

Conclusions: The outcomes gathered in this assessment provide compelling evidence that participation in a 30-minute online video discussion among 3 experts prompted changes in practice to provide better hyperkalemia management to their patients.

Funding: Commercial Support - Vifor

PUB144

Success of Virtual Patient Simulation at Improving Diagnosis and Management of Chronic Hyperkalemia

Amy Larkin, Donald Blatherwick. *Medscape Education, New York, NY.*

Background: We sought to determine if virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists related to diagnosis and management of hyperkalemia.

Methods: The intervention comprised a patient presenting at two different time points in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user's baseline (pre-CG) decisions using a McNemar's test to determine *P* values. The activity posted October 30, 2020; initial data was collected through March 10, 2021.

Results: To date, 86 nephrologists completed the activity (all decisions within at least 1 case) and were included. Significant improvements were observed after CG: Initial visit: Diagnose CKD stage 3b: 34% absolute improvement (8% pre-CG vs 42% post-CG; P<.01) Diagnose hyperkalemia: 29% absolute improvement (8% pre-CG vs 37% post-CG; P<.01) Initiate a potassium binder: 36% absolute improvement (22% pre-CG vs 58% post-CG; P<.01) Initiate loop diuretic: 57% absolute improvement (5% pre-CG vs 62% post-CG; P<.01) Discontinue oral naproxen: 10% absolute improvement (85% pre-CG vs 95% post-CG; P<.01) Order patient education: 12% absolute improvement (50% pre-CG vs 62% post-CG; P<.01) Order nutritional counseling: 15% absolute improvement (50% pre-CG vs 65% post-CG; P<.01) Follow-up visit: Diagnose chronic hyperkalemia: 36% absolute improvement (4% pre-CG vs 40% post-CG; P<.01) Continue potassium binder: 9% absolute improvement (89% pre-CG vs 98% post-CG; P<.05) Continue loop diuretic: 11% absolute improvement (87% pre-CG vs 98% post-CG; P<.05) Order patient education: 13% absolute improvement (47% pre-CG vs 60% post-CG; P<.01) Order nutritional counseling: 17% absolute improvement (36% pre-CG vs 53% post-CG; P<.01)

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to patient identification and management of hyperkalemia.

Funding: Commercial Support - Vifor

PUB145

Online CME Improves Clinician Understanding of Quality-of-Life Issues in Patients with Metabolic Acidosis

Amy Larkin, Donald Blatherwick, George Boutsalis. *Medscape Education, New York, NY.*

Background: We sought to determine if online continuing medical education (CME) could improve the clinical knowledge of nephrologists (nephs) and primary care physicians (PCPs) related to quality of life issues in patients with metabolic acidosis and emerging treatments options.

Methods: The effect of an online, 30-minute, CME-certified 2-expert discussion was analyzed to determine efficacy of online education. Three multiple-choice knowledge/competence questions and 1 self-efficacy confidence question were presented both before and immediately after each activity. A repeated pairs pre-/post-assessment study design, paired samples t-test for overall and McNemar's test at the question level (5% significance level, P <.05) assessed educational effect. The activity launched November 4, 2020 and data were collected through January 27, 2021.

Results: In total, 416 nephs and 502 PCPs answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation in both CME activities: Overall, 44% of nephs and 53% of PCPs improved their knowledge (P<.01 for both groups) 8% of nephs and 25% of PCPs demonstrated improvements identifying signs of excess acid retention (P=NS for nephs, P<.01 for PCPs) 23% of nephs and 19% of PCPs demonstrated improvements identifying effect of increasing sodium bicarb in patients with CKD and metabolic acidosis (P=NS for nephs, P<.01 for PCPs) 26% of nephs and 30% of PCPs demonstrated improvements recognizing effect of emerging treatment for metabolic acidosis (P<.01 for both groups) 36% of nephs and 45% of PCPs had a measurable improvement in confidence discussing QOL concerns with metabolic acidosis (P<.01 for both groups) Continued educational gaps: 19% of nephs and 39% of PCPs need additional education related to identifying excess acid retention 42% of nephs and 55% of PCPs need additional education related to effect of increasing sodium bicarb in patients with CKD and metabolic acidosis 38% of nephs and 52% of PCPs need additional education related to data on emerging treatment options for metabolic acidosis

Conclusions: This study demonstrates the success of online, video-based 2-expert discussion on improving knowledge of nephs and PCPs related to QOL issues with metabolic acidosis and emerging treatment options. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Tricida

PUB146

Nephrology Best Practice, Integrating Healthcare Education, and CKD: A Qualitative Perspective

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Background: Education and information seeking is pinnacle for patients with Long-Term Conditions (LTCs) like Chronic Kidney Disease (CKD) to take ownership of health and disease and navigate healthcare between health sectors. Patient and Public Involvement (PPI) is key to help understand gaps in health education. 1) Involving patients between two support groups to help understand which topics and subjects are pertinent to CKD patients; 2) Involving patients to understand whether, retrospectively there has been an educational neglect in healthcare; and 3) To understand how healthcare and education for CKD patients could be more integrated.

Methods: Two PPI workshops were implemented (May and June 2019) after reviewing NIHR INVOLVE best practice guidelines. Fourteen (14) topic tags were applied over 1-month (March and April 2020) between the Renal Patient Support Group (RPSG) (est.2009) and the Kidney Disease and Renal Support (KDARs) (est.2014) for Kids platforms. Group disclaimers encouraged informed consent. GDPR (2018) guidelines were implemented to ensure best practice surrounding confidentiality and data protection.

Results: Thematic Analysis was used to highlight findings, according to over-arching themes having used Nvivo-12 software to code and help understand where there are healthcare educational inefficiencies. Five themes were identified through this study including 1) Using Different Mediums to Collect Qualitative Data and Understanding Healthcare; 2) Reliability and Validity of using the Internet to Collect Data; 3) Healthcare, Patient and Public Involvement and Maintaining Confidentiality through Online Methods to collect Qualitative Data; 4) Advantages, Disadvantages and Limitations to Online Data Collection and Peer Support Groups and 5) Using Qualitative Methodology to Understand Educational Needs for CKD Patients.

Conclusions: Wider Allied Health Professionals (AHPs) could increasingly find themselves taking on roles, particularly where involvement is increasingly dependent bridging educational gaps and 'alleviating misinformation' through technology and 'online spaces'. **Conclusion:** This is the first UK retrospective study that examines educational gaps between online paediatric and adult CKD patients close to two decades (16 years), and highlights where further PPI-focused research would help understand where healthcare requires investment.

PUB147

What, If Any, Are the Nephrology Health Educational Needs of CKD Patients: A Qualitative Inquiry

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Background: An estimated 15 million patients in England have at least one Long-Term Conditions with the prevalence of CKD rising. The characterization of CKD at all stages is an important part of its management and allows the initiation of appropriate treatments with the aim of slow progression of kidney disease. Providing up-to-date, accurate health education is pinnacle for patients to take ownership of healthcare. Patients require educational support as part of healthcare and help navigate understanding with different healthcare professionals. The aims and objectives of this research was to understand how CKD patients should be encouraged to take ownership of healthcare through education.

Methods: The theoretical framework for this research involved an Inductive Content Analysis (ICA) approach where essentially qualitative data collection and analyses will help understand what if any, are the health educational needs getting perspectives from CKD patients and Health Professionals (HPs). ICA is particularly effective to help understand analysis in linking theory, or framework.19 participants between 4 cohorts, that included 6 General Practitioner (GPs), 4 Healthcare Scientists (HS), and 6 CKD Patients (CKDPs) were recruited and participated in telephone interviews.

Results: Majority of CKDPs were in between CKD4 and CKD5. Interviews allowed participants to put forward views and understanding, relating to healthcare education. Topic guides were developed for participant cohorts with several themes to collect data through one-to-one telephone interviews. NViVo-12 software provided opportunity to classify and arrange transcript context and glean insight to develop overall conclusions. Nine (9) main themes and several sub-themes were identified when coding for healthcare professionals (HPs), and Nine (9) main themes and several sub-themes identified when coding qualitative data for patients (CKDPs).

Conclusions: There needs to be a coordinated effort between patients and professionals, to understand how CKD education is more integrated with healthcare, and especially wherein involvement is end-to-end. This exploratory study provides evidence applying research to public health. Every effort has been made to reduce biases and diminish disparities. Point of Care Education (POCE) could be an integrated through online spaces and linked to Electronic Patient Records (EPRs).

PUB148

Chronic Hyponatremia: Challenges in Diagnosis and Management

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Introduction: Hyponatremia is manifestation of variety of disorders. Hyponatremia occurs as result of water intake exceeds greater than water excretion. Management becomes a challenge due to etiology and costly drugs.

Case Description: 46-year-old-male computer engineer who exercises 3 times a week, takes 25 grams of protein shake daily with no past medical history, not on meds, noted to have chronic sodium of ~ 126 mEq/L with stable BMI 26. His only complaint was mild fatigue. His exam was normal with a negative orthostatic. Labs: Sodium 126 mEq/L, Potassium 3.6 mEq/L, uric acid 2.8 mEq/L, Creatinine 0.65 mg/dL, Serum Osmolality 266 mOsm/kg, Urine sodium 72 mEq/L, Urine potassium 60.1 mEq/L, specific gravity 1.018, Urine Osmolality, 626 mOsm/kg H2O and Copeptin 6.2 pmol/L. Renal, adrenal, and thyroid function are normal. Imaging of brain, chest and abdomen is negative for pathology. He underwent colonoscopy with suprep which provided the least amount of volume load and Ure-Na prescribed to keep his serum sodium stable during the bowel prep. Max sodium achieved was 130 mEq/L after 30 g bid of Ure-Na. It was discovered later, his brother was noted to have serum sodium of 115 diagnosed at age 20 and maintained on sodium bicarb but was never tested genetically, nor achieved normal sodium levels.

Discussion: Labs were consistent with SIADH however he had undetectable copeptin level and negative workup for malignancy. Due to family history with negative workup for any other etiology, he likely has Nephrogenic Syndrome of Inappropriate Diuresis (NSIAD). NSIAD is caused by gain-of-function mutation in AVP receptor type 2 located on long arm of X chromosome (Xq28). Genetic confirmation for NSIAD is pending and if positive will need to test other family members. Management for chronic hyponatremia was challenging as fluid restriction was not realistic to adhere to as sugested by his high urine (Na+K) and high urine osmolality > 500mOsm/kg. Ure-Na was useful at time of bowel prep to avoid worsening of hyponatremia, however never achieved normal sodium even after 30 g bid Ure-Na. Vaptans were not tried as are more costly than Ure-Na and unclear efficacy in NSAID. Patient did not want to pay $80 of Urena, and he increased his protein intake to 75 g daily with fluid restriction 1.5 L/day, which maintained his sodium level at 130.

PUB149

Spontaneous Regression of Hyperammonemic Encephalopathy, Lactic Acidosis, Gastric Mucosa Injury, and Hepatic Portal Vein Gas After Infusion of 5-Fluorouracil

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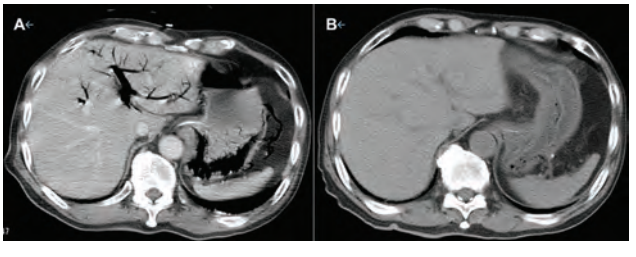
Introduction: 5-fluorouracil (5-FU) therapy is associated with hyperammonemic encephalopathy and lactic acidosis. 5-FU has a direct toxic effect on the gastric mucosa. Hepatic portal venous gas (HPVG) is caused by various factors including bowel necrosis and gastroduodenal ulcers.

Case Description: A 79-year-old man was referred to the nephrology department owing to lactic acidosis. He had a history of hypopharyngeal carcinoma. Two days prior to the consultation, he was started on 300 mg of carboplatin and 4000 mg/m^2 of 5-FU as a continuous intravenous infusion. On the consultation day (day 1), he was experiencing confusion and had a GCS score of 11/15. There was a significant increase in NH_3 (>500 μg/dL) and lactate levels (19 mmol/L). Abdominal contrast-enhanced computed tomography (CT) showed HPVG and gastro-omental venous gas (Figure A). Subsequently, we performed an upper gastrointestinal endoscopy, which revealed acute ulcers with erythema. Infusion of 5-FU was stopped, and intravenous lansoprazole were started. Eight hours after onset, the patient gained a normal level of consciousness with a GCS score of 15/15. Lactic acidosis (4.2 mmol/L) and hyperammonemia (64 μg/dL) also improved. On day 2, CT showed no HPVG or gastro-omental venous gas (Figure B). A final diagnosis of lactic acidosis, hyperammonemic encephalopathy, gastric ulcers, and HPVG caused by 5-FU was made.

Discussion: In this case, a plausible explanation for the findings is that the two rare manifestations of adverse drug reactions due to 5-FU occurred simultaneously. First, hyperammonemic encephalopathy and lactic acidosis were caused by 5-FU. Hyperammonemic encephalopathy and lactic acidosis are rare adverse drug reactions to 5-FU. Second, 5-FU caused gastric mucosal injury; subsequently, gastric mucosal injury caused HPVG. HPVG was diagnosed after infusion of 5-FU and disappeared the following day. To the best of our knowledge, there are no reports of HPVG caused by venous infusion of 5-FU. This case suggests that 5-FU infusion causes gastric mucosa toxicity; therefore, we propose that gastric ulcers may cause HPVG.



PUB150

Methanol Poisoning Diagnosed by Brain MRI

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Introduction: Methanol poisoning is deadly yet remains relatively common. Delays in diagnosis increases the risk of irreversible organ damage and death. In the absence of serum or urine levels, radiological findings may be useful in diagnosis. We report a unique case of methanol toxicity where we made the diagnosis based on characteristic brain MRI findings as timely serum or urine levels were unavailable.

Case Description: 81-year-old woman presented with altered mental status, poor appetite, lethargy and two episodes of vomiting en-route to the emergency room. On examination, her vital signs were normal but she was mildly agitated, oriented to person only. Initial blood work was significant for a low Bicarbonate level of 10mEq/L, Anion Gap 22, creatinine 0.81 mg/dL, serum Osmolality 403 mOsm/kg with calculated osmolality 296 mOsm/kg and Arterial Blood Gas (ABG) showing pH 7.29 and pCO2 24. Her CT head showed no acute changes with white matter microvascular ischemic disease. Because of high osmolar gap anion gap metabolic acidosis, patient was given intravenous Fomepizole. Overnight, her condition deteriorated requiring intubation and mechanical ventilation. Her repeat ABG showed worsening acidosis with pH 6.9 and pCO2 19. She was subsequently started on sodium bicarbonate drip. Further work up was negative for serum methanol, ethanol, salicylate, blood alcohol and 5-oxo-proline levels. Her acidosis gradually improved but her mental status continued to remain poor for which she had a brain MRI which showed extensive parenchymal brain abnormality, leukoencephalopathy and basal ganglia involvement reminiscent of acute methanol toxicity and thus a diagnosis was made. Unfortunately, her mental status remained poor and after consulting with palliative care, decision was made to prioritize patient comfort and terminal extubation.

Discussion: Characteristic MRI findings in methanol toxicity are high T2 signal suggestive of necrosis of lentiform nucleus with predilection for the putamen. There may be necrosis of lobar white matter with sparing of subcortical fibers and hemorrhagic transformation. Our patient had similar findings as well. An extensive ingestion history is crucial when evaluating high osmolar gap. However, in the absence of timely blood work and ingestion history, like in our patient, brain imaging with MRI may be integral to diagnosing methanol poisoning.

PUB151

Hypertonic Pseudohyponatremia with Seizures: A Treatment Dilemma

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Introduction: Hyperosmolar hyperglycemic non ketotic syndrome (HHS) with seizures can cause brain damage and rapid correction of plasma sodium (pNa) and plasm glucose (pGL) can cause osmogenic demyelination (OD). If untreated it causes death due to cerebral edema. We lack guidelines for fluid and the rate of correction of hyponatremia in HHS. We describe a patient with hyponatremic seizure due to very high plasma glucose (pGL). Hyponatremia occurs with extracellular water shift and corrects as pGL improves as water shifts intracellularly. The seizures in HHS are due to high plasma osmolarity (pOsm) from high pGL. The protocols for HHS mandate saline infusion to repleat volume and simultaneous insulin infusion for pGL. Each infusion alone can correct pNa and pGL. We present a case of pseudohyponatremia with seizures and the dilemma we faced.

Case Description: A 55-yr-old female diabetic unwell for a few days had a seizure. She received levetiracetam on the way to the hospital where she was unconscious and volume depleted. Her pGL was 1452 mg/dl, pNa 115 mEq/L, HCo3 of 21 mg/dl and a pH 7.37. HHS was diagnosed as the plasma osmolality (pOsm) was 320 mOsm/kg. Her urine sodium was 42 mg/dl, osmolality was 448 mOsm/kg and no ketones. With infusion of saline and insulin her pNa was 123 mEq/L and 128mEq/L in 3 and 6 hours while pGL was 1158 and 709 mg/dl and pOsm 315 and 302 mOsm/Kg respectively. A 0.225% saline was infused to reduce correction rate and pNa was 128 mEq/L for 2 days while pGL continued to fall. She made a complete recovery in 6 days.

Discussion: HHS has greater mortality than DKA. HHS with seizures may get treated with vasopressin receptors antagonists (VRA) or hypertonic saline causing an acute rise in the pNa and pOsm enhancing OD. There are no guidelines for correcting HHS seizures with pseudohyponatremia. In our case we used hypotonic saline to slow down the correction rate. We feel that saline infusion alone corrects volume depletion and reduces pGL and pNa merely by the dilutional effect. Simultaneous infusion of saline and insulin may be unnecessary and can be harmful due to a precipitous drop. There is no role for VRA, hypertonic saline or medications in the management peudo hyponatremic seizures. We propose that pOsm should guide the correction rate rather than pNa or pGL and only saline may be used initially to avoid rapid correction and OD. The mortality may be due to rapid correction.

PUB152

Online Dysnatremia Correction Calculators: Consistency and Practice Guideline Adherence

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Background: Online calculators for sodium correction in dysnatremia are frequently used by non-nephrologists. We assessed 5 popular calculators which use the Androgue-Madais equation for practice guideline adherence and reproducibility in a theoretical 80 year old, 100 kg (72 inch) male.

Methods: Hypernatremia case: Na^+ 150 meq/L. *Guideline-based Rx*: Estimated water deficit 4.2 L. Replacement target 2.1 L in the first 24 hours, plus 1.5 L insensible losses. Infusate: 150 ml/hr D5W. **Hyponatremia case:** Na^+ 115 meq/L, euvolemic with acute/severe symptoms, normal serum K^+. *Guideline-based Rx:* Immediate treatment: 3% NaCl, 100 mL over 10 minutes up to 3 times; Na^+ increase ≤ 6-8 mEq/L in first 24 hours. Alternative using the Androgue-Madias equation: 3% NaCl at 32ml/hr, with frequent Na^+ determination.

Results: See Table. **On-line Calculators for Hypernatremia:** Water deficit calculated in 3 (range 3.6-4.3L). Insensible loss calculated in 1. Replacement target defaults: 140-145 mEq/L Na^+ at 10-24 hours. **On-line Calculators for Hyponatremia:** One discusses volume status, acuity, and symptoms. Only 2 indicate rapid correction should be used for severe symptoms. Default correction rate range: 6-12 mEq/L/day. Calculated rate of 3% NaCl: range 32-64 mL/hr. Only 1 calculator incorporated infusate K^+, and recommended Na^+ and infusate rate redetermination.

Conclusions: The 5 calculators correctly use the Androgue-Madias formula to determine infusate rate of hypertonic or hypotonic fluids in dysnatremia. However, defaults may yield rates that exceed safe correction rate; 4/5 had no discussion of chronicity, symptom severity, or need for frequent Na^+ determination/infusate rate recalculation. These may contribute to unexpected adverse outcomes. *The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.*

Comparison of Online Calculator Results with Guidelines

Calculator	Hypernatremia Calculations				Hyponatremia Calculations		
	Water Deficit (L)	Default Na+ Target (mEq/L)	D5W Rate (mL/hr)	Duration (hrs)	Immediate Rx	Safe Na Correction Rate (mEq/L/d)	3% NaCl Rate (mL/hr)
Guideline	4.2	145	150	24	Yes	6-8	32
1	None	140	170	20	None	8-12	64.1
2	None	145	232.5	10	None	12	34.5 x 30 hr
3	3.57	145	None	None	Yes	8	32
4	3.6	140	170	20	None	12	64
5	4.29	140	None	None	None	8	42.29

PUB153

Mass Poisoning from Ethylene Glycol at a US Military Base

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Introduction: Ethylene glycol (EG) poisoning occurs over 5000 times annually in the US, but a poisoning outbreak (3 cases within 72 hours) has not previously been reported. We describe on an EG poisoning outbreak in January 2021, presenting at William Beaumont Army Medical Center.

Case Description: Eleven soldiers presented to the emergency room over a twelve hour period after ingestion of an unknown alcohol, later identified as radar cooling fluid containing EG. Only the first two patients were symptomatic. Serum EG levels were not immediately available, therefore treatment decisions were based on surrogate markers (arterial pH, anion [AG] and osmolar [OG] gaps, serum bicarbonate [TCO2], lactate [Lac], and creatinine [sCr]).

Discussion: Two patients received immediate hemodialysis (HD) in combination with fomepizole (FOM) due to severe acidosis plus elevated OG and AG (Table). These patients developed acute kidney injury (AKI) with renal recovery occurring within a 3-week period. Two patients with elevated Lac received bicarbonate-based intravenous fluids (IVF) and FOM. Two patients received IVF only and required prolonged observation for worsening acidosis and/or AKI. Five patients with normal lab values were treated with IVF and observation. All patients received cofactors including thiamine and pyridoxine. All patients survived. The outbreak occurred in the setting of limited dialysis resources and FOM availability and in a community with widespread COVID-19 activity. Additional guidelines are needed to determine allocation of limited resources and optimal dialysis and FOM treatment course, and identify comorbid conditions which may prolong recovery. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government.

Patient	pH/TCO2 (mEq/L)	Lactate (mmol/L)	AG (mEq/L)	OG (mOsm/kg)	AKI	EG (mg/dL)	FOM	HD
1	6.93/8	1.99	22	30	Y	45	Y	Y
2	7.19/10	1.30	24	14	Y	20	Y	Y
3	7.36/24	1.25	12	7	N	6	N	N
4	7.34/26	2.12	11	-1	N	<5	Y	N
5	7.32/30	2.97	12	6	N	<5	Y	N
6	7.49/25	1.20	11	4	N	<5	N	N
7	7.43/26	0.85	11	1	N	<5	N	N
8	7.36/25	1.29	9	-1	N	<5	N	N
9	7.36/22	1.01	11	-1	N	<5	N	N
10	7.40/26	1.52	12	2	Y	<5	N	N
11	7.43/22	0.97	12	-6	N	<5	N	N

PUB154

Unexplained Hyperkalemia

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Introduction: Hyperkalemia is a life-threatening emergency that warrants prompt evaluation and treatment. Evaluation should include ruling out falsely elevated potassium (K) levels that would otherwise lead to unwarranted and potentially harmful therapies.

Case Description: A 69-year-old male with mantle cell lymphoma presented with multifocal pneumonia, septic shock, and acute hypoxic respiratory failure. He had an acute kidney injury (AKI) with a creatinine of 2.4mg/dL from 1mg/dL due to ischemic acute tubular necrosis. CVVHD was started for oliguria and volume overload, with a prescription of blood flow rate 250ml/min, dialysis flow rate 2L/hr (at 25mL/kg), 4mmol/L of potassium, 1.5mmol/L of calcium, and 35mmol/L of bicarbonate. On day 5 of CVVHD, he was switched to a 3mmol/L (K) bath due to (K) of 5-5.3mmol/L. Labs also showed worsening lymphocytic predominant leukocytosis due to underlying cancer. The initial whole blood (K) was 6.9mmol/L. He received calcium gluconate, dextrose, and insulin, with whole blood (K) 3 hours later of 7.7mmol/L. EKG obtained twice did not show signs of hyperkalemia. Repeat (K) obtained from an arterial blood gas analyzer was 4.9mmol/L.

Discussion: Pseudohyperkalemia is an in-vitro phenomenon in which serum (K) exceeds plasma (K). It can occur in patients with severe leukocytosis, erythrocytosis, or thrombocytosis. Clinical consequences of hyperkalemia are absent, and aggressive management is unnecessary as in-vivo (K) levels are unchanged. Plasma (K) contains both serum and clotting factors, which is why plasma is collected in tubes with anticoagulants like heparin. With extreme leukocytosis, the white blood cell membrane is fragile and prone to lysis from heparin. The release of even a minute amount of (K) from cells can notably raise 'measured' extracellular (K). Both serum and plasma (K) samples can be affected, but the impact on plasma seems to be higher. As plasma (K) is higher than serum (K), it is termed "reverse pseudohyperkalemia". If suspected, a repeat whole blood (K) sample should be collected by a point of care (blood gas) analyzer that does not contain heparin. Early recognition of false (K) elevations is thus crucial to prevent detrimental interventions.

	Prior to CVVHD	Day 1	Day 3	Day 4	Day 5
Whole Blood Potassium (mmol/L)	4.6				8:30am: 6.9 mmol/L 11:00am: 7.7mmol/L
Serum Potassium (mmol/L)	5.5	5.3	5.0	4.9	5.1
White Blood Cell Count (K/cu mm)	78.48	78.19	84.94	104.48	149.28

PUB155

The Risks of the Administration of the Newly Introduced Potent Potassium Binders in Pseudohyperkalemia: Two Case Series

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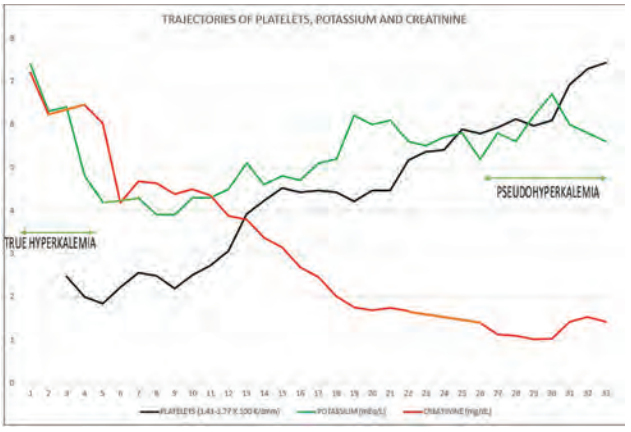
Introduction: Pseudohyperkalemia, first reported in 1955 by Hartmann and Mellinkoff, is a marked elevation of serum potassium in the absence of clinical evidence of electrolyte imbalance. Simultaneous serum potassium exceeds plasma potassium by >0.4 mmol/L. Pseudohyperkamlemia has mostly been associated with moderate to severe thrombocytosis or leukocytosis. Unmistakably, true hyperkalemia is potentially lethal. Nevertheless, inappropriate treatment of pseudohyperkalemia leading to severe hypokalemia is also life-threatening.

Case Description: Two patients with pseudohyperkalemia received inappropriate potassium binders: A 40-year-old African American male patient with sickle cell anemia with acute kidney injury, anion gap metabolic acidosis and true hyperkalemia subsequently developed pseudohyperkalemia secondary to post-sepsis thrombocytosis in the same hospitalization (Figure 1). He received over one week of sodium zirconium cyclosilicate before the diagnosis of pseudohyperkalemia was confirmed following the finding of a normal EKG with serum potassium of 6.7 mmol/L. A 77-year-old female with previously undiagnosed erythrocytosis and thrombocytosis from polycythemia vera had received over 3 months of Patiromer, for suspected renal tubular acidosis before the PCV was diagnosed and testing confirmed pseudohyperkalemia. Both potassium binders were promptly discontinued when pseudohyperkalemia was confirmed by simultaneous plasma versus serum potassium measurements. Subsequent potassium monitoring reverted to plasma potassium measurements only.

Discussion: Physicians must always give consideration to the plausibility of pseudohyperkalemia under appropriate clinical scenarios. One recurring mantra remains that true hyperkalemia in the absence of overt kidney dysfunction must always be viewed with circumspection and doubt. Iatrogenic life-threatening hypokalemia remains a real concern and must be avoided.



Serum potassium, creatinine and platelet count

PUB156

Symptomatic Hyponatremia and Possible Pulmonary-Renal Syndrome

Samuel A. Lazoff, Kambiz Kalantari. *University of Virginia, Charlottesville, VA.*

Introduction: Hyponatremia occurs in 15-30% of hospitalized patients and is associated with increased morbidity and mortality. Here we present a case of severe symptomatic hyponatremia, acute kidney injury, and dyspnea.

Case Description: A 59-year-old female with history of chronic obstructive pulmonary disease presented to the emergency department for recurrent falls and shortness of breath. She complained of confusion, difficulty with ambulation, and increased swelling in her bilateral arms/legs with 18 pound weight gain in one week. On examination she was hypotensive, tachycardic and tachypneic. There was jugular venous distention up the mid-neck, decreased breath sounds and 2+ pitting edema of all four extremities and the anterior abdominal wall. Laboratory results are shown in Figure 1. Chest X-ray showed bilateral infiltrates. Urine microscopy showed 20 – 30 erythrocytes, but no casts. She received multiple infusions of 3% NaCl and loop diuretics. Her mentation improved, but she eventually required kidney replacement therapy. Kidney ultrasound was unremarkable. Kidney biopsy showed hypercellular glomeruli and one cellular crescent. Immunofluorescence microscopy showed 1+ mesangial staining with IgA and C3 and electron microscopy showed mesangial immune deposits. She received pulse dose methylprednisolone and cyclophosphamide for treatment of rapidly progressive glomerulonephritis due to IgA nephropathy. She was then treated with continuous kidney replacement therapy with post filter 5% dextrose in water (D5W) replacement to avoid over correction of hyponatremia. She had a very high A-a gradient, but with aggressive ultrafiltration her respiratory status and oxygenation significantly improved. On hospital discharge, she had normal serum sodium concentration, but remained dialysis dependent.

Discussion: The severity of hyponatremia and a picture that suggested pulmonary renal syndrome were unusual. However, based on her response to treatment and further work up, her hyponatremia was related to severe volume overload. Her volume status stabilized with ultrafiltration and her serum sodium corrected appropriately by infusing D5W into the CKRT circuit, post-filter.

Initial Laboratory Values

Sodium (mmol/L)	115
Potassium (mmol/L)	5.8
CO2 (mmol/L)	22
BUN (mg/dL)	40
Creatinine (mg/dL)	2.4
Glucose (mg/dL)	57
Total Protein (g/dL)	5.6
Albumin (g/dL)	2.1
Hemoglobin (g/dL)	16.2
Urine sodium (mmol/L)	<20
Urine osmolality (mOsm/kg)	283
Urine protein: creatinine (g/g)	17.22

PUB157

Chronic Milk-Alkali Syndrome

Samantha M. Saggese, Manal Alotaibi. *Northwestern Memorial Hospital, Chicago, IL.*

Introduction: Milk-alkali syndrome is a common cause of hypercalcemia. Excessive calcium carbonate (antacid) consumption is a classic cause. We present a case of a 41 year old female with AKI, hypercalcemia and metabolic alkalosis due to dairy and supplemental vitamin D consumption.

Case Description: Our patient presented with abnormal labs (Table 1). She had no urinary frequency, abdominal pain, nausea, vomiting, constipation, or confusion on admission. She had mild pruritus and bilateral plantar foot pain and elbow pain. Her EKG was unremarkable. She received 2 liters of 0.9% saline and was started on continuous 0.9% saline intravenous fluids at 150 mL/hour upon admission. She drank a half-gallon of milk per day for the last two years. She consumed a Premier protein shake each morning with breakfast, which contains 50% of the daily value (DV) of calcium and 25% of the DV of Vitamin D. She rarely took antacids. She had a multivitamin containing 100% of the DV of Vitamin D and an additional Vitamin D supplement. Review of systems was positive for episodes of polyuria, urinary frequency, and dry mouth, for which she compensated with large volume fluid intake.

Discussion: Our patient was diagnosed with chronic milk-alkali syndrome. This syndrome is characterized by hypercalcemia, hyperphosphatemia, metabolic alkalosis, AKI and metastatic calcification. Hypercalcemia causes vasoconstriction, which decreases the glomerular filtration rate (GFR). It suppresses PTH secretion and leads to renal retention of phosphate. It activates the calcium-sensing receptor (CaSR) at the basolateral surface of Loop of Henle cells, inhibiting the Na-K-2Cl co-transporter, enhancing natriuresis and inducing volume depletion, which augments proximal reabsorption of calcium and bicarbonate. Alkalosis activates the pH-sensitive calcium channel, TRPV5, in the distal nephron, thereby contributing to calcium retention and hypercalcemia. Standard treatment is withdrawal of exogenous calcium and administration of intravenous normal saline. Furosemide is sometimes used in severe cases.

Lab Results

	Calcium (mg/dL)	Creatinine (mg/dL)	Bicarbonate (mEq/L)	Phosphorous (mg/dL)	iPTH (pg/mL)
2.5 years prior	9.7	1.08	29		
1.5 years prior	10.4	1.4	46		
2 weeks prior	12.2	4.57	38		
Admission	13.2	4.94	38	5.8	25
Discharge	10.7	4.34	32	4	
1 month post	10.6	3.38	27	3	27

PUB158

An Unexpected Cause of Hypokalemia

Zainab Obaidi, Jose M. Monroy-Trujillo. *Johns Hopkins University, Baltimore, MD.*

Introduction: A case of Hyperemesis Gravidarum "HG" that presented with hypokalemia in the setting of starvation ketosis and metabolic alkalosis.

Case Description: A 25-year-old female (G3P3) 9 weeks pregnant presented with intractable nausea and vomiting since pregnancy. She noted 40 pounds unintentional weight loss and denied similar complaints in the past, diarrhea, fever, rashes or vaginal bleeding. She presented to the ER 2 days prior and was treated with promethazine suppository, metoclopramide, thiamine tablets and given 1-liter IVF and discharged home with metoclopramide and dicyclomine. (See table 1) She was readmitted 2 days later due to worsening symptoms (see table for labs). She received 2 liters IVF, famotidine, promethazine suppository and IV antiemetics. Nephrology was consulted for persistent hypokalemia after repletion with 120 meq of potassium chloride over 24 hours leading to potassium increase from 2.7 to 2.9. Magnesium was 1.5 and repleted. On day 3, labs were notable for metabolic alkalosis (see table for VBG) with concurrent respiratory alkalosis (expected pCO2=40+ 0.6x(27-24=3)=41 mmHg). Urine electrolyes noted on table 1. The urine potassium/urine creatinine ratio was high at 3.3 mmol/L indicating renal losses. She was discharged home once PO intake improved.

Discussion: Our patient initially presented with anion gap metabolic acidosis in the setting of starvation ketosis noted on her urinalysis. However, after receiving IVF her bicarbonate increased rapidly unmasking metabolic alkalosis with underlying respiratory alkalosis. The metabolic alkalosis was likely in the setting of her HG. However, urine studies did not correlate as urine chloride was elevated = 85 mmol/L likely in the context of potassium chloride repletion that increased urinary chloride excretion. This case highlights renal potassium losses due to: 1) Bicarbonaturia (urine pH 6) in the setting of metabolic alkalosis 2) Ketonuria (as urinary ketones bind to potassium increasing excretion in urine). It is important to account for unmeasured anions in the workup of persistent renal potassium wasting.

Lab values	Emergency visit	Day 1 of admission	Day 3 of admission
Na (mmol/L)	135	135	137
K (mmol/L)	3.4	2.7	2.9
Cl (mmol/L)	96	95	101
HCO3 (mmol/L)	17	16	27
Anion gap	22	24	9
BUN (mg/dL)	15	15	2
Cr (mg/dL)	1.0	1.2	0.7
VBG (pH/pCO2/HCO3)	-	-	pH: 7.51/34/27
Urinalysis	+2 protein, sp gravity 1.031, urine pH 6, ++Ketones, 2WBC, 6RBC	+2 protein, sp gravity 1.026, urine pH 6, ++Ketones, 9WBC, 8 RBC	-
Urine Chloride (mmol/L)	-	-	85
Urine Potassium (mmol/L)	-	-	14.3
Urine Creatinine (mg/dL)	-	-	52

PUB159

Successful Therapy for Life-Threatening Hyperkalemia with Isotonic Sodium Bicarbonate and No Dialysis

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Introduction: Isotonic sodium bicarbonate (ISB) intravenously (iv) alone in acidotic pts was shown by K Schwarz, Circulation, 19:215, 1959 & Adler and Fraley in Kid Int, 12: 354, 1977 to cause up to a 3 mEq/L decrease in serum potassium (K) within 4 hours when 150-400 nM iv ISB was given. We treated a pt with a serum K of 9.8 mEq/L in sine wave EKG pattern who refused dialysis with ISB which brought her K to near normal in 14 hrs.

Case Description: A 90 yr old woman with Type 2 diabetes presented in sine wave, HR 30/min & systolic BP 80 mmHg with a K of 9.8 mEq/L. She ha3 mEq/Ld a baseline serum creatinine of 1.6 mg/dl with a K of 6.2 mEq/L & serum bicarbonate of 19 mEq/l. She was started on trimethoprim/sulfa 1 week earlier. Admission labs showed (mEq/L): Na 141, K 9.8, Cl 108, HCO3 13, serum creatinine 3.6 mg/dl, ph 7.2, UNa 43 mEq/L, UK 31 mEq/L, FE NA 1.8% & TTKG 0.5. The family & pt refused dialysis. She was given 3 amps of iv 10% calcium gluconate & her EKG converted to sinus rhythm. ISB (150 mEq of Na & bicarbonate/L) was started at 150 ml/hr along with sodium polystyrene resin 60 gm every 6 hours & 1 amp of Dextrose 50% (25 gm) followed by 10 U of reguiar insulin every 4 hrs. Labs in mEq/L showed: After 5 hrs: Na, 145 K 7.8, bicarb 16, glucose 156 mg/dl. After 10 hrs: Na135, K 6.8, Bicarb 20 glucose 185 gm/dl. After 14 hrs: Na 135, K 5.5, Bicarb 21 glucose 248 mg/dl, After 24 hrs: Na 142, K 3.3, Bicarb 28 glucose 157mg/dl, & TTKG .44.

Discussion: Our pt showed a 2 mEq/L decrease in serum K 5 h after a fast drip infusion rate of ISB giving 112 nM of ISB, a 3 mEq/l decrease after 225 nM ISB & 4.3 mEq/L after 315 nM ISB plus iv dextrose and regular insulin every 4 h. Sodium polystyrene resin works after 6 h and helped later lower the serum K. The low TTKG at the different times shows that increaed renal excretion did not account for the dramatic decrease in serum K. We Conclude: In acidotic pts ISB by continuous iv infusion along with q 4h iv dextrose and insulin can successfully reverse life threatning hyperkalemia without dialysis.

PUB160

An Interesting Case of Non-Anion Gap Metabolic Acidosis Secondary to Arginine Hydrochloride Infusion Therapy

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Introduction: Mitochondrial disorders are relatively common inherited disorders, the syndrome of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is a disorder characterized by hemiparesis, cortical blindness, or hemianopia, muscle weakness, seizures. Treatment of MELAS is critical, delay may result in cortical injuries, neurologic dysfunction and ultimately dementia. The pathophysiology involves reduced vasodilation. L-Arginine is a precursors to nitric oxide, which mediates vasodilation. Despite widespread use of arginine hydrochloride, there is limited understanding of its adverse effects, particularly metabolic acidosis.

Case Description: In our case report, we present a 60 year old male with MELAS who was brought in due to a 3 week progressive weakness, falls associate with poor appetite and failure to thrive. In the hospital, he became encephalopathic with RLL Aspiration pneumonia. Head CT showed ischemic changes. He was started on 30gm IV arginine HCl in 300ml of NS over 90 minutes. Day 1 of infusion, he developed hyperchloremic non anion gap metabolic acidosis with hyperkalemia. Due to hyperkalemia refractory to medical management and development of nonoliguric AKI due to ischemic ATN, the patient was started on CVVHD. His renal function recovered after two days with no further indications to continue dialysis, hypotension had also resolved with removal of vasopressor support.

Discussion: The pathogenesis of clinical features in MELAS has been attributed to the energy defect, causing dysfunction of the microcirculation thus poor perfusion. In our patient, who had hypoperfusion and encephalopathy, L-Arginine was the ideal treatment. The recommended infusion is standardized in adults. We suspect in our patient, the renal impairment resulted in the loss of renal excretion of bicarbonate combined with the relatively high arginine dose due to low body surface area resulted in severe acidosis. To prevent metabolic acidosis with the infusion of Arginine HCL, it should be dosed as per the BSA with close monitoring of the pH. The ability of the kidney to acidify the urine should be monitored by directly measuring the urine ammonia or the surrogate method like Urine anion gap or urine pH.

PUB161

Adrenal Tumor Causing Hyperaldosteronism Leading to Kaliopenic Nephropathy, Nephrocalcinosis, and Nephrolithiasis

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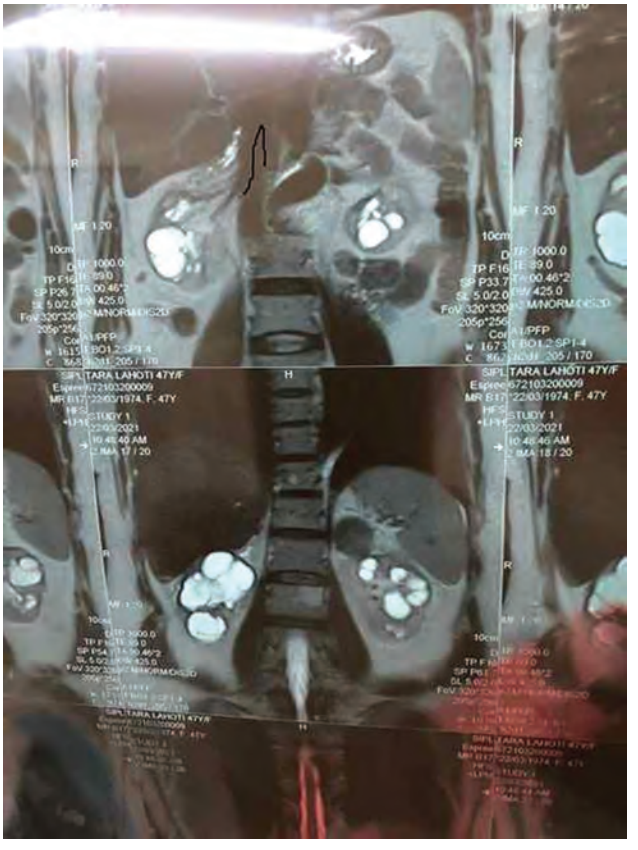
Introduction: Nephrocalcinosis is of rare occurence in a patient with hyperaldosteronism. We report a case of hyperaldosteronism associated with cytsic renal disease, nephrocalcinosis and nephrolithiasis.

Case Description: 40 yrs lady hypertensive presented for evaluation of deranged renal parameters. She had nocturia, polyuria without over the counter, herbal medicine use. She was on antihypertensive drugs including telmisartan. Previous records showed persistent hypokalemia in the range of2 .7 to3 meq/l. BP160/100 mm of hg without any postural drop. Abg showed metabolic alkalosis. Her urinary osmolality was 184mosm/kg with urinary ph 5.5, 24 hour urine was 3.5 L urinary sodium 200meq, potassium160meq, chloride250meq, citrate30mg/day(>40 mg/d) creatnine800 mg/d(20mg/kg/day), calcium260mg/d(4mg/kg/d), uric acid300mg/d(170-1300mg/d), phosphate20 mmol/d(13-40 mmol/d) TTKG was 9.5. Her aldosterone to renin ratio 366.905(<15). An MRI abdomen showed bilateral normal sized cystic kidneys with wall calcification and nephrocalcinosis bilateral renal stones and left adrenal mass lesion of the size of 4.1x3.5 cms which was heterogenously hypointense on out of the phase sequencing suggestive of malignant etiologyand a lytic lesion in the L3 vertebrae. The patient has been advised adrenelactomy and has been started on tab spironolactone and potassium citrate.

Discussion: Although cystic renal disese is common occurence with chronic hypokalemia, nephrolithiasis and nephrocalcinosisis is rare. This patient had adrenal mass lesion with chronic hypokalemia. Nephrocalcinosis can be explained by increased sodium and calcium loss and decreased citrate loss and increased ammonia associated compliment activation due to chronic hypokalemia with hyperaldosteronism.



MRI abdomen showing bilateral cystic kidneys with calcification and left adrenal mass

PUB162

The Role of a Patient Navigator in Reducing Health Disparities in a Distal Renal Tubular Acidosis Decentralized Clinical Trial

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Background: It is well documented that there are a multitude of health disparities that impede clinical trial enrollment in underrepresented racial and ethnic minorities. These disparities/barriers include systemic mistrust of the health system, deep-rooted fear of clinical trials, cultural and language barriers, as well as lack of education and socio-economic standing. Further compounding the complexities are decentralized clinical trials (DCTs) whereby patients may feel undervalued, unsafe, and less supported. Diverse trial participation is critical to understand therapeutic effectiveness in different populations; hence, the goal of the newly created role of industry-sponsored patient navigators will support the enriched enrollment and retention of a diverse and inclusive population in the ARENA2 trial for distal renal tubular acidosis (dRTA), a rare genetic disorder.

Methods: A patient navigation team was formed of English, Spanish, and French-speaking navigators with backgrounds in social services and education. Navigators received training about dRTA, clinical trials and ARENA2. The team collaborated to ensure all patient-facing materials aligned with relative cultural standards and reflected patient-friendly, appropriately translated lay terminology.

Results: The ARENA2 trial seeks to initiate enrollment June 2021 in the US and Canada. Navigators recorded native-language patient education videos about clinical trials, dRTA and ARENA2. Videos were uploaded to the ARENA2 website to inform

potential subjects and establish rapport. Native-language welcome packets that included information of the dedicated services and mapped out home care visits/expectations were created. Diverse and inclusive enrollment and retention rates will be compared to prior rare disease trials upon completion of the 12-week ARENA2 study.

Conclusions: Industry-sponsored, culturally sensitive, bilingual patient navigators are key stakeholders in clinical trials for rare disorders, especially DCTs, and can help reduce ethnic and racial disparities. The ARENA2 trial, will analyze and report on the patient navigator's unique role impacting trial enrollment and retention of Spanish and French speaking populations by addressing complex problems in underrepresented populations.

Funding: Commercial Support - Advicenne

PUB163

The Prevalence of Hyperkalemia and Associated Risk Factors in a General Population

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Background: Hyperkalemia has been related to the risk of cardiovascular events associated mortality. The object was to determine the epidemiology of hyperkalemia and associated risk factors in a rural Chinese population.

Methods: We performed a cross-sectional study of 10,281 participants in China in 2014. All participants completed a questionnaire, physical examination, and collected venous blood to detect serum creatinine, and inorganic ions (potassium, etc.), First void morning urine was collected to detect the albumin-creatinine ratio(ACR) and urine potassium. Hyper- and hypokalemia were defined as serum potassium levels >5.0 mEq/L and <3.5 mEq/L, respectively.

Results: The mean age of the study population was 55.4±10.0 years; 47.1% were males. The crude prevalence of hyper-and hypokalemia was 9.3% and 0.3%, respectively. The subjects with hyperkalemia had higher urine potassium-creatinine ratio (4.4±2.6 vs. 3.7±2.5, P<0.001) and potassium excretion fraction(60.1±48.9 vs. 54.1±46.5, P<0.001). In multivariate analyses, the individuals with decreased eGFR<60ml/min/1.73m^2 had a 3.17-fold increase in the odds of having hyperkalemia. Hypertension, diabetes, and high low-density lipoproteinemia(LDL) were significantly associated with the increased risk of hyperkalemia. However, the female was negatively associated with hyperkalemia even after excluding those with decreased eGFR. The ACEI use was not found to be independently related to hyperkalemia.

Conclusions: The male and participants with hypertension, diabetes and high LDL had an increased risk of having hyperkalemia. Physicians should raise awareness of high-risk groups.

Factors associated with hyperkalemia in the general population

Factors	OR (95%CI) Overall	OR (95%CI) Excluding eGFR<60ml/min/1.73m2
Age (per 1 yr)	1.00(0.99-1.01)	1.01(0.99-1.01)
Gender (male vs. female)	1.19(1.03-1.36)	1.18(1.03-1.36)
BMI (per 1Kg/m2)	0.98(0.96-0.99)	0.98(0.96-1.00)
Hypertension	1.21(1.02-1.42)	1.20(1.01-1.42)
Diabetes	1.19(1.01-1.40)	1.18(0.99-1.39)
LDL (per 1mmol/L)	1.20(1.10-1.30)	1.21(1.11-1.32)
Decreased eGFR(<60ml/min/1.73m2)	3.17(2.08-4.84)	—-
Microalbuminuria(ACR>30mg/g)	1.17(0.95-1.44)	1.10(0.88-1.36)
ACEI/ARBs use	1.12(0.87-1.43)	1.06(0.82-1.38)

BMI: body mass index; LDL: Low-density lipoprotein; eGFR: estimated glomerular filtration rate; ACR: albumin-creatinine ratio; ACEI/ARBs: angiotensin-converting enzyme inhibitor/ Angiotensin receptor blockers.

PUB164

A Suspected Case of Cerebral Salt Wasting (CSW) Syndrome in a Patient with Traumatic Subdural Hematoma: Revisiting a Long Debated Topic

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Introduction: It has long been debated whether CSW is a true entity causing hyponatremia in patients with central nervous system (CNS) pathology or whether the hyponatremia is actually secondary to SIADH while apparent salt wasting is due to underappreciated volume expansion. Literature agrees, for the most part, that CSW is a separate disease process and it has been mostly described in patients with aneurysmal subarachnoid hemorrhage. It has also been described in other forms of CNS pathology including traumatic brain injury, meningitis, and intracranial neoplasms. We present a unique case of symptomatic, severe hyponatremia and apparent renal salt wasting in a patient with subdural hematoma secondary to a traumatic head injury. It was transient and was successfully treated with hypertonic saline, mineralocorticoids, and salt tablets.

Case Description: A 30-year-old male with no significant past medical history presented to the hospital initially on 4/27/21 after a motorcycle accident that resulted in a subdural hematoma, minor cervical fractures, intraspinous ligaments strain, and lacerations. He was discharged on narcotic pain medications, gabapentin, and keppra for seizure prophylaxis. Serum sodium was 135mEq/L at the time of discharge. He returned on 5/5/21 after several days of feeling uncoordinated and having orthostatic symptoms. He was found to have evidence of volume depletion of physical examination. Computed tomography (CT) of the brain showed resolution of prior subdural hematoma. Serum sodium on admission was 115mEq/L. It later dropped to 112mEq/L post hydration with IV fluids composed of normal saline with 5% dextrose. Net sodium balance was calculated to be -60.4 mEq during that initial interval suggesting renal salt wasting. He eventually improved after several days of infusion with hypertonic saline, fludrocortisone, and salt tablets. His episode was transient as he maintained a normal serum sodium off hypertonic saline prior to discharge.

Discussion: We reexamined the proposed mechanisms behind CSW along with the different arguments for, and against it as a separate entity as they relate to this case. We also ecplored the key points of differentiation between CSW and SIADH while focusing on how they pertain to the management of these critically ill patients.

PUB165

Association of Serum Bicarbonate with Incident Gout in Patients with Advanced CKD

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Background: Patients with CKD are at increased risk for gout and alkalinization solubilizes uric acid. We sought to determine if baseline bicarbonate or change in bicarbonate was an independent predictor of incident gout in patients with CKD stages 3-5.

Methods: Optum's de-identified Integrated Claims-Clinical dataset of US patients (2007-2019) was queried to identify patients with non-dialysis CKD stages 3-5 with 2 consecutive serum bicarbonate values 12 to <30 mEq/L, 28-365 days apart, with data ≥1 year prior and ≥2 years of post-index or death within 2 years. Patients without pre-existing gout were followed for up to 11.5 years for diagnosed incident gout (ICD-9 or ICD-10 diagnosis codes 274.** excluding 274.11, M10.* or M1A). Cox proportional hazards models were used to examine predictors of incident gout, controlling for demographic characteristics as well as BMI, time-dependent change in serum bicarbonate; and baseline covariates eGFR, serum bicarbonate, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, high c-reactive protein, hypertension, diabetes, obstructive sleep apnea, irritable bowel syndrome, inflammatory bowel disease, Charlson Comorbidity score, and prescriptions for thiazide diuretics or metoprolol. Death was similarly evaluated as a competing risk.

Results: 125,551/136,067 patients (92%) had no evidence of gout during the pre-index period. During the period up to 11.5-years of follow-up (median 4.2 years), the following covariates were most strongly associated with incident gout: male sex (HR 1.69, 95% CI:1.63-1.76), Black or Asian race (HR 1.52, 95% CI:1.44-1.60 and HR 1.47, CI:1.23-1.75), and hyperuricemia (HR 1.40, 95% CI:1.27-1.55). Hispanic ethnicity (HR 0.82, 95% CI:0.73-0.92), low-income status (HR 0.90, 95% CI:0.85-0.94), higher baseline eGFR (HR 0.98, 95% CI:0.979-0.983, and lower overall comorbidity burden (HR 0.98, 95% CI:0.97-0.99) were associated with a lower risk of gout. Baseline serum bicarbonate and time-dependent change in serum bicarbonate were not associated with incident gout.

Conclusions: In this longitudinal analysis of patients with CKD, serum bicarbonate was not associated with the development of gout.

Funding: Commercial Support - Tricida, Inc.

PUB166

Hyponatremia in a Patient with Chyle Leak

Harish C. Nuthakki. *UT, Houston, TX*.

Introduction: Chylous ascites can cause a multitude of electrolyte abnormalities. Hyponatremia is not a very common presentation unlike hypernatremia in pts with chylous ascites. Here we present a case of hyponatremia in a patient with chylous ascites and the various management challenges we face while managing the hyponatremia.

Case Description: We present a case of a 75y old female with a history of papillary cancer of the thyroid status post thyroidectomy and left neck dissection, with worsening chyle leak from the surgical site with evidence of local recurrence of cancer with worsening left cervical lymphadenopathy. She presented with hypotension, which was treated by infusing 4L of normal saline over a period of 36 hours. She was also receiving 1.5L of free water daily with her tube feeds, which were 85% free water. On hospital day 3, she developed hypo-osmolar hyponatremia which reached the nadir over the next 48 hours, and nephrology was consulted. Patient's urine and serum studies showed a high ADH state and volume depletion. Her volume depletion is due to the chyle leak and she had concomitant high ADH state due to relapsing papillary thyroid cancer. Patient's chyle leak responded to IV octreotide and a low-fat diet with medium-chain triglyceride supplementation. The hyponatremia resolved with administration of oral sodium chloride tablets once the chyle leak was controlled.

Discussion: Patients with chylous ascites suffer volume depletion who can be a challenge to quantify secondary to the location of the leak. Excessive fluid administration, either isotonic or hypotonic can lead to severe life-threatening hyponatremia in these patients. Physicians should pay attention to the amount free water being administered through tube feeds in these pts with active malignancies as they are prone to high ADH states.

PUB167

SIADH-Related Hyponatremia due to a Non-Functioning Hemorrhagic Pituitary Adenoma

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Introduction: Determining the etiology of hyponatremia can be challenging. When euvolemic, one need consider a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH). This can be classified into two groups: ectopic production of ADH or release from the posterior pituitary gland related to disoders of the central nervous system, pulmonary disoders or drug administation. Mechanisms of posterior pituitary related hyponatremia are usually due to hypopituitarism or dysfunction of the pituitary adrenal axis. More rare, are reports of SIADH in patients with pituitary tumors and normal associated function. This is believed to be related to factors of mechanical stress.

Case Description: 39 year old female with no past medical history presented to the emergency department complaining of numbness and tingling of the bilateral upper and lower extremities. Serum sodium was found to be 122 mEQ/L. Urine osmolality 971 mOsm/kg and urine sodium 179 mmol/L. An initial CT scan showed fullness of the sella, possibly representing an underlying lesion. Subsequent MRI of the brain revealed a sellar/suprasellar lesion most consistent with a hemorrhagic pituitary adenoma. Neurohormonal axis proved to be intact and the tumor deemed non secreting. As such, the working diagnosis was SIADH caused by mechanical stress and inappropriate ADH release from the posterior pituitary. She was given a low dose (7.5 mg) of Tolvaptan with ensuing rapid correction of sodium, which required administration of DDAVP and D5W to slow down. Ultimately, salt tablets were started to help maintain an acceptable sodium range. Plan is for endoscopic transspenoidal resection of the pituitary mass.

Discussion: The clincal and laboratory features of this case were consistent with SIADH. There was hyponatremia, in the setting of euvolemia and high urine osmolality and urine sodium. Furthermore, the function of the pituitary gland remained normal on biochemical assessment. In such a scenario of increased ADH secretion, it is important to evaluate the anatomical interaction between the pituitary tumor and the hypothalamo-neurohypophysial system. The tumor may push the pituitary stalk upward leading to mechanical stress and the dislocated gland causing inappropriate ADH release. Such a description is a very rare occurence, but nevertheless need be considered as a cause of SIADH related hyponatremia.

PUB168

Hyponatremia and Hypothyroidism: Association or Causality?

Goutham Kondapi, Eric Krutel, Joel M. Topf. *Ascension St John Hospital, Detroit, MI.*

Introduction: Among the various etiologies of hyponatremia, one that is frequently called into question is hypothyroidism. Literature review repeatedly indicates that only the severe state of myxedema coma has shown a causality with hyponatremia. Data examining the incidence of hyponatremia in less severe hypothyroidism is conflicting; there is question as to whether there is any causality at all. Here we present a case of hyponatremia that is attributable to severe hypothyroidism without myxedema coma.

Case Description: 71-year-old female with a past medical history of hypothyroidism presented to the hospital following a fall and complaint of generalized weakness. Patient had a serum sodium of 111, initially thought to be SIADH given a low serum uric acid, urine sodium less than 20, and serum osmolality of 242. However, the patient had a TSH of 65.70 mcunits/mL with T4 less than 0.1 ng/dL. Patient was given normal saline with minimal sodium correction, and subsequently started on 2% NS with a DDAVP clamp. Patient was started on IV levothyroxine for treatment of her severe hypothyroidism. After 4 days of IV levothyroxine and hypertonic saline, her serum sodium reached 130, and she was discharged home on maintenance levothyroxine.

Discussion: The mechanism behind hypothyroid-induced hyponatremia is not well understood. Studies have suggested a hypothyroid state causes a decrease in cardiac output and peripheral vascular resistance, leading to decreased renal perfusion and decreased GFR. One study found that in patients with primary hypothyroidism before and after thyroid replacement, all had decreased GFR, with hyponatremia observed in greater than half the subjects. However, another study found hyponatremia to be uncommon in more short term hypothyroidism. Literature review has largely identified hypothyroidism-induced hyponatremia in myxedema coma. However, this patient presented not with symptoms suggestive of myxedema coma, but with an elevated TSH and no other attributable cause of her hyponatremia. Additionally, the low uric acid and urine sodium argue against a decrease in renal perfusion as the cause of ADH release. In summary, though some recent literature calls into question hypothyroidism causing hyponatremia, we present a case of profound hyponatremia in a patient with severe hypothyroidism without myxedema coma, which responded to treatment of her hypothyroidism as well as hypertonic saline.

PUB169

A Rare Case of Low-Dose Cyclophosphamide-Induced Symptomatic Hyponatremia

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Introduction: We report a case of severe acute symptomatic hyponatremia with generalized tonic clonic seizures after the first cycle of adjuvant chemotherapy with cyclophosphamide.

Case Description: We present a case of 62-year-old woman who was diagnosed with breast cancer and underwent lumpectomy followed by first cycle of chemotherapy with cyclophosphamide, dexamethasone, and doxorubicin. She received low dose, 15 mg/kg or 1,030 mg IV Cyclophosphamide. On the day of chemotherapy her sodium was 144 mEq/L. The next day the patient had a seizure at home. While in the Emergency Department she had another witnessed seizure. On physical examination vital signs were normal, patient showed altered mental status with no focal deficits. Laboratory: Serum sodium 127 mEq/L, CBC was normal; LFT and other electrolytes were in a normal range. Her head CT was normal. Patient's urine osmolarity was 432 mmol/L and urine sodium was 116 mmol/L. These findings were suggestive of SIADH. Infusion of 300 ml of NaCl 3% and water restriction improved the symptoms and corrected hyponatremia within 24 hours.

Discussion: Hyponatremia is a known but rare complication of cyclophosphamide. Initially it was thought that only high doses of cyclophosphamide (>40 mg/kg) could induce hyponatremia. However, cases of low-dose cyclophosphamide (<20 mg/kg), have been reported, though uncommon. We report a rare case of low dose cyclophosphamide-induced symptomatic hyponatremia. Our patient's rapid decline of sodium could have precipitated the seizure. Using hypertonic saline, hyponatremia resolved, and symptoms improved without neurological deficits. Cyclophosphamide-induced hyponatremia was first reported by Moses et al demonstrating antidiuretic hormone-like effect of Cyclophosphamide to retain water. More recent studies suggest a direct toxic effect of cyclophosphamide or its metabolites on renal collecting tubules and/or an antidiuretic hormone-like activity of cyclophosphamide metabolites. Thus, development of SIADH has been accepted as one of the mechanisms for cyclophosphamide-induced hyponatremia. Thus, physicians should have a low threshold to suspect cyclophosphamide-induced hyponatremia which can be life threatening.

PUB170

Von Hippel-Lindau Syndrome (VHL) Associated with a Breast Tumor

Fatima Cheema, Dawn Maldonado, Maritza Brown. *Mount Sinai Health System, New York, NY.*

Introduction: We present a case of a woman who was incidentally found to have a breast tumor at the same time that she was found to have several other cysts and tumors, and was ultimately found to have Von Hippel Lindau syndrome (VHL). The breast tumor association has not yet been described in VHL.

Case Description: A 21-year-old female presented to another facility with dysphagia and bilateral upper extremity weakness. CT and MRI of the brain demonstrated multiple cysts in the spinal cord extending to the brain stem. Her renal ultrasound findings were read as polycystic kidney disease. The patient underwent C5-C7 laminectomy and resection of the largest intramedullary tumor. Pathology report revealed grade 1 hemangioblastoma. She presented to our hospital 3 months later for dyspnea and tachycardia, so CT angiogram of the chest was performed to rule out pulmonary embolism. It incidentally revealed a right breast mass measuring 3.5x2.7 cm, a 1.9 cm liver lesion, and innumerable sub-centimeter hypodense masses in both kidneys. The dyspnea was attributed to pneumonia and atelectasis from her post-operative recovery. A repeat renal sonogram at our facility demonstrated small kidneys, so the diagnosis of PCKD was questioned and re-evaluated. Genetic testing ultimately returned positive for VHL-1. Her breast mass was found to be a BIRADS-4A lesion on ultrasound, and core biopsy demonstrated a fibroadenoma.

Discussion: VHL is a rare autosomal dominant disorder characterized by the presence of multiple benign and malignant tumors and a pathogenic variant of the VHL gene. VHL is a tumor suppressor gene that inhibits hypoxia-inducible transcription factor, thereby inhibiting hypoxia-induced vascular growth. Loss-of-function mutations hence lead to tumor growth in multiple organs. Tumors associated with VHL include infratentorial hemangioblastomas, retinal hemangioblastomas, renal cysts and pheochromocytomas. It remains unclear whether her breast fibroadenoma was associated with VHL. However, the literature on VHL remains limited, so we may not yet know all potential lesions associated with VHL. We therefore present this case to contribute to the literature on possible VHL presentations.

PUB171

Perineural Cysts in Polycystic Kidney Disease

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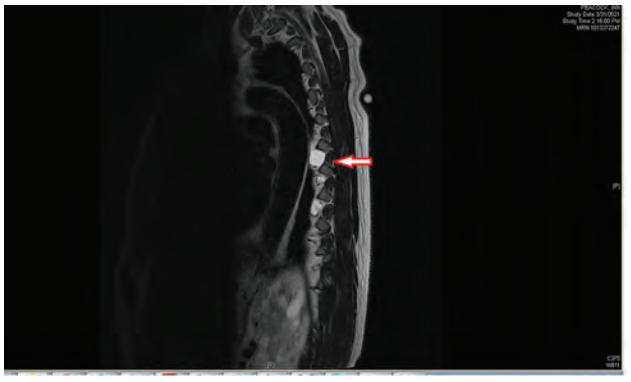
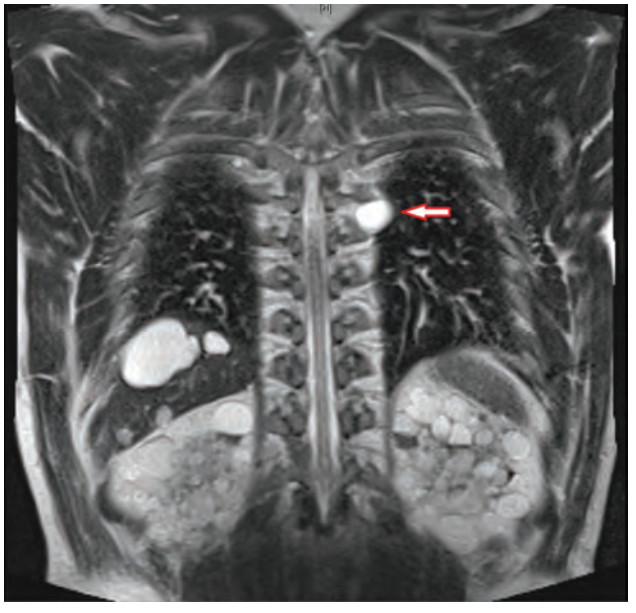
Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease characterized by cyst formation in the kidneys and other organs. In the nervous system, arachnoid cysts have been found in ~8% of patients with spinal meningeal cysts being far less commonly reported.

Case Description: A 51 y.o. man presented to the Nephrology clinic for ADPKD. He underwent an MRI of the abdomen to calculate his total kidney volume. Incidentally found were multiple T2 hyperintense lesions in the intercostal spaces, most prominent in the left paraspinal midthoracic spine. A dedicated MRI of the thoracic spine was subsequently performed which further characterized the lesions to reflect perineural cysts.

Discussion: Perineural cysts are benign pouches filled with cerebrospinal fluid (CSF) located at the nerve root canals along the spine. Only a few cases of spinal meningeal cysts/perineural cysts have been reported in association with ADPKD. Most cases are asymptomatic, but variable nerve root or spinal cord compression may be present. Low-back pain, radiculopathy, and headache due to cerebrospinal fluid leakage may also occur, thus, such symptoms in a patient with ADPKD should warrant further investigation for this condition.



Perineural cyst in thoracic spine



PUB172

The Importance of Family History in Evaluating Persistent Microscopic Hematuria

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Introduction: Alport syndrome (AS) is a condition caused by one or more mutations in *COL4A3-5* (1,2). These result in abnormal production of alpha chains 3, 4, and 5 of type IV collagen in the basement membranes of kidneys, cochlea, and eyes (2,3). Patients exhibit progressive glomerular disease that usually occurs with hematuria, sensorineural deafness, eye abnormalities, and/or leiomyomatosis (2-5). We present a case of presumed AS in a woman with persistent microscopic hematuria and preserved renal function.

Case Description: A 40-year-old woman with a history of Raynaud's syndrome and hypothyroidism was referred to nephrology for persistent microscopic hematuria. Hematuria was first noted in 2008 though renal function remained normal, and she had no significant proteinuria. Social history was non-revealing. The patient's family history was significant for multiple family members with End Stage Renal Disease (ESRD) requiring either dialysis or transplant. The patient underwent a renal ultrasound as well as serologic evaluation which were non-revealing. However, due to the patient's long history of hematuria in addition to her family history, a kidney biopsy was performed. Light microscopy and immunofluorescence were normal; however, electron microscopy demonstrated varying levels of basement membrane thickness. These findings are consistent with Alport syndrome. Genetic testing was performed to identify a mutation in type IV collagen but was unremarkable. Given the patient's family history, biopsy findings, and no identified pathogenic genetic variant, the patient will undergo whole exome sequencing.

Discussion: AS is generally an X-linked disease though other modes of transmission are possible (1-5). Patients with autosomal recessive and X-linked forms can have similar presentations with possible sensorineural hearing loss and visual abnormalities that are rare in patients with autosomal dominant forms. One of the most commonly observed renal manifestations of AS is persistent hematuria either microscopic or gross with the latter being very rare. Females with an X-linked form usually present with microscopic hematuria (4). AS is diagnosed by genetic testing and skin or renal biopsy. Genetic testing is preferred since it is highly accurate and non-invasive though cases of AS with no detectable mutations or copy number variants of *COL4A3-5* are reported (1,3).

PUB173

A Male Senior with Alport Syndrome in Digenic Inheritance of COL4A3 and 4A4

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Introduction: Alport syndrome (AS) sometimes show positive in alpha 2 (a2(IV)) and 5 (a5(IV)) chains of type IV collagen in the glomerular basement membrane (GBM). This could illustrate with the facts that; 1) a5(IV) in basement membranes of Bowman corpuse and cortex are normally immunofluoroscent in 20 % of autosomal recessive AS (ARAS) patient **1)**; and 2) autosomal dominant AS (ADAS) as well as normal kidney are known to be positive in a5(IV).

Case Description: A 21-year-old Asian male senior ("the patient") was referred to nephrology outpatient clinic due to persistent microscopic hamatourina for over fifteen years. No apparent kidney abonormality was found in echogram so was observed till fourth grade of elementary school. Not only himself but his mother and elder brother had hematouria; this brother recently had complained of low-tone hearing loss. The patient had no ocular defect nor hearing loss; no hypertension, diabetes, nor hypercholesterolemia. Serum Cr 0.95 mg/dl; urine RBC 30-100/HPF, beta2-MG 42 microg/L, and UP/Cr 47.9 mg/gCr. LM of the kidney was near normal. The routine IF examination for Igs and complement components were negative. a2(IV) and a5(IV) were not lack in immunofluorescence staining. EM show 10% area of GBM had irregular thinning; No EDD in glomeruli. SPEEDI-KID version 3.0 **2)** next generation sequencing covered throughly 99.2 % genes, as well as COL4A3, 4A4, 4A5, and 4A6 genes. A known c.G469C,p.G157R **3)**, and a known c.T4793G,p.L1598R **4)** mutation was detected in COL4A3 gene. Novel c.G929A,p.R310Q was detected in COL4A4 gene. No mutation in 4A5 and 4A6 genes. The diagnosis of AS was made of persistent microscopic hematouria, type IV collagen gene mutations, and family history of nephritis. His mother also had a known D682G mutation in COL4A4 **3)**, as well as a known G157R mutation in COL4A3 **3)**. His elder brother has not been investigated so far.

Discussion: Two mutations in COL4A3 gene were located in another chromosome so indicated as having heterozygous compound mutations in COL4A3 gene of the patient. ADAS sometimes occur within a family; Its genetic manner, autosomal dominant, could differ symptoms among them. The patient had two individual gene mutations in COL4A3 and 4A4, which has severe clinical features as digenic inheritance **4)**. **References 1)** Pediatr Nephrol 2014;**29**:1535-44. **2)** Clin Exp Nephrol 2017;**21**:63-75. **3)** Plos One 2013;**8**:e71381. **4)** Pediatr Nephrol 2015;**30**:1459-65.

PUB174

A Rare Case of Gordon's Syndrome

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Introduction: Pseudohypoaldosteronism type II (PHAII) or Gordon's Syndrome, is a rare inherited form of hypertension. It is characterized by hyperkalemia, metabolic acidosis, normal GFR, and a low renin state[2]. The first case was described in 1964[4] with only a few hundred cases being discovered since, making each diagnosis an important and unique discovery[3]. There are increasing studies investigating the alteration of genetic pathways leading to disease. In this case, a young male presents for persistent hyperkalemia and was diagnosed with Gordon's syndrome.

Case Description: A 33-year-old caucasian male presented to the emergency room with the chief complaint of abdominal pain. Family history is significant for a daughter who has a history of recurrent hyperkalemia of unknown etiology. Initial vital signs were within normal limits, including blood pressure. Labs revealed potassium of 6.4, a mild non anion gap metabolic acidosis, and serum creatinine of 1.26 with no prior diagnosis of chronic kidney disease. Urine potassium was 12.3 mmol/L and consideration of inappropriate renal retention of K was made. Cortisol and aldosterone levels were normal. Renin level was low at < 2.1pg/mL. He was treated with potassium binders as well as sodium citrate inpatient with improvement in hyperkalemia. Upon follow-up, hyperkalemia recurred despite an improved SCr of 0.9. Genetic testing revealed a variant in the WNK4 gene consistent with Gordon's Syndrome. The patient was started on 12.5 mg of hydrochlorothiazide and has missed all follow-up appointments to date.

Discussion: The discovery of this rare, inherited disorder has lead to the understanding of potassium and sodium handling along the distal convoluted tubule (DCT)[4]. The main disturbance involved is the activation of the thiazide-sensitive NaCl cotransporter (NCC) at the DCT[4]. Mutations in WNK1 and WNK4 genes were found to further increase the activity of the NCC as well as decrease surface expression of ROMK[1]. There are also findings that a chloride shunt is present[1]. It is with these studies that we have been able to identify the causation of pathogenesis and subsequent treatment. Our patient presents as a unique case as this autosomal dominant mutation was found later in life as well as being normotensive which can be present in ~20% of cases[3]. Regardless of presentation, one must consider this rare disorder as treatment can be lifesaving.

PUB175

Market Research Studies Across Primary Hyperoxaluria (PH) Subtypes: PH1, PH2, and PH3

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Background: PH is a family of ultra-rare genetic disorders causing hepatic oxalate overproduction that can result in recurrent kidney stones, life-threatening kidney damage, and systemic oxalosis. There are 3 known subtypes of PH (PH1, PH2, and PH3). PH1 was the first subtype to be characterized and is the most studied. While PH2 and PH3 are less well understood, increasing evidence suggests that they have more severe clinical consequences than previously thought.

Methods: Several market research studies (table 1) were conducted to better understand PH disease burden across subtypes. All data are physician-reported. Copies of medical charts or genetic test reports were not provided for verification purposes.

Results: Across all studies, respondents reported a large subset of PH patients with moderate to severe renal disease. Specifically, the percentage of patients in CKD Stage 3 or worse was the following: — PH1: 87% (Study 1), 56% (Study 2), and 39% (Study 3) — PH2: 92% (Study 1), 68% (Study 2), and 55% (Study 3) — PH3: 83% (Study 1), 41% (Study 2), and 48% (Study 3) Stone burden was similar across PH subtypes: — Average of 3.24 (PH1), 3.92 (PH2) and 4.95 (PH3) stones in the last year (study 1) — 62% (PH1), 71% (PH2), and 61% (PH3) of patients with no renal impairment presented with 3 or more stones in 5 years (study 3). Nephrocalcinosis was reported in 48% (PH1), 61% (PH2), and 38% (PH3) of patients (study 1). The rate of hospitalizations and emergency room visits was comparable across PH subtypes: 63% (PH1), 64% (PH2), and 57% (PH3) (Study 1). Management of PH3 is qualitatively the same as PH1 and PH2. Hyperhydration, stone removal procedures, and vigilant monitoring of disease progression (study 3) are standard of care.

Conclusions: Results from these completed market research studies suggest that severe disease burden and progression is consistently reported across PH1, PH2, and PH3.

Funding: Commercial Support - Dicerna Pharmaceuticals

Table 1: Market research studies

	Design	Respondents	Total n of PH Patients	Data Type
Study 1	Survey-based medical chart	29 nephrologists & urologists	89	In-depth medical data
Study 2	Survey	200 nephrologists, urologists, & primary care physicians	419	Patient segmentation by disease burden
Study 3	Survey + qualitative interviews	85 nephrologists & urologists	644	Patient segmentation by disease burden and PH3 disease management

PUB176

Improvement in Metabolic Control in Patients with Distal Renal Tubular Acidosis (dRTA) After Switching from Standard of Care to ADV7103

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Background: Patients with dRTA present with hyperchloremic metabolic acidosis leading to poor growth as well as compromised bone and kidney health. Current standard of care (SoC) requires a multiple dose regimen with reported poor adherence which may render metabolic control difficult. We describe three patients switched from SoC to a prolonged-release galenic formulation of potassium bicarbonate and potassium citrate with twice daily dosing (ADV7103).

Methods: Three patients with clinically confirmed dRTA (18Y-M, 22Y-F, 16.5Y-F) enrolled in the ARENA2 Phase 3 study (NCT03644706) prior to COVID-19 interruption. Plasma bicarbonate and potassium levels were measured >12 months pre-study initiation on SoC, baseline screening, and 3, 6, & 12 months after participants were switched to ADV7103. Adverse events, palatability, patient satisfaction and adherence rates (estimated proportion of treatment effectively taken based on study drug retrieval) were also reported.

Results: All three patients demonstrated low plasma bicarbonate levels with SoC (< 22 mmol/L) 12 months prior to baseline screening. All patients receiving ADV7103 recorded normal plasma bicarbonate from 3 to 12 months after enrolment. Plasma potassium levels (3.0, 4.3 and 2.8 mmol/L respectively at baseline) were normal for the duration of the trial on ADV7103. One patient reported dyspepsia at 8 months on ADV7103 but resolved with symptomatic treatment. Palatability and patient satisfaction were greatly improved switching from SoC to ADV7103. Adherence rates by 12 months improved from average (50-75%) or good (75-90%) to excellent (>90%) for 2 patients and improved from poor (<50%) to good (75-90%) for one patient. One patient, an adolescent, reported a tremendous positive impact on growth velocity and lifestyle and is reluctant to return to SoC.

Conclusions: All patients maintained normal levels of plasma bicarbonate and potassium after switching from SoC to twice daily dosing with ADV7103. All three patients demonstrated better adherence with ADV7103 as compared to SoC. This small cohort of patients reported improved palatability and satisfaction with ADV7103 treatment as reasons for improved medication adherence and this increased adherence is believed to have had a direct impact on the overall metabolic control achieved throughout the study.

Funding: Commercial Support - Advicenne Pharmaceuticals

PUB177

A Curious Case of Isolated Glucosuria

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Introduction: Glucosuria exceeding 25 mg/dl is pathological and is known as frank glucosuria. Glucosuria can be grouped into two categories; defective absorption of glucose and overflow glucosuria. Conditions such as hyperthyroidism, pregnancy, fever, and exercise tend to decrease the renal threshold for glucose thereby resulting in glucosuria. Here we present a case of persistent isolated glucosuria likely due to primary renal glucosuria in a healthy 52-year-old female in the absence of any secondary etiology.

Case Description: A 52-year-old female was evaluated for incidental finding of glucosuria. She was a healthy individual with no history of diabetes mellitus or gestational diabetes, dysuria, polyuria or polydipsia, chronic kidney disease or kidney stones. Home medications included simvastatin, trazodone and a combined OCP. Hemoglobin A1c was mildly elevated at 5.9 with glucose of 121. Dipstick urinalysis showed pH of 5.5, specific gravity of 1.008 with trace glucosuria. In our workup, we were not able to identify any specific cause for our patient's glucosuria. Her HgbA1c was in the prediabetes range however multiple random blood glucose readings were normal. Based on the available information, we suspect that she might have rare genetic mutation in SLCA52 gene responsible for persistent glucosuria.

Discussion: Glucosuria in a non-diabetic patient is rarely observed in the general population. Primary renal glucosuria (PRG) is an autosomal dominant condition caused by a mutation in the SLC5A2 gene. A defect in this transporter disrupts the kidney normal function of maintaining glucose homeostasis. Based on a few case reports, PRG has not been associated with any renal dysfunction however polyuria, enuresis and later a mild growth and pubertal maturation on long term follow ups has been reported. In rare cases, episodic dehydration and ketosis during pregnancy and starvation have been reported. Few case reports have also linked isolated glucosuria to autoimmune diseases like Graves and undifferentiated connective tissue disease. Our case here emphasizes on the importance of monitoring isolated glucosuria in the general population. Majority of the patients presenting with glucosuria also have concomitant diabetes mellitus or chronic kidney disease, however glucosuria in the absence of comorbid conditions is a rare phenomenon which warrants further evaluation and close monitoring for worsening kidney function.

PUB178

Variants of MTHFR and FGG Genes Are Associated with Levels of Leptin but Not Adiponectin in Colombian Pediatric Lupus Nephritis

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Background: Pediatric Systemic Lupus Erythematosus (pSLE) is a chronic autoimmune disease with unknown etiology. Pediatric Lupus nephritis (pLN) has a worse prognosis and morbidity. Leptin/adiponectin and SNPs in *MTHFR* and *FGG* genes are known to be risk factors that influence development of atheromatosis and cardiovascular disease. The aim of this study was to evaluate the association of serum leptin and adiponectin and SNPs of *MTHFR* and FGG genes in pLN Colombian Caribbean patients.

Methods: A case-control study (98/100) was carried out in Colombian children. The sample groups were selected from a pLN cohort by simple random sampling. Serum concentrations of leptin and adiponectin were determined by ELISA. SNPs in *MTHFR* (A1298C rs1801131) and *FGG* (C10034T-rs2066865) genes were genotyped by qPCR. p-values < 0.05 mean significant statistical

Results: Serum leptin and adiponectin levels were significantly increased in pLN patients (24.7%; 28.9%) compared to control group ($P < 0.001$; $P < 0.001$) respectively. There was no significant association between *MTHFR* rs1801131 or *FGG* rs2066865 SNPs and pLN neither in codominant (P=0.29; P=0.89) nor in allelic models (P=0.88; P=1), respectively. No association was observed between pLN, serum adipokines and *MTHFR*/*FGG* SNPs (*P=0.51; P=0.52)*, respectively. The AG genotype of *FGG* gene rs2228570 SNP was significantly associated with serum leptin levels (*P*=0,0161).

Conclusions: In our population, no association was observed between pLN with the SNP variants of the two gene systems studied nor between pLN and adipokines. However, results in this study found an association between the FGG polymorphism and categorized concentrations of leptin.

Funding: Government Support - Non-U.S.

	pLN (*n*=98)				Control (*n*=100)			
Leptin levels	<1 ng/ml	1-15 ng/ml	>15 ng/ml	*P	<1 ng/ml	1-15 ng/ml	>15 ng/ml	*P
rs1801131 (MTHFR)								
GG, *n* (%)	0 (0)	3 (4.4)	2 (8.3)		1 (10)	8 (9.5)	0 (0)	
TT, *n* (%)	5 (100)	52 (76.5)	13 (54.2)	0.16	8 (80)	62 (73.8)	0 (0)	0.86
GT, *n* (%)	0 (0)	13 (19.1)	9 (37.5)		1 (10)	14 (16.7)	0 (0)	
rs2066865 (FGG)								
AA, *n* (%)	1 (20)	2 (2.9)	0 (0)		0 (0)	2 (2.4)	0 (0)	
AG, *n* (%)	3 (60)	24 (35.3)	10 (41.7)	0.10	0 (0)	37 (45.1)	0 (0)	**0.016**
GG, *n* (%)	1 (20)	42 (61.8)	14 (58.3)		10 (100)	43 (52.4)	0 (0)	
	pLN (*n*=98)				**Control (*n*=100)**			
Adiponectin levels	<5 µg/ml	5-30 µg/ml	>30 µg/ml	*P	<5 µg/ml	5-30 µg/ml	>30 µg/ml	**P
rs1801131 (MTHFR)								
GG, *n* (%)	2 (5.1)	1 (3.3)	2 (7.1)		9 (10.8)	0 (0)	0 (0)	
TT, *n* (%)	29 (74.4)	23 (76.7)	18 (64.3)	0.85	61 (73.5)	9 (81.8)	0 (0)	0.51
GT, *n* (%)	8 (20.5)	6 (20)	8 (28.6)		13 (15.7)	2 (18.2)	0 (0)	
rs2066865 (FGG)								
AA, *n* (%)	0 (0)	0 (0)	3 (10.7)		2 (2.5)	0 (0)	0 (0)	
AG, *n* (%)	18 (46.2)	13 (43.3)	6 (21.4)	0.027	34 (42)	3 (27.3)	0 (0)	0.52
GG, *n* (%)	21 (53.8)	17 (56.7)	19 (67.9)		45 (55.6)	8 (72.7)	0 (0)	

*Contingency table. *: p <0.05 Chi square, ¥: Bonferroni correction, pLN: Pediatric Lupus Nephritis, MTHFR: Methylenetetrahydrofolate reductase, FGG: Fibrinogen gamma chain*

Table 1. Comparison between genotypic frequency of MTHFR/FGG SNPs and leptin/adiponectin levels in pediatric lupus nephritis patients and control group

PUB179

Magnitude of the Potential Screening Gap for Fabry Disease in Manitoba, Canada

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Background: Fabry disease is a rare disorder caused by deficient activity of -galactosidase A (GLA) and often leads to heart, kidney, and nerve damage. Fabry disease can be treated with enzyme replacement therapy, improving quality of life, but it often goes undiagnosed as neonatal screening programs suggest its true prevalence is much higher than what has been reported clinically. Given its low frequency, mass screening for Fabry disease is impractical. However, a targeted screening program of high-risk individuals may uncover previously unknown cases. Our objective was to use population-level administrative health databases to identify patients at high risk of Fabry disease.

Methods: We conducted a retrospective cohort study of all residents of Manitoba, Canada between 1998 and 2018. Using databases housed at the Manitoba Centre for Health Policy, we ascertained a cohort of patients without a diagnosis of Fabry disease who had at least one of the following high-risk conditions: idiopathic hypertrophic cardiomyopathy, ischemic stroke <45 years of age, kidney failure or proteinuria of unknown cause, peripheral neuropathy. We excluded patients with known contributing factors to these high-risk conditions, including, where appropriate, diabetes, hypertension, autoimmune diseases. cancer, glomerulonephritis, and polycsysitc kidney disease. Those who remained and did not have evidence of GLA testing were considered to have a 0.5-4.0% probability of having Fabry disease.

Results: A total of 145,466 individuals had at least one high-risk condition. Of those, 1,386 remained after applying exclusion criteria. Only 22 of 1,386 (1.6%) had GLA testing, leaving a screening gap of 1,364 individuals of which 932 were still alive and residing in Manitoba as of December 31 2018. We estimated that screening these individuals would yield between 4 and 37 new cases of Fabry disease.

Conclusions: Administrative health databases may be a useful tool to identify patients at higher risk of Fabry disease or other rare diseases. Further directions include designing a program to screen these individuals for Fabry disease.

PUB180

Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) with UMOD Gene Mutation as a Rare Cause of CKD in a Young Patient with Family History of ESRD

Saira Sajid, Katerina Hysi, Naveed N. Masani, James Drakakis. *NYU Winthrop Hospital, Mineola, NY.*

Introduction: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is caused by mutations in the UMOD gene (ADTKD-UMOD). It is characterized by slowly progressive chronic kidney disease usually first noted in teen years and progressing to end stage renal disease (ESRD) between the third and seventh decades. Hyperuricemia and gout are hallmark features, presenting from an early age or developing over time. This is considered a rare and often underrecognized diagnosis and in fact, clincial features have been shown to poorly predict ADTKD-UMOD. As such, our case highlights the need for genetic testing to help define the etiology of renal disease guided by a relevant family history.

Case Description: 28 year old male with a past medical history of hypertension and serum creatinine 1.8 mg/dL presented for evaluation. Workup revealed small kidneys bilaterally (8.3 cm and 7.9 cm on right and left respectively) and lack of significant proteinuria or hematuria on urinalysis. Family history was very significant and included the patient's father, paternal grandfather and paternal uncle, all with ESRD having been on dialysis. Additionally, serum uric acid was noted to be 12.1 mg/dL. Genetic testing ultimately revealed a likely pathogenic variant in the UMOD gene associated with autosomal dominant tubulointerstitial kidney disease 1 (ADTKD1) also previously known as familial juvenile hyperuricemia nephropathy 1, glomerulocystic kidney disease with hyperuricemia and isosthenuria and medullary cystic kidney disease 2.

Discussion: ADTKD is a rare genetic kidney disease most commonly caused by mutations in the UMOD gene. It is characterized by early onset hyperuricemia and gout with development of slowly progressive renal failure with tubulointerstitial disease. There is usually no proteinuria or hematuria, and imaging may show medullay renal cysts. Pathogenic UMOD mutations cause protein misfolding, retention in the endoplasmic reticulum (ER) and mistargeting of uromodulin in the thick ascening limb of the loop of Henle. This results in tubulointerstitial damage via ER stress and reduced urinary uromodulin excretion. This case illustrates the lack of distintive clinical and diagnostic features of inherited interstitial kidney diseases, making them an underrecognized and underreported entity. Physican awareness and accurate family history can be of great benefit.

PUB181

Proteinuria Behind the Scenes: An Occult Diagnosis of Alport Syndrome in a Woman via Genetic Testing

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Introduction: Alport Syndrome is a rare disease amongst children and adults. The diagnosis is a clinical challenge for adult nephrologists. We illustrate a case demonstrating the use of genetic testing to confirm the diagnosis.

Case Description: The patient is a 23-year-old woman who presented with nephrotic syndrome. She was found to have proteinuria of 3.2 grams, glomerular hematuria, and a creatinine of 1.6 mg/dL. The patient endorsed a family history of End Stage Kidney Disease (ESKD) in her sister. A complete serologic work-up and renal ultrasonography were negative. Kidney biopsy was performed, which showed Focal Segmental Glomerular Sclerosis (FSGS) with diffuse foot process effacement. The patient was started on steroids and lisinopril. After 6 months, the patient did not improve. Genetic testing for Alport Syndrome was positive for the *COL4A4* mutation, confirming a diagnosis of autosomal Alport Syndrome despite a lack of classic symptoms.

Discussion: Alport Syndrome affects one in every 5000 to 10000 adult Americans and causes 0.2% of all ESKD cases in the United States. The pathophysiology involves a lamellated glomerular basement membrane with abnormal collagen IV composition. The majority (85%) of cases are inherited in an X-linked pattern via the *COL4A5* mutation. Autosomal recessive, and less commonly autosomal dominant, patterns are seen with mutations in the *COL4A3* and *COL4A4* genes. It is characterized by progressive renal failure, hematuria, hearing loss, and ocular abnormalities. Kidney biopsy in such patients has been reported to show FSGS, as in our patient. In the appropriate clinical context, the gold standard for diagnosis remains genetic testing. Treatment involves supportive care and RAAS blockade to slow the progression to ESKD. In 2021, the use of novel genetic testing can be more accessibly done in the clinic setting. These tests can uncover various renal pathologies which may otherwise have gone undiagnosed, as is what occurred in our case. Therefore, we believe the more routine use of genetic testing by nephrologists allows for better overall patient care.

PUB182

Genetic Testing to Help Navigate the Spectrum of Type IV Collagen Nephropathy

Katerina Hysi, Saira Sajid, James Drakakis. *NYU Winthrop Hospital, Mineola, NY.*

Introduction: Single gene mutations as an attributable cause of chronic kidney disease (CKD) are becoming increasingly elucidated. Those specifically recognized as being quite impactful involve type IV collagen. While these have been classically associated with Alport's syndrome, advances in genetics have permitted further understanding of the role type IV collagen plays in the pathogenesis of other causes of CKD. The spectrum of genetic hematuria syndromes spans entities ranging from thin basement membrane disease to X-linked Alport syndrome. There is wide variability in phenotype which depends on an interplay of sex, genotype and chromosome activation.

Case Description: 33 year old male with past medical history of excess BMI, and hypertension presented after routine UA displayed proteinuria and hematuria (serum creatinine 0.9 mg/dL). 24 hour study revealed proteinuria of 1.9 g per day and several repeat UAs had ongoing proteinuria and blood/RBC. Family history was significant for the patient's brother and father both with microhematuria. Kidney biopsy showed focal segmental & sclerosing glomerulopathy, perihilar variant (mild) with glomerulomegaly, diffuse GBM thinning (mean 230 nm) and rare GBM lamellations, most consistent with collagen IV nephropathy. Genetic testing revealed heterozygosity for a pathogenic deletion involving the COL4A4 gene, which is associated with both autosomal dominant and autosomal recessive Alport's syndrome.

Discussion: Thin basement membrane nephropathy (TBMN) is an entity within the spectrum of genetic hematuria syndromes which historically was considerated to be a benign hereditary condition characterized by thin basement membranes and microscopic hematuria without significant proteinuria or progressive kidney disease. Recent evidence and understanding of type IV collagen mutations has shown that the prognosis of TBMN may not always be so benign. In fact, 29% of patients heterozygous for mutations in COL4A3/4 develop CKD and 15% progress to ESRD. Phenotypes can be rather variable

along this genetic continuum and where TBMN specifically fits remains an area of ongoing discussion. Our case utilized genetic testing to confirm a deletion in the COL4A4 gene, after kidney biopsy findings were consistent with collegen IV nephropathy. The associated perhilar varient of FSGS and glomerulomegaly could be considered a risk factor for escalated CKD progression.

PUB183

MAGED2 Mutation with Bartter's Syndrome in Adult Patients

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Introduction: MAGED2 mutation is associated with a transient antenatal form of Bartter's syndrome that can be severe enough to lead to death.

Case Description: 43-year-old woman with a history of pituitary adenoma on cabergoline and levothyroxine, referred to nephrology for hypokalemia, hypocalcemia and hypomagnesemia dependent on replacement therapies, frequent lower extremity muscles cramping and weakness post exercise, with frequent ER visits for vomiting and hypokalemia. A diagnosis of Bartter versus Gitelman's syndrome was raised. Her Blood pressure on average is 90 systolic (80-100, asymptomatic). She noticed worsening LE edema and systolic up to 110 lately. Renin and aldo were elevated (36 and 51 respectively). FeNa was 0.03%, FeK of 6.76% and FeCa of 0.1%. The low urinary calcium (3mg/dl) was pointing towards a Gitelman's syndrome. MRI of the abdomen showed possible liver hemangioma, simple cyst of the left kidney and otherwise normal kidneys. As a kid, the patient had a constant craving for salt, had muscle cramping while sleeping, had lower extremity edema especially after puberty, and when she was 20 she would have a 9 lbs fluctuation in her weight in one day. Patient's mother had a pregnancy complicated by polyhydramnios and gave birth to a sister who suffered from nephrocalcinosis and died soon after birth. The patient has a daughter with an avid need to eat salt. She was started on spironolactone and enalapril which improved her edema, blood pressure and resolved the need for potassium. She remained on magnesium, calcitriol and calcium carbonate. Her recurrent vomiting improved after decreasing cabergoline. A genetic panel was order and revealed and X-linked MAGED2 heterozygous mutation, normally defined as variant of uncertain significance [P268L and c>T in exon 4]

Discussion: MAGED2 is linked to a transient form of antenatal Bartter's syndrome including nephrocalcinosis and symptoms resolve by 1.5 years of age. The mutation present in this patient however, is not described previously and is the first mutation of MAGED2 to cause a Bartter's syndrome that remains pathogenic at an adult age. This might be due to the fact that MAGED2 was described in relation to Bartter's syndrome in 2016 and the focus is on a pediatric population. Learning points: MAGED2 mutation can have a variable phenotype within the same family. MAGED2 mutation can cause Bartter's syndrome that is not limited to the perinatal period.

PUB184

Renal-Limited Thrombotic Microangiopathy in the Setting of Thrombomodulin Mutation

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Introduction: Thrombotic microangiopathy is a pathological condition comprised of microvascular thrombosis involving any organ of the body leading to thrombocytopenia, Coombs-negative microangiopathic hemolytic anemia, and organ damage. Common causes of primary TMA are STEC-mediated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and atypical hemolytic uremic syndrome. AKI secondary to TMA in severe Hypertension is not an uncommon scenario, however it is important to rule out primary TMA as a cause of Hypertension. Our case involves a very young male, who presented with elevated Creatinine and severe Hypertension, whose renal biopsy showed renal-limited TMA, with subsequent genetic panel showing Thrombomodulin mutation.

Case Description: This is a 29 year old African ancestry male with known history of Hypertension, diagnosed 1 year ago, not on any antihypertensive medication. Patient presented to the ED with chest pain with BP of 230/110 mm Hg. Blood work remarkable for serum Creatinine of 4.9, unknown baseline, K of 3 and serum bicarbonate of 27. Urinalysis remarkable for sterile pyuria with WBC of 100 and UPCR of 1.5 g/g Patient was admitted under the impression of hypertensive emergency. All the work up for secondary hypertension, including PRA/serum Aldosterone and Renal Doppler were negative. Serology work up for glomerulopathy including ANA, ANCA, Anti Cardiolipin Ab, Anti GBM Ab, HIV, Hepatitis, Anti PLA2R Ab, C3/C4 were negative. Renal fucntion has not improved despite hypertension management, and renal biopsy was performed, which showed findings suggesetive of severe TMA. Haptoglobin and LDH were not suggestive of presence of MAHA, Hemoglobin level and Platelet counts were never low. Genetic panel for aHUS was sent, which showed THBD mutation, for which Ravalizumab was initiated, with the plan of 3 to 6 months treatment with close monitoring of renal function.

Discussion: Though most patients with TMA will present with the hematologic abnormalities of MAHA and thrombocytopenia, there are some that never demonstrate those features and only present with acute renal injury and Renal-Limited TMA. High degree of suspicion of underlying dysregulation of alterenative pathway of complement is required, especially if patients do not improve with standard supportive care. Some of those mutations could present with Renal-Limited TMA without features of systemic TMA

PUB185

Endogenous Ouabain (EO) and Body Composition in Frail Subjects

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Background: The Na/K-ATPase is a highly selective receptor for cardiotonic steroids (CTS) such as ouabain and digoxin. At pharmacological concentrations used in the treatment of cardiac conditions, CTS modulate the ion-pumping function of Na/K-ATPase. At much lower concentrations, in the range of those reported for endogenous CTS in the blood, they stimulate hypertrophic growth of cultured cardiac myocytes through initiation of a Na/K-ATPase-mediated and reactive oxygen species (ROS)-dependent signaling.

Methods: As inflammatory mechanisms may be involved in the pathophysiology of hypertension and in endothelial dysfunction and atherosclerosis via reactive oxygen species, inflammatory and oxidative stress markers were studied in elderly frail subjects under basal condition.

Results: Males showed increased circulating EO (Male 189.8±8.22 vs Female 157.8 nM/L, p=0.0007adjusted for BMI, age, number of drugs taken). Mental health index was not associated with circulating EO levels contrary to what is reported in an experimental model. Conversely, a direct relationship between EO and muscle mass was observed (Pearson 0.236 p = 0.042).

Conclusions: We conclude that EO is a novel determinant of body composition in the presence of reduced renal function in elderly.

PUB186

An Atypical Case of Nodular Glomerulosclerosis

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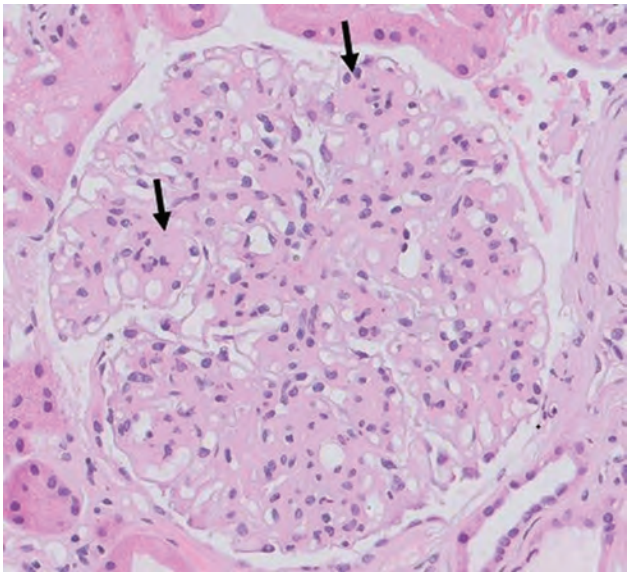
Introduction: Nodular glomerulosclerosis (NG) is a pathological lesion characterized by expansion of the mesangium and increased lobularity. They are typically found in diabetic nephropathy. Other conditions associated with NG include MPGN, paraproteinemias, and chronic ischemic lesions. In rare cases, the lesion may be idiopathic, (ING).

Case Description: The patient is a 67yo female with a medical history of chronic kidney disease, hypertension, hyperlipidemia, and tobacco use (quit 20 years prior). She has no history of diabetes and her most recent hemoglobin A1C value was 4.5. She presented to the hospital with dyspnea and worsening kidney function and nephrotic range proteinuria (3.9g/g). Her serological evaluation, which included SPEP, ANCA, ANA, hepatitis serologies, and serum complement proteins, were all unremarkable. Because of this, she underwent a kidney biopsy. Diffuse and nodular glomerular mesangial expansion was noted on light microscopic evaluation (arrows). She had evidence of advanced disease with 40% interstitial fibrosis and tubular atrophy. On electron microscopy, the patient had no discrete immune-type or organized deposits. She was noted to have a thickened GBM and diffuse podocyte foot process effacement. Unfortunately, she developed progressive renal dysfunction and was started on dialysis.

Discussion: NG is most commonly associated with diabetic nephropathy. However, nondiabetic NG can also be seen secondary to a number of conditions or as a primary condition, known as ING. Clinical risk factors for ING include obesity, hypertension, and tobacco use. Heavy tobacco use is one of the strongest risk factors. In the largest series published to date, the median tobacco consumption was 52 pack-years, and 43% of patients with former smokers, which demonstrate the importance of careful history-taking in identifying risk factors for this disease.



PUB187

Fibrillary Glomerulonephritis in a Patient with Long-Standing Hypertension, Proteinuria, and Advanced CKD: Not Everything Is Hypertension

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Introduction: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease that mostly affects patients in their fifth or sixth decade of life. Clinical manifestations include elevated creatinine, hypertension (HTN), hematuria, and proteinuria. FGN has been associated with monoclonal gammopathy, autoimmune diseases and viral infections. However, many of the cases ultimately have no precipitating factor identified.

Case Description: We present a case of a 65 years-old man with history of diabetes mellitus for 6 years without retinopathy, HTN and chronic kidney disease (CKD) who presented to our hospital with acute kidney injury after increasing dose of lisinopril for uncontrolled hypertension. Physical exam was unremarkable except for high BP 154/85 mmHg, and mild lower extremity edema. Laboratory studies revealed a serum creatinine of 4.13mg/dL (baseline 2.9 mg/dL, eGFR 22 ml/min/m^2), UPCR of 7.1 g/d, UA showed 10 RBCs and 3+ protein. No RBC on repeat UA. He was negative for Hepatitis B, C, and ANCA, anti-GBM, ANA, and anti-dsDNA Ab. C3,C4 were normal, SPEP showed no M spike, and elevated kappa/lambda ratio of 1.81 (89.7 / 49.6 mg/L). Renal biopsy revealed 20-30% interstitial fibrosis, diffuse, moderate to severe mesangial expansion by eosinophilic deposits with segmental mild increase in mesangial cellularity, polyclonal IgG-dominant smudgy mesangial staining with capillary loop extension with kappa/lambda light chain shift, and mesangial and subendothelial deposits with non-branching randomly arranged fibrils (7-21 nm). A Congo red stain was negative for amyloidosis. Immunohistochemical staining for DNAJB9 was positive, supporting the diagnosis of FGN.

Discussion: This case highlights the importance of pursuing a kidney biopsy in patients with worsening proteinuria and kidney function even without active sediment and negative work up for GN. In patients with long standing history of HTN, it is not uncommon to blame HTN as the cause of the CKD. However, diseases such as FGN although rare should always be considered as part of our differential diagnosis. Whether we should treat with immunosuppression or continue conservative management in this patient with advanced chronic kidney disease is debatable but knowing the diagnosis of FGN will certainly help to establish a better prognosis.

PUB188

Is This Primary or Secondary Membranous Nephropathy?

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Introduction: The definition and management of membranous nephropathy (MN) has rapidly evolved over the past decade, following the identification of PLA2R-Ab. A host of other target antigens have been discovered including thrombospondin type 1 domain-containing 7A, neural epidermal growth factor-like 1, and semaphorin-3B. Primary membranous nephropathy is considered to involve a humoral autoimmune response to a normal podocyte antigen, in the absence of known secondary etiologies including autoimmune diseases, infections, malignancies and certain drugs.

Case Description: We present a 72 Y male with medical conditions including HTN, pre-diabetes, grade 1 obesity, CAD, and remote history of laryngeal cancer, who presents to nephrology clinic for evaluation of lower extremity edema and proteinuria of 11 gms. Labs are consistent with nephrotic syndrome, and he is subsequently started on Furosemide and Lisinopril. His GFR is preserved with serum creatinine of 0.9 mg/dL. Additional work up includes HEP B/C, HIV, SPEP/UPEP/FLC, and ANA, which are negative but PLA2R-Ab is markedly elevated (PLA2R IFA positive with titer of 1:500 and PLA2R ELISA positive at 250.00 RU/mL). The patient refuses renal biopsy. In the absence of a biopsy, a mutual decision is made to treat the patient with rituximab. However, after two doses of rituximab 1g spaced two weeks apart, the patient fails to achieve clinical or biochemical remission within 6 months. The need for a biopsy is again discussed to further determine treatment options, and is eventually done. Biopsy suggests features of secondary MN, including mesangial expansion, intracapillary leucocytes on light microscopy (LM), IgG (1 and 3) and IgM, C3 and C1q deposits, absent PLA2R stain on immunoflourescence (IF), and subepithelial, intramembranous as well as subendothelial electron dense deposits on electron microscopy (EM). A thorough assessment for secondary causes of MN remains unremarkable. A CT head/neck, chest, abdomen, and pelvis is also obtained which does not reveal any malignancy.

Discussion: Although the biopsy findings are suggestive of a secondary MN, the significantly high titer of PLA2R-Ab have persisted. The patient is offered an alkylating agent based therapy, but has opted to enroll in an ongoing clinical trial on anti-CD 38 therapy. He remains under surveillance for possible secondary etiologies due to his biopsy findings, while awaiting his response to anti CD-38 therapy.

PUB189

Two Clinical Scenarios Leading to the Diagnosis of Staphylococcus Infection-Associated Glomerulonephritis

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Introduction: Historically, infection-associated glomerulonephritis (IAGN) has been associated with group A streptococcal infections. At this time, staphylococcus infection-associated glomerulonephritis (SAGN) has become more prevalent in developed countries. We describe two different patients and clinical scenarios, who merge at the diagnosis of SAGN.

Case Description: The first patient is a female in her 60s who had recently been treated for methicillin sensitive staphylococcus aureus (MSSA) bacteremia. Three weeks later she was admitted with heart failure exacerbation and started on diuresis. Labs showed creatinine of 2.22, from baseline of 0.9, and proBNP was 30,583. Her respiratory status improved, however her creatinine increased day by day, peaking at 6.9, and she became oliguric. Renal biopsy showed IgA dominant immune complex mediated diffuse segmental proliferative glomerulonephritis consistent with post-staphylococcal glomerulonephritis. Immunofluorescence showed granular mesangial staining for IgA and C3. She was started on hemodialysis and was discharged to inpatient rehab. The second patient is a 19 year-old female who was transferred for treatment of tricuspid valve endocarditis and methicillin resistant staphylococcus aureus (MRSA) bacteremia. After transfer her renal function worsened, with peak creatinine of 3.5 from a baseline of 0.6. She became oliguric and hyperkalemic, and hemodialysis was started. A few days later, she developed a necrotizing small vessel vasculitis and was treated with prednisone for presumed leukocytoclastic vasculitis. This resulted in improvement in her renal failure. After steroids were stopped her renal function again worsened. Renal biopsy showed diffuse segmental proliferative and necrotizing glomerulonephritis with crescent formation; immunofluorescence revealed granular mesangial and capillary staining for IgA and C3. Steroids were restarted with plans for a lengthy taper, and she was discharged a few days later.

Discussion: SAGN has become a prevalent cause of infection-associated glomerulonephritis. Clinicians should recognize the broad risk factors associated with SAGN as staphylococcus infections are exceedingly common. Including the more elusive differentials including SAGN can aid in providing appropriate and swift management with antimicrobials, and possible hemodialysis support.

PUB190

Something Out of Nothing: A Rare Case of Pulmonary Renal Syndrome with Pauci-Immune Glomerulonephritis and Diffuse Alveolar Hemorrhage with Negative Serologies

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Introduction: Pauci-immune (PAN) crescentic glomerulonephritis (CrGN) is one the most common etiologies of rapidly progressive glomerulonephritis. PAN CrGN presents as CrGN with little or no immunoglobulin staining and negative serological workup aside from a positive antineutrophil cytoplasmic autoantibody (ANCA). Patients with PAN CrGN usually have underlying systemic small vessel vasculitis, but in rare cases, it is not associated with vasculitis or ANCA. ANCA-negative PAN CrGN is often isolated to the kidneys, but here we present a case in association with severe diffuse alveolar hemorrhage (DAH).

Case Description: A 66-year-old Hispanic woman with no significant medical history presented with four days of fatigue and dysphagia. On admission she was hypoxic on room air, and her physical exam was remarkable for crackles bilaterally. Initial laboratory results revealed anemia (5.2 g/dL), hyperkalemia (6.3 mmol/L), and AKI with serum creatinine of 4.5 mg/dL. Urinalysis showed dysmorphic RBCs and proteinuria. A computed tomography scan of the chest/abdomen/pelvis was obtained and revealed multifocal pulmonary consolidations. The patient developed hemoptysis and a bronchoscopy showed DAH. The ICU team proceeded to intubate her as the hemorrhage continued to worsen. Further workup revealed a positive ANA titer of 1:40, but otherwise negative serologies, including MPO-ANCA, anti-GBM, and anti-dsDNA. Kidney biopsy showed necrotizing CrGN with negative immunofluorescence. She was diagnosed with PAN ANCA-negative vasculitis with associated DAH and nephritis and was started on

pulse-dose steroids and IV cyclophosphamide. Afterwards, her creatinine began trending down and urine output improved. The patient was discharged with a regiment of daily oral cyclophosphamide and steroid taper.

Discussion: We present a unique case of pulmonary-renal syndrome with negative serologies including ANCA. Based on most recent results from PEXIVAS trial, plasmapheresis was not considered to be part of the treatment plan and not doing plasmapheresis did not affect outcome.

PUB191

A Case Report of ANCA-Negative Vasculitis Presenting with Pauci-Immune Glomerulonephritis

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Introduction: Crescentic glomerulonephritis (GN) is a severe form of GN characterized by a rapid decline in kidney function. Pauci- immune GN is one of the most common causes of rapidly progressive GN and is usually associated with positive antineutrophil cytoplasmic antibody (ANCA). We present a rare case of ANCA negative pauci- immune GN that was successfully treated with immunosuppression.

Case Description: A 17-year-old girl without significant PMH was admitted to the hospital with abdominal pain and diarrhea. She initially had dark colored urine but became anuric shortly thereafter. On admission, she had a blood pressure of 139/83 mmHg (98 percentile), Pulse of 87 bpm and Temp of 98.3 °F. Physical exam was unremarkable. Initial laboratory investigation revealed creatinine of 11.9 mg/dl. Urinalysis was positive for proteinuria and hematuria. Protein to creatinine ratio was 28 g/ g. Urine microscopy showed RBCs with dysmorphic features. ANA, ANCA and anti GBM antibodies were negative. C3 and C4 were normal. Viral serology was negative. Kidney biopsy was consistent with small vessel vasculitis with pauci-immune necrotizing GN. She has initially required dialysis for several sessions but her kidney function improved after we started her on steroids and cyclophosphamide with subsequent improvement of her condition.

Discussion: Pauci-immune crescentic glomerulonephritis is one of the most common causes of rapidly progressive glomerulonephritis. The majority of patients with pauci-immune had circulating ANCA. Some patients with pauci-immune crescentic glomerulonephritis lack ANCAs. There are recent studies about the association between anti LAMP 2 antibody and ANCA negative pauci-immune GN.

PUB192

Atypical Presentation of Anti GBM Disease in an Elderly Woman with No Hematuria and Subnephrotic Proteinuria

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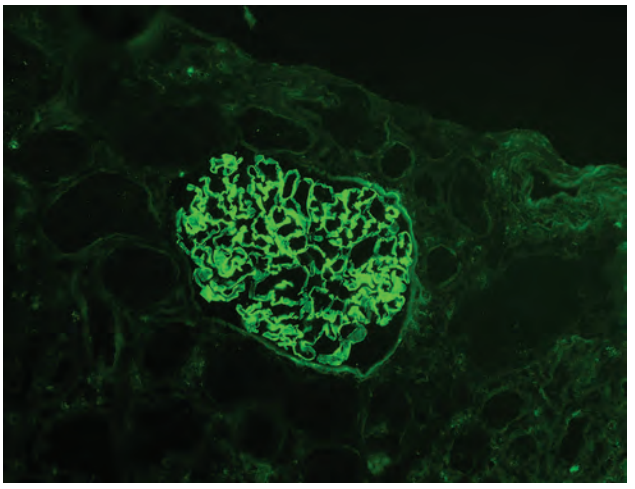
Introduction: Atypical anti GBM disease forms a small minority of patients in this rare and aggressive condition. Atypical disease usually presents with milder disease and typical histopathology and good prognosis. However, presentation without hematuria is unique.

Case Description: A 69-year-old lady with a background history of hyperlipidaemia, hypothyroidism and rheumatoid arthritis presented with a 4-week history of nausea and lethargy. She had been initiated on Pantaprazole and noted to have renal dysfunction with creatinine at 214 μmol/L 4 weeks later. She had no respiratory symptoms. Urine protein/creatinine ratio was elevated at 108 mg/mmol and she had leucocyturia and no hematuria. The vasculitic screen revealed positive anti GBM titre at 135 CU (QuantaFlash chemiluminescence assay; normal range <20CU). A renal biopsy revealed necrotising glomerulonephritis and distinctive linear IgG deposition on glomerular basement membrane. She underwent daily plasma exchange for one week and subsequently initiated on alternate daily exchanges. She was initiated on pulse Methylprednisolone 500 mg daily for three days followed by oral prednisolone 1 mg/Kg and oral cyclophosphamide 2 mg/Kg. Her renal function continues to improve with creatinine at 177 μmol/L.

Discussion: The initial presentation was suggestive of interstitial nephritis esopecially with the drug history. However, the anti GBM serology and the typical histopathological features were consistent with a diagnosis of anti GBM disease resulting in appropriate therapy. Hence the teaching points from this case are that anti GBM disease can present in an atypical manner and absence of hematuria does not rule out an aggressive glomerulonephritis and timely investigation with a renal biopsy and appropriate management can prevent end stage kidney disease.



Immunofluorescence with IgG antibody with linear staining of glomerular basement membrane

PUB193

IgA Nephropathy and Lupus Nephritis: A Subtype or a Separate Entity?

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Introduction: The relationship between IgA nephropathy (IgAN) and lupus nephritis (LN) is controversial, some feeling the 2 can co-exist while others feel that IgAN could be a subtype of LN. We present a case of SLE that had features of IgAN on kidney biopsy which we treated as lupus nephritis resulting in recovery of renal function.

Case Description: A 51 year old female with undifferentiated connective tissue disease consistent with SLE was evaluated for AKI, proteinuria with protein to creatinine ratio of 5.76 grams, and microscopic hematuria. Lab investigation showed neg p-ANCA, c-ANCA, PLA2R Ab, DNA Ab, anti-GBM with normal C3 and slightly high C4. Around this time she was noted to have GI ulcers on scoping. Kidney biopsy was performed and sample was sent to Arkana lab. It showed 22 total glomeruli 2 of whicher were globally sclerosed, no segmental sclerosis or arteriolar hyalinosis, mild interstitial fibrosis and tubular atrophy, severe arterial intimal fibrosis, negative congo red stain for amyloid, and 1 glomerulus on toluidine blue stained sections. LM had crescents in 7/14 glomeruli. IF had 1/7 glomeruli that were globally sclerotic. There was 3+ amounts of mesangial deposits of IgA. 3+ amounts of lambda light chain and 2+ amounts of kappa light chain were seen in a similar pattern. Kappa and lambda light chains stained equally in small casts and in tubulointerstitial regions. EM showed mild effacement of foot processes. The mesangium was not expanded and there were a moderate number of mesangial electron-dense deposits. Pathology reported this as IgA–Crescentic glomerulonephritis and stressed that though an unusual pattern, it was consistent with diffuse class IV lupus nephritis. We treated her with Euro-lupus protocol using glucocorticoid and cyclophosphamide with good recovery of renal function.

Discussion: LN is a known complication of SLE and it normally has distinct characteristics on kidney biopsy. IgG deposits are commonly seen on IF in LN but IgA deposits are uncommon. Secondary forms of IgAN can present in patients who have mucosal infections or ulcerations which may have contributed to IgA deposition in our patient. Currently we do not have criteria to precisely differentiate whether these two entities (IgAN and LN) can co-exist. We feel our patient represents a distinct subtype of LN based on clinical history, biopsy findings and response to treatment.

PUB194

Hemoptysis in Mixed Cryoglobulinemia

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Introduction: Mixed cryoglobulinemia(MC) is a small vessel immune complex vasculitis caused by polyclonal cryoglobulin deposition in major end organs. Pathogenesis has been associated with viruses including hepatitis C and HIV, plasma cell dyscrasias, and connective tissue diseases. Clinical presentation varies but pulmonary manifestations are generally rare. We present a unique case of mixed cryoglobulinemia presenting with kidney, skin and lung involvement.

Case Description: A fifty-seven-year old female with a history of alcoholic cirrhosis, chronic kidney disease, diastolic heart failure was initially found to have a petechial rash during admission for syncope at an outside hospital. Her lab workup noted progressive acute kidney injury, cryoglobulin consisting of IgG kappa, polyclonal IgG and IgM lambda, low complement levels, positive rheumatoid factor, and negative HIV, hepatitis C, and ANCA. Skin biopsy revealed leukocytoclastic vasculitis. Kidney biopsy showed proliferative glomerulonephritis with necrotizing arteriolitis. She was treated with intravenous solumedrol for MC but developed hemoptysis followed by acute hypoxemic respiratory failure. Bronchoscopy with bronchoalveolar lavage(BAL) revealed thin bloody secretions in the right upper and middle lobe of the lung. Culture and gram stain

noted methicillin sensitive staph aureus(MSSA). Patient was given rituximab, antibiotics and was transferred to a tertiary center for consideration of plasmapheresis and bone marrow biopsy. Although course of antibiotics improved respiratory status, hemoptysis persisted raising suspicion for lung involvement of cryoglobulinemia. Patient's rash, kidney function, and hemoptysis improved with steroids and an additional rituximab dose. Patient did not undergo plasmapheresis. Bone marrow biopsy was negative for evidence of clonal plasma cell disorder.

Discussion: Pulmonary disease in MC includes cough, dyspnea, and rarely hemoptysis. Hemoptysis from diffuse alveolar hemorrhage (DAH) is documented as a clinical feature of cryoglobulinemia with an estimated incidence of 0.4– 4%.We report a case of mixed cryoglobulinemia with persistent hemoptysis despite antibiotics. No sequential BAL done to investigate DAH. MSSA pneumonia noted on BAL is likely a complication of immunosuppression with intravenous steroids. Our case is a valuable addition to the few cases of hemoptysis in MC described in the literature.

PUB195

Management of Infective Endocarditis-Related Glomerulonephritis

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Introduction: Antibiotics can be effective and curative if infective endocarditis (IE) infection is mild. However, in severe cases of IE, surgical intervention is necessary to restore integrity of heart value and to halt or cure IE related glomerulonephritis (GN).

Case Description: 28-year-old male with Crohn's disease, hepatitis C(viral load >10,000,000 IU/ml), admitted at an outside hospital (8/10-9/15) with creatinine (Cr) of 1.28 mg/dL (baseline Cr 0.83 mg/dL) after intravenous (IV) drug use resulting in methicillin-sensitive S. aureus tricuspid valve (TV) endocarditis with septic emboli to right shoulder, lung, and left hip. Renal biopsy: subendothelial and mesangial deposits with >60% foot process effacement consistent with membranoproliferative glomerulonephritis (MPGN). He was treated with IV oxacillin and no surgical intervention. Readmitted to our hospital on 9/19 with hypertensive urgency (173/123 mmHg), anasarca and gross hematuria. Labs:Cr 2.4 mg/dL (discharge Cr 2.09 mg/dL), WBC 17/nL, proBNP 30,000 ng/L, albumin 0.9 g/dL, and low C3 level. Urinalysis with hematuria and protein Ur/Cr Ur ratio 40 grams. C4, hemoglobin, liver function, platelet count, and coagulation were normal. ANCA and cryoglobulins were negative. Duplex of renal arteries and veins was negative for thrombosis. Serum Ascites Albumin Gradient (SAAG) score was 0.3 g/dL, not consistent with portal hypertension. Echo: severe TV regurgitation, moderate pericardial effusion, and global hypokinesis with an ejection fraction of 40% and 1.5 cm vegetation. He underwent TV DeVega annuloplasty. Hospital course complicated by hemorrhagic shock with acute tubular necrosis and right hemithorax requiring VATS. Outpatient follow up, 3 months later, he was on Coreg only with blood pressure (120/80 mmHg), albumin 3.8 g/dL, stable Cr 1.79 mg/dL, remains without edema and pending hepatitis C treatment.

Discussion: Despite~6 weeks of antibiotics and negative bacteremia, the persistent hypocomplementemia suggests failure to control the infection as seen by worsening renal function, hypertensive urgency, nephrotic proteinuria, and anasarca. By undergoing a repair rather than replacement of TV not only resulted in lower operative mortality but also achieved a higher long-term survival, both from cardiac and renal standpoint. MPGN was related to his IE and not hepatitis C as he had resolution of his proteinuria and stable Cr after his surgical intervention.

PUB196

Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID) with Fibrillary Deposits Progressing to Macrophage-Driven Systemic Vasculitis: An Autopsy Case

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin (Ig) deposits (PGNMID) is a renal-limited glomerular disease characterized by disordered glomerular Ig deposits.

Case Description: Here, we report the case of a 62-year-old Japanese woman undergoing hemodialysis 5 years after PGNMID onset. After kidney failure, prednisolone treatment for managing PGNMID was discontinued. Thereafter, fever of unknown origin (FUO), multiple vascular occlusions in the brain, fingers, and retina were observed. Finally, the patient died of hemorrhagic cerebral infarction 8 months after kidney failure.

Discussion: Autopsy revealed the presence of subendothelial fibrillar deposits in differently sized vessels. Furthermore, electron microscopy revealed that macrophages phagocytosed the deposits and underwent autophagy. Liquid chromatography-mass spectrometry (LC/MS) analysis was performed to diagnose IgG1κ type PGNMID. Furthermore, MS revealed that the deposits contained an amyloidogenic protein, which was responsible for the systemic deposition and macrophage-driven systemic vasculitis, eventually resulting in FUO and vasoocclusive disease. Furthermore, macrophage-driven vasculitis in the present patient was suggested to be markedly influenced by pyroptosis, a form of pro-inflammatory cell death peculiar to phagocytes. Systemic PGNMID reported in the present case is a rare subtype of PGNMID.

PUB197

Urinary GADD45G Protein Excretion Predicts IgA Nephropathy Progression

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Background: Growth arrest and DNA damage 45G (GADD45G) is a family of proteins involved in DNA damage response and cell growth arrest. We have previously shown that GADD45G promotes apoptosis leading to acute and chronic kidney injuries (KI 2008; Am J Nephrol 2009; PLoS One 2019). In this study, we show evidence that urinary GADD45G protein can predict progression of IgA nephropathy (IgAN).

Methods: IgAN patients were included in the study if they did not have acute kidney injury on the day of sample collection and had at least one follow up serum creatinine (SCr) measurement after renal biopsy. A 50% or greater increase of serum creatinine levels was used as an endpoint of deterioration of renal function. ELISA assay was performed using a Human GADD45G ELISA kit. Renal biopsy tissue was stained with a monoclonal mouse anti-GADD45G antibody.

Results: Forty-five patients were enrolled in this study whose renal biopsy revealed IgAN. Urinary GADD45G and urinary protein concentrations were 1.89±1.82 μg/g and 1.47±1.98 g/g, respectively. Urinary GADD45G showed a significant positive correlation with SCr-slopes and with urinary protein. The SCr-slope of the highest tertile group (above 1.95 μg/g) of urinary GADD45G was significantly higher than that of the lowest tertile group (below 0.90 μg/g). Urinary protein was significantly higher in the highest tertile group compared to the other tetile groups. Univariate Cox regression analysis showed that urinary GADD45G was significantly associated with deterioration of renal function. Kaplan-Meier test showed a significant difference in event-free survival for deterioration of renal function between patients with the highest urinary GADD45G tertile vs. the other tetile groups. The area under the receiver operating characteristics (ROC) curve indicated urinary GADD45G had a good performance in predicting renal outcome. The cut-off point of 1.67 μg/g was determined from the ROC curve. This cut-off point yielded a positive predictive value of 36.8% and a negative predictive value of 100%. Immunohistochemistry showed that GADD45G was expressed in all biopsy samples of IgAN whereas no staining was noted in normal control tissue. Staining was mainly detected in the cytoplasm of renal tubules.

Conclusions: In the present study, we showed that urinary GADD45G excretion is significantly associated with kidney disease progression in patients with IgAN.

PUB198

Expanding the Differential: Goodpasture's Disease in the Setting of the COVID-19 Pandemic

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Introduction: The 2020 COVID-19 pandemic was a challenging time in healthcare. Physicians struggled with limited resources, overwhelming patient volume and limited knowledge of COVID-19. During this period many hypoxemic patients with pulmonary infiltrates were empirically managed as COVID-19 patients. However, anchoring to COVID-19 diagnosis narrows differentials and potentially lead to missed diagnosis. Herein we highlight a case of delayed Goodpasture's disease diagnosis in the setting of COVID-19 pandemic.

Case Description: A 51 year old male was admitted for several days of malaise, diarrhea and decreased oral intake. On arrival the patient was hypothermic 88.6 °F, BP 122/67 mm Hg, SpO2 91% on room air. On exam he was encephalopathic, diffusely edematous with sonorous wheezes. Initial labs notable for (mEq/L): Na 135, K 7, Cl 107, low CO_2 8, significantly elevated BUN 184 and Cr 27.9. CT chest showed bilateral airspace opacities, renal ultrasound was unremarkable. Initial diagnosis was sepsis secondary to presumed COVID-19 infection despite several negative COVID tests. Emergent hemodialysis was complicated by hypotension and hypoxemia requiring intubation. The patient rapidly deteriorated requiring 3 vasopressors. Autoimmune serologies resulted several days later were negative (ANA, ANCA, C3, Anti-dsDNA Ab, Hepatitis B/C, HIV, SPEP with immunofixation) with the exception of positive anti-GBM IgG Ab (>8). Renal biopsy was unattainable given his tenuous clinical status; however, bronchoscopy performed revealed bloody aliquots consistent with alveolar hemorrhage. The patient was subsequently started on cyclophosphamide, pulse dose steroids and plasmapheresis. Respiratory status steadily improved allowing ventilator liberation. The patient underwent several more cycles of immunosuppression, plasmapheresis during hospitalization and was discharged after 80 days. 1 year later the patient remains dialysis-dependent.

Discussion: This case illustrates the unique challenges of diagnosing Goodpasture's Disease (GD), a rare immune complex-mediated small vessel vasculitis characterized by alveolar hemorrhage and renal insufficiency, during the COVID-19 pandemic. Similarities in their presentation (pulmonary infiltrates, hypoxemia, renal failure) led to our patient being initially treated for COVID-19. However, maintaining a broad differential is essential as the treatment for GD and COVID-19 are vastly different.

PUB199

The Alteration of Neutrophil Nuclear Morphology: A Potential Predictor for Corticosteroid Response in IgA Nephropathy

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Background: In patients with active IgA nephropathy (IgAN), immunosuppressive treatment using corticosteroid is widely used. It should be useful to detect a poor corticosteroid responder in advance. Neutrophils are the most abundant white blood cells (WBC) in circulation, representing a first line of defense from daily environmental insults. Recently, there have been reported associations between an alteration of neutrophil nuclear morphology and treatment responses in patients with infection, cancer, and autoimmune diseases. In these states, the neutrophil nuclear breaks down, then the nucleosome components extrude. The aim of study is whether an alteration of neutrophil nuclear morphology associates with poor corticosteroid response in IgAN.

Methods: We investigated IgAN patients starting corticosteroid therapy between July 2020 to March 2021. We excluded patients with apparent infection or cancer. We defined the alteration of neutrophil nuclear morphology as neutrophil blebs (NB) with Giemsa stain (Figure 1). The participants with NB greater than the median NB were grouped in the high-NB group and the rest were in the low-NB group.

Results: We enrolled five biopsy-proven IgAN patients; number of female, 4; median age, 51 [interquartile range (IQR): 41-57] years old; median WBC count, 7700 [IQR: 6100-9550] /mL; median eGFR, 58.5 [IQR: 56-69] ml/min/1.73m^2; median CRP, 0.06 [IQR: 0.01-0.64] mg/dL; median UP, 0.7 [IQR: 0.2-1.4] g/gCr; median NB, 53.2 [IQR: 37.6-69.2] % at baseline. The high-NB group showed the significantly decrease in UP than that low-NB group after 4 weeks from the initiation of corticosteroid therapy (p=0.0516). There was no differences in eGFR.

Conclusions: The alteration of neutrophil nuclear morphology could predict the response to corticosteroid therapy in IgAN patients.

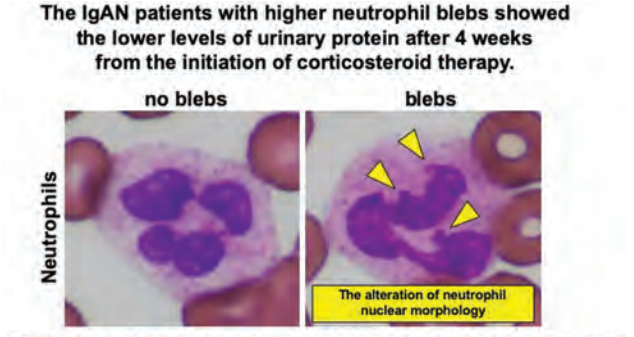

Figure1 The differences between neutrophils with no blebs and blebs

PUB200

Repeat Kidney Biopsy During Remission Induction in Crescentic C3-Dominant Glomerulonephritis

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Introduction: C3 glomerulopathies are rare kidney diseases characterized by complement dysregulation in the glomerular microenvironment, resulting in complement C3-dominant depositions in kidney biopsy samples. To date, it remains elusive which histopathological lesions in C3-dominant glomerulonephritis (GN) are susceptible and effectively eliminated by aggressive immunosuppression and therapeutic plasma exchange (PEX) treatment or indicators of treatment response. In this report, we describe histopathological and ultrastructural findings in repeat kidney biopsies during remission induction with steroids, PEX and intensive protocol cyclophosphamide (CYC) in a case of severe crescentic C3 GN.

Case Description: We here report the case of a 53 years-old man with relapse of severe crescentic C3 GN and histopathological findings in repeat kidney biopsies during remission induction. Crescentic C3 GN developed within less than 2 weeks, associated with severe acute kidney injury. After initiation of aggressive immunosuppressive therapy including PEX treatment, dialysis treatment was still required based on clinical and laboratory markers of kidney injury. In a repeat biopsy after initiation of remission induction, no regression of previous observed crescentic GN was observed. However, no C3c was detectable, associated with an almost complete regression of previous observed ultrastructural deposits. Based on these observations, we continued aggressive remission induction and achieved partial recovery of kidney function with sufficient diuresis and discontinuation of dialysis treatment.

Discussion: Histopathological and ultrastructural findings in C3 GN may be helpful to conclude individual treatment response independent of clinical and laboratory markers of kidney injury and further emphasizes the value of repeat kidney biopsies in cases of severe crescentic C3 GN.

PUB201

Nile Red Fluorescence and Spectroscopy Reveal Unique Lipid Droplet Distribution and Physicochemical Changes in Glomerulonephritis

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Background: Abnormalities in lipid deposition and lipid droplet (LD) accumulation have not been well established in glomerulonephritis (GN). Nile Red (NR), a well-known lipophilic stain for intracellular LDs, is a solvatochromic fluorophore that provides high-resolution spatial assessment of lipid distribution and chemistry. Solvatochromatic spectroscopy is a sensitive imaging modality with the potential to characterize the subtle, early changes in lipid chemistry associated with glomerular injury and disease.

Methods: A total of 72 kidney biopsies of histologically diagnosed glomerular diseases including minimal change disease, membranous nephropathy, primary FSGS, class IV lupus nephritis (LN), ANCA-associated vasculitis, and IgA nephropathy (IgAN), and healthy tissue controls were retrieved from the Biobank for the Molecular Classification of Kidney Disease. Quantitative spectral analysis of NR emission patterns were performed on NR-stained biopsies to generate unique physicochemical profiles for each type of GNl. Segmented regions of biopsies (glomeruli, tubules, and interstitial) were imaged using confocal microscopy allowing for LD quantitatation using an algorithm developed in MATLAB.

Results: Lipid droplet distribution greatly differed between the GN with IgAN and LN demonstrating the highest number LDs in glomeruli. By spectral analyses, control tissue showed significant differences in lipid polarity profile between histological compartments of the kidney (glomeruli, interstitium and tubules). Tubules consistently displayed more lipid rich domains compared to interstitial and glomerular regions. In diseased states, these patterns varied between GNs, with glomerular regions becoming more polar (for example in LN) and tubular regions (predominantly for IgAN). Within histologically identical disease types, we noted distinct populations based on lipid profiles, suggesting significant variance within GN.

Conclusions: Nile Red spectral analysis of human kidney tissue provides unique insights into lipid physicochemical changes in GN. Marked variance within identical disease types suggests that histological determinants of GNs are limited and sensitive techniques such as high-resolution imaging and spectroscopy can identify earlier changes in disease.

PUB202

ANCA Vasculitis: Detecting It Early

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Introduction: Renal limited vasculitis (RLV) is part of the spectrum of antineutrophil cytoplasmic autoantibody (ANCA) vasculitis and includes granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). GPA and MPA present with kidney and pulmonary involvement. RLV tend to present later in the disease course given the lack of extrarenal symptoms that are seen with GPA and MPA. They can progress into having GPA and MPA with development of extrarenal manifestations. Here we present a case in which renal limited vasculitis is diagnosed early in its course.

Case Description: 54 year Hispanic male with no medical history was admitted with atrial fibrillation, acute heart failure, hyperthyroidism and melena. Patient had no history of recurrent sinus or respiratory infections. On exam, patient had a saddler nose deformity from an accident as a child and lower extremity edema. Creatinine (Cr) was 0.54 on admit and was also 0.54 in the emergency room one week prior. Urinalysis had large blood with >100 RBC/HPF and 30mg/dL protein. Patient was diuresed aggressively for 3 days with a furosemide drip and with a mild bump in creatinine from 0.73 to 1.16. The patient's renal function deteriorated even after losartan and furosemide were discontinued and nephrology was consulted when Cr was 2.23. Evaluation showed ongoing microscopic hematuria. Serologic studies were ordered and renal biopsy was performed. Biopsy showed pauci-immune necrotizing glomerulonephritis (GN) with crescents. C3 and C4 were low and C-ANCA and anti-proteinase 3 were strongly positive. Despite induction therapy with Solumedrol followed by weekly rituximab x 4 doses, renal function continued to decline. Due to aggressive clinical course, he was started on plasma exchange x 7 treatments. Despite interventions, he became oligo-anuric and required initiation of dialysis. Although he has had some recovery of renal function and is no longer oligo-anuric, he remains dialysis-dependent.

Discussion: Renal limited vasculitis is confirmed by kidney biopsy, and commonly shows necrotizing GN with crescents in the early stages. As the disease progresses, the lesions become more sclerotic. Untreated glomerulonephritis can progress to end stage renal disease within weeks. Treatment requires pulse methylprednisolone with 500 to 1000mg/day for three days followed by oral prednisone along with cyclophosphamide or rituximab. In rapidly decline in Cr continues, plasmapheresis is warranted.

PUB203

Unexpected Severe Thrombocytopenia Linked to Mixed C- and P-ANCA-Positive Vasculitis

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Introduction: The Anti-Neutrophil Cytoplasmic Autoantibody (ANCA)-associated vasculitis are a rare group of disorders that affect multiple organ systems with a peak age of 65-74 years. It encompasses several diseases including Granulomatosis with polyangiitis, Microscopic polyangiitis and Eosinophilic granulomatosis with polyangiitis. Few cases have been able to demonstrate the existence of mixed ANCA vasculitis related to severe refractory thrombocytopenia.

Case Description: We report a 74-year-old male with Past Medical History of Hypertension and Chronic Kidney Disease (CKD) Stage IV that came to our hospital complaining of fatigue and decrease urinary output since 5 days. Physical exam was remarkable for bilateral crackles and lower extremity edema. Initial labs showed evidence of anemia and thrombocytopenia of 5.8 g/dl and 66 $10^3/\mu L$ respectively. Multiple electrolytes abnormalities were found including acute kidney injury over CKD: serum creatinine 7.23 mg/dl (baseline: 3.85), marked azotemia BUN:101 mg/dL and metabolic acidosis: 13 mEq/L. Patient was admitted with diagnosis of volume overload to start emergent renal replacement therapy along with PRBC transfusion. Follow up labs revealed evidence of hemoglobin optimization (10.2 g/dl), improved azotemia (65 mg/dL) and metabolic acidosis (19.3 mEq/L). Further work-up sent by nephrology service showed evidence of high levels of Proteinase 3 ANCA antibodies: 4.9 U/ml and Myeloperoxidase ANCA antibodies: 96.4 U/ml. Decision was made to start induction therapy with Rituximab and high dose pulse IV steroids. Despite aggressive treatment, clinical course continued to deteriorate with thrombocytopenia reaching critical values of 19 $10^3/\mu L$. Other causes in the differential diagnosis were rule out such as Thrombocytopenia Purpura, Chronic lymphocytic leukemia, HIV, Hepatitis C, Thrombotic thrombocytopenia purpura, among others, which indicated an association between mixed ANCA vasculitis and severe thrombocytopenia.

Discussion: This case illustrates a routinely found inpatient lab abnormality not generally seen in this rare vasculitis type. It is important to keep a wide-ranging differential diagnosis in patients presenting with refractory thrombocytopenia concomitant to advance renal failure. Prompt identification and suspicion of ANCA vasculitis can lead to early start of induction therapy which can delay the progression to end stage kidney disease.

PUB204

Atypical Haemolytic Uremic Syndrome in Lung Transplantation and Treatment with Eculizumab: Our Experience

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Background: Atypical haemolytic uremic syndrome (aHUS) is a clinical entity characterized by acute kidney injury, thrombocytopenia and microangiopathic hemolytic anemia. There are several cases of AHUS in non-renal solid organ transplants described in the literature, included lung transplant. Kidney and patient survival are compromised by this complication because of the lack of an effective treatment. Eculizumab is C5 complement factor specific blocker already administered in another kind of secondary aHUS with encouraging results

Methods: We analys six lung transplants in a retrospective single-center study between 2018-2020 who developed an aHUS and were treated with eculizumab. Clinical and analytical data were collected along the follow-up. Principal outcome was to explore haematologycal and renal response after treatment with eculizumab.

Results: We included a total of six patients(83% female) with a median age of 57 years at the time of transplantation. Induction and maintenance immunosuppressive therapy were based on tacrolimus, mycophenolate and prednisone. Baseline serum creatinine after lung transplantation was 1.1 mg/dl(0.9-2.4). Two patients developed an aHUS in the immediate post-transplant, one of them died because of surgical complications. Another four patients developed an aHUS 59 months(33-95) after transplantation. Previously of thrombotic microangiopathy, three patients were on treatment with everolimus instead of mycophenolate and two lung transplants have cytomegalovirus reactivation. At the aHUS onset, median serum creatinine was 4mg/dl(2.4-5-7) and acute dialysis was performed in 50% of patients. Median hemoglobin was 7.2g/dl(6.9-7.7), platelet count was 32x1000/μL(17-58), and DHL was 1343 U/L (581-1597)at the start of eculizumab despite having treated the trigger. After a median of 6 doses of eculizumab, the five surviving patients had haematologycal and renal response. No patients underwent chronic dialysis. Serum creatinine was 2.2 mg/dl(1.7-2.3), hemoglobin 9.8g/dl and platelet count 159x1000/μL at the end of follow-up.

Conclusions: AHUS is a critical complication in lung transplantation, shortly related with immunosuppressive therapy. Patients are at risk of end stage renal disease. Eculizumab treatment appears promising.

PUB205

Proliferative Glomerulonephritis with Monoclonal Immune Deposits: A Continued Treatment Conundrum

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Introduction: Proliferative Glomerulonephritis with Monoclonal Immune Deposits (PGNMID) is a rare entity characterized by abnormal light chain, heavy chain, or intact immunoglobulin deposits. Patients generally are Caucasian, female, >50 years-old, and present with renal dysfunction and nephrotic-range proteinuria. Pathogenesis involves clonal plasma or B-cells depositing abnormal monoclonal proteins into the kidneys. The clone however is rarely found, and this contributes to the lack of a standard treatment regimen.

Case Description: A 32-year-old Caucasian male with PMH of uncontrolled HTN, chronic microscopic hematuria, and anemia presented with hypertensive emergency (220/111 mmHg) and acute kidney injury (BUN: 58 mg/dl & SCr: 4.41 mg/dl). UA showed microscopic hematuria and proteinuria. 24-hr urine protein was 8.5 g/24hr. Renal US was unrevealing. Other studies were negative including autoimmune panel, SPEP, UPEP, C3/C4, serum FLC, anti-PLA2R, anti-THSD7A, illicit drug screen, endocrine (HgbA1c, renin, aldosterone, catecholamines) and infectious (hepatitis panel, HIV, antistreptolysin-O). A kidney biopsy showed a membranoproliferative pattern with cellular/fibrocellular crescents, 15% interstitial fibrosis, predominant lambda IgG3 and C3 granular capillary loop staining, and numerous subendothelial, mesangial and paramesangial immune complex deposits on EM. A bone marrow biopsy showed hypocellular marrow trilineage hematopoiesis. No clonal cells were identified. He was started on prednisone 80 mg x 4 weeks. Renal function deteriorated and so he was treated with Rituximab (4 doses, 375 mg/m2/dose; briefly interrupted by COVID-19 infection). Absolute CD20 count 4 weeks after this treatment showed 1 cell/mcl with no improvement in renal function or proteinuria.

Discussion: PGNMID is challenging to treat due to its rarity, and here we highlight a case without detectable clone or monoclonal protein in serum/urine that failed prior published effective treatment strategies. The reconstitution of CD20 cells shortly after treatment completion may suggest that a stronger dose or treatment is necessary to achieve clinical response. Daratumumab (a monoclonal anti-CD38 antibody) was recently studied in an open-label phase 2 study to treat 11 PGNMID patients, and this is our next step. Our case highlights the evolving treatment modalities of PGNMID.

PUB206

A Case of Class IV Diffuse Proliferative Lupus Nephritis in a Hispanic Woman with Underlying Systemic Lupus Erythematosus

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Introduction: Glomerulonephritis is the major cause of morbidity and mortality of SLE. Lupus nephritis is characterized by immune complexes deposition in the mesangium leading to complement activation resulting in hypocomplementemia. Studies show that up to 60% of adults with lupus develop renal involvement and it has been well established that Hispanic patients show poorer outcomes than Caucasians despite advances in treatment. Kidney biopsies are paramount in patients with an exacerbation of symptoms as it will establish a diagnosis, help to define treatment strategy, and determine response to treatment.

Case Description: A 41-yo-Hispanic-Woman with a PMH SLE without previous renal involvement, secondary Sjogren's hypertension, heart failure and NASH liver cirrhosis presented to the ER with worsening SOB, difficulty swallowing, and anasarca. Symptoms started two weeks prior and had progressively worsened. Patient was hypertensive, tachypneic, had positive JVD, wheezing in lung bases, +1 pitting edema in the lower extremities and hyperpigmentation of the skin on the face, neck and upper extremities. CXR showed pulmonary edema. Labs showed WBC 11.1, Hgb 10, plt 192, Cr 0.9, BUN 17, CO2 19, UA 3+ blood, 3+ proteinuria, negative LE, nitrates. BNP 1170. Other labs showed Protein/Cr > 2.000, ESR 94, CRP 4.5, ANCA negative, ANA 10, dsDNA 2.7, CENP antibody 0.9, Jo1 antibody 0.6, SCL 70 antibody <0.6, Smith antibody 3.1, SSA/RO 103, SSB/LA 0.9, UR1RNP 3.7, C3 54, C4 <5, RNA polymerase III Ab 37, Cardiolipin Ab IgM <12, Cardiolipin Ab IgG 14. HIV, Hepatitis C, and Hepatitis B were negative. Kidney biopsy showed class IV diffuse proliferative lupus nephritis with a component of Lupus anticoagulant. The patient was started on angiotensin receptor blocker, Prednisone 60 mg BID, Mycophenolate 1000 mg BID and Eliquis 5 mg BID.

Discussion: Kidney biopsies are imperative when establishing a cause of new onset proteinuria in a patient with history of SLE. Goal of treatment is to produce strong immunosuppression in order to reduce kidney inflammation in a timely manner and prevent flares, which decreases the long term risk of renal failure. Despite early recognition strategies and advances in treatment, Hispanic patients are likely to present with class IV or V lupus nephritis and are subsequently more likely to develop CRF compared to Caucasian patients.

PUB207

IgA Nephropathy (IgAN) and Focal Segmental Glomerulosclerosis (FSGS) in a Patient with Crohn's Disease (IBD) on Infliximab

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Introduction: IgA nephropathy and FSGS are common conditions which can coexist in the same patient either due to the nature of the underlying nephropathy, or to the use of anti-inflammatory agents. We present a case of IgAN and FSGS in a patient treated with anti-tumor necrosis factor-α therapy (aTNF-α) for IBD

Case Description: A 21-year-old male with diffuse IBD on semi-monthly Infliximab, presented with nephrosis manifesting as 4.2 grams proteinuria, hypoalbuminemia to 2.8 g/L, and hyperlipidemia. He had no complaints, was normotensive, and had a normal physical exam. Labs demonstrated BUN 15 mg/dl and Creatinine 0.8 mg/dl, normal complement C3 and C4, Urinalysis with 3+ protein, 1+ blood, 10 RBC/HPF, and 7 WBC/HPF. Renal biopsy showed extensive mesangial IgA deposits, diffuse foot process effacement, and tip variant FSGS in a single glomerulus. These findings presented diagnostic and therapeutic challenges since it was unclear whether the aTNF-α induced the FSGS, the IgAN, both, or neither

Discussion: IgAN is the most common nephritis in the developed world and is characterized by mesangial IgA deposition with varying degrees of proliferation. Primary FSGS is one of the most common patterns of nephrosis in adults. The use of aTNF-α for non-renal diseases, has been reportedly linked to the occurrence of FSGS, as well. Though there may be a link between the aTNF-α and the FSGS in our case, FSGS has also been reported in patients with IgAN, irrespective of aTNF-α use and may have prognostic significance. As for the IgA itself, a causal linkage between aTNF-α therapy and IgAN is tenuous as such reports may represent IgA deposition associated with the underlying condition such as ankylosing spondylitis or Crohn's disease This case is a rare example of combined pathology with IgAN and FSGS in a patient treated with aTNF-α that has an undefined primary cause. Despite the diffuse foot process effacement and evidence of FSGS lesions, we opted to treat this as drug induced nephropathy. We withheld the aTNF-α and are monitoring for recovery. We have a low threshold to initiate steroids for primary FSGS in the absence of near-term remission

PUB208

Double Positive Glomerulonephritis: A Disease Associated with Unfavourable Outcome Requiring Aggressive Treatment: A Case Report and Review of Literature

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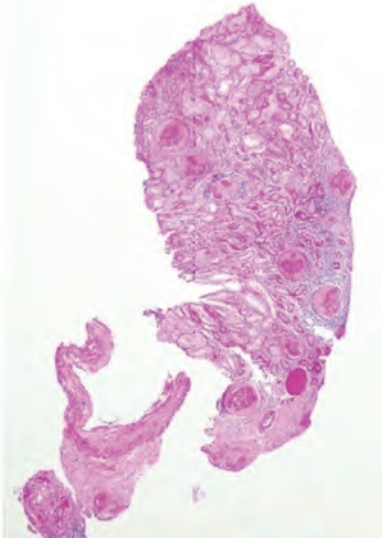
Introduction: Co-presentation with both ANCA and anti-GBM Ab is not unusual and associated with worst outcome (Tab.1); the prevalence of double-positivity in Good-Pasture Syndrome (GPS) is higher (30-38%) than in ANCA-associated vasculitis (AAV) (5-14%).

Case Description: A 70-year-old woman was admitted with a severe respiratory distress and AKI (stage 3) requiring urgent dialysis. Laboratory tests revealed high titer of ANCA (MPO >134 IU/ml, PR3 20 IU/ml) and anti-GBM Ab (54 IU/ml). Histopathological renal analysis showed chronical lesions (Fig. 1). Steroids, plasma-exchange and Rituximab were therefore administered. A sensible improvement of respiratory insufficiency, but no recovery of renal function was observed.

Discussion: Double-positive patients show hybrid features: the acute phase, similarly to GPS, is characterized by frequent lung hemorrhage, warranting plasma-exchange sessions; the subacute phase, like AAV, by high rate of recurrence, requiring a more intense and prolonged maintenance immunosuppressive regimen. Renal biopsy represents a useful diagnostic tool to establish chronicity degree and to speculate about pathogenethic contribution of each component. The worst renal outcome and higher risk of relapse require a careful follow-up.



10 glomeruli (8 global and 2 segmental sclerosed), 60-70% of tubulointerstitial fibrosis and moderate arteriolar intimal fibrosis (PAS stain 100x)

	Anti-GBM+	ANCA+	Double positivity
Age (years)	52	58-65	62
Incidence (milion/year)	1	20	
Lung			
Respiratory insufficiency (%)	75	25-75	75
Alveolar Haemorrage (%)	40-60	10-12	45-50
Kidney			
Acute Kidney Injury (%)	80-90	65-70	100
Dialysis (%)	60	28	70
1-year prognosis			
Dialysis (%)	80-95	-	55-60
Renal recovery (%)	44	88	53
Mortality (%)	13	10	17
Recurrence (%)	0	37	22

PUB209

A Rare Case of Severe AKI from Fibrillary Glomerulonephritis

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Introduction: Fibrillary glomerulonephritis (GN) is an uncommon disorder found on less than 1 percent of native kidney biopsies done worldwide. Due to its rare prevalence, the association of this disorder with other diseases is not fully understood. Here we present a case of a 60 year-old woman with a history of hypertension and untreated Hepatitis C who presented with acute oliguric kidney injury and was subsequently found to have biopsy proven fibrillary GN.

Case Description: 60 year-old woman with history of hypertension and Hepatitis C presented with shortness breath and back pains. Labs on admission showed an elevation in BUN and Cr to 121 mg/dL and 7.69 mg/dL respectively. Other findings included an elevated globulin gap of 4.6 g/dL and a urine dipstick with minimal proteinuria. Renal ultrasound was negative for obstruction and showed normal sized kidneys. Serum and urine protein electrophoresis with immunofixation revealed the presence of free monoclonal lambda light chains. Beta-2 microglobulin level was elevated to 12.4 mg/L. These clinical and laboratory findings raised suspicion for light chain cast nephropathy secondary to multiple myeloma and so renal and bone marrow biopsies were performed. Bone marrow biopsy showed no abnormal plasma cell clones, suggesting against a diagnosis of multiple myeloma. Furthermore, no lytic lesions were noted on skeletal survey. Renal biopsy showed findings consistent with fibrillary GN as well as acute pyelonephritis even though patient experienced no symptoms of urinary tract infection during the entirety of the hospitalization. She was started on intravenous antibiotics, and her renal function returned to near normal on day 14 of hospital stay. She was discharged home with appropriate Nephrology and Oncology follow up.

Discussion: Fibrillary GN is a poorly understood cause of renal failure. Treatment of the disorder is based on the underlying cause if one can be found. Approximately 30-50% of cases are associated with a hematological malignancy, autoimmune disease, monoclonal gammopathy, or Hepatitis C infection. For our patient, the renal biopsy failed to show monoclonal immunoglobulin deposits, suggesting that the most likely association was the underlying Hepatitis C. Also, the finding of acute pyelonephritis on the biopsy likely indicates an entirely separate (though still possibly related) disease process which probably also contributed to the renal injury.

PUB210

A Case of TAFRO Syndrome with Two Consecutive Renal Biopsies Following the Pathological Course of the Kidney

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Introduction: Renal involvement of TAFRO syndrome consist of diffuse glomerular endothelial injury. But due to thrombocytopenia and deterioration of general condition, there are few reports on kidney biopsy results. We report a rale case of TAFRO syndrome with two consecutive renal biopsy which shows pathological time course of endothelial injury from acute to chronic phase.

Case Description: A 20-year-old female who presented with high fever, pleural effusion, ascites, thrombocytopenia, lymph node enlargement, and proteinuria around 1.0g/day. First, she was diagnosed as systemic lupus erythematosus and treated with prednisolone. But she showed poor response to the therapy. Then she was transferred to our hospital and received renal biopsy for definite diagnosis. The renal specimen showed no evidence of immune complex nephritis, but showed diffuse global swelling of endothelium and expansion of subendothelial space. TAFRO syndrome was diagnosed based on 3 major and 2 minor criteria. She was treated with oral prednisolone and tocilizumab, and once CRP titer became negative. But 3 weeks after first tocilizumab treatment, her CT images revealed worsening of ascites, lymph node swelling. CRP titer again became positive, and massive proteinuria appeared. We considered the situation as relapse of the disease and reduced the interval of tocilizumab doses. A second renal biopsy was performed two months after the first one to investigate the cause of the large amount of proteinuria. Interstitial fibrosis was observed in 15% of renal cortex. Glomeruli showed global collapse or focal segmental double contour. One glomerulus showed mesangiolysis and endocapillary hypercellularity. No thrombosis was observed on PTAH staining, and partial loss of CD31 staining was confirmed in a damaged glomerulus. Owing to the enhanced treatment, she achieved remission for one year.

Discussion: The pathological course of renal damage associated with TAFRO syndrome was observed at an interval of two months, and the second renal biopsy showed both active inflammation and advanced organic damage such as fibrosis of the interstitium and double contour, suggesting that solid anti-inflammatory treatment should be required from the beginning of the disease.

PUB211

Complement Inhibition with a Short Course of Eculizumab for Refractory Vasculitis

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Background: Systemic vasculitis (SV) is a life-threatening disease and, in some cases, refractory to intensive multi-immunosuppressant drugs. Complement hyperactivation has gained interest in the pathogenesis of the SV. We report the efficacy of the short course of C5-inhibitor (eculizumab) in refractory cases of lupus nephritis (r-LN) and refractory ANCA-associated glomerulonephritis (r-AGN).

Methods: In this retrospective study, nine consecutive patients were included (r-LN:n=3 and r-AGN:n=6). All patients were previously treated with three or more drugs: corticosteroids(n=9), mycophenolate(n=9), rituximab(n=8), immunoglobulins(n=5), therapeutic plasma exchange (n=4), cyclophosphamide(n=1), and belimumab(n=1). Eculizumab was considered for use in off-label indication in patients with progressive renal deterioration (worsening creatinine, protein-to-creatinine ratio) or developing a high-risk lethal complication after the induction immunosuppressive therapy. The histologic lesson observed were: a) r-LN: Type VI (n=1), Type V (n=1), and type IV (n=1), and b) r-AGN: sclerotic (n=3), and malignant hypertension+/-thrombotic microangiopathy (n=1), in two patients who developed pulmonary haemorrhage, no renal biopsy was performed.

Results: Mean age (SD): 54(17) years. Median (min-max) of follow-up: 23(2-48) months. Overall, 2(22%) patients are in chronic renal replacement program (one r-AGN patient who was dialysis dependent at presentation, and presented a complement H mutation, and one r-LN within 12 months after the onset eculizumab). 8 patients showed hypocomplementemia. As a whole the mean (95%CI) eGFR (EPI-CKD), increased: 8.0 (-3.0 to 19.1) ml/min/1.73m2 (P = 0.13). In r-AGN, the mean (95%CI) eGFR increased :13(-1.8 to 28,25), P= 0.07; while in r-LN, a slight change was observed: -2.1(-24.8 to 20.59), P = 0.72. The median(p25-p75) protein-to-creatinine ratio decreased from 2.6 (1.6-5.5) to 0.6(0.4-1.2) mg/mg (P= 0.01). The eculizumab doses [median(p25-p75)] required in r-LN and rAGN patients were: 8400 (7800-10200) mg and 3150 (2475-5700) mg, respectively. No major side effects were recorded.

Conclusions: The coadjuvant complement inhibition with eculizumab stabilized or increased renal function and decreased proteinuria significantly in refractory vasculitis. The short course of eculizumab seems to be highly effective in r-AGN, and also was associated with lower doses needed.

PUB212

Lupus Nephritis Presenting with Positive PR3-ANCA and Decreased ADAMTS13

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Introduction: Lupus nephritis is a well-described entity. The simultaneous presence of ANCA abs is rare and is related to poor prognosis. Positive patients usually have MPO-ANCA. We present a case of biopsy-proven Class IV/V Lupus nephritis with PR3-ANCA and decreased ADAMTS 13 activity in an AA man.

Case Description: This 46-year-old AA man with no known past medical history presented to the ED for two weeks of SOB, leg, and scrotal swelling. He denies any associated symptoms. He denies using any other OTC medications and illegal drugs. On exam, vital signs were stable. He had 2+ pitting edema in LE bilaterally, scrotal and penile edema. Other systems were unremarkable. Labs were significant for Hg 5.1, Platelets 106, K 6.9, CO2 9, BUN 78, Cr 10.2, and Albumin 2.4. UA showed dysmorphic RBCs and proteinuria, and Urine protein/creatinine of 9. COVID-19 testing was negative. HIV1&2, RPR titer, hepatitis panel, rheumatoid factor, ASO screen were all negative. Renal U/S showed normal-sized kidneys and no hydronephrosis. ANA, ANA titer, and anti-dsDNA returned elevated at >10,1:640 and 9.9IU, respectively. PR3-ANCA was also positive, but MPO-ANCA negative. C3 and C4 at 0.4g/L and 0.14g/L, respectively. ADAMTS-13 activity decreased to 40%. The rest of the work-up was negative. Kidney biopsy confirmed lupus nephritis, Class IV, and V, with ~50% cellular crescents. Moderate to advanced interstitial fibrosis and tubular atrophy ~50%. EM showed two globally sclerotic glomeruli. IF showed a full-house with IgG, IgA, C3, C1q, kappa, and lambda. Unfortunately, kidney function did not recover, and hemodialysis was started, and he was treated with MMF, Methylprednisolone, and with plasma exchange.

Discussion: ANCA positivity, although not common, is a well-described entity but not understood in lupus nephritis patients. Most of these patients present with MPO-ANCA rather than PR3-ANCA. This subset of patients usually presents clinically differently with distinct histopathological features. Long-term follow-up in these patients is also needed to better understand this disease process in lupus nephritis patients.

PUB213

Novel Prognostic Marker of ANCA-Associated Glomerulonephritis: Is It C3?

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Introduction: Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is known as a systemic vasculitis with unknown etiology. AAV has a predilection for affecting the respiratory tract and kidney parenchyma. Hypocomplementemia with low C3 levels at granulomatosis with polyangitis or Microscopic polyangitis diagnosis, may be responsible for worse survival and renal prognosis. We are reporting lowest C3 level in a patient of ANCA associated glomerulonephritis (GN) leading to rapidly deteriorating renal functions.

Case Description: A 78 years old female with history of Diabetes Mellitus complicated with retinopathy, hypertension, end stage renal disease on hemodialysis. She initially presented for workup of proteinuria and worsening renal functions. Her workup showed positive P-ANCA with low C3 levels. Patient did not consent for biopsy. Her kidney functions kept on worsening rapidly and she was started on hemodialysis within a period of two years from the onset of chronic kidney disease.

Discussion: The complement system has been proposed to play an important role in pathogenesis of AAV. A low C3 serum level in AAV patients at diagnosis is associated with worse long term patient and renal survival. When the kidneys are involved, AAV typically gives rise to rapidly progressive renal failure and necrotizing cresentic GN. The study by Augusto et al. showed evidence that even if serum C3 levels are within normal range low C3 values are associated with worst renal outcomes. Lower than normal C3 levels as in our patient could have more significance in terms of patients poor renal outcome even in the absence of biopsy. This raises a question, is C3 a novel independent prognostic marker for AAV?

Patients Laboratory Data

	11/2017	12/2018	04/2019	08/2019	12/2019
BUN mg/dl	23	60	78	97	109
Cr mg/dl	0.94	2.48	3.34	4.53	10.8
GFR ml/min/1.73m2	60	18	13	9	3.5
Alb/Cr	1377	2780			
C3 mg/dl			76	63	
C4 mg/dl			24	25	
P-ANCA			positive	1:1280	

PUB214

A Case of Biopsy Proven Kidney Restricted AL Amyloidosis Leading to Diagnosis of Multiple Myeloma

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Introduction: Monoclonal gammopathy is defined by presence of a monoclonal immunoglobulin in plasma, urine or both produced by clonal plasma cells. It could be associated with hematologic malignancy, smoldering, MGUS or a relatively new term monoclonal gammopathy of renal significance. We present a case of monoclonal gammopathy associated with renal damage leading to the diagnosis of multiple myeloma.

Case Description: A 69 year old male with history significant for hypertension, CAD, PVD presented to the office with bilateral lower extremity swelling extending up to his trunk and significant weight gain over the past month. Laboratory investigations revealed serum albumin of 2.6g/dl, cholesterol 300mg/dl, LDL 187mg/dl. Urine analysis revealed macroalbuminuria with a urinary protein-to-creatinine ratio of 14,314g/g in the setting of a normal serum Cr of 0.89. SPEP followed by serum immunofixation showed an M-spike which was difficult to quantitate. Kappa to lambda ratio was low at 0.06. Extensive work up to determine the etiology for nephrotic syndrome was performed which was followed by a kidney biopsy, showing lambda light chain deposition on immunofluorescence and positive birefringence of congo red stained material under polarized light. Electron microscopy showed haphazardly arranged fibrils and foot process effacement, consistent with amyloid deposition and nephrotic syndrome respectively. An echocardiography, skeletal survey and PET scan obtained to exclude any other organ involvement, were insignificant. Patient was referred to hematology-oncology and he underwent a bone marrow biopsy which showed 10-20% involvement by a plasma cell neoplasm. With the information gathered, the diagnosis of AL amyloidosis with multiple myeloma was made. The patient later underwent therapy with CyBorD whereafter his swelling improved.

Discussion: An unimpressive SPEP should not be ignored. In the setting of high clinical suspicion, work up should always be followed by kidney and bone marrow biopsy. About 12-15% of patients with renal AL amyloidosis have associated multiple myeloma which require treatment with chemotherapeutic agents. Even though our patient fits into the monoclonal gammopathy associated with hematologic malignancy, MGRS is an evolving topic which deserves considerable attention because many of these entities benefit from clonal based therapies.

PUB215

Hematuria and Proteinuria in a Patient of Cypriot Descent

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Introduction: C3 glomerulonephritis (C3GN) caused by a mutation in complement Factor H-related protein 5 (CFHR5) is endemic in patients of Cypriot descent. CFHR5 nephropathy bears a striking resemblance to IgA nephropathy (IgAN). We present a case of CFHR5 nephropathy in a Cypriot patient who was initially diagnosed with IgAN and highlight the importance of family history, labs, renal biopsy, and genetic testing in diagnosis of CFHR5 nephropathy.

Case Description: A 22-year-old male of Cypriot and Greek descent presented in June 2019 with recurrent microscopic hematuria and proteinuria in the setting of upper respiratory tract and gastrointestinal illness. Blood pressure was 132/78 and he had no edema. Serum creatinine (SCr) was 1.6 mg/dL (SCr was 0.7 in 2012, 1.0 in 2018, and 1.3 in 2019). Urinalysis revealed microscopic hematuria and proteinuria. Spot urine protein/Cr ratio (UPCR) was 580 mg/g Cr. Serologic workup was unremarkable. He was diagnosed initially with IgA nephropathy. Due to slowly progressive renal dysfunction, a renal biopsy was performed in January 2020, which showed mild mesangial hypercellularity, segmental duplication of basement membranes, and glomerular C3 deposits. Immunofluorescence was negative for IgG, IgM, C1q, light chains, or fibrin. Electron microscopy revealed segmental mesangial, subepithelial, and subendothelial immune-type electron dense deposits with segmental duplication of glomerular basement membranes. He was diagnosed with C3GN. Genetic testing confirmed the CFHR5-CFHR5 fusion gene that has been causally linked to C3GN by a gain-of-function effect leading to overactivation of the alternative complement pathway. He was treated conservatively with Lisinopril 10 mg daily. Home blood pressures remain stable. SCr remains 1.5 to 1.9 mg/dL and UPCR remains 610 to 810 mg/g Cr.

Discussion: CFHR5 nephropathy is endemic in patients of Cypriot descent. Therefore, a high index of suspicion for CFHR5 nephropathy should be maintained in Cypriot patients presenting with nephritic syndrome. The presentation of CFHR5 nephropathy bears a striking similarity to IgAN. The main distinguishing features of CFHR5 nephropathy vs. IgAN are its familial nature and absence of IgA deposition. Therefore, family history, renal biopsy, and genetic testing for CFHR5 mutation are critical in establishing a diagnosis of CFHR5 nephropathy.

PUB216

Benralizumab Monotherapy Substitution Therapy in Symptomatic Asthma Exacerbations of Eosinophilic Granulomatosis with Polyangiitis

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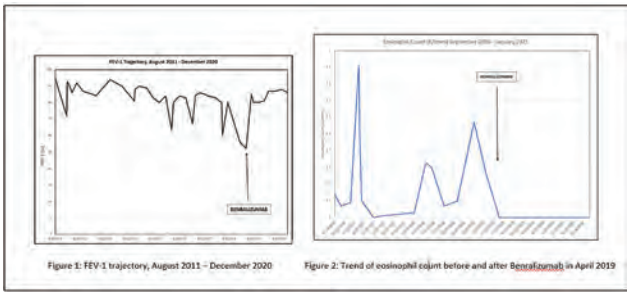
Introduction: There is increasing interest in the use of the biologicals including anti-interleukin 5 and anti-interleukin 5 receptor antibodies in the management of steroid-resistant or steroid-dependent eosinophilic granulomatosis with polyangiitis (EGPA). Benralizumab, an anti-IL 5 receptor antibody is steroid sparing. We describe successful substitution Benralizumab montherapy in EGPA.

Case Description: In late 2005, a 38-year old male was diagnosed with multisystemic illness that included asthma, polyarthrits and nephrotic syndrome. Urine protein creatinine ratio was 11.6 (<0.11) mg/mg. He had 20.3% eosinophils (absolute count 1160 K/cmm) on his differential and erythrocyte sedimentation rate was 50 mm/hour. Standard serology/immunology work up was negative. Serum creatinine was slightly above recent baseline at 1.1 mg/dL and albumin was 2.3 mg/dL. A kidney biopsy demonstrated minimal change disease and EGPA was diagnosed. He achieved early remission with corticosteroids and IV cyclophosphamide and was later continued on combination prednisone and MMF. Nevertheless, he had repeatedly experienced severe asthma exacerbations, falls in FEV-1 and associated eosinophilia (Figure 1). In April 2019, he was started on Benralizumab, 30 mg subcutaneously every 4 weeks for 3 doses and thereafter every 8 weeks. His asthma symptoms resolved, eosinophil count promptly dropped to zero and he was weaned off mycophenolate mofetil and prednisone, 14 and 16 months, respectively, after starting Benralizumab (Figure 2). FEV-1 trajectory has been most impressive with Benralizumab monotherapy (Figure 1).

Discussion: We describe the successful Benralizumab substitution monotherapy in EGPA with eosinophilic asthma. We support calls for larger trials of the biologicals in EGPA.



Composite showing impact of Benralizumab montherapy on FEV-1 (Figure 1) and Eosinophil count (Figure 2) after its introduction in April 2019.

PUB217

Infection-Related Glomerulonephritis: Is It Only Related to Infection?

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Background: Infection-related glomerulonephritis (IRGN) encompass a wide relationship between active bacterial infection and associated glomerular lesion. The treatment relies on eradication of infection. The role of immunosuppression (IS) is still in debate. We aimed to assess factors that could be related to kidney and patient outcomes in a series of IRGN patients.

Methods: Clinical and outcome data from patients >18y, with histologic and laboratory diagnosis of IRGN, were collected retrospectively. Pathologic patterns were reviewed and evidence of simultaneous infection was confirmed.

Results: Fifteen patients (12 male; mean age 70±10y) were included; 33% were diabetic and 33% had alcoholic habits. Median baseline eGFR was 78.7mL/min. All presented haematuria and proteinuria, 53% in nephrotic range. Median SCr at admission was 3.7mg/dL. C3 was decreased in 60% and IgA levels were elevated in 40%. The commonest infection site was skin (47%) and Staphylococcus aureus infection was the most prevalent. The most common pathologic patterns were mesangial (86.7%) and endocapillary proliferative GN (93.3%), 60% with crescentic proliferations. IF showed mesangial and capillary C3 deposits (93%), 60% of cases were IgA-dominant. All patients were treated with antibiotics and 73.3% underwent IS. All developed kidney dysfunction (median SCr 6.1mg/dL), 60% needing RRT. In hospital mortality was 20%. At discharge 26.7% remained RRT-dependent and 46.7% had AKD; only one patient presented total recovery. At 3mo of follow-up (n=12), one new patient had total recovery, 33.3% remained RRT-dependent and 66.7% had median eGFR 40.0mL/min. At 12mo (n=11) one patient died (unrelated cause); 36.3% remained with CKD, 36.3% maintained RRT and 27.3% maintained recovery. Data related outcomes regarding IS and IgA dominance showed that neither influence recovery. During follow-up a new episode of infection was detected in 50% of cases, most of them with AKI associated.

Conclusions: Overall IRGN had poor kidney outcome and it seems that treatment with IS did not improve that, although it is important to highlight that all patients IS-treated had more severe disease. Patients with IgA-dominant IRGN had better eGFR. Our results correspond to a small series of a single centre; therefore, future research is needed to better understand risk factors for outcomes.

PUB218

A Descriptive Study of the Demographic, Clinical, and Biopsy Findings at the Time of IgA Nephropathy (IgAN) Diagnosis

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Background: In patients with IgAN, higher proteinuria, glomerulosclerosis, and tubular atrophy are associated with poor outcomes. We summarize the demographic, laboratory, and biopsy findings of an IgA nephropathy cohort from the US southwest.

Methods: We identified patients diagnosed with IgAN between 2002 to 2016 on whom data was available within 30 days of the biopsy. We summarized the data by calculating n (%), mean (SD), or median (IQR) as appropriate. We compared the clinical data at biopsy stratified on Oxford IgA nephropathy (MEST-C) classification.

Results: We identified 67 patients with IgAN (Figure 1). Approximately half of the cohort was female and most of the patients identified as Hispanic (40.3%) or Native American (22.5%). The mean biopsy age was 37.7 years with a median serum creatinine and spot urine protein to creatinine ratio of 2.35 mg/dl and 3.3 g/g, respectively. Most biopsies had segmental sclerosis (88.5%) and cortical tubular atrophy (62.3%). On the Oxford classification, patients' with M1, E1, and S1 lesions had a lower creatinine level and higher urinary RBCs and serum creatine compared to those with M0, E0, and S0 lesions, respectively (Figure 2a). T lesions were positively correlated with creatinine and proteinuria. The majority of the biopsies stained negative for C1q and positive for C3 on immunofluorescence (IF) microscopy (Figure 2b).

Conclusions: This IgA cohort was predominantly Hispanic or Native American. Most of the patients had established CKD, proteinuria, segmental sclerosis, and tubular atrophy at the time of the diagnosis. At the time of biopsy, higher T lesions were associated with an increased creatinine level and a trend towards increased proteinuria. On IF, C3 was

positive with a negative C1q pointing towards alternate and/or mannose-binding lectin complement pathway activity.

Demographic variables		Laboratory variables	
N; N (%)	67 (100)	Age (Years); mean (SD)	37.7 (15.6)
Female; N (%)	31 (46.3)	Cr (mg/dl); median (IQR)	2.35 (1.80)
Race and Ethnicity; N (%)		Blood on UA; n (%)	
White/Hispanic	13 (19.4)	Large	36 (62.1)
Native American/ Not Hispanic	11 (16.5)	Moderate	7 (12.1)
Hispanic/Unknown	8 (11.9)	Small or trace	13 (22.4)
White/Unknown	7 (10.4)	Negative	2 (3.4)
Unknown/Hispanic	6 (9)	RBCs (per high power field); median (IQR)	21 (86.0)
Native American/Unknown	4 (6)	Spot urine protein to creatinine ratio (g/g); median (IQR)	3.30 (4.7)
Other	15 (26.8)		
Biopsy variables; Oxford MEST Score; N (%)			
M0	29 (47.5)	T0	21 (34.4)
M1	30 (49.2)	T1	24 (37.7)
E0	27 (44.3)	T2	15 (24.6)
E1	32 (55.5)	C0	35 (57.4)
S0	7 (11.5)	C1	22 (36.1)
S1	54 (88.5)	C2	3 (4.9)

Figure 1: Demographic, laboratory, and biopsy variables at the time of the kidney biopsy

	M0 (N=29)	M1 (n=30)	p value
RBCs (per HPF); Median (IQR)	14 (97)	26.50 (75.00)	0.568
UPCR (g/g); Median (IQR)	2.00 (2.40)	5.65 (5.88)	0.085
Cr (mg/dl); Median (IQR)	2.28 (2.40)	1.33 (1.45)	**0.028**
	E0 (N=27)	**E1 (N=32)**	
RBCs (per HPF); Median (IQR)	8 (36.25)	54.50 (129.25)	**0.044**
UPCR (g/g); Median (IQR)	2.65 (3.20)	3.70 (4.90)	0.433
Cr (mg/dl); Median (IQR)	1.70 (1.71)	1.80 (2.04)	0.785
	S0 (N=7)	**S1 (N=54)**	
RBCs (per HPF); Median (IQR)	48.00 (97.00)	21.00 (87.00)	0.336
UPCR (g/g); Median (IQR)	1.60 (5.30)	3.45 (4.38)	0.452
Cr (mg/dl); Median (IQR)	0.90 (0.80)	1.77 (2.41)	**0.039**
	T0 (N=21)	**T1 (N=21)**	**T2 (N=15)**
RBCs (per HPF); Median (IQR)	41.50 (122.50)	36.00 (86.00)	8.00 (16.00)	0.312
UPCR (g/g); Median (IQR)	2.50 (5.30)	3.05 (2.30)	4.40 (4.00)	0.980
Cr (mg/dl); Median (IQR)	0.91 (1.00)	1.81 (1.92)	2.58 (3.05)	**0.000**
	C0 (N=35)	**C1 (N=22)**	**C2 (N=3)**	
RBCs (HPF); Median (IQR)	25.50 (85.25)	28.00 (123.00)	56.00 (54.00)	0.824
UPCR (g/g); Median (IQR)	2.80 (4.10)	3.45 (4.68)	15.70 (23.15)	0.209
Cr (mg/dl); Median (IQR)	1.70 (1.59)	1.60 (3.08)	2.30 (2.65)	0.825

Figure 2c: The association of Oxford classification with urine RBCs (cells/HPF), spot urine protein to creatinine ratio (g/g), and serum Cr (mg/dl) at the time of the biopsy. Kruskal-Wallis rank sum test used for comparisons between groups.

	C1q (Yes/%)	C3 (Yes/%)	p value
Could not be assessed	2 (3.3)	2 (3.3)	<0.001*
Absent	51 (85.0)	2 (3.3)	
Trace	6 (10.0)	3 (5.0)	
1+	1 (1.7)	19 (31.7)	
2+	0 (0.0)	21 (35.0)	
3+	0 (0.0)	14 (23.3)	

Figure 2b: C1q and C3 staining on immunofluorescence microscopy. *Pearson's Chi-squared test

PUB219

Diabetic Nephropathy: A Great Mimicker or Mistaken Identity

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Introduction: Monoclonal gammopathy of renal significance (MGRS) is often a challenging diagnosis due to wide spectrum of disease and difficulty in establishing a pathogenic link between monoclonal proteins and kidney disease. Here, we describe a biopsy 'proven' diabetic kidney disease in a non-diabetic patient, diagnosed as membranoproliferative glomerulonephritis (MPGN) years later with robust clinical response to treatment.

Case Description: A 68-year-old male with stage 3A-B CKD, hypertension and monoclonal gammopathy of uncertain significance (MGUS) was referred to renal clinic for second opinion on biopsy 'proven' diabetic kidney disease in 2013 despite never being a diabetic. A repeat kidney biopsy in 2020 for persistent proteinuria revealed MPGN with segmental subendothelial electron dense deposits (Figure 1). Unfortunately, IF was inconclusive due to inadequate sample. After ruling out other etiologies, he was treated as MGRS with velade and dexamethasone with excellent clinical response with improvement in renal function and resolution of proteinuria (Figure 2).

Discussion: This case brings up an interesting clinical question: could the original diagnosis of diabetic nephropathy be early changes related to MGRS and was it a mistaken identity? Serial kidney biopsies are rarely done in MGRS but could provide guidance as illustrated by our experience.

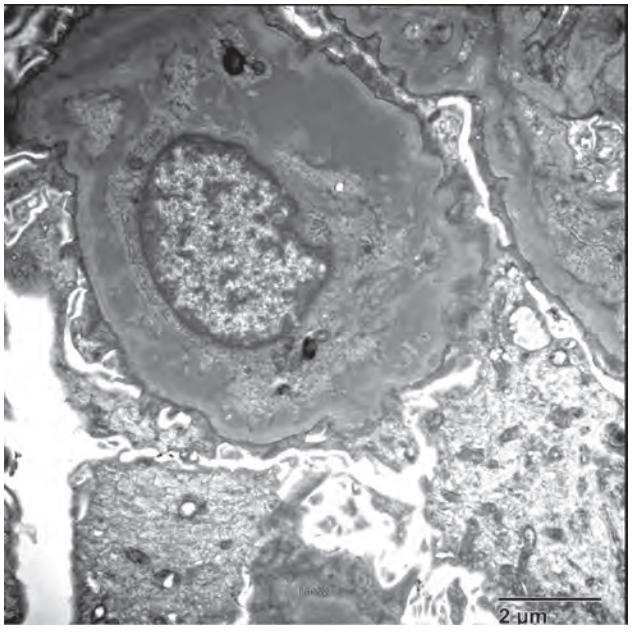
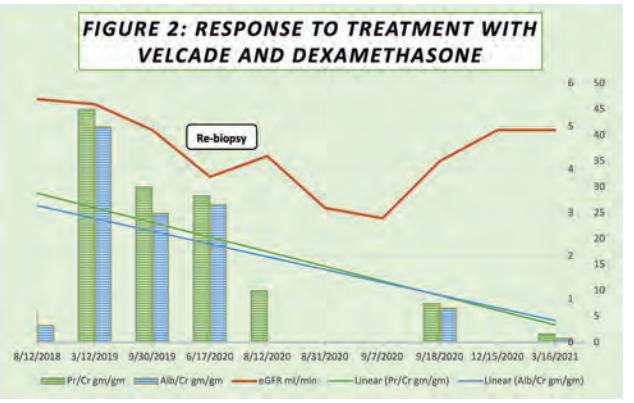


Figure 1: Electron microscopy with sub-endothelial deposits



PUB220

AKI Associated with Anticoagulant-Related Nephropathy in a Newly Diagnosed IgA Nephropathy

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Introduction: Anticoagulant-related nephropathy (ARN) is a type of acute kidney injury (AKI) that may be caused by anticoagulation with warfarin and other anticoagulants. It is an underestimated cause of AKI with poor renal prognosis. AKI is probably resulting from glomerular hemorrhage and the characteristic pathologic findings consist of obstruction of renal tubules by red blood cell casts, which do not contain Tamm-Horsfall protein.

Case Description: A 58-year-old Caucasian man presented with AKI stage 3 (serum creatinine 5.9mg/dL) complaining of macroscopic hematuria. Two months ago, he underwent aortic valve replacement with a mechanical valve and he began taking acenocoumarol as an anticoagulant agent (serum creatinine 0.9mg/dL). He also presented INR 2.2, several dysmorphic erythrocytes in urinary sediment and 24-h urinary protein excretion 5g/day. The renal biopsy revealed mild mesangial hypercellularity, acute tubular necrosis with occlusive red blood cell casts and interstitial inflammation. The immunofluorescence presented mild mesangial deposits of IgA (2+) and C3 (1+). We consider that the cause of AKI was anticoagulant-related nephropathy rather than IgA nephropathy because there was no history of prior infection and the presence of numerous RBC tubular casts could not be explained just by these glomerular findings (mild mesangial proliferation, as well as mild deposits of IgA by immunofluorescence). Due to the severe interstitial nephritis, pos prednisolone 1mg/Kg/daily was added to his treatment, with a gradual reduction in 4 months and acenocoumarol was replaced by tinzaparin. After 1year renal function remains stable at creatinine level 2.5mg/dL, proteinuria <1gr/24h, without microscopic hematuria.

Discussion: This case report highlights an unusual severe cause of AKI "anticoagulant-related nephropathy", in which the majority of patients remains hemodialysis dependent. Patients with underlying glomerulopathies, associated with hematuria are predisposed to be risk factors. Considering the poor renal prognosis, it highlights the necessity for close vigilance of renal function, as well as, urine sediment in patients, who begin on anticoagulation, especially with pre-existing renal diseases, including glomerulopathies and those with glomerular hyperfiltration.

PUB221

Eculizumab for Treatment of Recurrent Pregnancy-Triggered Atypical Hemolytic-Uremic Syndrome with a Mutation in Complement 3: A Case Report

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Introduction: In atypical hemolytic-uremic syndrome (aHUS), thrombotic microangiopathy (TMA) often develops due to mutations in complement-related genes or autoantibodies to complement regulators. Anti-C5 monoclonal antibodies (eculizumab and ravulizumab) are expected to improve prognosis. However, the significance of genetic testing is unknown. We report a case of pregnancy-triggered aHUS that was successful with plasmapheresis and eculizumab administration.

Case Description: A 37-year-old Japanese female who had a twin pregnancy underwent a scheduled cesarean section at 37 weeks gestation. On the second day after her delivery, she developed thrombocytopenia, hemolytic anemia, and renal dysfunction. TMA was suspected, and plasma exchange (PE) was started on the 3rd day after her delivery, and steroid pulse was started on the 4th day, and then prednisolone 60 mg/day was administered. Since Shiga toxin-producing *Escherichia coli* in her stool was negative and both ADAMTS13 activity and inhibitor were normal, the patient was clinically

diagnosed with aHUS. Her clinical findings tended to improve, so PE was interrupted after eight times; however, aHUS relapsed due to a urinary tract infection 15 days after her delivery. We decided that eculizumab was necessary because of the relapse of aHUS due to the infection even under high doses of steroids. Eculizumab was administered 22 days after her delivery, and her clinical findings improved. After that, the pathogenic variant C3 p.Ile1157Thr was identified by genetic testing. Since aHUS due to C3 gene mutation has been reported to have a high recurrence rate, eculizumab administration was continued every two weeks.

Discussion: When thrombotic thrombocytopenic purpura (TTP) and aHUS are suspected in patients with TMA, PE should be started as soon as possible, and eculizumab administration should be considered when aHUS is diagnosed by ADAMTS13 testing. In the case of aHUS, genetic testing is essential because it enables the definitive diagnosis and the prediction of prognosis.

PUB222

Severe AKI: A Case of Histiocytic Glomerulopathy

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Introduction: Histiocytic glomerulopathy(HGP) is a rare and potentially life-threatening cause of acute kidney injury(AKI) which can occur coincident with macrophage activation syndrome(MAS) or hemophagocytic lymphohistiocytosis(HLH). HGP has also been recognized secondary to viral infections and autoimmune diseases(AD). Early identification with renal biopsy(RB) to exclude other forms of rapidly progressive glomerulonephritis(GN) and to initiate prompt treatment is of utmost importance to improve outcomes. We present a case of AKI secondary to HGP in the setting of acute viral illness

Case Description: 52-year-old male with DM, HTN presented(Pre-Pandemic) with 4 days of fever, chills, myalgia with severe hand joint stiffness and pain. On exam, he had hand swelling and tenderness. Labs noted hemoglobin11.9, platelet(plt)69000, bicarbonate(CO2) 23, BUN 47, creatinine(Cr) 3.4 mg/dl, urinalysis(UA) with >1000mg protein, 11 red cells and 10 white cells. UA and Cr(0.8) was normal one year prior. Other tests noted a 24 hour urine protein of 4gm, TSat 12%, ferritin 295, ANA(1:320), anti ds-DNA 1:80, elevated EBV and Parvovirus IgM and IgG, positive EBV nuclear antigen, low C3<8(14-44), C4- 46(88-165), ESR 64 with negative cryoglobulin, hepatitis B, C, anti-GBM, RF, ANCA, urine immunofixation and serum protein electrophoresis. By day 2 of admission, he became oliguric with urine output(UO)<500cc/day, CO2 decline to 19 a hyperuricemia. RB demonstrated endocapillary histiocytes, endothelial cell swelling with mild IgM deposits and 80%foot process effacement. With supportive therapy (IV fluids, holding ACE, analgesics) his arthritis resolved. By day 4, UO increased, SCr improved to 1.5 and plt normalized. Anemia persisted and was treated with IV iron

Discussion: HGP has been reported secondary to acute viral illnesses and may be associated with MAS in the settings of AD and malignancies. When associated with MAS or HLH, multiorgan failure may be life threatening prompting early immunosuppressive treatment. Though rare, HGP should be considered in the differentials of acute GN prompting early renal biopsy. If clinical picture is severe, treatment with steroids and calcineurin inhibitors may be renal and life saving. In our patient, with a more benign course of HGP likely due to EBV, clinical improvement was rapid with supportive care alone. Without RB, appropriate treatment for other forms of GN, microangiopathic injury or vasculitis might have been delayed

PUB223

A Case of ANCA-Associated Vasculitis (AAV) in Patients with Systemic Sclerosis (SSc)

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Introduction: AAV in patients with SSc has been reported rarely. As both diseases can present with renal involvement, diagnosis is challenging. We report the case of a 56 y.o. male with hx of SSc who was admitted for proteinuria AKI found to have biopsy-proven P-ANCA-associated crescentic glomerulonephritis.

Case Description: 56 YOM with PMH of SSc, recent hx of sinus and ear infection and progressive B/L SNHL who presented with systemic symptoms. He was seen by Rheumatology in 2013, found to have + ANA 1:1280 homogeneous, SCL-70 and low C3 and diagnosed with SSc. He has progressive bilateral hearing loss in the past five months with B/L ear discharge and otalgia S/P multiple Abx and steriod courses. On the admission, he was vitally stable. His labs are significant for Cre 13.77 mg/dl from Cre baseline 1.1 mg/dl. UA with hematuria, proteinuria, and pyuria with no casts. UPCR 4.93 mg/dl. Renal US showed with B/L renal enlargement and no hydronephrosis. He started on iHD urgently. Further labs were significant for + ANA 1:1280, SCL70, and MPO 595, C3 is low. Anti-GBM was negative. Hemolysis labs and peripheral smear were negative. A kidney biopsy showed severe allergic interstitial nephritis, focal necrotizing arteritis, and few lesions of focal crescentic glomerulonephritis. He treated with Solumedrol x 3 doses and then started on a Prednisone taper. He received his first dose of Rituximab in the hospital and ultimately had renal recovery. Of note, his hospital course was c/b peripheral parasethesia and EMG showed multiple mononeuropathies, consistent with a vasculitic polyneuropathy. He was discharged and received his second dose of Rituximab. His kidney function, UPCR and MPO titers continued to improve.

Discussion: His AKI is likely related to AAV with overlap SSc. He also has severe interstitial nephritis, which would indicate some drug induced trigger for AAV. There have been rare reports of patients with SSC with ANCA. However, the majority of these patients do not manifest AAV. Studies showed an association between ANCA positivity in patients with SSc and increased mortality and poor prognosis. These findings suggest that ANCA should be tested early in patients with SSc. AAV in SSc is rare with conflicting data about renal outcomes. Rapid recognition is essential for prompt initiation of treatment. Kidney biopsy is the gold standard diagnostic test.

PUB224

ANCA Negative, Yet Pulmonary Embolism Positive

Latoya N. Gayle, Deborah A. Fein. *Englewood Health, Englewood, NJ.*

Introduction: Pauci immunue glomerulonephritis(GN) with negative ANCA serology occurs in ~1/3 of pauci immune GN patients. ANCA negative patients are thought to have a lower incidence of extra-renal involvement but poorer renal prognosis than those who are ANCA-positive. We present a case of ANCA-negative Pauci-immune Rapidly Progressive GN(RPGN), returning 4 weeks after diagnosis with pulmonary embolism(PE)

Case Description: A 39-year-old male presented(pre-pandemic) with 2 weeks of fever and chills. For ~3 years, he has had intermittent arthralgia, dyspnea, facial and ankle swelling with gross hematuria and a 12lb weight gain 2 months prior to admission. Baseline creatinine(Cr) was 1.3(0.7-1.3mg/dl) a month prior. On admission Cr was 2.6, Alb 3mg/dl and Urinalysis noted protein 100mg/dl, RBC 20-30 and WBC 10-20. A 24 hour urine protein measured 8g/day. Serologies were positive for dsDNA1:10 and Antistreptolysin O, with negative ANA, ANCA, anti-GBM, SPEP, Hepatitis B, C, HIV and normal C3/C4. Renal sonogram noted normal sized kidneys with increased echogenicity. A renal Biopsy was done and Methylprednisolone pulse therapy commenced. His renal biopsy showed focal necrotizing and crescentic GN with negative IF, consistent with pauci-immune GN. Cr peaked at 3.6 and IV Cyclophosphamide was given. He was discharged on Prednisone with Rituximab given 2 weeks later.4 weeks after discharge, Cr improved to 1.3, however he represented with SOB, pleuritic chest pain and hemoptysis. CT chest revealed acute bilateral PE. Malignancy work-up and lower extremity dopplers were negative. He had normal IgG, A, M, antithrombin III, prothrombin gene analysis, protein C,S activity and factor X with negative Lupus anti-coagulant and antiphospholipid Ab. He was started, then discharged on Enoxaparin for anticoagulation

Discussion: Renal disease manifests as a pauci-immune GN in ANCA-Associated Vasculitis(AAV).~ 1/3 of patients with pauci immune vasculitis are ANCA negative. Whether these patients should be included in the spectrum of AAV or are a separate pathophysiologic mechanism is unknown. Our patient presented with RPGN and a PE after initial treatment despite negative ANCA panel and current evidence suggesting a lower incidence of other organ involvement. The presence of an underlying pulmonary vasculitis could not be excluded. We postulate that all patients with ANCA negative RPGN should be followed for additional organ involvement and further study of this patient population is warranted

PUB225

Autologous Mesenchymal Stromal Cell Therapy for Idiopathic Nephrotic Syndrome: The MESNEPH Study

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Background: Corticosteroids represent first-line treatment of idiopathic nephrotic syndrome (INS). However, 60-80% of patients present multiple relapses and require steroid-sparing immunosuppression with significant toxicity. New therapeutic approaches with a better safety profile are needed. Mesenchymal stromal cells (MSC) exert immunomodulatory functions, regulating cells of both adaptive and innate immune systems.

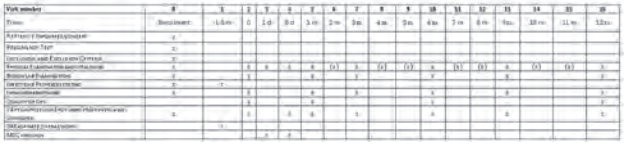
Methods: Approximately 20 patients (age-range 5-40 years) with multi-relapsing INS (≥2 relapses despite prednisone and/or ≥1 other immunosuppressive steroid-sparing agent) in remission will be recruited. After screening and informed consent, a bone marrow aspirate will be performed, followed by a 6-12 week MSC-expansion period during which oral immunosuppression will be maintained. Each patient will receive 2 intravenous infusions of 1-2x10^6/kg autologous MSCs 7 days apart. One month after the first infusion, all concomitant immunosuppressive therapy will be tapered and withdrawn. The observational phase will last 12 months after the first MSC infusion (Table 1). This is a prospective, phase 1 open-label non-randomized multicentric study evaluating the safety and efficacy of autologous bone-marrow derived MSC treatment in patients with severe frequently-relapsing or steroid-dependent INS.

Results: The study is ongoing, last patient visit is expected in July 2021.

Conclusions: The study will primarily assess the feasibility and safety of this approach for the treatment of severe INS. Secondarily, it will evaluate treatment effect on INS relapses, immunosuppressive therapy dose and toxicity, kidney function at baseline and 12 months after MSC infusion.

Funding: Government Support - Non-U.S.

Table 1



PUB226

Safety and Efficacy of Avacopan (CCX168) in a Pediatric Patient with C3 Glomerulopathy

Marina Vivarelli, Maria Arena, Federica F. Zotta, Andrea Cappoli, Ines D. L'Erario, Marco Busutti, Francesco Emma. *Division of Nephrology and Dialysis - Bambino Gesù Pediatreic Hospital IRCCS, Rome, Italy*.

Introduction: C3 glomerulonephritis (C3GN) is a subtype of C3 glomerulopathy, characterized by alternative pathway complement activation and intense C3 immunofluorescence on renal biopsy. C5a is a potent pro-inflammatory mediator of the complement system, whose chemotactic effects are mainly mediated by the interaction with complement C5a receptor (C5aR) expressed on the cell surface. Avacopan is an orally administered selective inhibitor of C5aR.

Case Description: An 11-year-old female with biopsy-proven C3GN was initially treated with three intravenous (IV) boluses of methylprednisolone then tapered to oral prednisone (PDN) given with mycophenolate mofetil (MMF) and an angiotensin-converting enzyme inhibitor (ACE-i). Complete remission was achieved, PDN was stopped, and MMF and ACE-i were maintained. Twelve months following remission, due to relapse of proteinuria (urinary protein/creatinine ratio [UPCR] 1.19 mg/mg), a second course of PDN therapy was started and cyclosporin (CyA) was added to the therapy. A high level of C5b9 was found. Since the patient never achieved complete remission, she was enrolled in the ChemoCentryx ACCOLADE study, which was a randomized, double blind, placebo controlled study. Patients received avacopan or matching placebo for the first 26 weeks, followed by open-label avacopan in all patients for the following 26 weeks. At the end of the open-label phase, her UPCR was 2.09 mg/mg. Following avacopan, a progressive reduction of proteinuria of approximately 0.5 mg/mg was observed. In the last 4 weeks of the study, avacopan was discontinued, and an increase in proteinuria (UPCR 0.7 mg/mg) was observed, which continued to >1 mg/mg in the subsequent weeks. The patient also reported increased fatigue. After about 3 months, authorization for compassionate use of avacopan was obtained and the patient experienced improvement in her physical well-being and a reduction of proteinuria of approximately 0.5 mg/mg. CyA was discontinued, but it was rapidly reintroduced due to a transient increase of proteinuria. In the following months, proteinuria remained low despite the interruption of MMF. At the last follow up (+16 months from open-label start) UPCR was 0.29 mg/mg and the drug was well tolerated.

Discussion: To the best of our knowledge, this is the first report on the use of avacopan in a pediatric case of C3GN.

PUB227

Rituximab for Steroid-Dependent Minimal Change Disease in Adults

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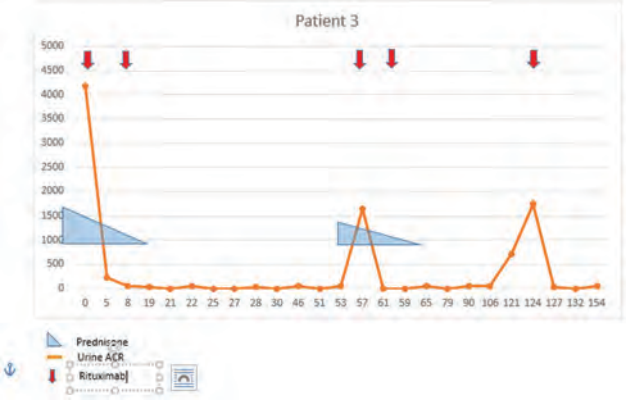
Introduction: Minimal change disease (MCD) accounts for 15% of adult nephrotic syndrome, out of which 25% have frequently relapsing nephrotic syndrome and 30% become steroid dependent. Here we report four cases of relapsing or steroid dependent MCD in adults who were treated with rituximab and their long term follow up.

Case Description: Retrospective chart review of 4 adult patients with relapsing or steroid dependent minimal change disease treated with rituximab at the University of Virginia with more than 6 months follow up following rituximab infusion.

Discussion: The table shows a summary of demographics and laboratory values for these patients. All four patients achieved complete remission and remained steroid free, at least 18 months following treatment with rituximab, although 2 had relapses that responded to another dose of rituximab. One case was treated with immunosuppressive drugs for decades and had developed several complications.

CLINICAL CHARACTERISTICS OF THE PATIENTS

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Female	Male	Male
Age at diagnosis	78	69	5	22
Age at the time of rituximab infusion	80	69	22	23
Duration of follow-up	4 years	1 year	9 years	3 years
Serum Cr, presentation	1.2	3.6	1	1.5
Urine ACR (mg/g)	8600	11900	4200	4600
Previous Rx	-	-	Cyclosporine + Prednisone	-
Biopsy	Normal LM, severe foot process effacement on EM	Diffuse foot process effacement superimposed on arterionephrosclerosis	Normal LM, severe foot process effacement on EM	ATL mild mesangial expansion, mesangial IgA(3+), C3 (2+, IgM (2+, IgG (1+), severe foot process effacement on EM
Number of rituximab infusions	3	2	5	1
No. of relapses after rituximab	2	0	1	0
Duration of remission after last dose of rituximab	19 months	12 months	18 months	14 months



PUB228

Dapsone-Induced Methemoglobinemia in a Patient with Minimal Change Disease

Misha Varma, Khaled Shawwa. *West Virginia University, Morgantown, WV*.

Introduction: Dapsone is commonly used as a second line medication in treatment and prevention of pneumocystis pneumonia. Its use has been associated with life-threatening conditions, namely methemoglobinemia.

Case Description: A 34-year-old female presented to Nephrology clinic for evaluation of proteinuria in the setting of weight gain. She had 4 prior pregnancies with one complicated by HELLP and another by preeclampsia. A week prior to presentation, she reported waking up with significant swelling in her face and legs. She had a protein to creatinine ratio of 12 grams/gram of creatinine at her primary care's office. Her serum albumin was 1.9 gram/deciliter. Her other serological workup was negative or normal. Her hemoglobin A1C was 5.1%. The patient does not take NSAIDs or OTC medications. A kidney biopsy showed minimal change disease. Prednisone was started at 1mg/Kg along with Atovaquone for PCP prophylaxis. Patient had a prior history of anaphylactic reaction to Bactrim. Given COVID19 pandemic, Pentamidine administration has been restricted due to droplet isolation. Atovaquone was subsequently replaced with Dapsone due to poor palatability. The patient was hospitalized for worsening dyspnea with new oxygen requirement two weeks later. Her oxygen partial pressure at room air was 32 mmHg with a normal A-a gradient. She had lost 10 pounds and was no longer on diuretics. The patient was euvolemic on exam. An echocardiogram was unremarkable. A CTA of the chest to assess was negative for pulmonary edema and pulmonary embolism. The patient had new anemia (hemoglobin was 11.3 from a baseline of 14 g/dL). She did not have signs of hemolytic anemia (LDH, bilirubin, haptoglobin and peripheral smear were normal). Her methemoglobin levels were then tested given recent initiation of dapsone and were found to be elevated at 11.5%. Dapsone was consequently discontinued, and she was transitioned back to Atovaquone after taking it with food. Discontinuation of dapsone resulted in significant symptomatic improvement without further need of supplemental oxygen.

Discussion: Methemoglobinemia a is rare but serios adverse event of Dapsone. Teaching points: - Knowledge about options for PCP prophylaxis is essential when using high dose steroids in the treatment of glomerular diseases. - It is important to counsel and monitor patients being started on Dapsone for potential side effects (hemolytic anemia and methemoglobinemia).

PUB229

Kidney Function in Patients with Lupus Nephritis Followed Up for a Very Long Time

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Background: Most investigations of long-term kidney outcomes in patients with lupus nephritis (LN) focus on end-stage kidney disease (ESKD), but seldom on the proportion of patients left with chronic kidney disease (CKD). Both CKD and lupus are non-traditional risk factors for cardiovascular morbidity. We therefore looked at the development of CKD in a subset of LN followed for a very long time in an LN clinic.

Methods: A retrospective chart review was conducted in biopsy-proven LN patients followed for ≥10 years in a single-center, multidisciplinary LN clinic. Patients with CKD were defined as having an eGFR <60 ml/min/m^2, and those with ESKD as having an eGFR <15 ml/min/^{2} or requiring permanent kidney replacement therapy. eGFR was determined by the clinical laboratories the patients used and was race adjusted. Results were analyzed with descriptive statistics.

Results: 72 patients were followed for a median of 17.1 years (range 10 to 38.7) after LN was confirmed by kidney biopsy. The mean (± standard deviation, SD) age at diagnostic biopsy was 31.8±14.1 years. 21 patients were of African ancestry, 4 were Asian, and 47 were White. ESKD developed in 12 patients (16.7%) after a median of 14.6 years. At the time of last follow-up, 27 patients (37.5%) had CKD with a mean (±SD) eGFR of 40.4±13.0 ml/min/1.73m^2. Of the 27 patients who developed CKD, 21 experienced at least one episode of eGFR <50 ml/min/1.73m^2 that lasted for at least 6 months. Of the other 6 CKD patients, 4 (67%) had at least one 6 month (or longer) episode of proteinuria >3.5 g/d.

Conclusions: These data suggest that over 50% of LN patients may be at risk for developing ESKD or CKD if followed for 10 or more years. Almost all of these patients had sustained periods of kidney injury resulting in eGFR <50 ml/min/1.73m^2, nephrotic-range proteinuria, or both preceding ESKD or CKD. Immunosuppression may not be sufficient to prevent CKD in LN. These patients may benefit from intense anti-progression therapy.

PUB230

Staphylococcus aureus Infection-Related IgA Vasculitis with Kidney Involvement

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Introduction: IgA Vasculitis (IgAV), a systemic small vessel vasculitis with IgA dominant/co-dominant immune deposits, is characterized by purpura, arthralgias, and kidney involvement (IgAV with nephritis; IgAV-N). *Staphylococcal*, including methicillin-resistant *Staphylococcus aureus* (MRSA), infection with glomerular IgA deposits known as IgA-dominant infection related glomerulonephritis (IgA-IRGN), is a variant of IRGN whose management remains controversial.

Case Description: A 46-year-old White male with diabetes, lumbar discitis with recurrent MRSA bacteremia, and normal kidney function [baseline SCr 0.7 mg/dl] presented with bilateral lower extremity palpable purpura and petechiae, polyarthralgia, diarrhea; without urinary complaints. Concomitant MRSA bacteremia without an adequate source (despite interrogation of lumbar hardware) or evidence of endocarditis was found. Skin biopsy revealed leukocytoclastic vasculitis with direct IF (+) for IgA, C3, and fibrin confirming IgAV. Urinalysis revealed nephritic sediment. Sr albumin was 2.3 g/dl; random UPCR was 3 g/g. Workup including lupus serologies, cryoglobulins, ANCAs, Anti-GBM, RF, ASO, Hepatitis B/C, HIV, paraproteinemia testing were negative. Complements were normal. SCr on admission was 0.8 mg/dl; peaked to 1.4 mg/dl on the 3rd hospitalization day likely in setting of contrast-related AKI, multifactorial ATN, and potential IgAV-N secondary to MRSA infection. He was started on IV vancomycin, IV methylprednisolone, IVIG, and dapsone. SCr returned to baseline on 5th day. Oral prednisone 60 mg/d with a rapid taper was started. Rash, kidney function, and proteinuria improved; hence a kidney biopsy wasn't pursued. Blood cultures turned negative; he was discharged on IV daptomycin/ceftaroline and prednisone taper X 6 weeks.

Discussion: Kidney histopathological features of IgA-IRGN are similar to those of IgAN/IgAV-N. Correct diagnosis is imperative as IgAN and IgAV-N likely necessitate immunosuppressive (IS) treatment, while initial IS can exacerbate infection in IgA-IRGN. In our patient, skin biopsy clinched diagnosis of IgAV, and was treated with IS given widespread systemic disease, and antibiotics, with rapid improvement of kidney function abating need for kidney biopsy. Individualized approach for the management of IgA-IRGN is therefore warranted.

PUB231

Treatment Dilemma of Immune Complex Deposition of Unclear Significance in Hypocomplementemic Urticarial Vasculitis Syndrome

Kara Kaplan, Rima Kang. *The Ohio State University Wexner Medical Center, Columbus, OH.*

Introduction: Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare autoimmune disorder with recurrent urticaria, glomerulonephritis, and arthritis. Literature reports 50% or more of patients with HUVS have renal involvement that can be delayed up to a decade after diagnosis and portends a poorer prognosis. Treatment is aggressive immunosuppression.

Case Description: 36 year old female with HUVS diagnosed July 2020 and anxiety was admitted in April 2021 with HUVS flare and intermittent microscopic hematuria. Rheumatology and Dermatology followed. Vitals remained stable. Euvolemic with unremarkable exam, no rash. No signs of systemic lupus erythematosus. Creatinine 0.5mg/dL and hemoglobin 8-9mg/dL, at baseline. Urinalysis: moderate blood, RBC >20/hpf, no WBCs, no bacteria. 24 hour urine PCR 0.20. Renal ultrasound unremarkable. Urine sediment negative for dysmorphic RBCs or casts. Negative infectious workup. Glomerulonephritis workup: positive ANA 1:320 speckled, C3 64mg/dL, C4 18mg/dL, beta 2 glycoprotein IgM antibody 73.3 cu. Remainder of workup negative. Renal biopsy with scattered mild glomerular immune complex deposition, mildly thickened arteries but no active disease. Due to unclear significance of renal pathology and patient preference, no further immunosuppression pursued other than hydroxychloroquine with frequent lab monitoring. One month after discharge, HUVS skin manifestations worsened and she was started on mycophenolate mofetil 1000mg BID at the time of writing.

Discussion: There is a high rate of kidney involvement in HUVS. Early HUVS renal involvement can manifest as intermittent microscopic hematuria, such as this case. The patient also had rare immune complex deposition in HUVS. Renal biopsies may capture this early, subclinical disease. This can lead to a treatment dilemma of whether to wait for renal disease progression to become clinically significant or to treat subclinical disease with non-regimented immunosuppressants with the quandary of how to monitor therapy response, such as frequent renal biopsies. Renal biopsy monitoring is not ideal in all patients, especially those with anxiety; therefore, expectant monitoring was pursued. Due to the rarity of the disease, there is no standard treatment for HUVS renal involvement. More research is needed to determine optimal therapies, especially for subclinical disease.

PUB232

Treatment with Rituximab in Patients with Idiopathic Membranous Nephropathy: A Case Series and Literature Review

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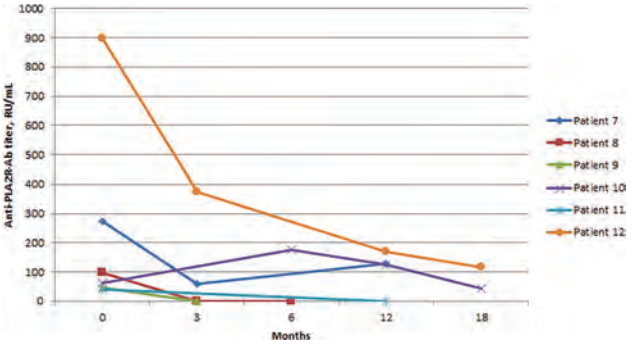
Background: Membranous nephropathy (MN) is a major cause of nephrotic syndrome in adults. This study aimed to evaluate the effect of rituximab (RTX) in patients with idiopathic MN (iMN) who have a high risk of progression.

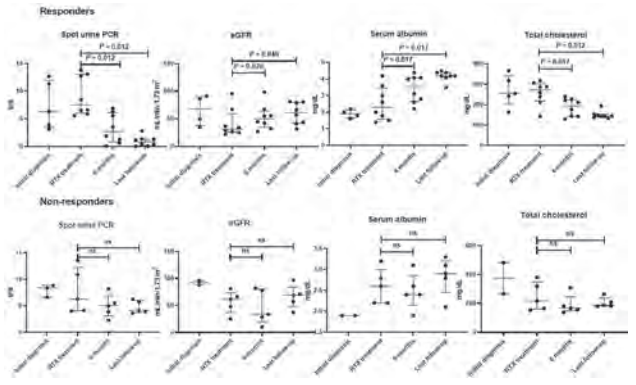
Methods: We retrospectively analyzed data of 13 patients with iMN, who received RTX treatments from January 2014 to July 2020. RTX was indicated in patients with iMN with severe proteinuria and decreasing estimated glomerular filtration rate (eGFR) in the previous 6 months despite other immunosuppressive therapy.

Results: The patients were predominantly male and with a mean age of 55.3 years, median eGFR, 37.0 mL/min per 1.73 m^2 (interquartile range [IQR], 26.3–66.5); serum albumin level, 2.6 g/dL (IQR, 1.9–3.1); and spot urine protein-to-creatinine ratio at baseline, 6.6 g/g (IQR, 5.7–12.9). In a median follow-up of 22 months, 8 patients (61.5%) achieved complete or partial remission. In responder group (n = 8), median eGFR increased from 31.5 to 61.5 mL/min/1.73m^2 (p = 0.049) and serum albumin level increased from 2.3 to 4.2 g/dL (p = 0.017) from RTX initiation to last follow-up. Antiphospholipase A2 receptor antibody (anti-PLA2R-Ab) was positive in 6 among 7 tested patients, which markedly decreased in responder group. There were no adverse events after RTX.

Conclusions: This study suggests that RTX is a safe and effective treatment option for patients with iMN who have a high risk of progression. Individualized therapy based on anti-PLA2R-Ab titer would be needed for better outcomes.



Changes in antiphospholipase A2 receptor antibody of each patient.



Changes in outcomes between responder group and non-responder group.

PUB233

Sometimes an Ultrasound Scan Before the Kidney Biopsy Is Enough: An Unexpected Case of Rapidly Progressive Renal Failure(RPRF)

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Introduction: RPRF is a clinical diagnosis in patients with progressive renal impairment of short duration. The underlying etiology may be a primary renal disease or a systemic disorder. Early definitive diagnosis of RPRF is essential to reverse progression to end-stage kidney disease.

Case Description: Male patient, 64 yo, referred to us after hospitalization elsewhere for RPRF with nephritic-like syndrome. PMH: DM2 history. At age 58 (2015) aortic valve replacement with bioprosthetic valve for severe stenosis. HPI: after 4 months of persistent low-grade fever with a TIA, in March 2021 the patient referred to the ER for epigastric pain and fever. A worsening of renal function was found (creatinine 2.3 mg/dl). During hospitalization, further renal function worsening (creatinine 6.1 mg/dl) and a positive blood culture for E.faecalis treated with amoxi/clav. Renal biopsy was planned. On 03/26/21 the patient was admitted to our clinic, we detected creatinine 6.2 mg/dl, proteinuria <1g/day, normal serologic workout. Urinary sediment revealed dysmorphic erythrocytes. At abdominal ultrasound: kidneys of normal dimensions, hyperechoic, reduced cortico-medullary differentiation, normal vascular resistance. The same procedure revealed hypoechoic splenic lesions due to probable ischemia. On physical examination severe systolic heart murmur. Transesophageal echocardiogram showed an infective endocarditis on the prosthetic aortic valve, so renal biopsy was not performed because cardiac surgery was mandatory. He started antibiotic therapy with ceftriaxone and ampicillin, after 2 weeks renal function improved (3.8 mg/dl). On 05/04 he underwent valve substitution with a mechanical prosthesis. Discharged on 05/26 with creatinine 3.14 mg/dl.

Discussion: Clinical history and carefully evaluation of radiological and serological investigations are mandatory before kidney biopsy. Unfortunately without a renal biopsy it is not possible to have a precise diagnosis.

Etiopathogenetic hypotheses of our case nephropathy

	Present signs	Absent signs
Post-infectious glomerulonephritis	dysmorphic hematuria, proteinuria <3 g/day	15 days after infection onset, C3 consumption, oedema, hypertension
Rapidly progressive glomerulonephritis	dysmorphic hematuria, loss of renal function >50% in a short period, proteinuria <1g/day	ANCA pos, complement consumption, therapy needed for renal function improvement
IgA nephritis	dysmorphic hematuria, proteinuria <2 g/day, complement normal levels, hyperchromic urine	48h after respiratory or gastrointestinal infection onset, IgA high levels
Endocarditis-associated glomerulonephritis	microhematuria, moderate proteinuria, renal function improvement during antibiotic therapy	Rarely with rapidly progressive manifestations, complement consumption, circulating immune complexes, elevated rheumatoid factor, type III cryoglobulinemia
Septic embolization	hematuria, proteinuria <3g/day; marked loss of renal function, only partial improvement	No spontaneous improvement of renal function, embolism/indirect signs evidence

PUB234

A Case of Malignancy in NELL-1 Membranous Nephropathy

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Introduction: The predominant target antigen for primary membranous nephropathy (MN) has been Phospholipase A2 receptor (PLA2R), which is present in approximately 70% of cases. Neural epidermal growth factor like 1 protein (NELL-1) was recently identified as one of four new antigens in a distinct type of primary MN. NELL-1 membranous nephropathy was found to be the first candidate antigen highly prevalent in malignancy associated MN, seen in nearly 33% of all cases. We will review a case of NELL-1 membranous nephropathy.

Case Description: A 54-year-old Caucasian female presented from her PCP's office with shortness of breath, left flank/lower back pain, and bilateral lower extremity edema for four days. Physical exam exhibited BP 170/99 mmHg, nontender cervical lymphadenopathy (LAD), left CVA tenderness, and 2+ pitting edema. Initial lab studies were significant for elevated D-dimer, hypoalbuminemia (Alb 1.7g/dL), and nephrotic range proteinuria (UPCR 13.5g). Imaging revealed bilateral subsegmental pulmonary emboli, a left renal vein thrombosis, and extensive bilateral LAD (axillary, supraclavicular, mediastinal, and left periaortic retroperitoneal). Given concerns for a podocytopathy due to a possible lymphoma, the patient underwent an unremarkable extensive serologic workup and a renal biopsy. Her biopsy revealed NELL-1 membranous nephropathy, with diffuse (3+) fine granular staining along glomerular capillary loops for NELL-1 and numerous subepithelial deposits with severe foot process effacement. The patient underwent a bone marrow biopsy, excisional right axillary/cervical lymph node biopsies, PET scan, infectious work up, and age-appropriate malignancy screenings, which were all non-diagnostic for a malignancy. Her biopsies showed reactive lymphadenopathy with concern for evolving B-cell lymphoproliferative disorder with plasmacytic differentiation. Given her biopsy findings and NELL-1 MN, the patient was treated with rituximab.

Discussion: NELL-1is a rare emerging subtype of MN that has been identified in both primary MN and malignancy associated nephropathy. A thorough malignancy workup is warranted in all patients diagnosed with NELL-1 MN. More research is needed in the association between NELL-1 and specific cancers, in hopes of guiding future treatments for this disease.

PUB235

Vitamin D Status and Its Association with PTH in 73645 Caucasian Outpatients

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Background: 25-hydroxyvitamin D (25(OH)D) inhibits the synthesis of PTH. However, the limited size of clinical studies to date has only allowed a relatively crude analysis of the relationship between 25(OH)D and PTH.

Methods: We investigated this relationship in 73645 patients (Figure 1).

Results: The relationship between 25(OH)D and iPTH has three phases: an initial drop in iPTH (25(OH)D: 0~20 ng/ml); a horizontal phase (25(OH)D: 20~60 ng/ml): a final drop in iPTH (25(OH)D: ≥60 ng/ml). A Cox regression analysis of these three phases considering age, sex, 25(OH)D, calcium, phosphate, and creatinine showed that in the initial phase age (RR: 0.20 ; CI: 0.09~0.31, p<0.0001), sex (RR: 15.84; CI: 11.40~20.28; p<0.0001), 25(OH)D (RR: -1.73; CI; -2.22~-1.25; p<0.0001), and creatinine (RR: 45.52; CI: 42.87~48.16; p<0.0001) are independently correlated with iPTH, whereas in the second horizontal phase age (RR: 0.14 ; CI: 0.09~0.20, p<0.0001), sex (RR: 14.84; CI: 13.01~16.66, p<0.0001), calcium (RR: -10.73; CI: -17.81~-3.64; p=0.003), phosphate (RR: -19.19; CI: -23.46~-14.92; p<0.0001), and creatinine (RR: 46.36; CI: 45.30~47.41, p<0.0001) are relevant. In the third phase, only sex (RR: 17.94; CI: 5.38~30.50, p=0.005) and creatinine (RR: 42.07, CI: 35.39~48.74, p<0.0001) play a significant role. Analyzing the relation between iPTH and 1,25-dihydroxyvitamin D (1,25(OH)2D) in a subset of the study (N=2441) revealed that serum 1,25(OH)2D concentrations have no effect on iPTH concentrations in subjects with normal kidney function.

Conclusions: In conclusion, circulating 1,25(OH)2D does not contribute substantially to the regulation of iPTH in healthy subjects. Presumably, serum 25(OH)D that is converted to 1,25(OH)2D after megalin-mediated uptake in the parathyroid chief cells plays the critical role. The relationship between 25(OH)D and iPTH has three phases. Factors correlating independently with PTH in the different phases differ substancially. 25(OH)D is only relevant in the first initial phase.

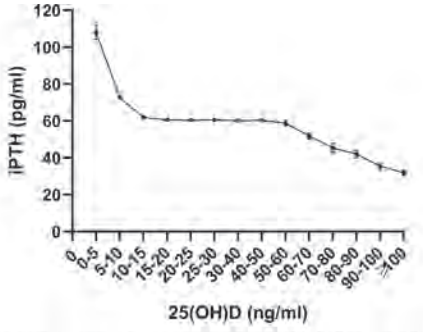

Figure 1. Relationship between serum 25(OH)D and iPTH (Mean ± SEM).

PUB236

Metabolic Features of Patients Older than 80 Years Receiving Total Parenteral Nutrition (TPN)

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Background: Advances in surgical and interventional techniques has extended the use of TPN in patients unable to receive enteral support. Metabolic abnormalities in "elderly" individuals receiving TPN has been reported > 65 yo but few focusing on > 80.

Reduced GFR, low muscle mass, and multiple comorbidities create unique management challenges. Use of a multidisciplinary approach as described may mitigate TPN associated electrolyte derangements and mortality. For this retrospective study we report some of the clinical parameters associated with "extreme" elderly patients receiving TPN.

Methods: A TPN team consisting of a nephrologist/intensist, abdominal/critical care surgeon, dietician and surgical PA met daily at 1030 to consider all referrals and create orders by 1230 for a TPN specialty pharmacist review followed by administration at 1730. 38 patients between 1/1/2019-12//15/2020 receiving CENTRAL parenteral nutrition (no PPN) were included. Metabolic complications of 1 or more times were reported.

Results: Baseline Characteristics (n=38) Gender: 45% male, 55% female Mean Age (range): 86 years (80-98 years) BMI <19 kg/m2: 18% BMI 30-39 kg/m2: 24% Severe Malnutrition: 66% HbA1c >6.5%: 5% GFR <60 mL/min/1.73m2: 34% TPN Characteristics Mean days on CPN (range): 14 days (4-39 days) Mean energy dose: 26.7 kcal/kg Mean protein dose: 1.7 gm/kg Caloric distribution: 26% protein, 50%CHO, 24% lipid Metabolic Complication%(n = 38) Hyperglycemia (blood glucose >200 mg/dL) 50%(19) Hypoglycemia (blood glucose <60mg/dl)3%(1) Hypertriglyceridemia (>400mg/dL)0%(0) Hypokalemia (<3 mEq/L)8%(3) Hypophosphatemia (<2 mg/dL) 18%(7) Hyponatremia (<135 mEq/L)63%(24) Hypernatremia (>145 mEq/L)24%(9) Low potassium (< 3.5 mEq/L) in 1st 2 days on TPN 32%(12) Low phosphorus (<2.5 mg/dL) in 1st 2 days on TPN 34%(13)

Conclusions: Expected "refeeding" hypo K and PO4 were observed but critical levels <2 and 1.5 respectively and early fatalities not encountered given daily monitoring and aggressive supplementation. Very frequent hyponatremia largely of the "SIADH Type" was mitigated by fluid restriction and/or high osmolar load. Na levels < 125 or >150 were not seen after initiation of TPN. We believe that a concerted multidisciplinary team approach is extremely useful in provision of the high risk "TPN medication".

PUB237

Comparison of the Triglyceride and Glucose Index in Predicting CKD Among Hypertensive Population: Six Southern China Community Cohorts

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Background: Hypertension (HTN), as a major disease concern around the world that impacts middle-age and elderly population. We intend to explore the relationship between HTN and CKD through a new insulin-related index: Triglyceride and glucose index (TyG).

Methods: A cross-sectional cohort study of six populations in the southern coastal town of Wanzhai (Zhuhai, China) was carried out over 4 months. Group assignment criteria were: Systolic Blood Pressure (SP) ≥140mmHg with or without a Diastolic Blood Pressure (DP) ≥90mmHg or self-reported currently under treatment with anti-hypertensive medications for the hypertensive case group; while the control group population had normal blood pressure and no previous history of HTN. CKD was defined with the following criteria for diagnosis: urinary albumin/creatinine ratio (ACR)≥30mg/g with or without an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2.

Results: Lipid and glucose metabolic index TyG showed a correlation with the occurrence of CKD in the hypertensive population. In binomial logistic regression analysis, the risk of occurence of CKD was 1.503 (odds ratio) with the 95% confidence interval (CI) of each standard deviation of TyG lying between 1.127-2.003 (p<0.05). Area under the curve (AUC) of a receiver operating characteristic (ROC) was 0.5807 (p<0.001; 95% CI: 0.5337–0.6278), showing the utility of TyG as a prognosticator of CKD in people with HTN.

Conclusions: TyG may predict the prevalence of CKD occurence among hypertensive population of Southern China.

PUB238

Renal Artery Stenosis: Ticking Bomb

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Introduction: Untreated renal artery stenosis leads to poorly controlled and difficult to manage hypertension, congestive heart failure, and progression of renal disease. A high index of suspicion is essential for clinical diagnosis and to potentially reverse a condition with narrow time window.

Case Description: 82-year-old female with poorly controlled blood pressure, 27 pack year smoking history, quit 2007 was evaluated for worsening creatinine of 2.64 mg/dL, eGFR 16, 8/24/2020 (cr 1.29 mg/dL, eGFR 37,11/5/2019). Each time a RAAS antagonist was given, this would result in decreased renal function and would improve off it. Blood pressure 180/90, BMI 28, +2 edema. Labs: proBNP 9,317 pg/ml, LDL 137 mg/dl, Protein creatinine ratio 1.588 mg/g, 3+ dipstick. Serology for proteinuria was negative. Renal ultrasound: right kidney 8.7cm with cortical tissues are echogenic and markedly thin consistent with areas of atrophy and left kidney 10.5 cm with normal cortical thickness and echogenicity. Renal duplex: aortic velocity 95.4cm/s peak systolic, right renal artery 134.5cm/s peak systolic and left renal artery 386.8cm/s peak systolic. Resistive index right kidney average of 0.55 and left kidney 0.72. Renal artery to aortic velocity ratio 1.4 on right and 4.1 on left. Echo: moderate to severe concentric LVH, abnormal diastolic relaxation. After left renal artery stent placement, her creatinine was 1.31 mg/dL from 2.11 mg/dL. A month later after addition of losartan to carvedilol and Lipitor her creatinine was 1.2 mg/dl eGFR 42, protein creatinine ratio 745 mg/g with no edema, "more energy" and blood pressure 110/60.

Discussion: She has solitary left functioning kidney due to right renal atrophy. When RAAS antagonist was introduced her kidney function deteriorated demonstrating it was dependent on angiotensin, behaving as bilateral stenosis. She developed poorly controlled hypertension, edema, proteinuria, LVH and diastolic dysfunction. Combination of ultrasound and duplex showed a window of opportunity to intervene on viable kidney tissue with an atherosclerotic lesion. She was safely placed on ARB to further reduced her risk of progression of renal and heart disease.

Renal Artery Stenosis

PUB239

Epithelial Overexpression of Human ACE2 in Mice as a Model for Studying Renal Disease

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Background: ACE2 is an integral part of the renin angiotensin system (RAS) and is highly expressed at the brush border of epithelial cells of the renal proximal tubule. Within the lumen, ACE2 is poised to metabolize angiotensin II and extinguish its effects as part of the counter-regulatory arm of the RAS. Use of transgenic mouse models has been essential in exploring the cardiovascular and renal functions of ACE2. Limitations in using mouse models for SARS was overcome by generation of mice expressing human ACE2 (hACE2) downstream of the keratin 18 promoter (K18-hACE2) by McCray *et al* 2007. K18-hACE2 mice express hACE2 in epithelial cells throughout the body and have proved valuable for the study of SARS-CoV and CoV2 viral infectivity and pathogenesis. Here, we investigate whether K18-hACE2 mice might serve as a unique tool with which to study the role of ACE2 in the intra-renal RAS.

Methods: We assessed ACE2 activity in urine collected from K18-hACE2 mice (obtained from Jax and bred in our own colony) and their wildtype littermates. Urine was collected over 24 hours in individual metabolic cages, and enzymatic activity was determined using an ACE2 activity assay. Duplicate samples tested for each animal.

Results: Our lab has a longstanding interest in the role of ACE2 in the kidney and our preliminary experiments demonstrate that K18-hACE2 mice have significantly increased ACE2 enzymatic activity in the urine compared to wildtype littermates (1597.0±379.74 vs 396.0±143.92, p=0.013).

Conclusions: The increased urinary ACE2 activity suggests that there are elevated levels of ACE2 reaching the kidney. While this seems most likely due to increased expression of renal epithelial ACE2, soluble ACE2 derived elsewhere and able to reach the lumen of the nephron must also be considered. Thus, K18-hACE2 mice with increased urinary ACE2 activity can serve as a model to examine the effect of ACE2 and the RAS on kidney diseases such as hypertension and acute renal injury.

Funding: Other NIH Support - NIH TL1 TR002371, 5T32GM109835-03

PUB240

Nephrotic Syndrome Secondary to Paraneoplastic Syndrome of Leukemia

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Introduction: Paraneoplastic glomerulopathies are rare manifestations of neoplastic disease that must be differentiated from iatrogenic renal injury. Nephrotic Syndrome is one of the most frequent presentations of paraneoplastic glomerulopathies. Such findings might serve to identify prognosis of disease course. It has been reported that solid tumors are associated with membranous nephropathy while lymphomas are associated with minimal change disease. While the incidence of paraneoplastic glomerulonephropathies in Chronic lymphocytic leukemia (CLL) is unknown and rare. CLL is one of the most common type of leukemia in Western countries. It is commonly observed in elderly patients but is hasn't been associated with renal gromeluropathies. Recent studies suspected that leukemic cells might have certain properties that lead to the development of nephrotic syndrome.

Case Description: This is the case of a 82 y/o male patient with past medical history of hypertension, hypothyroidism, and prostate cancer that presented to the hospital with complaints of edema. Associated symptoms were malaise, poor urinary output and nauseas. Physical examination was remarkable for generalized edema with pitting edema +2 on lower extremities. Initial laboratory work up was remarkable for findings of acute renal injury accompanied by oliguria and proteinuria +3. Despite foley placement and diuresis no major improvements on renal function was observed. Due to constant deterioration he was started on hemodialysis with adequate response but further work up for nephrotic syndrome was requested. ANCA and ANA was negative as well cryoglobulin. Complement such as C3 and C4 were within normal limits. Fat Pad biopsy was performed. Report was remarkable for changes suggestive of membranous

glomerulonephritis. In addition, due to sudden decrease in hemoglobin levels and elevated light kappa chains bone marrow biopsy was performed. Report was remarkable for changes suggestive of CLL.

Discussion: This case exhibits a patient that did not presented with symptoms or findings suggestive of CLL at the time of renal injury. Therefore, this case strongly underlines the importance of performing a bone marrow biopsy to patients that present with abnormal electrophoresis and immunofixation in order to detect lymphoproliferative disorder. Early detection can help to treat such disease at early stages and avoid further complications that might affect patient's prognosis.

PUB241

A Case of Immune-Complex-Mediated Glomerulonephritis Associated with Pembrolizumab

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Introduction: Immune checkpoint inhibitors (ICI) are changing the way we treat cancer. However, these agents have various systemic adverse events that may preclude their use and cause poor patient outcomes. ICI-associated acute kidney injury is an emerging complication of this treatment.

Case Description: An 80-year-old man diagnosed with metastatic adenocarcinoma of the lung with high PDL-1 expression was evaluated for new-onset proteinuria and elevation of serum creatinine. The patient had completed four cycles of carboplatin, pemetrexed, and pembrolizumab at the initial evaluation. His only complaint was foamy urine. Vital signs were remarkable for elevated blood pressure. The physical exam was unremarkable. Laboratory data showed serum creatinine of 1.8mg/dl (baseline of 1.18mg/dl, two months prior), blood urea nitrogen of 24mg/dl, and serum albumin of 3.3g/dl. Urinalysis showed proteinuria, and moderate blood with 9 RBC/HPF. A spot urine protein/creatinine ratio of 10.8 g/g. A kidney biopsy was performed, which showed immune complex-mediated glomerulonephritis, with a membranoproliferative and diffuse segmental endocapillary proliferative pattern of glomerular injury.

Discussion: Kidney immune-related adverse events occur in about 2-5% of patients receiving ICI therapy. Recently there has been increasing recognition of its association with glomerular diseases. Several differential diagnoses were considered that could have instigated these pathological findings. Ultimately, our team had a high clinical suspicion that they were associated with ICI therapy. After a multidisciplinary discussion, the decision was to hold pembrolizumab and start prednisone at a 1mg/kg dose. The patient responded well to therapy, was discharged home with prednisone taper; subsequent protein/creatinine ratio had a striking improvement to 1.8g/g. The serum creatinine was back to baseline. To our knowledge, this is the first case reported of pembrolizumab-associated immune-complex glomerulonephritis. Patients undergoing ICI therapy require close monitoring for potential kidney adverse events. Physicians must remain vigilant and should be able to recognize a potential glomerular injury from ICI therapy.

PUB242

Renal Cell Carcinoma Incidentally Discovered in Native Kidney During Imaging for Superior Vena Cava Obstruction

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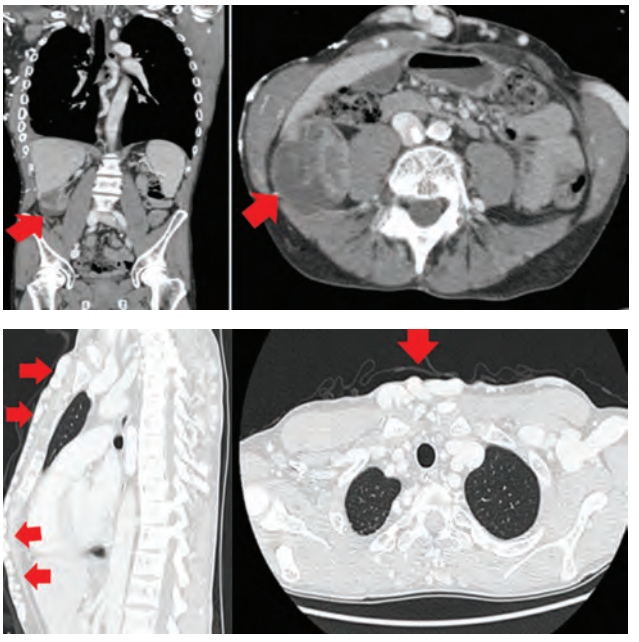
Introduction: Papillary RCC accounts for approximately 15 % of all kidney cancers, and these can be divided into type 1 and type 2 subtypes based on histopathologic features. As with clear cell cancers, papillary RCC originates from the proximal tubule, but these tumours are morphologically and genetically distinct malignancies. The initial information on their molecular pathogenesis was derived from cases arising in patients with hereditary forms of RCC.

Case Description: 37-year-old male patient with recurrent FSGS post renal transplantation currently on dialysis. He had aneurysmal AV dialysis fistula and he had CT Scan to evaluate superior and inferior vena cava obstruction which picked up a large complex heterogeneous well-defined mass arising from the lower pole of the atrophic right kidney highly suspicious for renal cell carcinoma (image 1). CT venogram showed chronic obstruction of SVC. This has resulted in extensive varicosed collateral veins in the anterior lateral chest wall and abdominal walls (image 2). The dilated collaterals drain into the femoral veins bilaterally. The patient undergone SVC angioplasty followed by elective right Nephrectomy. The renal mass histology showed Type II papillary renal cell carcinoma, G3. No extrarenal extension or renal sinus invasion identified.it was graded as pT1b pNx (AJCC 8th edition). As per EUA Guidelines for CT scan control at 6 months, 1 year, 2 years, 3 years then every 2 years for 10 years.

Discussion: Treatment approach For localized disease, the general approach to treatment of localized in clear and non-clear cell renal cell carcinomas. Surgical resection offers the best chance of cure.



PUB243

Immune Checkpoint Inhibitor (ICPI)-Associated Hypopituitarism Presenting as Severe Hyponatremia

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Introduction: ICPI has improved the prognosis for patients with advanced malignant disease. However, as their use increases, it is important to be aware of their potential side effects that require prompt attention. Here, we report a case that presents with life-threatening severe hyponatremia from secondary adrenal insufficiency as the first sign of hypopituitarism secondary to ICPI therapy.

Case Description: A 67-year-old man with a past medical history significant for metastatic clear cell type renal cell carcinoma, status post radical right nephrectomy, and adrenalectomy. He was found to have a metastatic lesion to his lungs and was initially treated with Pembrolizumab along with Axitinib for almost one year. 5 months later, He was found to have a metastatic necrotic mass in the right renal fossa and was started ipilimumab/nivolumab x 4 cycles followed by maintenance monthly nivolumab. Almost 4 months after being initiated on ICPI therapy and almost 3 weeks after the last dose, labs showed severe hyponatremia with serum sodium of 115 mmol/L with serum osmolality of 249 mmol/L. Clinical examination was suggestive of euvolemia. Urine osmolality of 510 with Urine sodium of 59 was consistent with the diagnosis of the syndrome of inappropriate antidiuretic hormone release (SIADH). Further workup included 8:00 AM cortisol of 0.5 mcg/dl increasing up to 9.3 mcg/dl in two hours after Cosyntropin 250 mcg IV stimulation along with inappropriately normal levels of ACTH of 18.4 pg/ml suggestive of secondary adrenal insufficiency. Additionally, relatively low TSH (with low free T4) along with low LH were suggestive of pituitary insufficiency. FSH and prolactin were within normal range. MRI brain was without any evidence for pituitaritis. No laboratory or clinical evidence for hypoaldosteronism. The patient was treated with the addition of hydrocortisone and levothyroxine. Follow-up labs at one month showed serum sodium of 132 meq/L.

Discussion: This case is an excellent illustration that hyponatremia in the patients receiving checkpoint inhibitors could be from hypocortisolemia. Extensive work up to detect pituitary insufficiency should be considered in such cases as hyponatremia could present as the initial sign of pituitary insufficiency.

PUB244

TMA Associated with Hypereosinophilic Syndrome

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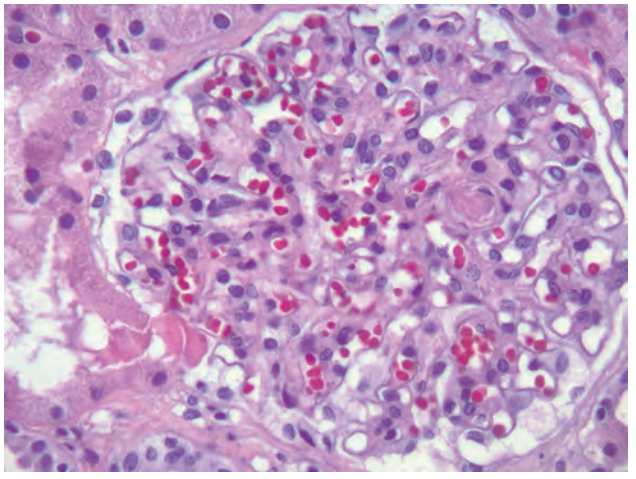
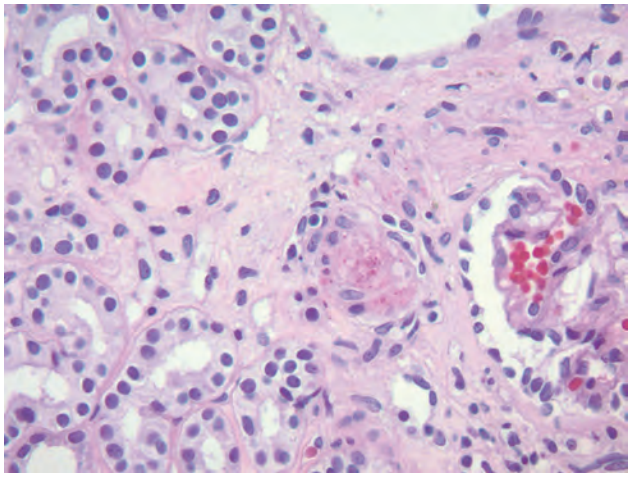
Introduction: Thrombotic microangiopathy (TMA) is a rare but serious form of renal injury that can be a manifestation of an array of conditions, including malignancies. Here we illustrate a case of renal TMA due to hypereosinophilic syndrome associated with PDGFRA gene rearrangement.

Case Description: A 29 year-old male presented with endocarditis-like features and findings of myocarditis on cardiac MRI. He was found to have AKI with creatinine up to 2.0 mg/dL, six months prior his creatinine was 0.96 mg/dL. Laboratory data was notable for peripheral eosinophilia, sub-nephrotic range proteinuria, and urine sediment showed many dysmorphic red blood cells. FISH testing showed FIP1L1-PDGFRA fusion rearrangement. A kidney biopsy was performed which revealed an acute TMA with

focal glomerular capillary thrombosis, multifocal arteriolar thrombosis, and arteriolar fibrinoid necrosis (Figures 1, 2). The patient was started on imatinib with improvement of creatinine to 1.75 mg/dL.

Discussion: Hypereosinophilic syndrome with PDGFRA mutation has been associated with renal TMA in only a few reported cases. It has been hypothesized that eosinophil granule proteins lead to the endothelial injury and platelet activation that precipitates this form of renal injury. This case highlights the importance of early diagnosis of AKI in these patients and the need for prompt treatment.





PUB245

Deep Analysis of AKI and CKD in Allogeneic Stem Cell Transplantation: A Big Data Approach

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Background: Acute kidney injury (AKI) is a common complication in allogeneic stem cell transplantation (ASCT). Although it is thought that in the majority of patients this injury is short lived in some patients, the damage persists for more than 3 months progressing into chronic kidney disease (CKD). So far, just a few publications have shown robust data based on larger patient populations. The aim of this project is to analyze the incidence and severity of AKI in ASCT and the transition into CKD.

Methods: Between 2000 and 2019, 1,401 patients underwent ASCT in our clinic. For 1,099, a detailed history of creatinine (n=184,056) could be extracted from the Clinical Data Warehouse. The classification of AKI was carried out in accordance with creatinine criteria of KDIGO classification at the respective stages (AKI 1, 2, 3). For AKI, an increase in serum creatinine of ≥ 0.3 mg/dl (26.5 micromol/l) within 48 hours or an increase in serum creatinine to ≥1.5 times baseline was used. Persistence of impaired renal function beyond day 90 was defined as CKD. An algorithm was programmed for the analysis of the big data and classification of the AKI / CKD. Retrospectively, the results were validated by a colour-coded representation of renal function.

Results: Between January 1, 2000 and December 31, 2019, 184,056 creatinine levels were enriched for 1,099 patients for the period from day -42 before to day +118 after ASCT. The overall incidence of AKI was 87% (n=956). 782 (71%) Patients have shown an AKIN 1, 145 (13%) an AKIN 2 and 29 (3%) an AKIN 3. During the observation period 122 (11%) patients died. For 32% (204/644) the transition to CKD has been observed.

Conclusions: AKI after ASCT is the rule and not the exception. As the vast majority of patients show AKIN 1 it might be often clinically overlooked. However early intervention might mitigate the development of long term renal impairment. Automated detection (AKI alert systems) as well identification and avoidance of factors contributing or aggravating injury (e.g., conditioning, immunosuppression, perfusion, inappropriate dosing of drugs) might minimize long-term renal complications in ASCT.

PUB246

Gemcitabine-Induced TMA: A Rare Side Effect Associated with High Mortality: A Case Report of Partial Response to Eculizumab

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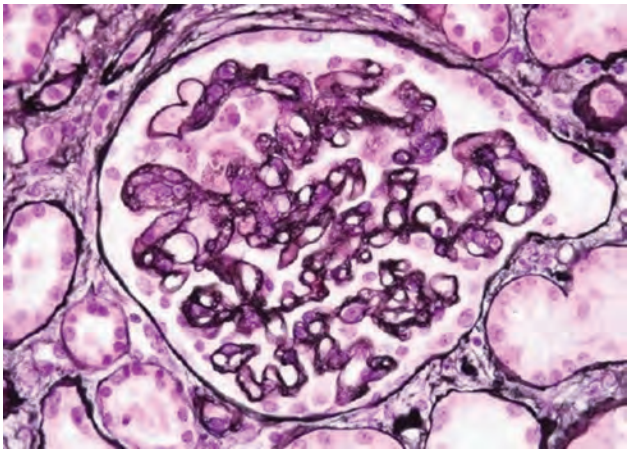
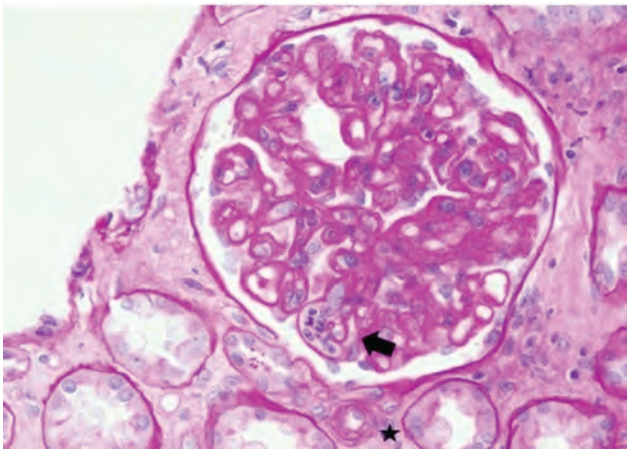
Introduction: Thrombotic Microangiopathy (TMA) is a well-known complication in cancer, and it could be secondary to neoplasm itself or to its treatment. Gemcitabine-induced TMA is rare, but associated with high mortality rate and negative renal prognosis.

Case Description: A 71-year-old woman treated with Gemcitabine for recurrence of endometroid carcinoma developed a rapid progressive kidney injury, hypertension and pulmonary edema. Laboratory tests revealed signs of TMA. Histological analysis showed both acute and chronic TMA signs (Fig. 1). Upon suspicion of GiTMA, antiblastic therapy was discontinued and, in order to prevent complement activation, Eculizumab was administered. According to literature, a sudden improvement of blood count was observed. Because of worsening of renal function, dialytical treatment was started. Histologically chronical lesions were documented (Fig.2).

Discussion: GiTMA is mostly misdiagnosed, because blood count instability and renal impairment could recognised multiple triggers in neoplastic patients. An early diagnosis enables drug withdrawal and complement system inhibition: the only measures that seem to be associated with increased survival and a better renal outcome.



Focal mesangiolysis, glomerular basement membrane reduplication (Silver Jones stain; 400x)



Mesangiolysis, endocapillary proliferation (arrow), glomerular basement membrane reduplication; arteriole (asterisks) free from TMA signs (PAS stain; 400x)

PUB247

Electrolyte Disorders Associated with the Use of Immune Checkpoint Inhibitors: A Single-Center Cohort

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Background: Electrolyte imbalances have been reported in association with exposure to immune check point inhibitors (ICI). However, the incidence of these disorders has not been widely established. Herein, we report a single center experience on the incidence of electrolyte abnormalities associated with ICI therapy as well as risk factors associated with their development.

Methods: We conducted a retrospective review of medical records searching for patients who received ICI over a 10-yr period at Ochsner Health. Demographic and clinical characteristics were extracted up to 1 year post ICI treatment. Common Terminology for Cancer Adverse Events version 5.0 criteria were used to grade the severity of electrolyte abnormalities. Risk factors were examined by logistic regression.

Results: A total of 102 patients were identified. The mean age was 64 ± 11 years, 43% women, 82% of white race. Pembrolizumab was the most commonly used ICI (46%), followed by nivolumab (26%) and atezolizumab (15%). The mean baseline glomerular filtration rate is 58 ml/min. ICI was more frequently administered to patients with lung cancer (47%). The incidence of hyponatremia (<134 mEq/L) and severe hyponatremia (<124 mEq/L) were 17% and 2%, respectively. Hypocalcemia (<8.4 mg/dL) was observed in 7%, whereas 11% experienced hypomagnesemia (<1.5 mg/dL) and 3% hypokalemia (<3.4 mEq/L). Melanoma was found to be numerically associated with hyponatremia, but not statistically significant (OR 3.1, 95% CI 0.7-14.8). White race was associated with 3 times greater risk of hyponatremia with ICI therapy (OR 3.5, 95% CI 1.2- 9.9). Although co-administration of cisplatin, underling chronic kidney disease and use of SSRI are known risk factors associated with hyponatremia, those variables were not associated with hyponatremia in our cohort, suggesting that hyponatremia secondary to use of ICI could be mediated by a mechanism independent of those variables.

Conclusions: Exposure to ICI is associated with the development of electrolyte imbalances. In our study, white race was identified as factor having 3 times higher odds of hyponatremia. Further studies are needed to examine race and other factors and the risk of hyponatremia in patients treated with ICI.

PUB248

Spontaneous Tumor Lysis with Normal Electrolytes

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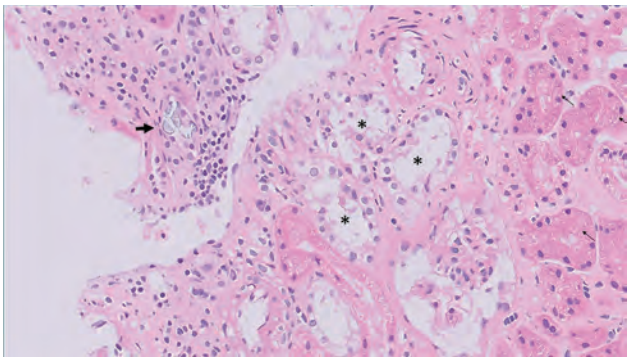
Introduction: Tumor lysis syndrome (TLS) leading to renal failure can occasionally occur prior to treatment in highly proliferative hematological malignancies. We present a case of AKI due to spontaneous TLS without the typical antecedent electrolyte derangements normally expected with TLS.

Case Description: A 76-year-old male with no prior medical history presented to the emergency room with abdominal pain and weight loss. CT scan revealed a gastric mass, ascites and abnormal liver consistent with cirrhosis. Gastric biopsy revealed diffuse large B cell lymphoma. He initially had a bland UA and a slight increase in baseline creatinine. The primary team treated him for hepatorenal syndrome with no response. His renal function rapidly deteriorated and he became anuric. A follow up UA showed protein and blood. Although the uric acid (UA) was 13.7 mg/dL, the phosphorous and potassium remained in their normal ranges leading us away from a diagnosis of TLS and toward the possibility of a rapid progressive glomerulonephritis. On biopsy the renal tubules contained calcium oxalate and calcium phosphate crystals with vacuolization of the tubular epithelial cells and tubular changes consistent with prior uric acid crystal deposition. The glomeruli were normal. At this point the uric acid level had risen to 25 mg/dl. Rasburicase was initiated and the patient eventually recovered renal function.

Discussion: In TLS, tumor cells lyse and release their intercellular electrolytes and purines (which are metabolized to uric acid) leading to elevated potassium, phosphorus and uric acid. Rarely the potassium and phosphorus can be normal. Our patient had renal failure further limiting the excretion of potassium and phosphate, making the normal levels of these electrolytes especially notable. Identifying the mechanism of normokalemia and normophosphatemia in spontaneous TLS may give us insight on how to diagnose it earlier, thus leading to earlier treatment.



H&E with calcium oxalate crystals (arrow), tubular lumen that likely contained uric acid crystals (asterisks)

PUB249

Bladder Amyloidosis as a Rare Cause for Hematuria

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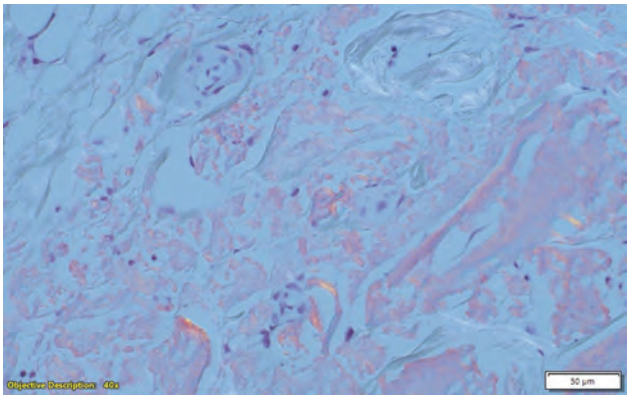
Introduction: Urinary tract amyloidosis involvement can mimic transitional cell carcinoma, with haematuria and irritative symptoms. Bladder amyloidosis has slow progression to systemic disease. More than 50% of bladder amyloidosis can be diagnosed as bladder carcinoma. Histological examination with congo-red stain remain important. Tests like bens-johns proteins serum electrophoresis, abdominal fat biopsy and serum amyloid P component can help to differentiate primary and secondary amyloidosis.

Case Description: 60 yo male, presented with on and off frank haematuria with TURB done 9 years ago. CT Contrast enhanced images confirmed an enhancing polypoidal soft tissue density/wall thickening of the bladder wall projecting within the lumen on the right lateral aspect along the bladder base, suspicion of malignancy was high so patient underwent Transurethral bladder tumour resection for solid tumour in the bladder trigone.

Discussion: Tumour biopsy showed extensive deposition of faint eosinophilic material in lamina propria, basement membrane, and submucosa and focally in muscularis propria with formation of chunky separate pieces present in artificially created spaces. Extensive deposition is also seen in the wall of blood vessels focally. The material was diffusely positive for Congo red stain with apple-green birefringence, consistent with amyloid. Immunohistochemical staining for kappa and lambda light chains was performed and shows dual positivity of the amyloid material, but with stronger staining on the lambda side, suggestive for AL type. SPEP Elevated beta globulins. UPEP and immunofixation showed glomerular Proteinuria selective for albumin&negative Bence Jones protein. Creatinine ranged between 111 – 144 micromole/L. the patient had negative investigations for systemic amyloidosis. The patient was advised to start colchicine, but he was not compliant with medication or follow up. No other pathology would explain his haematuria.



PUB250

Pattern of Renal Diseases Detected on Renal Biopsy at Pakistan Institute of Medical Sciences (PIMS) Islamabad

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Background: Renal biopsy is an important tool for evaluation and diagnosis of glomerular, vascular, tubulointerstitial and genetic kidney diseases. It helps in determining the stage of disease, making treatment protocol and predicting prognosis as well Purpose of the study is to find out pattern of renal diseases diagnosed on renal biopsies.

Methods: This is retrospective analysis done from February 2012 to April 2018. This data was taken from pathology department of Pakistan Institute of Medical sciences Islamabad Pakistan. These were adult patients above 18 years who underwent percutaneous renal biopsy due to some clinical indications. Their data was analyzed for spectrum of kidney disease on renal biopsy

Results: Total biopsies were 254. Most common lesions were glomerular lesions. Among them primary forms were found. Most common GN found was Membranous Nephropathy (14%), second most common lesion was Focal segmental glomerulosclerosis (FSGS) (12.5%) followed IgA Nephropathy (10.6%) Membranoproliferative glomerulonephritis MPGN (9.1%). Most common secondary glomerular lesion was found was Lupus Nephritis (7.8%). Other lesions were chronic kidney disease (12.5%), Interstitial fibrosis with tubular atrophy (IFTA) (5.9%)., Rapidly progressive GN (5.9%), Renal cortical necrosis (4.3%), Acute tubular necrosis (ATN) (4.3%), IgM Nephropathy 2%, chronic tubulointerstitial disease (TID) (2.4%), Diabetic Kidney disease (DKD) (2%) Minimal Change Disease (2%), Amyloidosis AA (1.2%), HTN (0.8%), pos-streptococcal GN (0.8%), Postinfectious GN (0.4%), diffuse proliferative GN (0.4%). In young patients' glomerular lesions were common whereas in middle age and elderly Chronic tubulointerstitial diseases and DKD were the common lesions.

Conclusions: In review of renal biopsies most common histological lesion found was membranous nephropathy (12.5%) followed by focal segmental glomerulosclerosis (FSGS) (12.5%) and IgA Nephropathy (10.6%).

PUB251

Can Antinuclear Antibody (ANA) Be Monoclonal? A Case Report of Unusual Immunofluorescence Findings in a Patient with Monoclonal Gammopathy of Uncertain Significance (MGUS)

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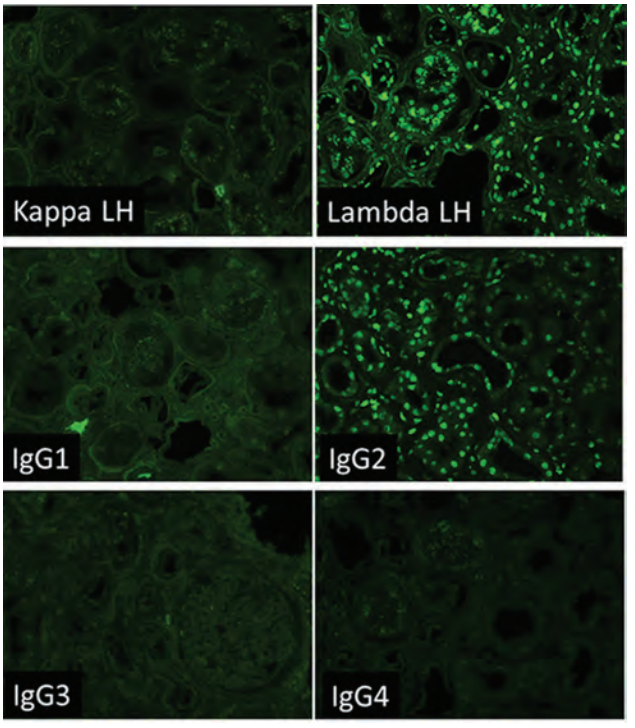
Introduction: Nuclear staining by immunofluorescence in a kidney biopsy is often seen in patients with positive ANA in the serum. These ANA are usually polyclonal, but herein we report an unusual finding by immunofluorescence of IgG2 lambda monoclonal nuclear staining in a patient with MGUS.

Case Description: The patient is a 72-year-old Caucasian male with a history of diabetes mellitus type 2 (hemoglobin A1c is 6.1%) who was recently treated with hydralazine, and he was found to have positive ANA (homogenous pattern, > 320), but after discontinuation of hydralazine the ANA decreased to 21. He had positive P-ANCA (positive MPO, 4) and negative C-ANCA (negative PR3). Also he has positive anti-double-stranded DNA. His serum creatinine was 1.7 mg/dl (1 mg/dl baseline), proteinuria 0.34 gm/24h. He did not have monoclonal protein in the urine, but in the serum by immunofixation there was IgG lambda monoclonal protein (two monoclonal bands were noted). He has elevated serum both kappa and lambda light chains with normal kappa-to-lambda light chain ratio. Kidney biopsy showed acute tubular necrosis (ATN), moderate chronic kidney injury and there was no evidence of immune complex deposition, monoclonal immunoglobulin deposition or amyloid. Immunofluorescence showed positive nuclear staining for IgG (IgG2 subclass only) and lambda but not kappa light chain (Fig 1). These findings raise the possibility that his ANA are of monoclonal origin.

Discussion: Our case demonstrates the unique pattern of IgG2 lambda monoclonal nuclear staining by immunofluorescence in the patient with MGUS. The prevalence of this type of findings is not well studied.



PUB252

The Use of Bone Wax to Position and Secure the Kidney for Intravital Analysis in Mice Using an Abdominal Imaging Window

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Background: Intravital imaging is a powerful technique for evaluating inflammatory processes, cell migration, tubule and blood flow, cyst development, and injury and repair responses in vivo in live kidneys. Combining this with the use of an abdominal imaging window (AIW) allows for long-term in vivo visualization. However, the challenge has been preventing the kidney from repositioning in the AIW over the course of the study. Previous methodology utilized a cyanoacrylate adhesive to attach the kidney to the window or gauze placed under the kidney to stabilize it against the window, thus facilitating the acquisition of images. In our hands, both approaches cause scaring and fibrosis that have complicated our analysis. Here we compare a bone wax approach to secure the kidney with that of gauze.

Methods: AIW implantation surgery was done on 8 to 10 week old wild type mice and the kidneys were positioned and secured in the window using sterile gauze or bone wax (n=4 each).

Results: Our results show that sterile gauze can cause adhesion reactions with the surrounding tissue, including the kidney, making it difficult to visualize and image the kidney for more than 3 days post window insertion. In addition there are inflammatory reactions, and the kidney frequently adhered to the AIW coverslip preventing imaging of cell movements, cilia responses, and flow within the renal tubule. Bone wax is an inert and malleable substance that is used for bone recovery surgeries and therefore should not result in an intense inflammatory response. In contrast to the results obtained with sterile gauze, using bone wax to secure placement of the kidney in the window resulted in a far less inflammatory reaction and reduced adhesions and fluid accumulation within the window. Using bone wax, we can now easily follow the kidney for 2 - 3 weeks after surgery with minimal complications.

Conclusions: We conclude that bone wax is a superior approach for long-term intravital renal imaging. The longer time frame provided by using bone wax for longitudinal renal visualization will allow us to evaluate the initiation and expansion of cysts, to image renal injury responses and cell movements, and to analyze tubule flow and cilia responses.

Funding: NIDDK Support

PUB253

Renal Tuberculosis: An Uncommon Presentation of a Common Disease: Case Report

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Introduction: Guatemala is an endemic country for tuberculosis (TB) with 3 500 cases per year, 85% correspond to pulmonary presentation. Genitourinary tuberculosis is uncommon, it is considered a severe form of extrapulmonary TB; it is secondary to infection with Mycobacterium tuberculosis complex with a long-standing dysuria, sterile pyuria, fever and consumptive symptoms. We present the case of an atypical renal TB having hematuria and fever as the only clinical features.

Case Description: A 54-year-old Guatemalan male came to the emergency room with a history of intermittent fever during the last year that worsens in the last 2-weeks. He lived in a rural area at the southern-coast of Guatemala. No previous medical history, no pets at home. The fever was between 38.3-40º (100-104ºF) with no predominant pattern during the day. On admission, normal vital signs, dehydrated with no other sign or symptom at physical examination. Initial laboratories with WBC 6 500, Hb 13gr/dl, SCr 0.86mg/dl, BUN 15mg/dl, normal LFTs and electrolytes. Chest X-ray with no evidence of pneumonia or other pulmonary disease. Urinalysis with microscopic hematuria with >30 RBCs per hpf, 40% of dysmorphism; no WBC in three consecutive urinary test. Urinary protein-creatine ratio15mg/g. Negative urine culture. ANA, ANCAs, C3, C4 were negative. Infectious disease tests were negative (FilmArrayâ, TORCH, blood culture, SARS-Cov2, HIV, HBV, HCV, lumbar puncture). Considering hematuria from urological origin we perform a uro-CT which was negative for kidney stones, masses or other anatomical abnormalities. Urine Ziehl-Nielsen stain was negative but with a positive result for acid fast bacilli in urine Kinyoun stain (figure 1). A multidrug therapy was started with isoniazid, pyrazinamide, ethambutol, rifampicin. Forty-eight hours later the fever disappeared until discharged.

Discussion: Renal TB has a prevalence of 10% worldwide and 20% in Latin-America mainly from pulmonary origin. The reported cases have higher prevalence in developing countries, male gender, immunosuppressed state as in HIV infection and post transplanted. It is an under diagnosed disease that can lead to CKD. The diagnosis of renal TB must be considered in patients with dysuria, hematuria, pyuria with negative urinary cultures.

PUB254

Real-Time Percutaneous Kidney Biopsy Experience: Is There a Change in the Trend of Complication?

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Background: Percutaneous kidney biopsy (PRB) is essential in establishing diagnosis and guides in the treatment of renal diseases. The procedure of kidney biopsy has evolved through technique and procedural refinements. Bleeding and its consequences are the most concerning complications of kidney biopsy. This is a UK renal centre experience to report the post-kidney biopsy bleeding complications.

Methods: We included all patients (inpatient and day case) who underwent PRB between January 2014 and Dec 2016. Biopsy was performed using a 16-gauge biopsy needle with a spring-loaded trigger device. Pre-biopsy parameters such as Blood pressure, haemoglobin, platelet counts and coagulation studies of patients were recorded. Data on kidney biopsy outcome were collected retrospectively. Bleeding complications were macroscopic hematuria, drop in haemoglobin requiring blood transfusion or requiring intervention radiology. Statistical analysis was performed.

Results: A total of 458 kidney biopsies were carried out with 58.9% male and 53.1% as day case. There was a 2.4% technical failure and 96.9% histological adequacy. Indications for kidney biopsy were acute kidney injury (37.1%), nephrotic syndrome (24.5%), proteinuria (17.7%) and hematuria (8.2%). Histopathology diagnoses were IgAN (12.2%), pauci-immune glomerulonephritis (10.4%), tubulointerstitial nephritis (9.3%), FSGS (7.6%), diabetic nephropathy (7.1%) and membranous glomerulonephritis (6.4%). Bleeding episodes were seen in 19(4.3%) with 3(0.6%) having haematoma and 1(0.2%) inpatient had embolisation. Day case (2.1%) compared to in-patient (6.8%) kidney biopsy and platelet count (>150 x 10^9) had less bleeding complication ($p< 0.05$). Mean serum creatinine is higher among in-patient kidney biopsy (361.93 ±216.41 vs. 151.21 ± 94.26, p= 0.005). In-patient kidney biopsy were older, had lower hemoglobin and higher INR ($p< 0.05$). Lower mean hemoglobin (104.42 ± 15.39 vs. 115.35 ± 21.03, p=0.025) and higher mean serum creatinine (413 ± 288.41 vs. 242.16 ± 185.72, p=0.005) were reported in those who had hematuria. We reported no nephrectomy or death.

Conclusions: We report a low post kidney biopsy bleeding complication. Day-case procedure has a lower rate of kidney biopsy bleeding complication when compared to in-patient kidney biopsy.

PUB255

Variation in Interpretation of 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) in Children with Confirmed or Suspected Hypertension (HTN) by Canadian Pediatric Nephrologists and Cardiologists

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Background: ABPM is more accurate compared to a single office-based blood pressure (BP) measurement. However, it is unclear how physicians interpret ABPM and make management choices, especially where evidence supporting recommendations is limited. This survey's goal is to study ABPM interpretation variation by HTN category and disease among pediatric nephrologists and cardiologists.

Methods: Survey content included physician demographics, ABPM indications, interpretation, and management. The same questions were asked of all respondents, except kidney-related conditions which were only shown to nephrologists.

Results: The survey was sent to 196 physicians, with 69 (35.2%) responses. Most respondents were age 45+, in practice for 11+ years and university-based. Table shows significant differences in ABPM interpretation for BP load, isolated systolic and diastolic HTN, and between nephrologists and cardiologists for different conditions (not all data included in abstract table). Rates of HTN treatment are lower than guidelines recommendations.

Conclusions: There is significant practice variation among physicians in ABPM interpretation and management. Gaps in guidelines create ambiguity regarding management decisions for different ABPM parameters. A more protocolized approach may help to standardize practice.

Initiation or alteration of antihypertensive treatment with respective ABPM parameters in various conditions

ABPM Parameter	Condition	Nephrologists (n=32)	Cardiologists (n=37)
Isolated systolic hypertension	Essential hypertension	19 (59.4%)	14 (37.8%)
	Congenital heart disease	27 (53.1%)	13 (35.1%)
	CKD stage 1-4/dialysis/kidney transplant	23 (71.9%)	n/a
	Renovascular hypertension	21 (65.6%)	
Isolated diastolic hypertension	Essential hypertension	9 (28.1%)	11 (29.7%)
	Congenital heart disease	11 (34.4%)	10 (27.0%)
	CKD stage 1-4/dialysis/kidney transplant	16 (50.0%)	n/a
	Renovascular hypertension	16 (50.0%)	
BP load >25% with normal mean BP	Essential hypertension	17 (26.6%)	2 (5.4%)
	Congenital heart disease	20 (31.3%)	3 (8.1%)
	CKD stage 1-4/dialysis/kidney transplant	14 (43.8%)	n/a
	Renovascular hypertension	25 (39.1%)	
Isolated daytime hypertension	Essential hypertension	18 (56.3%)	13 (35.1%)
	Congenital heart disease	19 (59.4%)	13 (35.1%)
	CKD stage 1-4/dialysis/kidney transplant	21 (65.6%)	n/a
	Renovascular hypertension	22 (68.8%)	
Isolated nighttime hypertension	Essential hypertension	11 (34.4%)	9 (24.3%)
	Congenital heart disease	12 (37.5%)	9 (24.3%)
	CKD stage 1-4/dialysis/kidney transplant	18 (56.3%)	n/a
	Renovascular hypertension	15 (46.9%)	

PUB256

An Electronic Health Record (EHR) Algorithm to Identify Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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Background: ARPKD is an important cause of pediatric chronic kidney disease, hepatic fibrosis, and portal hypertension. Its rarity makes it difficult to collect larger-scale natural history data and to identify patients for clinical trials.

Methods: We developed an EHR-based algorithm to identify ARPKD patients at a single site in PEDSnet (v3.9, 1/2009-7/2020), a national pediatric learning health system. A training/testing cohort consisted of 50 clinician-confirmed ARPKD patients and 150 non-ARPKD controls (enriched for patients with cystic/dysplastic diagnoses). A random forest was implemented to classify patients as cases and non-cases, with variable importance permutation-based, with high performance (precision 98%, recall 94%). The algorithm was applied to a denominator of 45,186 patients with either a nephrology visit, a GI visit + a liver diagnosis, or a NICU visit to classify patients as cases or non-cases. Two clinicians blinded to model case classification used a standardized form to review 97 patients with ≥1 ARKPD diagnosis (not included in original training/testing cohort) and classify them as ARPKD or non-ARPKD.

Results: The key model selection features were number of visits with an ARPKD diagnosis code and presence of a hepatic fibrosis diagnosis code. Table 1 shows patient characteristics. Of 97 patients reviewed, clinicians excluded 5 as indeterminate, and classified 56 as non-ARPKD and 36 as ARPKD [positive predictive value (PPV) of ≥1 ARPKD diagnosis 39%]. The algorithm identified 23 true positives, 17 false positives,

13 false negatives, and 39 true negatives; model performance: sensitivity 64%; specificity 70%; PPV 58%; negative predictive value (NPV) 75%.

Conclusions: An EHR-based algorithm improves PPV for identifying patients with ARPKD compared to diagnosis code alone and has relatively good NPV for excluding ARPKD in non-ARPKD patients with an ARPKD diagnosis code in their chart. Further chart reviews of incorrectly classified patients will allow algorithm refinement to improve performance.

Funding: NIDDK Support

Table 1: Demographic and clinical characteristics

Characteristic**	Denominator (n = 45,186)	Training/testing cohort (n = 200)		Chart review cohort (pts with ≥1 ARPKD diagnosis)* (n = 97)		True positive model ARPKD cases (n = 23)
		ARPKD (n = 50)	Controls (n = 150)	Model cases (n = 42)	Model non-cases (n = 55)	
Age at initial visit (yrs)	0.6 (0.0, 6.9)	0.6 (0.0, 5.6)	0.2 (0.0, 3.7)	2.2 (0.4, 8.5)	0.5 (0.0, 7.8)	3.7 (0.7, 8.1)
Follow-up time (yrs)	6.1 (1.7, 11.2)	9.5 (6.1, 13.1)	6.1 (0.4, 8.5)	3.9 (0.8, 10.4)	6.0 (0.3, 11.1)	4.2 (1.0, 10.7)
Female sex	20,273 (45%)	22 (44%)	67 (45%)	16 (38%)	28 (51%)	<11[#]
Age at first ARPKD diagnosis (yrs)		2.6 (0.1, 9.2)		4.85 (0.9, 12.1)	4.5 (0.1, 14.2)	4.7 (1.2, 10.5)
Follow-up time since ARPKD diagnosis (yrs)		7.4 (4.6, 11.8)		2.98 (0.78, 7.5)	2 (0.1, 5.5)	3.0 (0.6, 7.6)
Number of ARPKD diagnoses (per person-yr)		6.4 (2.1,10.0)		0.8 (0.6, 3.2)	0.2 (0.1, 1.0)	2.3 (0.8, 6.0)
Pts with >1 nephrology visit	14,459 (32%)	46 (92%)	109 (73%)	32 (76%)	28 (51%)	20 (87%)
Number of nephrology visits (per person-yr)	0.37 (0.1, 1.43)	4.8 (2.6, 10.6)	1.6 (0.7, 4.7)	3.4 (1.0, 6.5)	0.7 (0.35, 2.1)	5.0 (1.9, 8.9)
Pts with >1 GI visit	14,911 (33%)	45 (90%)	72 (48%)	28 (67%)	15 (27%)	20 (87%)
Number of GI visits (per person-yr)	0.8 (0.28, 2.5)	1.8 (0.7, 2.3)	1.4 (0.8, 3.2)	1.9 (0.6, 4.2)	0.8 (0.3, 1.7)	3.0 (0.9, 5)
Pts with >= 1 NICU visit	14,459 (32%)	10 (20%)	43 (29%)	<11[#]	15 (15%)	<11[#]

* Patients meeting the following criteria: included in denominator, not included in training/testing cohorts, ≥1 ARPKD diagnosis
** Continuous data presented as median (interquartile range) and categorical data as N (%)
# Exact counts/% not provided for groups with <11 individuals

PUB257

Nitromethane Fuel Toxicity Causing False Elevation of Serum Creatinine

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Introduction: Nitomethane along with methanol is a common component of model airplane fuel, rocket fuel and race car fuel. Reports of nitromethane exposure causing falsely elevated creatinine by its interference with the Jaffe reaction analysis has been reported in adult literature with limited pediatric data being available.

Case Description: 12 year old male with past medical history significant for major depressive disorder on prozac, H/o medium chain acyl-CoA dehydrogenase (MCAD) deficiency on a low fat diet and levocarnitine. Patient had prior admissions for self-harm and presented after ingesting about a mouthful of Torco race fuel. On initial evaluation in outlying ER, he was hemodynamically stable with heart rate of 97 per minute, respiratory rate of 16/min with saturations of 97% on room air and BP recorded at 130/67. Initial lab check showed a normal creatinine at 0.69 mg/dl. Patient was transferred to our hospital for administration of fomepizole as methanol is a main component of Torco race fuel. On arrival, repeat labs in 5 hours showed an increase in creatinine to 1.73, which slowly started coming down to 1.39, 48 hours into admission. He remained normotensive through the course of stay and further studies including urine studies for protein came back normal. No azotemia and blood urea nitrogen remained normal at 13-15 mg/dl through the length of stay. Cystatin -C levels done on hospital transfer returned normal at 0.68 mg/L. With serum methanol levels returning negative, patient was transferred to inpatient psychiatry ward.

Discussion: This is a pediatric case report on Torco race fuel ingestion in which the ingredient nitromethane ($CH_3 NO_2$) caused a false elevation of serum creatinine. The standard assay for creatinine uses the Jaffe reaction, where interaction happens between creatinine and alkaline picrate. Nitromethane by its reactive methyl component interacts with alkaline picrate producing a cromophore that closely resembles the creatinine picrate complex, causing false elevation of creatinine. Enzymatic assay of creatinine, which is not widely used will not get affected by nitromethane. False elevation of creatinine in a patient with methanol and nitromethane ingestion can force the physician to do unnecessary procedures such as dialysis and should be kept in mind.

PUB258

Long-Term Renal Outcomes of Congenital Ureteropelvic Junction Obstruction

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Background: Congenital ureteropelvic junction obstruction (UPJO) is often diagnosed in adulthood. Current literature is lacking in evaluation of long-term renal outcomes for adult patients with UPJO.

Methods: We queried service members diagnosed with UPJO from the U.S. Military Health System electronic health records. We assessed demographic, laboratory, radiology, stenting/pyeloplasty and outcome data. We assessed the impact of intervention regarding development of chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR)<60ml/min/1.73m$^{2)}$, hypertension (HTN) (blood pressure >130/80mmHg), and changes in renal excretory function on radionuclide scans.

Results: We identified 108 individuals diagnosed with congenital UPJO; mean follow-up of 7 years. 55% had right-sided, 40% left-sided and 5% bilateral UPJO. Mean age at diagnosis was 25 years (n=10 at <18 years; n=98 at ≥ 18 years); 95% male; 69% White, 15% Black. At diagnosis, mean BP was 130/78 mmHg; mean eGFR 86ml/min/1.73m^2; and 22% had proteinuria ≥ 30mg/dL. 85.2% had pyeloplasty and 23.4% had lone stent placement. 14% developed eGFR<60 ml/min/1.73m2. 9.5% of patients with intervention developed stage 3 CKD vs. 21.4% of those without intervention (p=0.42). Intervention was not associated with development of HTN in adjusted logistic regression analysis (OR 0.30, 95% CI 0.08-1.20). Intervention significantly reduced the proportion of patients with delayed cortical excretion and T½ emptying time with right-sided UPJO only (Table).

Conclusions: Approximately 14% of our young adult cohort with congenital UPJO developed CKD. Intervention improved cortical excretion and T½ emptying time with right-sided UPJO only. The views expressed are those of the authors and do not reflect official policy of the Dept of the Army/Navy/Air Force, Dept of Defense, or US government.

Variables	Pre Procedure	Post Procedure	P value
Left sided and bilateral UPJ obstruction			
Kidney size (ultrasound), cm (n=8)	13.1	12.7	0.22
Differential function (%) (n=35)	42.6	43.1	0.83
Delayed cortical excretion	18/33 (55%)	11/30 (37%)	0.06
T½ emptying time (Lasix scan), min (n=28)	24.1	22.8	0.78
Right sided and bilateral UPJ obstruction			
Kidney size (ultrasound), cm (n=11)	13.0	12.1	0.08
Differential function (%) (n=41)	39.0	38.6	0.77
Delayed cortical excretion	22/41 (54%)	16/44 (36%)	0.01
T½ emptying time (Lasix scan), min (n=31)	33.2	20.0	0.018

PUB259

Prevalence of Secondary Hypertension in Children with a New Diagnosis of Hypertension: A Meta-Analysis

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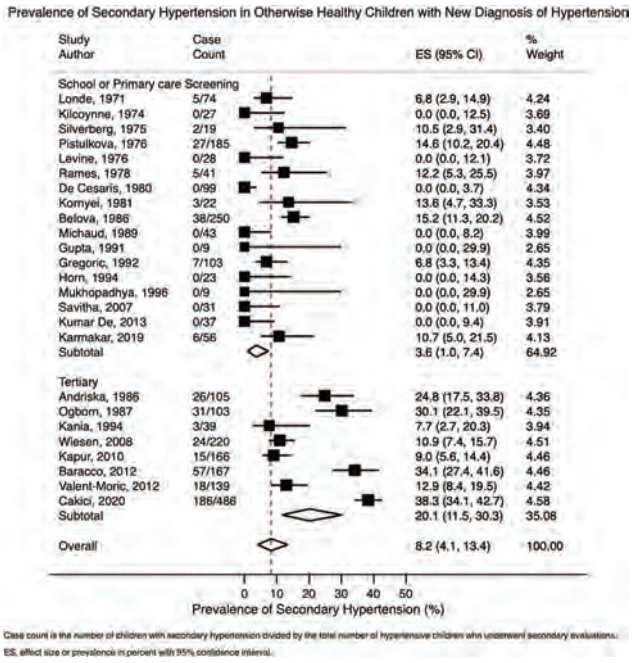
Background: Secondary hypertension (HTN) in children is associated with an increased risk of end organ damage and treatment resistance. For asymptomatic children with HTN identified on screening, the prevalence of secondary HTN is unknown.

Methods: MEDLINE, EMBASE, Web of Science, and Cochrane Library were searched for studies reporting rates of secondary HTN in children aged 0-19 years who underwent evaluation for HTN. We identified studies that diagnosed HTN based on at least 2 outpatient blood pressure readings and included children without any known comorbidities associated with HTN. Two authors independently extracted the study-specific prevalence of secondary HTN in children with HTN of unknown cause. Prevalence estimates were pooled in random effects meta-analysis.

Results: For the 18 prospective and 7 retrospective studies included, there was a median of 56 (range, 9-486) participants with HTN in each study. Although studies applied different diagnostic criteria for HTN, 20 of 25 studies used a blood pressure percentile-based approach. The pooled prevalence of secondary HTN was 8.2% (95% CI: 4.1-13.4%). Studies conducted in primary care or school settings reported a lower prevalence of secondary HTN (3.6% [95% CI: 1.0-7.4%]) than studies conducted in referral clinics (20.1% [95% CI: 11.5-30.3%]). When stratified by study setting, there were no significant subgroup differences according to study design, participant age range, HTN definition, blood pressure device, or study quality.

Conclusions: The low prevalence of secondary HTN in otherwise healthy children with a new diagnosis of HTN reinforces current guidelines to avoid extensive diagnostic testing for secondary causes in most hypertensive children ≥6 years old.



PUB260

Building the Bridge Between Pediatric and Adult Nephrology: A Quality Improvement (QI) Approach for Health Care Transition (HCT)

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Background: HCT from pediatric to adult-focused care in patients with renal disease continues to be difficult, we know that an inadequate HCT process can lead to poor patient outcomes. Various studies have demonstrated utilization of a HCT clinic as a means to improve communication and satisfaction between adolescents/young adults (AYA) and providers. This abstract highlights a QI approach conducted in the pediatric nephrology department of a children's hospital in collaboration with adult nephrology providers at an affiliate hospital in the Southwestern USA.

Methods: A dedicated transition team was created at the pediatric nephrology section which participated in transition needs assessment (Fig. 1). Part of this assessment involved surveys to pediatric faculty (n = 14), who rated the current transition process. A pilot group of patients was proposed to lead this effort with initiation of a novel form of transition clinic; 2-step transition clinic to tackle lack of a dedicated transition clinic. This clinic provides patient interaction with their renal providers and multi-disciplinary support in at least two different health care settings, pediatrics followed by adult.

Results: Multiple barriers were identified by initial needs assessment including lack of standardized transition procedure. Ease of transition was rated as 2.5 out of 5 (a 5 being easiest transition). During this endeavor, our team was able to build a framework for HCT along with strengthening ties with our adult colleagues. We collected surveys from patients at the time of 2-step transition clinic (n= 10) which was overall reassuring however 50% of the patients felt "somewhat ready for transition" highlighting the need for better transition preparedness.

Conclusions: The needs assessment underscores areas to target for intervention. We propose that implementation of the new standardized process including our 2-step transition clinic will result in enhanced patient satisfaction and HCT outcomes with potential areas for improvement.

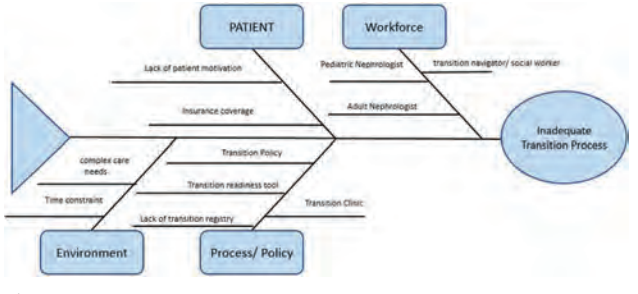

Fig.1

PUB261

Clinicopathological Characteristics of Focal Segmental Glomerulosclerosis (FSGS) in a Pediatric Patient Population

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Background: FSGS is a major cause of steroid resistant nephrotic syndrome and is a major cause of end stage renal disease in children. FSGS may progress to chronic kidney disease if untreated, however, treatment is only ameliorative. Few studies are available that characterize the histological and clinical features of FSGS in pediatric patients (pts) at time of kidney biopsy.

Methods: A retrospective cohort study was performed within the Arkana Biopsy database (January 1, 2016 to May 31, 2020) among pediatric pts who met the following study criteria: ≤17 years of age, ≥1 FSGS positive biopsy, and no prior kidney transplant. Outcomes evaluated included clinical and histologic characteristics.

Results: Of 3,157 renal biopsies performed among pts ≤17 years during the study period, 167 (5.3%) FSGS cases were identified, and 164 pts evaluated met study criteria. In this sample, 44.5% were female and mean (SD) age at biopsy was 11.4 (4.8) years. About one third of pts were White (33.5%), 25.6% African American, 12.2% Hispanic and 1.2% Asian. Median (Q1 - Q3) urine protein to creatinine ratio/24-hour urine protein for 61.0% of patients with available data was 3.0 (1 - 9) g/g, and approximately a third of pts (34.2%) had a diagnosis of hypertension. The majority of pts had absent/no comment indicated for arteriosclerosis (82.3%) and arteriolosclerosis (90.9%) and nearly half of FSGS pts (49.4%) had severe foot process effacement (≥80%). The most common FSGS type was "not otherwise specified" (71.3%), while 13.4% of pts had tip lesion, followed by perihilar (8.5%) and collapsing (6.7%) FSGS. Approximately 25.0% of pts had 0% interstitial fibrosis and tubular atrophy (IFTA), 52.4% had 1-<25% IFTA, 17.1% had IFTA 25%-<50% and 4.9% had IFTA ≥ 50%. Most pts (79.3%) exhibited <25% glomerular sclerosis while 9.2% had ≥50% GS.

Conclusions: FSGS in this pediatric population was associated with low degrees of glomerular sclerosis, interstitial fibrosis and tubular atrophy, but severe foot process effacement was common. When comparing to data reported in a companion abstract in adult pts with FSGS, the lower levels of sclerosis and fibrosis observed in these pediatric FSGS pts, suggest that early and effective intervention could potentially aid long term renal survival.

Funding: Commercial Support - Travere Therapeutics

PUB262

Impact of Hypertension on Health-Related Quality of Life in Childhood-Onset Systemic Lupus Erythematosus

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Background: Childhood oneset SLE can significantly impact Health-related quality of life (HRQOL) due to disease manifestations and its associated therapies. Hypertension is another chronic disease that can impact the HRQOL in children despite its "silent nature." In cSLE, secondary HTN can occur in up to 70%, due to nephritis and/or medications (i.e. steroids). We aim to assess the impact of HTN on HRQOL in patients diagnosed with active SLE aged 7-18 years in the Texas Children Hospital (TCH).

Methods: A total of 10 subjects met inclusion criteria: diagnosis of SLE as determined by a Pediatric Rheumatologist, age 7-18 years, new onset disease or flare from 11/2020 to 4/2021. Subjects were excluded if unable to complete the questionnaire, BMI >32, or eGFR<60. We classified hypertension using ambulatory BP monitoring (ABPM). HRQOL was measured by both patient and parent proxy using disease-specific SMILEY© (Simple Measure of Impact of Lupus in Youngsters) tool. We used Jamovi software to analyze demographic data.

Results: Median age was 17 (IQR 13-18) years. HTN was diagnosed in 40% by casual BP measurement and 70% by ABPM. Median Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was 13(10-18). Median SMILEY score was 60 (57-64). While there was no clinically significant differences in the parent report scores, patients with attenuated nocturnal BP dipping had lower child reported scores (Table1). Child reported SMILEY© scores correlated inversely with Mean 24hr systolic and diastolic load (r=-0.7, -0.9), mean wake SBP and DBP load (r=-0.7, -0.7), and sleep DBP load (r=-0.76).

Conclusions: In cSLE, ambulatory BP patterns significantly impact HRQOL. These initial conclusions suggest that HTN may impact HRQOL in cSLE.

Table 1 Median SMILEY© scores stratified by nocturnal BP dipping status at enrollment.

	ABPM Diagnosis	All=10 (IQR)	Normal Dipping (N=5)	Attenuated Dipping (N=5)	Absolute Mean Difference (SED)
Child Report	Global HRQoL	4 (3-4)	4	4	0 (0.3)
	Global SLE	3(3-4)	3	4	-1(0.1)
	Effect on Self	16 (15-17)	16	16	0 (0.6)
	Limitations	18 (17-20)	24	18	6 (1.3)
	Social	17 (13-18)	17	16	1 (0.4)
	Burden of SLE	19 (15-23)	18	18	0 (0.9)
	Total Score	60 (57-64)	61	57	4 (2.5)

PUB263

Parenteral Iron and Erythropoietin Effects on FGF-23 and Cardiac Function in Young Dialysis Patients

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Background: Elevated fibroblast growth factor 23 (FGF23) levels are associated with left ventricular hypertrophy (LVH) and diastolic dysfunction (DD). Recent preclinical and adult studies have shown that parenteral iron (Fe) supplementation and erythropoietin (EPO) may increase FGF23 production and circulating levels. Whether treatment with EPO or Fe could increase FGF23 levels and adversely contribute to LVH and DD in pediatric patients maintaining hemodialysis (HD) remains largely unknown.

Methods: Adolescents (n=20, median age 16 years) maintained on HD (average dialysis vintage 30 ± 17 months) were studied. All were treated with EPO, with or without concomitant parenteral Fe sucrose and all received intravenous paricalcitol for secondary hyperparathyroidism. C-terminal FGF23 (cFGF23), biochemical markers, and sequential echocardiograms (conventional and tissue Doppler, ECHO) were analyzed longitudinally twice, 6 months apart. LV dimensions, including IVST (interventricular septal thickness) and markers of diastolic function with peak early (E), late (A) diastolic flow velocities, and corresponding mitral annular velocities (Em, Am) were measured, and adjusted to Z-scores according to age and gender.

Results: Whereas the cumulative average EPO dose was similar in Fe-treated and untreated patients (10,056 ± 5,445 and 10,818 ± 7,935 Units/week/6 months, respectively), the initial and final cFGF23 levels remained similarly elevated in both groups. Prevalence of DD improved from 22% to 12% during the study period. LogFGF23 values correlated with Am (r= -0.7) and Em/Am (r= 0.7) Z-scores (both $p<0.05$) in Fe-treated patients. The doses of EPO and Fe did not correlate with markers of diastolic function, but EPO correlated with the IVST Z-score (r= 0.7, $p<0.05$). The cumulative paricalcitol dose did not correlate with markers of diastolic function but inversely correlated with IVST Z-score (r= -0.5, $p<0.05$)

Conclusions: Treatment with EPO, irrespective of parenteral Fe supplement, hemoglobin, and ferritin levels did not result in consistent elevations of cFGF23 levels. While the FGF23 levels correlated with worsen markers of diastolic function, the overall prevalence of DD improved overtime. The administration of paricalcitol may have contributed to the improvement of DD and the LVH.

Funding: Clinical Revenue Support

PUB264

Is It Time to Update the Age-Specific Pediatric Normative Serum Creatinine Ranges?

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Background: Diagnosis of abnormal kidney function is routinely based on serum creatinine (SCr) value. SCr in children increases with growth and normative values therefore vary with age. However, due to lack of availability of large number of blood samples from healthy children, most laboratories combine the SCr reference ranges in up to 5-year age group blocks, resulting in an upper limit that can be 2.3 to 2.6 times higher than the lower limit for that age block. As a result, a child with subnormal kidney function (GFR < 90 mL/min/1.73m2) who is near or at the younger end of the age in a specific age group block, can still have SCr value below the upper limit of reference range and thus will remain unflagged on the reported result. This may result in a missed diagnosis of decreased kidney function. Similarly, a diagnosis of acute kidney injury (SCr increase >1.5 above baseline) can also be missed as the increased SCr value can still fall within the reference range for that age group. In research studies, missing baseline creatinine values are customarily back calculated from eGFR equations with a presumed GFR of 120 mL/min/1.73m2. Our objective was to calculate age specific SCr reference ranges for children 2 – 18 years, and copmpare them with current age group block reference ranges.

Methods: We used bedside Schwartz equation (eGFR = height*0.413/SCr, where 0.413 is the constant k) to calculate estimated creatinine (eCr) = height*0.413/GFR. We calculated the eCr reference ranges by inserting 3rd percentile for height and GFR of 120 mL/min/1.73m2 for the lower limit, and by inserting 97th percentile for height and GFR of 90 mL/min/1.73m2 for the upper limit. Height values for respective ages were obtained from the CDC reference charts.

Results: The calculated theoretical reference ranges are shown in the Table. The upper limit of eCr values are only 1.6 times higher than the lower limit in contrast to the current reference ranges where the upper limit is 2.3 to 2.6 times higher than the lower limit for its age group block.

Conclusions: We believe that by switching from age group blocks to age specific normal SCr ranges the possibility of missing subnormal kidney function will be minimized. The calculated values need to be further validated.

Age (Yrs)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
eCr (Lower limit)	0.27	0.30	0.33	0.35	0.37	0.39	0.40	0.42	0.44	0.45	0.47	0.49	0.51	0.53	0.55	0.56	0.56
eCr upper limit	0.43	0.47	0.51	0.54	0.57	0.61	0.64	0.67	0.70	0.72	0.75	0.79	0.82	0.84	0.86	0.87	0.87

PUB265

Are Mutations in the Alpha-Hydroxy Acid Oxidase (HAO1) Gene Not as Harmless as Described?

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Introduction: Alpha-hydroxy acid oxidase (*HAO1*) catalyzes the oxidation of glycolate into glyoxylate in hepatic peroxisomes. Patients with homozygous *HAO1* mutations have massively elevated urinary glycolate excretion (Uglyc), but are said to be clinically asymptomatic.

Case Description: We present three pediatric patients, who either developed clinical sequelae, here urolithiasis (UL), or surprisingly had hyperoxaluria. First patient now 10 years of age, developed UL at age 6 years, which was treated by lithotripsy (stone analysis: 100% whewellite). Currently, he has 2 small stones in left kidney. Recent 24 h urine excluded elevated urinary oxalate excretion (UOx, 0.35-0.43), but high glycolate UGlyc (3.34-4.78 mmol/1.73m^2/d). His grandfather also had recurrent UL, but normal Uox and Uglyc. Patient 2 was 6 months of age at diagnosis of elevated Uox and Uglyc (1.37 and 7.01 mmol/1.73m^2/d, respectively). He has 3 relatives with a history of UL, elevated Uox/creatinine ratio was found in 2/3, and in the boys mother. Genetic evaluation for primary hyperoxaluria (PH) was negative. In patient 3 screening for organic acids detected elevated Uox: 1.56 and Uglyc: 7.04 mmol/1.73m^2/d. Genetic testing for PH was negative. Vitamin B6 though let to decline in Uox. Uglyc remained significantly elevated. Homozygous (family) mutations in *HAO1* were found also in parents, sister and in newborn brother. Father and sister also had elevated Uox (1.09 and 0.92) and Uglyc (4.19 and 4.75 mmol/1.73m^2/d). The newborn has a massively elevated Uglyc/creatinine ratio, but no hyperoxaluria.

Discussion: In the contrary to current understanding, patients with *HAO1* mutations can express a renal phenotype. We do not have an adequate explanation for UL in patient 1, as only Uglyc is elevated and no other risk factor is found. GO inhibition is used as therapeutic target in patients with PH1, which reduces Uox, but elevates Uglyc. Even more problematic to explain is the significant hyperoxaluria in patients 2 and 3 (after excluding secondary reasons). Therefore, the link between *HAO1* (loss of function) mutations and UL, or hyperoxaluria, respectively, clearly needs further clarification.

PUB266

Characterization of Adolescents with Persistent Albuminuria in a Region with a High Prevalence of ESRD of Unknown Etiology

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Background: We report high prevalence of ESRD of unknown etiology. Affected group was between 20 and 30 yo. We screen adolescents for chronic kidney disease (CKD).

Methods: Pts with Albuminuria-creatinuria ratio (ACR) ≥30 mg/gr or GFR ≤75 ml/min were reevaluated. Ultrasound (US) and tomography were performed. Renal bx was performed in pts with persistent albuminuria (PA).

Results: We include 482 pts, mean age 13.3(±1.5), 53.9% were male. We detect 17 pts (3.53%) with PA. US did not show abnormalities. 16 bx were performed.(Table1)

Conclusions: The characteristics of the biopsies are suggestive of established histological damage. Potential genetic and contaminants should be searched.

Histologic Description

Characteristics	N=16, n (%)
LM Glom. Size, m(SI)	177 nm (42)
LM Mesangial Proliferation	6(37.5)
LM Interstitial Nephritis	1 (6.2)
LM Glomerulomegaly	2 (12.5)
LM Glomerulosclerosis	2 (12.5)
LM Mild Interstitial fibrosis	2 (12.5)
LM Podocyte prominence	4 (25)
LM Reabsorption Proteins	5 (31,2)
LM Tubulitis	2 (12.5)
IF Mesangial IgA	1 (6.2)
IF Mesangial IgG	3 (18.7)
IF GBM IgG	2 (12.5)
IF C1q Mesangial ++	1 (6.2)
IF Mesangial kappa and lambda focal traces	3 (18.7)
IF IgM +	1 (6.2)
Negative IF	9 (56,2)
EM % Foot process effacement, med(IQR)	20 (15 - 30)
EM GBM Thickening	6 (37.5)
EM Increased of lysosomes	10 (62.5)
EM Microvillous Degeneration	9 (56.2)
EM Increase of Tubular Lysosomes	1 (6.2)
EM Cytoplasmic Tubular Vacuolization	2 (12.5)
EM Endothelial Edema	1 (6.2)
EM Mesangial electron-dense deposits	3 (18.7)
EM Paramesangial sclerosis	1 (6.2)
EM Paramesangial deposits	1 (6.2)
HD Secondary FSGS	2 (12.5)
HD IgA Nephropathy	1 (6.2)

LM: Light microscopy IF: Immunofluorescence EM: electronic microscopy HD: histologic diagnosis

PUB267

More Than "Getting High," Be Aware of Cannabis-Induced AKI: A Report of Two Pediatric Cases

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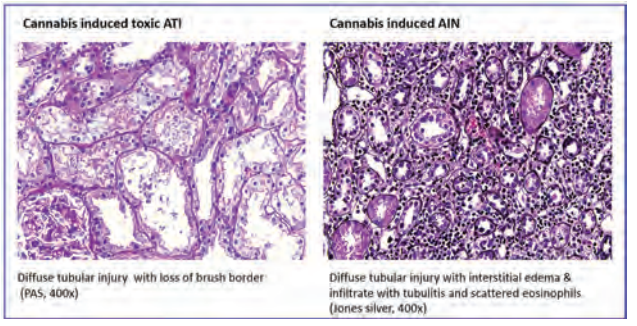
Background: Cannabinoids (synthetic > natural) can have deleterious effects on kidneys. We report 2 cases of cannabis-induced acute kidney injury (AKI) with acute tubular necrosis (ATN) and acute interstitial nephritis (AIN).

Methods: Case Series

Results: Two adolescents were cared for in 2021, presented with elevated serum creatinine (S. Cr). At presentation S. Cr was 1.7- 5.4 mg/dL, peaked at 5.4-6.6 mg/dL. Both patients developed acidosis. Patient 2 had hypokalemia, hypophosphatemia, and hypomagnesemia. Urine drug screen was positive for cannabinoids. Both patients admitted to using natural cannabis predominantly and smoking cannabis joints daily for a few weeks- a month prior to admission. Urinalysis showed proteinuria, leukocyturia, heme+ without RBCs in urine, hyaline casts. Renal bladder sonogram: echogenic kidneys. Kidney biopsy revealed ATN in patient 1 and AIN in patient 2 (Fig2). ATN was managed conservatively, while the patient with AIN received steroids. Both patients responded well with improvement in kidney function.

Conclusions: Though the endocannabinoid system (ECS) has been found to play a beneficial role in renal homeostasis and improvement of tubular cell survival; long-term stimulation and alterations to the ECS can lead to kidney damage as reported here. It is interesting to note that 2 patients predominantly used natural cannabis and reported that they assumed that natural cannabis is safe. A thorough history including drug use should be obtained in cases of AKI, particularly where the cause is not apparent and AKI does not improve with hydration. Awareness of this could lead to early diagnosis, management, and appropriate counseling, which might potentially decrease kidney damage and scarring.

		Patient 1	Patient 2
Age (yrs)		16	15
Ethnicity		Caucasian	Caucasian
Gender		Male	Male
Drug usage		Cannabis joints & synthetic cannabis	Cannabis joints & synthetic cannabis
S. creatinine (mg/dL)	At admission	1.7	5.4
	Peak	5.4	6.6
	At discharge	1.4	3.1
Serum Electrolytes	Potassium	Low-normal	low
	Magnesium	normal	low
	Phosphorus	normal	low
	Bicarbonate	low- normal	low
Serum complement (mg/dL)		C3: 112, C4: 13.4	C3: 167, C4: 31.8
CBC			Normal WBC count. No eosinophilia
Urinalysis		2+ protein, 2+ blood, 8 RBCs/HPF, 10 WBCs/HPF, no glucose or casts	SG 1.006, pH 6.5, 1+ protein, trace blood, 1 RBCs/HPF, 35 WBCs/HPF, 1+ Glucose, 1+ ketones, 4 hyaline casts
Kidney & bladder sonogram		Isoechoic kidneys (RT 12.0 cm, LT 12.1 cm)	Hyperechoic kidneys (14 cm each)
Biopsy	diagnosis	Severe toxic ATN	Acute interstitial nephritis
	LM	diffuse dilation and vacuolization involving 80-90% tubular profiles. Normal glomeruli.	Diffuse (70-80%) lymphocyte predominant AIN with edema & scattered tubulitis with scattered eosinophils (up to 20) involving ~30% tubules. Normal glomeruli.
	EM	2+ global granular mesangium with segmental chunky capillary loop deposits for C3	No immune complex staining.
	IF	Mild increase on GBM thickness. No subepithelial or subendothelial or mesangial deposits. No TBM immune complex deposits.	Normal GBM without any sub epithelial or sub endothelial deposits. Interstitium shows edema, lymphocytes, with deposits along TBM.
Management		Conservative. - Ionotropic PRN for about a week. - Fluid restriction followed by generous fluid intake.	- Solumedrol 1g IV daily x 3 days → daily prednisone 60 mg x 4 weeks. - Magnesium, Potassium, Bicarbonate supplementation temporarily. - Correction of Vitamin D deficiency
Effects on other organs		Seizures at presentation that resolved after admission. EEG normal. Not on anti-epileptic medications.	Cannabis hyperemesis syndrome
Outcome		Discharged to out of state hospital	Follow up and complete recovery



PUB268

Involvement of Succinate Dehydrogenase (SDH) in Deceased Kidney Donors' Inflammation

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Background: Succinate is a Krebs cycle intermediate that is converted to fumarate by succinate dehydrogenase (SDH). SDH activity depends indirectly on the oxygen availability. In deceased renal donation, hypoxia associated to ischemic process can increase renal succinate formation and induce the infiltration of immune cells producing TNF-α, increasing inflammation, renal epithelial apoptosis, as well as leukocyte recruitment, binding and migration, which can lead to renal graft damage. Moreover, increased levels of IL-1β promoting inflammation. We aim to demonstrate that succinate pathway is an important player in early and late inflammation in deceased kidney transplants.

Methods: Relative gene expression of SDH complex genes (SDHA, SDHB, SDHC and SDHD), HIF-1a and inflammatory factors were quantified by qPCR in RNA samples from deceased donors. Succinate levels were measured in serum from deceased kidney donors at the time of donation.

Results: Circulating succinate levels in serum from deceased donors were significantly higher than in healthy volunteers ($p=0.002$). In kidneys samples from deceased donors, gene expression of all four subunits of SDH complex were downregulated before transplantation ($p<0.001$ for all of them) whereas HIF-1α was increased compared to living donors ($p<0.001$). SDHA, SDHB and SDHD gene expression at 4 months after kidney transplant is positively correlated with graft renal function (CKD-EPI). In kidneys from deceased and living donors, SDHA, SDHB and SDHD are negatively associated with recruitment (MCP-1), adhesion (ICAM-1) and activation (IL-1β) of monocyte.

Conclusions: Our results indicate that low gene expression of SDH in kidneys from deceased donors could result in reduced activity of SDH that would reduce the ability to transform succinate to fumarate resulting in succinate accumulation, increasing inflammation that can influence on kidney transplantation outcomes.

PUB269

Lymphoproliferative Disease After Kidney Transplantation: Describing Our Experience

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Background: Post-transplant lymphoproliferative disorders (PTLD) are one of the most common malignancies in kidney transplant (KT) recipients. Immunosuppressive therapy and Epstein Barr Virus (EBV) play a main role in their pathogenesis.

Methods: In this study we retrospectively analyze the characteristics, clinical evolution and treatments of a group of KT recipients performed between 1986 and 2020 in a single center.

Results: We included 31 patients (64.5% males). Polycystic kidney disease was the most frequent cause of renal failure. Before KT a 6.5% of the patients presented another malignancy, 10% were EBV seronegative and one received immunosuppressive therapy secondary to his primary disease. Mean age at KT was 43±12 years. 68% of the KT came from brain-dead donors. The most frequent immunosuppressive regime consisted in tacrolimus, mycophenolic acid and prednisone (61.3%). Basiliximab and Timoglobulin were used in the same proportion for the induction therapy (22.6%). Before PTLD appearance the immunosuppressive therapy was reduced in the 54.8% of the recipients. 13% of them presented acute allograft rejection. The majority of PTLD were diagnosticated between 2016 and 2020. Median time to develop PTLD was 13 years. 54.3% of the patients presented with extranodal involvement. Although all the patients positivized EBV serology, 60% of them had undetectable EBV viral load. The main therapeutical strategy after PTLD consisted in a reduction of the immunosuppressive

therapy. In this way, 28.6% of the recipients was treated with monotherapy with a calcineurin inhibitors and 21.5% with monotherapy with a mTOR inhibitor. In other hand 16.7% received a combination of tacrolimus with a mTOR inhibitor. Rejections were not observed in our group and all the patients presented a preserved kidney function at the end of follow up. Four recipients died because of PTLD. The remaining 27 presented a complete response or stabilization of the disease.

Conclusions: Most of the PTLD were detected between 2016-2020. The time from transplantation to PTLD appearance was long, being EBV viral load negative in the majority of the cases. Graft survival after chemotherapy and reduction of immunosuppressive therapy was excellent, with a low risk of rejection and a good prognosis for hematologic disease. It is possible that a reduction in immunosuppression in selected patients could prevent the development of PTLD.

PUB270

Shorter Antibody-Mediated Rejection-Free Survival in Persistence Preformed DSA vs. Clearance After Kidney Transplantation: A Single-Center 10-Year Experience in Thailand

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Background: Preformed donor specific anti-HLA antibodies (pre-KT DSA) is one of the leading causes of post kidney transplant antibody mediated rejection (ABMR). Decrease level of pre-KT DSA by pre-transplant desensitization is one of the best available methods to lower risk of ABMR after transplantation. Post-transplant follows up of DSA to determine the persistence or clearance of DSA should reflect transplant outcomes. This study aimed to compared outcomes between patients who have persistence and patients who have clearance of DSA after kidney transplantation.

Methods: This retrospective cohort enrolled pre-KT DSA positive (CDC-AHG negative) kidney transplant recipients (KTR) at King Chulalongkorn Memorial Hospital from 2009 to 2018. Post-transplant DSA was tested by Luminex single-antigen assays and divided patient in to two groups 1) DSA clearance (<1000 MFI) and 2) DSA persistence (>1000 MFI). The outcomes were evaluated that comprise biopsy-proven acute rejections, including acute antibody-mediated rejection (ABMR) and acute T cell-mediated rejection (TCMR), subclinical or borderline rejections, and graft loss and mortality. Complications following KT and other associated risks were also assessed.

Results: There were 47 KTR enrolled. The mean pre-KT DSA (MFI) level was 931.37. Sixty percent of patients underwent pre-transplant desensitization. The median follow-up time was 5.7 years after transplant. The persistence DSA group (n=17) had higher rate of ABMR than DSA clearance group (n=30), with hazard ratio (HR) of 4.47 (95% CI, 1.48 – 13.45, p=0.008). Factors associated with persistence DSA include the recipient's age of over 40 years old, higher number of HLA A/B/DR mismatch, and lower tacrolimus levels at six months.

Conclusions: DSA should be monitored in kidney transplant patient with pre-KT DSA. The persistence of pre-KT DSA after kidney transplantation is associated with higher rate of ABMR. Surveillance allograft biopsy should be performed in patient with persistence DSA for early detection of rejection.

PUB271

Angiosarcoma in a Kidney Transplant Recipient with Fibrillary Glomerulonephritis

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Introduction: Kidney transplant recipients are at increased of developing malignancy. Angiosarcomas (AS) are aggressive tumors arising in either blood or lymphatic vessels. Fibrillary glomerulonephritis (FGN) has been described in the setting of malignancies. Here we present a case of metastatic angiosarcoma that developed in a patient with a history of end-stage kidney disease (ESKD) secondary to FGN.

Case Description: A 66-year-old female with ESKD secondary to FGN underwent a five-antigens mismatch living unrelated donor kidney transplant with thymoglobulin and methylprednisolone induction. Pre-transplant workup showed no malignancy. Immunosuppression included tacrolimus, mycophenolic acid, and prednisone. Three months post-transplant, she had a scalp lesion diagnosed as eczema, which improved partially with topical steroids. Four months post-transplant, the lesion increased in size and developed abdominal discomfort with distention. Imaging showed widespread lymphadenopathy, numerous liver lesions, splenomegaly, and ascites. An excisional lymph node biopsy from the neck revealed AS. She developed acute kidney injury with gross hematuria. Urine microscopy revealed numerous intact RBCs but no other abnormal findings. Due to volume overload with low serum albumin (2 g/dl), she was given intravenous albumin and furosemide, and her creatinine improved. Tacrolimus and mycophenolate were stopped, and sirolimus was started. Weekly paclitaxel was initiated, but she developed febrile neutropenia and deconditioning after the second dose, for which she opted out for further chemotherapy. Nine months post-transplant, follow-up showed dramatic clinical improvement with complete resolution of scalp lesions. Imaging showed markedly decreased conspicuity of low attenuation observations in the liver and a marked decrease in mesenteric and retroperitoneal lymphadenopathy. Kidney function remained at baseline.

Discussion: Angiosarcoma is a rare yet aggressive tumor with a poor prognosis in kidney transplant recipients. Here, the dramatic response may have resulted from lowering immunosuppressive drugs and starting chemotherapy. However, the anti-angiogenic activity of mTOR inhibitors is a possible explanation. Most reported AS cases developed from arteriovenous fistulas in kidney transplant patients. This is the first case of AS with FGN with an unexpected dramatic improvement.

PUB272

Recurrence of Scleroderma Renal Crisis After Kidney Transplantation

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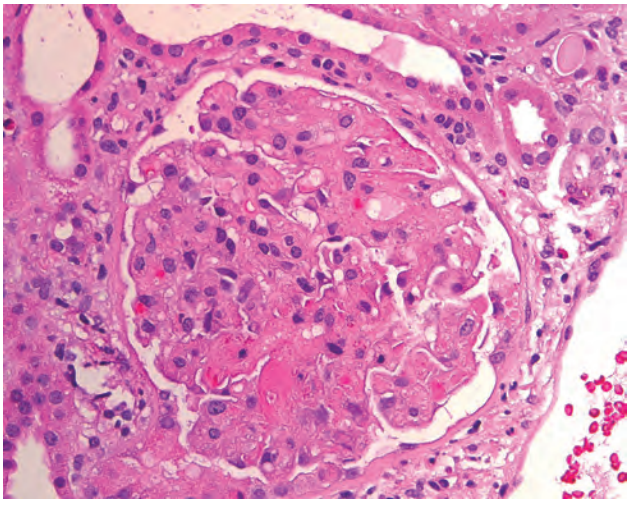
Introduction: Diffuse cutaneous Systemic Sclerosis (dcSSc) is a disease of generalized inflammation, vascular damage, and organ fibrosis. Scleroderma Renal Crisis (SRC), one of the most devastating complications of dcSSc occurs in 5-20% of patients and leads to end stage renal disease (ESRD) 20-50% of the time. SRC is characterized by malignant hypertension and acute kidney injury (AKI). Thrombotic microangiopathic anemia (TMA) and heart failure (HF) can also be seen. SRC patients with ESRD can undergo kidney transplantation (KT) with excellent graft survival. Recurrence of SRC in KT is very rare presumably because the renal vasculature is from a donor kidney without dSSc. We report a case of SRC in a patient post KT

Case Description: A 52-year-old male-to-female transgender patient with a history of ESRD due to SRC, who had a living unrelated KT 2 months prior to admission is admitted hypertension and pulmonary edema. She was found to have HF with reduced ejection fraction (37%) a new pericardial effusion and AKI. Kidney biopsy showed arterioles with thickened walls, bland arteriolitis with semi occlusive changes. She was diuresed and discharged home. She returned 2 weeks later with microangiopathic hemolytic anemia, thrombocytopenia, and worsening kidney function. Repeat kidney biopsy was consistent with TMA. Given her clinical presentation and her biopsy findings, a presumptive diagnosis of SRC was made. The patient was also found to have an antibody-mediated graft rejection. She received captopril, multiple sessions of PLEX, eculizumab, and belatacept, without response. She was initiated on dialysis where she remains today.

Discussion: SRC post KT is unusual but should be considered in the differential of AKI in the right clinical setting. Active dcSSc disease, use of steroids and calcineurin inhibitors may increase the risk of post transplant SRC



PUB273

Kidneys with Kidney Donor Profile Index (KDPI) >85% Can Be Used Successfully in Older Recipients

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Background: Kidneys with KDPI>85% have high discard rate approaching 50%, transplanted elderly patients over the age of 55 have lower risk of all cause mortality and death caused by cardiovascular disease compaired to their counterparts on dialysis .We present one year clinical outcomes of High KDPI > 85% kidneys when transplanted in elderly recipients.

Methods: Retrospective analysis of kidneys with KDPI >85% transplanted in UC Davis Medical Center between 1/1/ 2016 and 12/30/2018

Results: 67 patients received kidneys with KDPI >85% between 1/1/2016 and 12/30/2018, 77.5% were males, 52.2% diabetics, mean recipient age was 64.3years, 41.8% developed delayed graft function staying on dialysis for a mean of 17 days, 82% were alive after one year, 3 kidneys failed 81.5 % of kidneys were functioning after one years with amean creatinine of 1.4mg/dl.

Conclusions: KDPI >85% kidneys can be used successfully in older kidney recipients avoiding dialysis exposure and expanding the donor pool

Recipient characteristics

Total patients	67	
Males	53	77.5%
Females	14	22.5%
Age mean	64.3	
KDPI mean	91.7	
DM	35	52.2%
HTN	12	18%
PCKD	6	8.9%
GN	8	11.9%
others	6	9%
DGF	28	41.8%
Days on dialysis mean	17	
Patient survival 1 year	55	82%
Graft survival 1 year	53	81.5%
creatinine 1y mean	1.4mg/dl	
unavailable data	11	16%

PUB274

Risk Factors and Outcomes of BK Viremia Among Deceased Donor Kidney Transplant Recipients Based on Donor Characteristics

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Background: BK polyomavirus (BKV) and BKV nephropathy (BKN) are common infections among kidney transplant recipients (KTR). Risk factors and outcomes based on donor characteristics remain largely unknown, although some studies suggest BKV is donor derived. In particular, outcomes based on concordance or discordance for BKV among pairs of deceased donor KTRs receiving sister kidneys are unknown.

Methods: This was a retrospective study including all adult deceased donor KTRs at our center between 01/2014 and 12/2019 in which both donor kidneys were transplanted to two different recipients. Recipient pairs from each donor were divided into three groups based on concordance or discordance for BK viremia between the pair: "no BK-group" if neither KTR developed BKV, "discordant" if one KTR developed BKV but not the other and "concordant" if both KTRs developed BKV. Acute rejection (AR), graft failure and BKN were outcomes of interest.

Results: Of 578 KTRs, 336 (58%) were in no BK-group, 176 (30%) were discordant and 66 (11%) were concordant. Donors in the concordant group were younger, had lower KDPI, were less likely to be DCD, and had lower cPRA. Most of the recipient baseline characteristics were similar in all groups. In a multivariate analysis (MA) adjusting for significant factors, KTRs who had a donor with a higher BMI (HR: 0.97; 95% CI: 0.95-0.99; p=0.009) were less likely to develop BKV and those who received depleting induction were more likely to develop BKV (HR: 1.77; 95% CI: 1.26-2.51; p=0.001). There was no difference in the rate of AR, death censored graft failure (DCGF) or BKN among the groups. In MA, concordance was not associated with AR (HR: 0.83; 95% CI: 0.51-1.34; p=0.45), DCGF (HR: 1.77; 95% CI: 0.42-7.50; p=0.43) or BKN (HR: 1.02; 95% CI: 0.51-2.03; p=0.96). By K-M survival analysis, uncensored and DCGF were signficiantly lower in the concordant group (p=0.009 and 0.04 respectively), but not after removing grafts that failed within one year post-transplant. There was no difference in AR or BKN across the groups.

Conclusions: In this large study of 578 deceased donor KTRs, we identified donor BMI and depleting induction to be associated with BKV. Interestingly, concordance or discordance for BKV was not associated with detrimental outcomes.

PUB275

Risk of Rejection, Graft Failure, and Patient Death After Knee or Hip Replacement Surgery in Kidney Transplant Recipients

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Background: There remains a large debate about the timing of hip and knee replacement surgery (joint replacement) in the context of patients with end-stage renal disease (ESRD). Few studies have assessed the surgical complications of knee and hip joint replacement surgery after kidney transplantation; however, there is a paucity of data regarding risk-factors leading to joint-replacement surgery, as well as transplant outcomes. More studies are needed to assess the risk factors of joint replacement on transplanted kidneys in patients with ESRD.

Methods: This was a retrospective study analyzing all adult kidney transplant recipients (KTRs) at our university hospital who underwent hip or knee replacement between 2001 and 2017. Among KTRs with multiple joint replacements, only the first surgery was included. Risk factors for joint replacement and the incidence of rejection and graft survival were compared to controls using incidence density sampling at a 1:3 ratio based on the post-transplant interval.

Results: A total of 101 KTRs underwent joint replacement surgery during the study period. Although we attempted to select controls at a 1:3 ratio, this was not possible in all cases. However for each case, at least one control was selected, resulting in a total of 281 controls. The mean interval from KT to joint replacement was 3.9 ± 3.1 yrs. Patients needing joint replacements were older at time of KT (56 ± 11.7 yrs vs 50.7 ± 12.9, p <0.011) and White (94.1% vs 84%, p=0.01). In regression analysis, only older age was associated with an increased risk of needing joint replacements (HR: 1.04; 95% CI: 1.01-1.06; p =0.001). In multivariable analyses, the need for joint replacement was not associated with patient death (HR: 0.79, 95% CI: 0.52-1.18, p=0.25), death-censored graft failure (HR: 0.87; 95% CI: 0.48-1.56; p=0.64) or rejection (HR: 1.59; 95% CI: 0.77-3.29; p=0.21).

Conclusions: Our observational study suggests that hip or knee joint replacement after kidney transplantation is not a risk factor for acute rejection, graft failure, or patient death. Further studies are required to determine the risks of complications after joint replacement surgery.

PUB276

Transmitted Renal Hypouricemia in Living Donor Kidney Transplantation: A Case Report and Literature Review

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Introduction: Hypouricemia in kidney transplant (KT) recipients is rare since they usually have subnormal kidney function and/or use calcineurin inhibitors. Recently, hypouricemia has gained more interests due to recent progress in understanding of the role of uric acid transporters, and its recognition of renal hypouricemia (RHUC) as a disease, which often complicates kidney stones and exercise-induced acute kidney injury (EIAKI). We report a case of RHUC that developed in a recipient from a living donor with hypouricemia. Besides, we reviewed the previous literature on RHUC among KT recipients/donors for preventing potential complications.

Case Description: A 73-years-old Japanese man underwent KT, and the donor was his wife who had hypouricemia [serum uric acid (S-UA): 0.6 mg/dL]. Nine months after KT, the recipient's S-UA was low (1.5 mg/dL) with serum creatinine (S-Cr) of 1.56 mg/dL, and fractional excretion of UA (FEUA) was high (59.7%; normal <10%), indicating RHUC. Regarding the donor's information, S-Cr, S-UA, and FEUA were 0.95 mg/dL, 1.0 mg/dL, and 54.5%, respectively. To investigate further on the pathogenesis of RHUC in both the recipient and the donor, we performed genetic tests. The donor had a homozygous mutation of W258X in the *SLC22A12* gene and the recipient had a wild type of W258X.

Discussion: We eventually found 5 reports and 6 cases of RHUC in KT from a literature review based on past case reports on MEDLINE. According to the literature review, the incidence of urinary stone and EIAKI in either KT recipients or donors with RHUC were not determined due to a small number of patients in previous studies. However, we should focus on preventing these complications based on the evidence obtained from the general population, since both the recipient and the donor have a single kidney with significant hypouricemia, which potentially can be high risk for these complications. RHUC in donors transmits in recipients, which raise the caution for potential kidney stones or EIAKI in both recipients/donors after KT.

PUB277

Utilization of Donor-Derived Cell-Free DNA and Total Cell-Free DNA to Inform Treatment Decisions in a Pancreas Transplant Recipient with COVID-19 Infection and Active Rejection

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Introduction: Donor derived cell-free DNA (dd-cfDNA) is an established noninvasive biomarker for immunologic rejection of donor tissue in organ transplant recipients. The Prospera™ test, a SNP-based mmPCR methodology, evaluates dd-cfDNA levels as a fraction of total cfDNA. Atypical elevations in total cfDNA, as seen in immunologic responses, could affect the assessment of active rejection (AR). dd-cfDNA has been analyzed in patients undergoing kidney transplants, however, early data suggests that dd-cfDNA behaves similarly following pancreas transplant. Here we present the clinical course of a pancreas transplant recipient with COVID-19 infection for whom, serial dd-cfDNA testing was performed.

Case Description: A 51-year-old female received a deceased donor pancreas transplant in August, 2020. The patient was maintained on a triple immunosuppressive (IS) therapy regime, had stable amylase and lipase levels and no episodes of rejection. Six months later, the patient received the first dose of a COVID-19 vaccine, and the second dose three weeks later. The patient's spouse was diagnosed with COVID-19 and soon after, the patient had elevated pancreatic enzymes, 156 and 199 (prior labs 67 and 27) and presented with elevated temperature (100.4 F), cough, fatigue, loss of taste, diarrhea, myalgias and rhinorrhea. The patient was determined to have COVID-19 with a severity score of 2. IS was reduced and monoclonal ab therapy was initiated. dd-cfDNA fraction was 1.38%, indicated high-risk for AR, with corresponding total cfDNA elevated 10.2 multiples of the median (MoM). The patient was treated with Methylprednisolone 500 mg with a PO Prednisone tail. Three weeks later, the patient was negative for COVID-19 and IS was resumed. The dd-cfDNA fraction at this time was 1.59%, and total cfDNA decreased to 1.1 MoM. Subsequent weekly Prospera tests indicated dd-cfDNA fractions of 1.03%, 0.54%, and 0.81% with total cfDNA levels of 1.4 MoM, 1.3 MoM, and 0.94 MoM.

Discussion: Measurement of dd-cfDNA can guide IS management in pancreas transplant recipients with COVID-19 undergoing AR. Viral infections and anti-rejection therapies can influence total cfDNA. Thus, continued monitoring of both total and dd-cfDNA are needed to identify a true response to therapy.

PUB278

No Benefit of Prophylactic Surgical Drainage in Combined Liver and Kidney Transplantation: Our Experience

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Background: Contrasting results have emerged from limited studies investigating the role of prophylactic surgical drainage in preventing wound morbidity after liver and kidney transplantation. This retrospective study analyzes the use of surgical drain and the incidence of wound complications in combined liver and kidney transplantation.

Methods: A total of 55 patients aged >18 years were divided into two groups: the drain group (D) (n= 35) and the drain-free group (DF) (n= 20). Discretion to place a drain was based exclusively on surgeon preference. The primary outcome was the development of superficial/deep wound complications during the study follow-up. Secondary outcomes included the development of delayed graft function (DGF) of the transplanted kidney, primary non function (PNF) and early allograft dysfunction (EAD) of the transplanted liver, graft failure, graft and patient survival, overall postoperative morbidity rate and length of hospital stay.

Results: With a median follow-up of 14.4 months after transplant, no difference in the incidence of superficial/deep wound complications, except for hematomas, in collections size, intervention rate, PNF, EAD, graft failure and patient survival, was observed between the 2 groups. Significantly lower level of platelets, higher INR values, length of hospital stay, DGF and morbidity rates were reported postoperatively in the D group. Preoperative hypoalbuminemia and longer CIT were included in the propensity score for receiving a drain and were associated with a significantly higher rate of developing a hematoma post-transplant.

Conclusions: Absence of the surgical drain did not appear to adversely affect wound morbidity compared to the prophylactic use of drains in renal transplant patients during CLKTx.

Table 4. Postoperative outcomes analyzed

	DF group (n: 20)	D group (n: 35)	P value
Lowest PLT count (per ml) day 0-10, mean*/SE	33.65*/1.13	20.76*/1.1	**0.004**
Highest INR value day 0-10, mean*/SE	1.83*/1.06	2.16*/1.05	**0.04**
Wound-related complications, n (%)	11 (55)	22 (62.9)	0.57
Superficial, n (%)	2 (10)	5 (14.2)	0.64
Deep, n (%)	9 (45)	22 (62.9)	0.2
Superficial wound complications			
Subcutaneous Hematoma, n (%)	0 (0)	2 (5.7)	0.28
Wound dehiscence, n (%)	2 (10)	4 (11.4)	0.87
Wound infection, n (%)	0 (0)	1 (2.9)	0.45
Deep wound complications			
Hematoma, n (%)	4 (20)	18 (51.4)	**0.02**
Seroma, n (%)	4 (20)	2 (5.7)	0.1
Lymphocele, n (%)	1 (5)	1 (2.9)	0.68
Urinoma, n (%)	0 (0)	1 (2.9)	0.45
Abscess, n (%)	1 (5)	4 (11.4)	0.43
Any type of hematoma, n (%)	4 (20)	19 (54.3)	**0.01**
Max diameter peri-transplant collection (cm), mean±SE	8.47±1.31	8.32±0.81	0.92
Mean diameter peri-transplant collection (cm), mean±SE	6.77±0.95	7.15±0.72	0.77
Intervention on peri-transplant collection			
Any type[1], n (%)	4 (44.4)	7 (31.8)	0.5
IR percutaneous drainage, n (%)	4 (100)	3 (42.9)	0.06
DGF, n (%)	2 (10)	14 (40)	**0.02**
PNF, n (%)	0 (0)	0 (0)	N/A
EAD, n (%)	0 (0)	1 (2.8)	0.44
Death-censored renal allograft failure, n (%)	1 (5)	7 (20)	0.12
Death-uncensored renal allograft loss, n (%)	1 (5)	8 (22.9)	0.09
Death-censored hepatic allograft failure, n (%)	0 (0)	1 (2.8)	0.44
Death-uncensored hepatic allograft loss, n (%)	0 (0)	2 (5.7)	0.27
Death with a functioning graft, n (%)	0 (0)	1 (2.9)	0.43
Liver function indices at postoperative day 7			
Bilirubin level (mg/dl), mean*/SE	1.5*/1.16	2.51*/1.14	**0.02**
INR value, mean*/SE	1.14*/1.03	1.32*/1.03	**0.002**
AST level (U/l), mean*/SE	46.32*/1.14	43.32*/1.10	0.69
ALT level (U/l), mean*/SE	111.40*/1.19	87.86/1.13	0.26
Length of hospital stay (days), mean*/SE	14.78*/1.19	33.08*/1.16	**0.001**
Overall postoperative morbidity			
Clavien-Dindo grade ≥ 3, n (%)	9 (45)	25 (71.4)	**0.05**
CCI, mean±SE	36±5.1	59.2±4.6	**0.002**

[1] Nephrostomy, surgical or IR drainage

PLT, platelet, IR, Interventional Radiology; DGF, Delayed Graft Function; PNF, Primary Non Function; EAD, Early Allograft Dysfunction; CCI, Comprehensive Complication Index

PUB279

Albumin Preceding Simple Plasma Exchange in ABO-Incompatible Kidney Transplantation

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Background: In Japan, where very few deceased donor kidney transplants are performed, approximately 30% of living donor kidney transplants are ABO-incompatible. In these patients, pre-transplant antibody removal by apheresis is generally performed in addition to immunosuppressive therapy. Clinical problems include side effects such as allergic reactions, which are known to frequently occur in conventional plasma exchange (PEx) using fresh frozen plasma (FFP). In this study, we performed PEx using 5% albumin as the replacement fluid in the first half of the procedure followed by FFP.

Methods: PEx starting with albumin replacement fluid was performed in ABO-incompatible kidney transplant recipients (5 patients; 22 sessions). Of the total replacement volume (1.5 plasma volume), 5% albumin was used in the first half, and FFP in the latter half. The incidence of side effects was compared with that of recipients who underwent conventional PEx using FFP (18 patients; 39 sessions). We also studied the changes in coagulation factors before and after PEx using albumin.

Results: The incidence of side effects was significantly higher in recipients who underwent PEx using only FFP (29/39 sessions; 74.4%) compared to that of recipients who underwent PEx using albumin (6/22 sessions; 27.3%) (p<0.001). Among recipients who underwent PEx using albumin, there were only two sessions in which the patient had side effects including skin rash, redness, and itching, which were frequently observed in recipients who underwent PEx using FFP. The median [IQR] of fibrinogen and factor XIII removal rate was 31.6 [27.5, 42.5] and 31.0 [18.0, 44.4] %.

Conclusions: Recently, it has been reported that type AB soluble ABO substances (SAS) neutralizes ABO antibodies. In conventional PEx using FFP, antigen-antibody reaction of SAS and ABO antibodies is thought to induce allergic reactions. Our results suggested that there were fewer allergic reactions in recipients who underwent PEx starting with albumin replacement fluid, because ABO antibodies were removed by albumin first, making it difficult for SAS contained in FFP to react with ABO antibodies. In addition, because there was a slight decrease in the amount of coagulation factors using this method, studies should be made to determine the optimal ratio of albumin to use as the replacement fluid.

PUB280

Post-Transplant Nephrocalcinosis: A Single-Center Case Series

Aileen Wang, Vivek Charu, Colin R. Lenihan. *Stanford University School of Medicine, Stanford, CA.*

Background: Nephrocalcinosis is characterized by multifocal renal tubular and interstitial calcifications. Few studies describe the correlates and outcomes of post-transplant nephrocalcinosis. The goal of this study was to describe the characteristics of patients with nephrocalcinosis diagnosed on kidney transplant biopsy at our center.

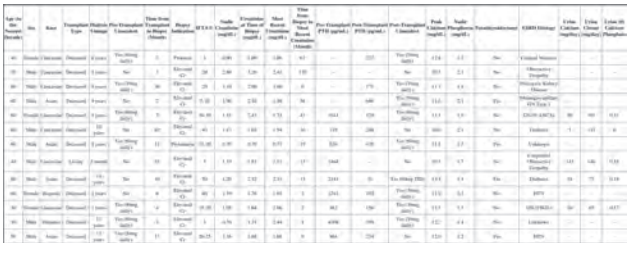
Methods: We searched all adult kidney transplant biopsy reports between January 2010 and May 2021. We excluded biopsies performed on a non-functioning transplant kidney and with a concurrent acute rejection or glomerulonephritis diagnosis. We identified 13 patients with nephrocalcinosis as a principle histological diagnosis.

Results: Patient characteristics and laboratory findings are shown in Table 1. Mean age was 49±13 years, 69.2% were male and 53.8% Caucasian. Time from transplant to biopsy was 15±18 months. Post-transplant nadir creatinine was 1.25±0.55 mg/dL. Creatinine at the time of biopsy was 1.9±0.72 mg/dL. Creatinine measured at mean of 28 months post-biopsy was 1.89±0.61mg/dL. Pre- and post-transplant parathyroid hormone levels were 1516±1192 and 264±190 pg/mL respectively. 4 patients underwent post-transplant parathyroidectomy for a parathyroid adenoma in all cases. 7 and 9 patients were prescribed cinacalcet pre- and post-transplant respectively. Hypocitraturia was found in all 5 patients with available urine studies.

Conclusions: Long dialysis vintage, markedly elevated pre-transplant parathyroid hormone level, and cinacalcet use were common in patients with post-transplant nephrocalcinosis. Further study is required to identify risk factors and treatments for post-transplant nephrocalcinosis.

Funding: Other NIH Support - National Institute of Allergy and Infectious Diseases, Grant/Award Number 1R25AI147369-01

Table 1



PUB281

Adenovirus and Clostridium difficile Coinfection in a Kidney Transplant Recipient

Katherine Rizzolo, Scott Davis. *University of Colorado, Denver, CO.*

Introduction: Adenovirus infection is associated with AKI (hemorrhagic cystitis, tubulointerstitial nephritis, or obstructive uropathy), fevers, and non-glomerular hematuria. Severe adenovirus infections are rare in solid organ transplants, manifesting within the first year of transplant. In this case, we report fever, AKI, and hematuria one year post kidney transplant due to co-infection of *Clostridium difficile* and adenovirus.

Case Description: 65 yo male status post deceased donor kidney transplant one year prior presented with five days of diarrhea and fever. Blood work revealed an acute kidney injury (AKI) from a baseline serum creatinine of 1.5 mg/dL to 2.3 mg/dL. He was found to be *Clostridium dificile* toxin positive and started on PO vancomycin and IV fluid. On hospital day 4, he began having high grade fevers to 40C, worsening creatinine to 5.9 mg/dL, and gross hematuria despite resolution of diarrhea. Urine microscopy revealed non dysmorphic red blood cells. Adenovirus blood and urine PCR returned positive >1 million copies/mL. Remainder of workup was negative. Biopsy was unable to be performed due to persistent bowel overlying the kidney. Tacrolimus was reduced to target a range of 4-7 ng/mL, mycophenolate was discontinued, prednisone was increased to 20 mg.

He received 5 days of 400 mg/kg IVIG with declining levels of adenovirus and resolution of fevers. Adenovirus became undetectable after four months and creatinine stabilized to 1.3 mg/dL

Discussion: This is the first case reported to our knowledge of *Clostridium difficile* coinfection with adenovirus. It is unclear whether the coinfection we report is due to viral immunomodulation or over-immunosuppression, further research will be needed in this area. Detection methods include direct antigen detection, molecular methods, viral culture, or histopathology. Kidney biopsy reveals acute tubular injury, necrosis, interstitial nephritis with pleiomorphic infiltrate, viral cytopathic changes. Treatment is reduction of immunosuppression; refractory cases may be treated with cidofovir, ribavirin, or IVIG. IVIG was used for our patient given its good safety profile compared with antiviral therapies, and theoretical rationale for reducing immunosuppression.

PUB282

Evaluation of Longitudinal Laboratory Data in Clinical Decision Support for Renal Allograft Longevity

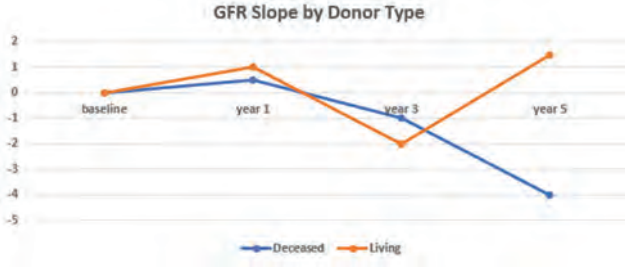
Marcus Garcia,[1] Monique Dodd,[1] Teofilo Borunda Duque,[1] Namita Singh,[2] Christos Argyropoulos.[2] *[1]TriCore Reference Laboratories, Albuquerque, NM; [2]University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Renal transplant is considered the preferred treatment for kidney failure. Pre- and post-transplant monitoring is a key factor influencing allograft longevity. The aim was to assess the value of longitudinal laboratory data for early identification of allograft dysfunction within the renal transplant population in NM.

Methods: This was a retrospective observational study evaluating lab data from Tricore Reference Laboratories for renal transplant patients, age 18-75, in NM between 1/1/10 and 12/31/10. TriCore is the largest lab in NM, serving the University of New Mexico (public) and Presbyterian (private) Hospitals. Following the standard of care clinical guidelines for identification of risks associated with renal allograft rejection, we evaluated estimated glomerular filtration rates (eGFR) for living and deceased allografts post-transplant over a 5-year period. Other labs such as urine protein excretion, complete blood count, comprehensive metabolic panel, hemoglobin A1C, immunosuppressive therapy, biopsy results, and history of ICD10 code (Z94.0) were also evaluated.

Results: A total of 575 patients were identified; 82.4% (474) and 17.5% (101) received allograft from deceased or living donor, respectively. Patients at risk for allograft dysfunction due to age were 15% (86) at <35 and 19% (108) at >65 years of age, respectively and 44% (85) required biopsy. eGFR was evaluated to determine allograft function over time (Figure 1). Average eGFR showed a reduction by 4 ml/min/1.73m^2 over a 5-year period in the deceased donor group and a 1.5 ml/min/1.73m^2 increase over a 5-year period in living donor group. There was a 3 ml/min/1.73m^2 reduction between year 1 and 3 in the living donor group.

Conclusions: Preliminary data results noted that allograft function declines in a linear pattern. This study demonstrates the value of longitudinal clinical laboratory data in the assessment of renal allograft longevity. Assessment of risk factors and care gaps enables early identification of allograft rejection and can ultimately improve patient outcomes.



PUB283

Kidney Transplant in African Americans and Associated Risk of Inferior Allograft Survival

Peter E. Umukoro, Muhammad S. Yaqub, Asif A. Sharfuddin, Oluwafisayo O. Adebiyi. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Inferior allograft outcomes have been previously reported among African Americans (AA) compared to non-African Americans (non-AA) in the intermediate and long terms. When these inferior allograft outcomes start to occur between AA and non-AA is unclear. Some have attributed loss of medicare insurance at 3 years post transplantation as responsible in part for these disparities in allograft outcomes between AA and non-AA. Our objective was to evaluate how soon after transplantation do AA begin having worse graft/survival outcomes compared to non-AA focusing on the short term as soon as 1 year post transplantation period. We hypothesized that there would be no difference between AA and non-AA in graft survival and function, acute rejection rates, and patient survival 1 year after a kidney transplant.

Methods: This is a single center retrospective cohort. 2096 study participants, mean (SD) age 51 (14.4) years, with 456 (21.8%) participants being AA who received a kidney alone transplant between 2005 - 2016 and were followed up for one year. We compared patient/graft survival and function at 1 year; 1-year rates of biopsy-proven acute rejection in AA versus non-AA. We used Cox proportional hazards models to estimate hazard ratios.

Results: No differences were observed in patient survival/surviving graft function. Graft survival with HR of 2.56 (95% CI: 1.03 – 6.35, p<0.04) and one-year acute rejection with HR of 1.73 (95% CI: 1.35 – 2.21, p<0.01) were worse in AA compared to non-AA after adjusting for age, sex, diabetes and donor type.

Conclusions: In this sizeable cohort with ethnic diversity, AA were at higher risk for worse graft outcomes even in the early post-transplant period compared to non-AA. Further studies evaluating factors including socio-economic determinants of health are needed to mitigate against poorer allograft outcomes.

Comparison of Allograft/Patient Survival at one year between African Americans and non-African Americans

Outcome	Hazard Ratios (HR)	95% Confidence Interval of HR	p-value
Death Censored Graft Failure At 1 Year	2.56	1.03 – 6.35	0.04
Graft Failure or Death at 1 Year	1.62	0.91 – 2.88	0.10
Acute Rejection Within 1 Year	1.73	1.35 – 2.21	<0.01
Patient Survival at 1 Year	1.17	0.54 – 2.53	0.69

All models were controlled for age at transplant, sex, diabetes (yes/no) and donor type (living donor versus deceased donor)

PUB284

Assessment of Donor-Derived Cell-Free DNA for Allograft Rejection in Kidney Transplant Patients More Than 1 Year from Transplant: Implications for Clinical Management

Mike Morgan, Sarah McCormick, Philippe Gauthier. *Natera, Inc., San Carlos, CA.*

Background: Detection of acute rejection in patients more than a year from kidney transplant (KT) relies on monitoring kidney function tests such as serum creatinine (SCr), BUN, protein:creatinine reactions and periodic assessment of donor specific antibody levels. Unfortunately, these metrics are lagging indicators of rejection and other injuries that may contribute to declining allograft function over time. In this setting, regular monitoring of donor-derived cell-free DNA (dd-cfDNA) can enhance the nephrologists's ability to detect and monitor acute changes in the allograft and to detect early injury caused by immunosuppression (IS) non-adherence. Here we examined the results of the Prospera™ test, a non-invasive single nucleotide polymorphism-based mmPCR methodology to evaluate dd-cfDNA levels, that was performed on patients >1 year from KT.

Methods: We contacted clinics with high-risk Prospera test results (dd-cfDNA >1%) for patients >1 year from KT. Based on the clinical follow-up, we classified the results as rejection, other injury, IS non-adherence or chronically elevated dd-cfDNA for an unknown reason.

Results: We identified 403 patients with Prospera tests performed between 366 and 14,554 days post-KT with a median time of 1445 days. Among test results, the median dd-cfDNA fraction was 2.19% (range: 1-20.73). Clinical follow-up was available for 115 cases with biopsy-matched results available for 24. Biopsy revealed rejection in 33.3% (8/24) of the cases: ABMR (62.5%, 5/8) and TCMR (37.5%, 3/8). An additional 8 biopsies showed pathological findings consistent with other allograft injury including diabetic/hypertensive nephropathy, BK nephropathy, interstitial fibrosis and tubular atrophy and other injury not classified as rejection. Elevated dd-cfDNA test results in patients without biopsy were attributed to IS non-adherence in 4 cases, as assessed by the physician, and to viral infection (1 CMV, 3 BK virus) in the remaining 4 cases. These findings resulted in referral to the transplant center for 3 patients, treatment for rejection for 1 patient, and serial testing and increased monitoring for 16 patients.

Conclusions: These findings provide real-world data that supports Prospera's utility in identifying allografts at high-risk for injury in patients more than 1 year from transplant.

PUB285

Subclinical Rejections on Kidney Transplant Recipients After COVID-19

Enzo C. Vasquez jiménez,[1,2] Bernardo Moguel,[1] Cesar Flores Gama.[1] *[1]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico; [2]Instituto de Seguridad Social del Estado de Mexico y Municipios, Toluca, Mexico.*

Background: The outcomes after COVID-19 and the associated immunosuppressive agents modification in kidney graft is unknown. We evaluated the presence of de-novo DSA and histopathologic findings in a group of kidney recipients after COVID-19 infection

Methods: Kidney recipients recovered from COVID 19 infection from March 31, 2020 to December 8, 2020 in a single transplant center in Mexico were enrolled. Four weeks after COVID-19 diagnosis, DSA and kidney graft biopsy were performed.

Results: A total of 20 kidney transplant recipients were enrolled. Immunosuppressive regimen was modified in 60% of patients, the most common modification was MMF reduction or withdrawn (35%). Allograft biopsy revealed that 70% had rejection; 20% were classified as active chronic rejection, 15% active ABMR, 20% mixed ABMR/TCMR rejection, 10% borderline for acute TCMR and 5% acute TCMR. Among allografts diagnosed with rejection, 57% were considered as subclinical. All borderline for acute TCMR and active ABMR with dnDSA were subclinical

Conclusions: The unusually high rate of acute rejections and the high number detected without allograft dysfunction in recipients recovered from COVID-19 should be an alert to others transplant centers to monitorize alloimmune response after COVID-19

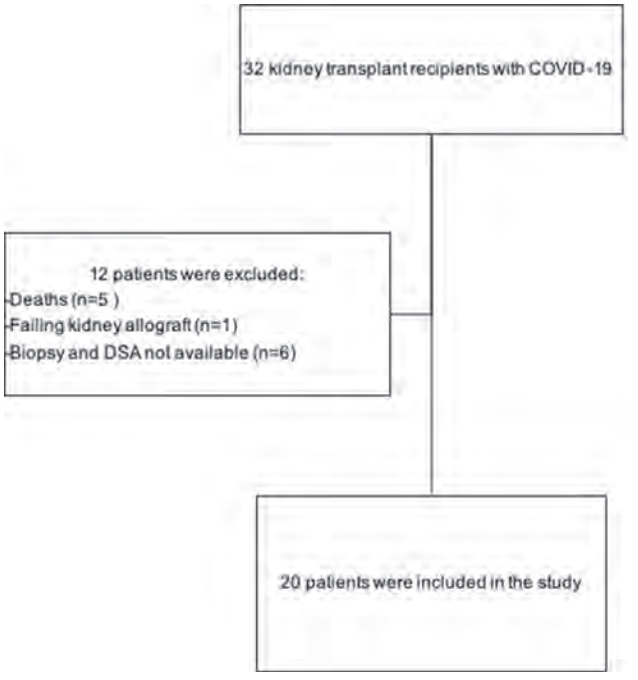


Figure 1. Study flowchart of kidney transplant recipients recovered from COVID-19.

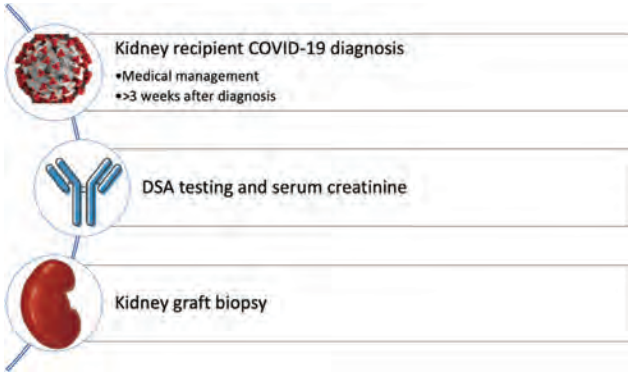


Figure 2. Brief description of the Study Methods.

PUB286

One-Year Follow-Up of Delayed Graft Function in Renal Transplant Patients Performed in Private Hospitals in the State of México, México

Armando Armenta,[2] Eduardo Mancilla,[2,3] José S. Aburto,[2,1] Jesús R. Pérez,[2,1] José R. González,[2,4] Marco S. Escalona,[2] Marcela E. Abasta,[5,2] Armando Armenta Alvarez,[3,2] Hirepan Armenta,[3,2] Delfilia Valle,[2,1] Andrea Armenta,[2] Guillermo Mondragón.[6,2] *[1]SSA, Toluca, Mexico; [2]Toluca Hospital, Toluca, Mexico; [3]Instituto Nacional de Cardiologia Ignacio Chavez, Mexico, Mexico; [4]Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico; [5]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; [6]IMTSC, Cuernavaca, Mexico.*

Background: Renal graft function delay (GFD) is defined as the need for dialysis in the first week after kidney transplantation (KT). The most common cause is acute post-ischemia tubular necrosis (ATN-pi). The survival reported in the literature of kidney grafts (KG) after one year with ATN-pi is about 89% for CDKT and 95% for LDKT. We report the evolution of KT made from May 1994 to December 2019 in two private hospitals in the City of Toluca, State of Mexico.

Methods: The data were obtained from the clinical records and were analyzed with student t-test and Chi2 for continuous or categorical variables respectively. The results are expressed as means with standard deviation, accepted as significant value of $p < 0.05$. SPSS 11.5 statistical program was used.

Results: We perform 28 KT: Male 19 (68%), Female 9 (32%). Age 36.5±14.89 years old (yo). Haemodialysis Pre-KT 22 (78.6%), CAPD pre-KT 6 (21.4%). Cause of CKD: Unknown 19 (68%), Diabetic Nephropathy 5 (17.9%), Others 4 (14.2%). LDKT 13 (46.4%), CDKT 15 (53.6%). The ATN-pi showed up 11 (39.3%), of these 10 with DCKT (90.9%) and 1 LDKT (9.1%). 0 HLA 23 (82.1%), 1 HLA 5 (17.9%). *Evolution post-KT RG function (with SCr mg/dl):* SCr one week post-KT ATN-pi 3.9±1.98 vs No ATN-pi 1.48±0.5 (p 0.0001). SCr one month post-KT ATN-pi 1.47±0.27 vs No ATN-pi 1.18±0.35 (p 0.02). SCr Three months Post-KT ATN-pi 1.25±0.3 vs No ATN-pi 1.13±0.26 (p NS). SCr six months post-KT ATN-pi 1.18±0.18 vs No ATN-pi 1.18±0.3 (p NS). SCr twelve months post-KT ATN-pi 1.25±0.16 vs No ATN-pi 1.18±0.24 (p NS). RG working one year after KT was 28 (100%). *Risk factors associated with the development of ATN-pi:* Male 10/11 with ATN-pi vs 12/13 No ATN-pi (p 0.03) (RR 8.8). DCKT 10 with ATN-pi vs 5 No ATN-pi (p 0.001) (RR 24). *Receptor age;* KT ATN-pi 43.9±12.73 yo vs No ATN-pi 32.11±14.97 yo (p 0.03). Diabetic Nephropathy ATN-pi 4 vs No ATN-pi 1 (p 0.04) (RR 9.1). Cold ischemia time with ATN-pi 14.7±4.9 hours vs No ATN-pi 5.7±8.4 hours (p 0.001). No other risk factors were found.

Conclusions: In our study sample, the incidence of Renal Graft function delay was 39.3%. ATN-pi was the only cause of GFD. The patient's survival and renal graft to a follow-up year was 100%.

PUB287

Challenges Treating Discordant Rejection in Simultaneous Kidney Pancreas Transplant (SPKT)

Fizza Abbas, Linyuan Wang, Arpita Basu. *Emory University, Atlanta, GA.*

Introduction: Discordant rejection in SPKT are uncommon wih limited data on outcomes. We present 2 cases of severe discordant acute rejections of the pancreas presenting early post-transplant (PTx).

Case Description: Patient 1 46-year-old lady underwent SPKT. 4 months PTx she was admitted, with abdominal pain and elevated pancreatic enzymes. CT abdomen was suggestive of transplant pancreatitis. She was treated for presumed pancreas rejection with IV Solumedrol. She was re-admitted 10 days later with significant rise in amylase and lipase. Pancreas biopsy showed moderate acute cellular rejection treated with IV solumedrol and ATG. Patient was readmitted 1 week later with elevated pancreatic enzymes and additional ATG was administered. In the following months while pancreatic enzymes normalized, she developed hyperglycemia needing insulin therapy. 9 months Ptx she is on an oral hypoglycemic agent. **Patient 2** 35-year-old lady underwent SPKT. 9 months PTx she was admitted with fever, elevated pancreatic enzymes elevation and acute kidney injury. Kidney biopsy showed no rejection. CT abdomen showed transplanted pancreatitis. She was treated for presumed pancreas rejection with IV Solumedrol. Patient was readmitted 4 days later with worsening pancreatic enzyme elevation. Pancreas biopsy showed severe acute cellular rejection which was treated with ATG. 12 months Ptx, pancreas and kidney allograft function are normal, however, blood sugars are elevated and being monitored without medications.

Discussion: Treatment of discordant acute pancreas rejection is difficult, particularly with congruent viremia. Large studies assessing allograft and patient outcomes post discordant rejection is needed to better care for this cohort.

Figure 1. Laboratory trends

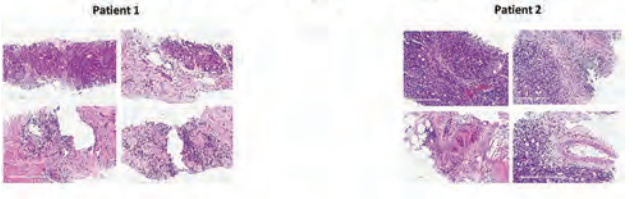
Patient 1

Labs	Hospitalization 1	Discharge 1 (Solumedrol x 3 doses)	Hospitalization 2	Discharge 2 (Solumedrol x 5 doses + ATG x 3 doses)	Hospitalization 3	Discharge 3 (ATG x 5 doses)	3months post rejection
Amylase(U/L)	187	92	611	360	702	559	21
Lipase(U/L)	248	107	1954	913	2982	1820	12
Creatinine (Baseline ~0.8mg/dl)	0.8	0.6	0.8	0.7	0.8	0.7	0.8
CMV PCR(IU/ml)	Undetectable		273		324		Undetectable

Patient 2

Labs	Hospitalization 1	Discharge 1 (3 doses IV Solumedrol)	Hospitalization 2	Discharge 2 (ATG x 5 doses)	3 months post rejection
Amylase[(U/L)]	361	336	492	247	39
Lipase	310	275	690	312	14
Creatinine(Baseline ~0.8mg/dl)	1.3	0.9	0.9	0.7	0.9
CMV PCR(IU/ml)	Undetectable		<35	<35	Undetectable
BK (copies/ml)	1430		667	2550	Undetectable

Figure 2. Pancreas Biopsy Pathology Findings



Findings:
- Acute Cellular Rejection, at least moderate
- Multifocal acinar inflammation with acinar cell injury
- Moderate septal inflammation
- Multifocal venulitis
- Mild intimal arteritis

Findings:
- Acute Cellular Rejection, severe
- Diffuse lobular inflammation (prominent neutrophils) with focal early necrosis
- Venulitis
- Arteritis with focal early fibrinoid necrosis
- Foamy arteriopathy

PUB288

Light Chain Deposition Disease (LCDD) Recurrence Post Kidney Transplant

Joel O. Adewuyi, Alfonso Santos, William L. Clapp. *University of Florida Health, Gainesville, FL.*

Introduction: Advanced Renal disease from LCDD does benefit from renal transplant but allograft survival may be shortened by LCDD recurrence. We report a case to support this

Case Description: 57-yr old male with history of multiple myeloma status post autologous peripheral blood stem cell transplantation (PBSCT) and ESRD due to IgG Kappa LCDD who got a diseased donor kidney transplant (DDKT) and developed recurrence of LCDD. Patient evaluated 4 years prior for creatinine 3.43mg/dL, proteinuria 7.4g/day, kappa light chain(KLC) 118.2mg/dL, lambda light chain(LLC) 13.8mg/dL, K/L ratio 8.5, serum protein electrophoresis (SPEP) with M-spike in gamma region, UPEP showed selective glomerular proteinuria, urine immunofixation with 2% of total urine protein being IgG kappa. Kidney biopsy showed:diffuse tubular and glomerular basement membrane staining for kappa light chain (KLC) 3+, weak basement membrane staining for IgG and albumin 1+, moderate -severe fibrosis, negative amyloid. Bone marrow biopsy: 30-40%, hypocellularity, atypical plasmacytosis, plasma cells with CD138 + up to 5% of marrow cellularity, CD56 +, and KLC restricted. Had 3 cycles of chemotherapy with partial response and autologous PBSCT to achieve complete response 1. Two years later, bone marrow and Kidney biopsies showed evidence of disease relapse. Had another cycle of chemotherapy and salvage PBSCT, follow up bone marrow biopsy negative for plasma cell abnormality. Started on PD due to worsening renal function. Allograft biopsy 9 months post DDKT done due to elevated serum creatinine and proteinuria showed recurrent LCDD (tubular basement membrane thickening and mesangial expansion with nodular accentuation, 3+ Linear staining for KLC, negative for lambda, focal glomerular staining for albumin 1+, Electron dense fine granular deposits along glomerular basement membrane) similar to native kidney biopsy prior to PBSCT. SPEP with M -spike 0.4 g/dl, K/L elevated at 11. He was started on chemotherapy for LCDD recurrence. Renal Allograft failed at 10 months post-DDKT and patient retuned to Hemodialysis

Discussion: This case illustrates that renal allograft survival is reduced in LCDD patients no matter the treatment used to achieve sustained hematologic response and this supports the need for more studies to establish the pathophysiologic mechanisms underlying LCDD recurrence in renal allograft which may serve as therapeutic targets

PUB289

Hypoalbuminemia Is a Risk Factor for Invasive Fungal Infections and Worse Outcomes in Infected Kidney Transplant Recipients

Aniruddha Srivastava, Fauzia Osman, Aahad N. Khan, Margaret R. Jorgenson, Neetika Garg, Fahad Aziz, Maha A. Mohamed, Didier A. Mandelbrot, Arjang Djamali, Sandesh Parajuli. *University of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: Serum albumin is a marker of overall health status. It is unknown if kidney transplant recipients (KTRs) with hypoalbuminemia are at an increased risk of invasive fungal infection (IFI) specifically, blastomycosis, coccidiosis, histoplasmosis, aspergillosis, and cryptococcus.

Methods: In this retrospective observational cohort study, all adult KTRs transplanted between 01/01/2001 and 12/31/2017 were included with serum albumin measured 3-6 months before selected IFIs and compared to matched controls using incident density sampling. KTRs were stratified into three pre-infection albumin levels: normal albumin ≥4.0 g/dL, mild hypoalbuminemia 3.0-<4 g/dL, and significant hypoalbuminemia <3.0 g/dL. Incidence models per 100 person-years and Cox proportional hazards were used to compare outcomes between groups.

Results: 113 KTRs with IFI and 348 controls were included in the study. Mean serum albumin level at the time of IFI was 3.1±0.62 gm/dl. The majority of infected KTRs had aspergillus (48.7%) followed by endemic fungal and cryptococcus infections. Infected KTRs were older at transplant (56±11 vs 53±14 years, p=0.02) with a higher incidence of delayed graft function (23.9% vs 5.8%, p<0.001). Basiliximab induction was more common in those with IFI (55.8% vs 47.4%, p=0.02). Calcineurin-inhibitor maintenance immunosuppression prevailed overall, but differed (85.9% vs 96.9%, p<0.001). Infected KTRs had lower serum albumin level with 7.1% normal, 50.4% mild, and 42.5% significant hypoalbuminemia; while in controls 18.7% had normal, 75.9% mild and only 5.5% significant hypoalbuminemia (p<0.001). The incidence rate of IFIs among normal, mild, and significant hypoalbuminemia was 3.6/100, 8.7/100, and 29.3 person-years, respectively. After multivariate analysis, mild hypoalbuminemia (HR: 2.2, 95%CI: 1.02-4.7) and significant hypoalbuminemia (HR: 5.0 95%CI: 2.3-11.2) had a significantly higher risk of IFI than normal albumin. A similar pattern of mortality and graft failure with hypoalbuminemia after IFI was observed.

Conclusions: These results suggest that hypoalbuminemia is associated with an increased risk of IFI as well as subsequent graft loss and mortality.

PUB290

Incident Fractures in Kidney Transplant Recipients: A Nationwide Cohort Study

Da won Kim,[1] Jaeseok Yang,[2] Myoung soo Kim,[3] Jeong hoon Lee,[4] Jin seok Jeon,[5] Hye Eun Yoon.[1] *[1]Catholic University of Korea, Seoul, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [4]Myongji University, Seodaemun-gu, Seoul, Republic of Korea; [5]Soonchunhyang University Hospital, Yongsan-gu, Seoul, Republic of Korea.*

Background: Increased fracture incidence is a challenging issue among kidney transplantation recipients (KTRs). This study investigated the incidence, location, and predictors of fracture following kidney transplantation (KT).

Methods: Data were obtained from the Korea Organ Transplantation Registry, a nationwide cohort study of KTRs. A total of 5403 KTRs who received KT between January 2014 and June 2019 were included. We estimated incidence rates and risk factors of fracture using Kaplan-Meier method and Cox proportional hazard model.

Results: At median follow-up of 31.6 (18.1 – 46.8) months, 79 patients developed incident fracture. The cumulative incidence of fracture was 2.23% at 5 years. The most frequent locations of fracture were foot (26.3%) and leg (25.0%). Older recipient age [hazard ratio (HR) = 1.038, 95% confidence interval (CI), 1.011 - 1.067; P = 0.007] and diabetes mellitus (HR = 2.404, 95% CI, 1.383 – 4.180; P = 0.002) at baseline were associated with higher risks for fracture after KT, while the use of anti-thymocyte globulin as induction therapy (HR = 0.233, 95% CI, 0.073 – 0.748; P = 0.014) and higher calcium * phosphorous product at 6 months post- transplantation (HR = 0.950, 95% CI, 0.906 – 0.995; P = 0.032) were associated with a lower risk of fracture.

Conclusions: The first 5 years after KT were associated with risks of peripheral skeleton fractures. Recipients' age, diabetes mellitus, induction therapy, and post-transplant calcium/phosphorus interaction may explain the risk. These results define the need of further studies to evaluate the reason for the fracture risks of KTRs.

PUB291

Outcome of 313 Czech Patients with IgA Nephropathy After Renal Transplantation

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Background: The recurrence of IgA nephropathy (IgAN) after kidney transplant is often with the range among 20 – 35 %. The main aim of our study was to evaluate the risk factors affecting the course of the disease after renal biopsy of native kidney and kidney transplant.

Methods: We evaluated clinical parameters and histological findings at the time of biopsy of native kidney and after kidney transplant in 313 Czech patients with IgAN during the follow up of 26 years. Logistic regression model, hypothesis test on binomial distribution and Kaplan-Meier survival curves were used for statistical analysis.

Results: Histologically verified recurrence of IgAN was confirmed in 23 individuals (46.0 %) of the total number of 50 (16.0 %) patients with IgAN with irreversible graft failure. Microscopic hematuria was detected just in 31 patients (62.0%) with graft failure. 10-years renal survival was unfavourable in patients with histologically confirmed recurrence of IgAN and microscopic hematuria in comparison with patients with recurrence of IgAN without microscopic hematuria. Using hierarchial clustering method patients with graft failure were divided into two groups according to the time from kidney transplant to graft failure (11.2 versus 6.1 years) which excellently correlated with the distribution of two groups based on the time from the renal biopsy of native kidney to end stage renal disease (5.9 versus 0.4 years). Body mass index, proteinuria, microscopic hematuria, histological evaluation of fibrosis and crescents at the time of renal biopsy of native kidney were confirmed for the differentiation into two groups.

Conclusions: The presence of microscopic hematuria together with histological verified recurrence of IgAN were confirmed to be unfavourable predictors of renal survival in our cohort of 313 Czech patients after kidney transplant (P<0.001). Higher age of donor kidney transplant, histological verified recurrence of IgAN, antibody mediated rejection and the onset of microscopic hematuria and proteinuria till one year after kidney transplant were confirmed for worse graft survival in multivariate Cox regression analysis in patients with original diagnosis of IgAN in native kidney biopsy.

PUB292

Symptoms and Occurrence of Hepatitis E in Solid-Organ Recipients: A Single-Center Experience of the Last Five Years

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Background: The Hepatitis E virus (HEV) can be found worldwide and the transmission is mainly fecal-oral. In Germany, transfection occurs especially from pork or beef, where genotype 3 is predominant. While most infections are asymptomatic, under immunosuppressive therapy a chronic (and fatal) course of Hepatitis E is possible. Regular testing is often missing due to lack of experience. Therefore, we retrospectively evaluated all solid-organ transplant patients in our tertiary care center with a positive diagnosis of Hepatitis E in the last five years.

Methods: All solid-organ recipients with positive HEV-RNA replication in the blood in the last 5 years were retrospectively analysed regarding disease manifestation, immunosuppressive therapy, and course of HEV infection. HEV-IgG or IgM alone were not sufficient for diagnosis.

Results: From 2015 to 2020 14 solid-organ transplant patients (4x kidney, 5x heart, 4x liver, 1x lung) were diagnosed with HEV in our center. All patients showed elevated transaminases before diagnosis. In total 3 patients experienced abdominal pain, two presenting with acute liver failure. Overall, HEV infection occurred after a median of 8.6 years after transplant, however 3 patients developed HEV within the first year after transplantation. The transmission path remained uncertain in all cases. Blood transfusions were never associated. Contaminated and/or undercooked meat was the most likely cause, especially as none of the patients were vegetarian. Regarding immunosuppressive therapy, 92 % (N=13) had a tacrolimus based regimen combined with either mycophenolic acid or m-Tor inhibitor. No significant differences between the two could be found. 10 out of 14 patients were treated with Ribavirin because of either persistent HEV-RNA or because of the severe course of the disease. In 4 patients HEV infection disappeared without specific treatment due to the reduction of immunosuppressive therapy. One patient developed a chronic HEV infection, which resolved after Ribavirin therapy.

Conclusions: HEV is a common cause of elevated transaminases in solid-organ recipients and should be considered for differential diagnosis. Therefore, we suggest a more precise instruction – even years after transplantation – regarding cooking rules.

PUB293

Vancomycin Nephrotoxicity Causing Renal Transplant AKI

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Introduction: Nephrotoxicity is a rather frequent side effect of vancomycin treatment. Attributes of vancomycin nephrotoxicity (VN) are well documented including its clinical manifestations and renal morphologic changes. However, VN has not been documented as the cause of acute kidney injury in the renal transplant setting.

Case Description: We herein reported the first three such cases. In each of these cases acute kidney injury developed concurrently with vancomycin treatment and resolved after its cessation. As compared with the general population VN in the renal transplant setting displayed some unusual clinical behaviors. Its development was rather capricious, being noted in some treatment episode, but not others even in the same patient. Acute kidney injury developed gradually in conjunction with a protracted vancomycin treatment, in contrast to a precipitous course in the non-transplant setting. However, renal transplant biopsies showed typical features of VN in each case

Discussion: VN is an exceptional but now well documented causes of acute kidney injury in renal transplant recipients. VN in this setting may display some atypical features setting it apart from that in the general population. However, renal transplant biopsy changes are characteristic and are amenable to a definitive diagnosis

PUB294

A Qualitative Exploration of Patient-Provider Communication Challenges After a Kidney Transplant

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Background: Kidney transplantation is a life-altering treatment, but symptoms and drug side effects persist for many patients post-transplant. Effective communication with the healthcare team (HCT) is key to address these, yet research shows patients find that challenging. Ineffective communication may lead to inadequate assessment and management of symptoms. Although communication is among patients' top research priorities, less than 5% of articles in the two leading transplant journals address it. To fill this gap, we conducted a qualitative exploration of communication challenges from recipients' perspective.

Methods: Within a larger study, we used Qualitative Description methodology to understand the quality of communication between patients and HCT post-transplant. Purposive recruitment was done via flyers (Jun-Dec2020). Patients with significant cognitive impairment or insufficient English were excluded. In-depth, semi-structured, individual interviews were recorded and transcribed verbatim. Directed content analysis framed the iterative development of codes.

Results: 7 recipients (4 males, ages 51-75, 4-15.5 years post-transplant) and 1 caregiver participated. Findings indicate a range of experiences, from regular contact with HCT to little perceived opportunity to communicate in-between clinic visits. Compared to pre-transplant care, communication was less frequent and many patients felt isolated, making it difficult for them to know where and how to seek information and support. Instead, patients relied on searching for information online, visiting family doctors or the emergency room. Some used phone/voicemail to reach HCT, but these were not always timely or efficient. Patients also raised the need for HCT to consider the uniqueness of each patient and their broader context, in addition to quantitative measures, in assessing their health. The diverse communication experiences also relate to patients' comfort with self-advocacy. While some proactively initiate conversation, others are more reserved.

Conclusions: Communication challenges between kidney transplant recipients and HCT contribute to feelings of isolation and difficulties navigating post-transplant life. Tailoring communication to individual preferences may improve patient-centered care.

PUB295

CMV-Associated Thrombosis in a Kidney Transplant Recipient

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Introduction: Cytomegalovirus (CMV) infection is a common infectious complication after kidney transplantation. Indirect effects of CMV infection include an increased risk of secondary infections, increased risk of acute rejection and chronic allograft dysfunction. However, it is not well known that CMV may also increase the risk of venous and arterial thrombosis. Here we present a case of acute deep venous thromboembolism associated with acute CMV disease in a kidney transplant recipient.

Case Description: A 64 year old male presented with 4 weeks of sore throat, cough, subjective fevers, and fatigue. 3 weeks prior, he presented to an outside hospital with flu-like symptoms and complaints of right calf pain. Imaging showed the right leg with totally thrombosed posterior tibial and peroneal veins as well as acute partially thrombosed popliteal vein. The patient was subsequently admitted to the hospital and found with a CMV PCR of 35,900 IU/ml, after which he underwent an esophagogastroduodenoscopy (EGD) and colonoscopy with biopsies confirming CMV in the lower esophagus consistent with CMV esophagitis. IV ganciclovir treatment was initiated with appropriate response seen.

Discussion: CMV belongs to the herpesvirus family that establishes latent infection following a primary infection. For patients who are CMV seropositive, the risk of CMV reactivation is highest in the setting of systemic immunosuppression. CMV infections may present with a wide array of syndromes ranging from meningoencephalitis to enteritis/colitis and hepatitis. In addition, CMV infection has been associated with thromboembolic events. Kidney transplant recipients show a high prevalence of thrombotic events compared with the general population. In short, acute CMV infection should be considered as a risk factor for venous thromboembolism. Therefore, diagnosis of acute CMV infection in patients with an acute thrombosis should redefine the thrombotic event as provoked rather than unprovoked, limiting the duration of anticoagulation treatment.

PUB296

Comparison of the Efficacy and Safety Between Anti-Thymocyte Globulin vs. Basiliximab in Deceased Donor Kidney Transplantation: A Multicenter Cohort

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Background: Induction immunosuppressant is decided upon the condition of deceased donors and recipients in deceased donor kidney transplantation (DDKT). Although anti-thymocyte globulin (ATG) is preferred in immunologically high risk patients, there has no clear evidences for the efficacy and safety of induction agent in DDKT. This study aims to compare the efficacy and safety between ATG and basiliximab (BSX) based on donor characteristics in DDKT.

Methods: A total of 724 kidney transplant recipients (KTRs) from 3 transplant centers were enrolled and ATG-DDKT group was 252 and BSX-DDKT group was 472. We investigated the impact of induction therapy based on donor age of 60, donor kidney with acute kidney injury (AKI) and kidney donor profile index (KDPI) score of 65% on post-transplant clinical outcomes in delayed graft function (DGF), acute rejection (AR), infectious complications, allograft and patient survivals.

Results: ATG-DDKT group had poor donor condition and highly sensitized recipients than BSX-DDKT group. DGF did not show statistically significant differences according to induction agent in terms of elderly/young donor, AKI/non-AKI, and high-KDPI/low-KDPI subgroups. Acute rejection and infection rate did not show meaningful differences. Death-censored allograft survival and patient survival rate between induction agents were also statistically irrelevant.

Conclusions: Our results suggest that though ATG was more frequently applied to poor donor condition and highly sensitized recipients, ATG was not inferior to BSX not only in aspect of survival rate but also DGF, AR and infection aspects. Therefore, as an induction agent, ATG should be considered in preference to BSX, especially in high-risk DDKT.

Funding: Government Support - Non-U.S.

Table 5. Risk factors for allograft failure in deceased donor kidney transplantation

	Unadjusted HR (95% C.I.)	P	Adjusted HR[a] (95% C.I.)	P
Induction therapy	1.225 (0.715-2.10)	0.460	0.713 (0.360-1.413)	0.332
Transplant years				
1996-2005	Reference		Reference	
2006-2012	0.760 (0.182-3.169)	0.706	0.601 (0.303-1.189)	0.923
2013-2019	0.440 (0.103-1.886)	0.269	0.376 (0.101-1.673)	0.931
Transplant centers				
Seoul St. Mary Hospital	Reference		Reference	
Uijeongbu St. Mary Hospital	1.187 (0.508-2.774)	0.692	0.742 (0.281-1.959)	0.547
Kyemyeoung Dongsan Hospital	0.551 (0.298-1.018)	0.057	1.025 (0.311-3.382)	0.968
Recipient age	0.971 (0.48-0.994)	0.014	0.984 (0.958-1.011)	0.253
Recipient gender	0.980 (0.607-1.582)	0.934	0.938 (0.545-1.613)	0.816
Recipient BMI	0.981 (0.914-1.054)	0.608	0.963 (0.892-1.040)	0.336
Donor age	1.020 (1.002-1.040)	0.034	0.999 (0.972-1.026)	0.931
Donor gender	1.726 (1.076-2.770)	0.024	0.686 (0.400-1.178)	0.172
Donor BMI	0.956(0.891-1.026)	0.215	0.973 (0.896-1.057)	0.521
Cold ischemic time	0.999 (0.997-1.001)	0.564	1.001 (0.998-1.003)	0.714
Prior KT	1.119 (0.535-2.340)	0.765	1.070 (0.449-2.548)	0.879
PRA class I+II>30%	0.845 (0.439-1.626)	0.614	2.458 (0.652-9.265)	0.184
Delayed graft function	1.301 (0.759=2.229)	0.338	0.569 (0.308-1.052)	0.072
BPAR	7.811 (4.711-12.953)	0.001	0.135 (0.075-0.244)	0.001
Deceased donor AKI	1.451 (0.892-2.358)	0.133	0.890 (0.496-1.597)	0.696
KDPI score	2.767 (1.626-4.708)	0.001	0.406 (0.186-0.889)	0.024

PUB297

Longitudinal Urine Inflammatory Profile During Renal Transplantation

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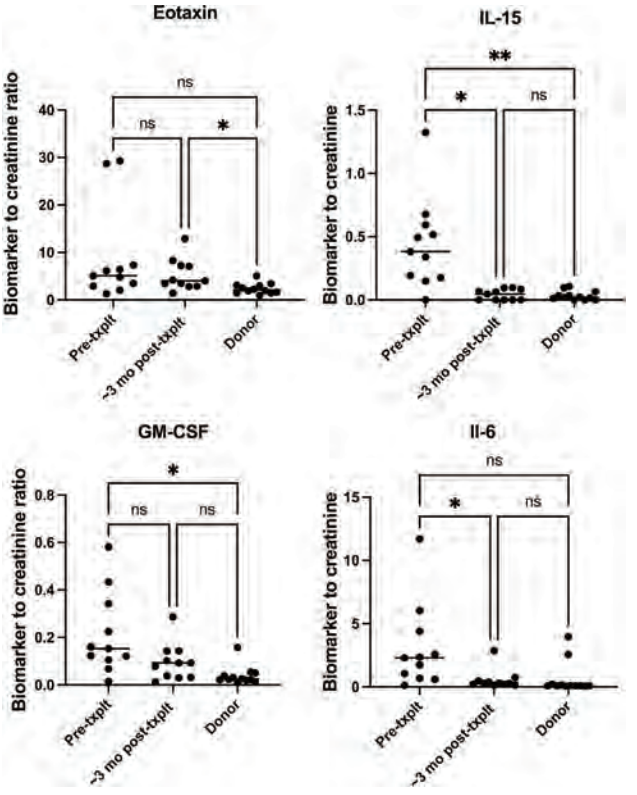
Background: In the year 2020, more than 5,000 living donor kidney transplants were performed in the United States. Kidney transplant recipients are subjected to several types of immunosuppressants in order to prevent rejection of the graft. Over-immunosuppression increases the risk of infectious complications and these patients require a delicate balance. Inflammatory profiles from the urine can help identify which biomarkers may guide clinicians in balancing over vs. under-immunosuppression.

Methods: Urine samples were obtained from 12 kidney donor-recipient pairs at a pre-operative visit ~1 week prior to or at time of transplant and then for the recipients, ~3 months following transplantation. The urine samples were analyzed using inflammatory urine biomarker profiles (Mesoscale Discovery). Urine levels were then normalized to urine creatinine values. Differences were noted between groups using the mixed-measures ANOVA, corrected for multiple comparisons with the Tukey test to get adjusted p-values.

Results: Results are presented in the figure, but it was identified that eotaxin urine levels were higher in post-transplant samples compared to donor samples; interleukin-15 levels were higher in pre-transplant samples compared to both donors and post-transplant samples; GM-CSF levels were higher in pre-transplant samples compared to their donors; and interleukin-6 levels were higher in pre-transplant samples compared to their post-transplant samples.

Conclusions: The urine inflammatory profile evolves over the transplant course between donors, pre-transplant recipients and transplant recipients. Although the transplant itself is typically accepted as a pro-inflammatory event, levels of biomarks in the urine tend to decrease post-transplant. Immunosuppression regimens may influence inflammatory profiles and warrant further investigation.

Funding: NIDDK Support



PUB298

A Study of Outcomes of Renal Transplantation from Deceased Donors in a Tertiary Care Centre from Southern India

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Background: In India, there are large number of end stage renal disease patients awaiting renal transplantation. Deceased donor reanl transplantation(DDRT) is one possible solution to this. So this study aimed to determine the outcomes of DDRT.

Methods: Total 126 DDRT recipients in a tertiary care hospital in southern India, between 2013 and 2020 were taken in to the study and the outcomes were retrospectively analysed.

Results: Out of 339 renal tranplants, 126(37%) were DDRT in the study period. Mean age at transplant was 38.3 years.77.7% were males and 22.3 % were femlaes. 73.8% patients received basiliximab, 26.2% received antithymocyte globulin for induction. Steroids, calcineurine inhibitors and mycophenolate mofetil were used for maintenance immunosupression. Over a mean follow up of 3.6 years, patient and graft survival rates were 85% and 92,6%, respectively, with a median serum creatine of 1.32 mg/dl. The incidence of delayed graft function(DGF) was 54.3%. The incidence of slow graft function was 33.4%. The incidence of immediate graft function was 12.3%. Prolonged cold ischaemia time was risk factor for DGF. Mean cold ischemia time was 4.2 hours.

Conclusions: Outcomes of DDRT showed successful results. So DDRT has a potential to expand donor pool and shorten the waiting list for renal transplantation. Increasing public awareness and good communication and a well trained team of transplant coordinators can help in improving the number of organ donations.

PUB299

Pressure Natriuresis and Diuresis Are Differentially Regulated Depending on Age and Sex

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Background: The renal capacity for handling salt and water is linked to hypertension. This study aimed to clarify the sex- and age-related natriuretic and diuretic differences in blood pressure (BP) regulation.

Methods: We analyzed two datasets: one from the E-SPECIAL trial, which evaluated the effect of a low-salt diet (LSD) on lowering albuminuria in 235 patients with nondiabetic chronic kidney disease, and the other from the Korean Genome and Epidemiology Study (KoGES), including 4,937 subjects.

Results: In the E-SPECIAL trial, BP was lower in premenopausal women (Pre) than in younger men (Y), and the gap disappeared between postmenopausal women (Post) and older men (O). LSD decreased urine sodium in Y, Post, and O but did not mitigate urine sodium in Pre. A positive correlation between BP and urine sodium was

observed only in the younger groups (Pre, Y). Urine volume was greater in Pre than in Y, and urine concentration was reciprocally lower in Pre than in Y. Urine volume was positively correlated with BP in Pre and negatively associated with BP in other groups. Urine volume and urine sodium were the most decisive factors for predicting BP in Pre. In the KoGES, BP was lowest in Pre. Urine sodium increased in Pre compared with Post, although sodium intake was not different. The correlation between BP and urine sodium augmented in younger groups (Pre, Y).

Conclusions: The pressure-natriuretic and pressure-diuretic responses were well conserved in Pre and mitigated in Post. Augmented natriuresis and diuresis might contribute to lower BP in Pre.

PUB300

Misoprostol-Induced Pulmonary Edema in a Pregnant Woman with ESKD Undergoing Induction of Labor Following SARS-CoV-2 Infection

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Introduction: Misoprostol can induce pulmonary edema in patients with end stage kidney disease (ESKD) undergoing induction of labor (IOL). Careful monitoring and interdisciplinary care is required in these complicated patients with tenuous respiratory status. We present a case of misoprostol-induced pulmonary edema in a pregnant women with ESKD requiring hemodialysis (HD) who may have been at higher risk of adverse effects due to recent SARS CoV-2 infection.

Case Description: A 21-year-old woman at 34 weeks, 6 days gestation in her first pregnancy and ESKD due to IgA nephropathy on home hemodialysis (HHD) was admitted for IOL. She had been hospitalized at 21 weeks gestation with severe SARS CoV-2 infection requiring ICU stay. She recovered and was discharged on HHD 6 hours, 6 days weekly. She required 2L supplemental oxygen upon discharge for a total of 7 weeks. Her BUN was maintained < 35mg/dl throughout her pregnancy. Prior to IOL, patient was euvolmic with oxygen saturation of 96% on room air, and patient was at her dry weight. IOL was initiated with two doses of vaginal misoprostol, 25mcg per dose, first dose at 8:37PM then another at 12:38AM. At 3AM she developed flash pulmonary edema. Her oxygen saturation dropped to 90% and B lines were seen in the apex of both lungs on point of care ultrasound. No clinical or laboratory signs of pre-eclampsia were found. Patient required urgent dialysis with 2L of fluid removal while she was in early labor, with resolution of symptoms. Given her tenuous fluid status, it was decided to perform primary cesarean section, which resulted in the birth of a healthy infant.

Discussion: Misoprostol has been identified as a possible cause of pulmonary edema in at least two cases of otherwise healthy asymptomatic patients. This is first report of misoprostol causing flash pulmonary edema in a patient with ESKD. Other prostaglandin analogues have been reported to cause pulmonary edema, and the FDA lists edema and myocardial infarction among possible cardiovascular adverse effects of misoprostol. We hypothesize that our patient was at higher risk of development of adverse effects due to her recent severe SARS CoV-2 infection.

PUB301

Predictors of Readmission in Patients with Advanced CKD and Colon Cancer: A Nationwide Analysis

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Background: It is well-documented that chronic kidney disease (CKD) and colorectal cancer (CRC) have an almost reciprocal effect, with CKD associated with development of CRC and viceversa. We attempt to explore predictors that increase the risk for 30-day readmission rates in patients with CRC and conconcomitant CKD.

Methods: A retrospective study of the 2017 National Readmission Database of adult patients readmitted within 30 days after an index admission for CRC with a concomitant diagnosis of CKD 4 and greater. We aim to identify 30-day readmission rate, mortality, healthcare related utilization resources, and independent predictors of readmission.

Results: A total of 5,678 patients with CKD were admitted with a diagnosis of CRC. The 30-day readmission rate was 28.3%. Main causes for readmission were sepsis, acute kidney failure (AKI), recurrent malignant or metastatic disease and pericarditis. Readmitted patients were more likely to be female (39.9% vs 37.1%; P=0.05), obese (15.2% vs 11.8%; P<0.01), develop AKI (37.6% vs 29.4%; P<0.01) and ileus (12.4% vs 8.7%; P<0.01). Readmission was associated with higher in-hospital mortality rate (1.5% vs. 0.1%; P<0.01), hypertension (2.2% vs 4.1%; P<0.01), and hemodialysis requirement (32.7% vs 36.4%; P=0.03). The total health care in-hospital economic burden of readmission was $104 million in total charges and $25.1 million in total costs. Independent predictors of readmission were prolonged length of stay, pleural effusion, and alcohol abuse. Factors preventative of readmission were younger age and disposition to a skilled nursing facility.

Conclusions: Readmissions in patients with CRC and comorbid advance stages of CKD (4 & 5) is associated with high morbidity and health care burden. Through this study we identified risk factors that can be targeted to help reduce this burden. Controlling these factors could help reduce re-admission rates and thus reduce morbidity and mortality. Similarly, focus on proper disposition planning can greatly improve outcomes.

Predictors of Readmissions

Variable	Adjusted odds ratio (95% confidence interval)	P value
Comorbidities		
Hypertension	0.73 (0.40-1.33)	<0.01
Obesity	0.88 (0.71-1.09)	<0.01
In-Hospital Complications		
Iron deficiency anemia	1.08 (0.88-1.32)	<0.01
Ileus	0.86 (0.66-1.12)	<0.01
Pleural effusion	1.40 (1.07-1.82)	<0.01

PUB302

Urinary Dickkopf-3 (DKK3) Uncovers Unapparent Progressive Kidney Injury in Patients with Chronic Obstructive Pulmonary Disease: An Etiological Study and Experimental Validation

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Background: Chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) represent global public health problems with high disease-related morbidity and mortality. However, the interaction between both diseases remains unclear.

Methods: In a novel murine model, cigarette smoke (CS)-induced lung injury was combined with a CKD model (CS-CKD model). In 2,314 patients of the prospective multi-center COSYCONET study, urinary Dickkopf-3 (DKK3), a renal tubular stress marker, was quantified. The association between urinary DKK3 and trajectories of FEV_1 and estimated glomerular filtration rate (eGFR), exercise capacity, risk of exacerbation, and mortality was determined (follow-up 37.1 months).

Results: In the CS-CKD model, CKD was associated with higher systemic and pulmonary inflammation, and the combination of CKD and CS significantly aggravated kidney inflammation as well as fibrosis and increased renal expression of DKK3. Abrogation of *Dkk3* attenuated kidney injury and pulmonary inflammation alike. In COPD patients, higher urinary DKK3 was associated with rapidly declining FEV_1 (OR 3.36, P<0.0001), higher risk for exacerbation, lower 6-minute walking distance, and higher all-cause mortality (HR 1.49, P=0.015). Importantly, higher urinary DKK3 was also associated with declining eGFR during follow-up (OR 2.23, P=0.0005). Neither eGFR nor proteinuria were associated with lung or kidney dysfunction during follow-up.

Conclusions: In summary, the present study identified a strong pathophysiological link between lung and kidney dysfunction, which is at least partially mediated by DKK3. Urinary DKK3 allows identification of COPD patients at increased risk for deteriorating pulmonary and kidney function as well as adverse outcomes. These patients might particularly benefit from preventive therapeutic strategies as a personalized-medicine approach.

PUB303

Outpatient Treatment Patterns of Hyperkalemia in the United States: The Design and Initial Findings from ZORA, an Observational Study

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Background: Hyperkalemia (HK) is a potentially life-threatening disorder due to alterations in cardiac conduction, which may result in arrhythmias and sudden death. Potassium binders is a key pillar in the outpatient treatment of HK, but conventional binders, including sodium polystyrene sulfonate (SPS), are generally poorly tolerated, lack palatability and have limited long-term efficacy – with suboptimal use as a consequence. New potassium binders (patiromer and sodium zirconium cyclosilicate [SZC]) with a more beneficial tolerability profile have become available, but contemporary real-world evidence on outpatient treatment patterns including these new therapeutic options is scarce. **Purpose**: To describe the characteristics and treatment patterns among patients with outpatient potassium binder treatment in the US.

Methods: This is an observational study including patients who filled an outpatient prescription for SPS, patiromer or SZC between 1 Jan 2018 and 30 Jun 2020, as identified in HealthVerity claims data linked with Quest Diagnostics laboratory data. Patient characteristics and binder treatment patterns will be described using standard descriptive statistics and survival analysis.

Results: The data set includes a random sample of 20,000 patients with a filled prescription for SPS, and approximately 20,000 patients with a filled prescription for a new binder (patiromer or SZC), over a data capture period of 30 months for patiromer and 12 months for SZC. Analyses on patient characteristics (such as demographics, HK severity, comorbidities, treatment history etc.) and their associations with outpatient treatment choice, as well as binder treatment patterns and trends over time, are ongoing and will be presented.

Conclusions: This study will identify important insights into the characteristics and binder treatment patterns among US patients with HK, and provide useful guidance to improve adherence to guidelines and optimize patient care.

Funding: Commercial Support - AstraZeneca

PUB304

eGFR calculation Without the Race Coefficient Obscures Obesity-Related Glomerulopathy in Female Adolescents

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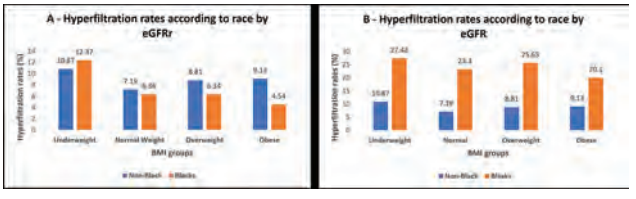
Background: Obesity is more prevalent among minorities, increasing the risk for cardio-renal morbidity. We explored interactions between race, body mass index (BMI), and the risk of hyperfiltration associated with Obesity Related Glomerulopathy (ORG).

Methods: We created a cohort of women and girls ages 12-21 from the New York area using their longitudinal electronic health records (EHR). Glomerular filtration rate (GFR) was estimated in two ways: I) using the standard age recommended formulae, and II) eGFRr –without a race-specific coefficient. Multivariate logistic regression was used to analyze the relative contribution of risk factors for ORG associated hyperfiltration, defined by a threshold of ≥135ml/min/1.73m^2.

Results: 7315 Black and 15,102 non-Black women and girls were evaluated for kidney function in parallel to body measures. Hyperfiltration was more frequent in Black compared to non-Black individuals when using standard eGFR but was lower after eliminating the race-specific coefficient. Black race was independently associated with hyperfiltration with standard eGFR calculation (OR=3.43, 95% CI 2.95-3.99) but the association was reversed when estimated by eGFRr (OR=0.56, 95% CI 0.45-0.70). Risk of hyperfiltration was higher for Black individuals across all BMI strata with standard eGFR estimates, but when estimated as eGFRr hyperfiltration filtration risk was reduced for overweight (OR =0.70 95% CI 0.54-0.89) and obese (OR=0.47, 95% CI 0.37-0.60) participants.

Conclusions: Estimated CKD prevalence among Black adolescents and young adults increases following removal of the race coefficient while fewer have evidence of obesity associated hyperfiltration. In the CKD range of GFR we should consider a gradual increase in the race coefficient to avoid underestimation of obesity related glomerulopathy in the high normal range of GFR

Funding: Other NIH Support - This project was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, through The Rockefeller University, Grant # UL1 TR001866, The Sackler Center for Biomedicine at The Rockefeller University, The Sackler Institute for Nutritional Science at the New York Academy of Sciences, and the Patient-Centered Outcomes Research Institute (PCORI) PCORnet Contract # CDRN-1306-03961., Private Foundation Support



Hyperfiltration rates according to race and the different formulae in Black individuals vs. non-Black individuals. Panel A – hyperfiltration calculated by eGFR according to BMI groups in Black (orange) and non-Black individuls (blue). Panel B hyperfiltration rates according to eGFRr in blacks (orange) and non-Black (blue) individuals.

PUB305

Inside CKD: Projecting the Global Clinical Burden of CKD Using Patient-Level Microsimulation

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Inside CKD *[1]Royal Prince Alfred Hospital Department of Neurology and Stroke, Camperdown, NSW, Australia; [2]AstraZeneca UK Ltd, Cambridge, United Kingdom; [3]University of Manitoba Faculty of Health Sciences, Winnipeg, MB, Canada; [4]HealthLumen Ltd, London, United Kingdom; [5]AstraZeneca, Gothenburg, Sweden; [6]North Bristol NHS Trust, Westbury on Trym, United Kingdom.*

Background: Chronic kidney disease (CKD) affects ~10% of the global population and disease progression is associated with increased risk of cardiovascular events, renal replacement therapy (RRT) and premature death. The trajectory of CKD and related costs are critical considerations for public health and policy planning. Using country-specific, patient-level microsimulations, *Inside CKD* models the global clinical and economic burden of CKD from 2021 to 2026.

Methods: We used the *Inside CKD* microsimulation to project the clinical burden of CKD in Canada, the UK and the US. We constructed a virtual *general* population for each country using national survey data and relevant published literature. Data inputs included country demographics and the prevalence of CKD, RRT, comorbidities, and complications. CKD stages were defined as discrete health states consistent with Kidney Disease: Improving Global Outcomes (KDIGO) 2012 recommendations. We conducted model validation and calibration using established methods for health economic modelling. Analyses from additional countries in the Americas, Asia-Pacific and European regions are underway.

Results: Preliminary results show that the prevalence of CKD stages 1–5 is projected to increase from 13.35% to 14.22% in Canada, from 13.48% to 13.98% in the UK, and from 14.88% to 15.57% in the US from 2021 to 2026 (**Table**). The number of patients receiving RRT annually is projected to increase from 42 064 to 47 582 in Canada, from 69 796 to 75 051 in the UK**,** and from 797 638 to 823 050 in the US, between 2021 and 2026 (**Table**).

Conclusions: *Inside CKD* projects that the prevalence of CKD will continue to rise in Canada, the UK and the US over the period 2021–2026 with a corresponding increase in the annual RRT burden. These data demonstrate that CKD continues to pose a significant global challenge to public health and demonstrates the continued need for national policies aimed at early intervention.

Funding: Commercial Support - AstraZeneca

Projected increase in CKD stages 1–5 (including undiagnosed) and RRT from 2021 to 2026

N (%)* 2021 → 2026	Canada	UK	US
CKD stages 1–5 (including RRT)	5 080 589 (13.35%) → 5 636 032 (14.22%)	9 193 406 (13.48%) → 9 708 680 (13.96%)	49 551 955 (14.88%) → 53 281 919 (15.57%)
RRT (all modalities)	42 064 (0.11%) → 47 582 (0.12%)	69 796 (0.10%) → 75 051 (0.11%)	797 638 (0.24%) → 823 050 (0.24%)

*Percentages expressed as a proportion of total projected country population

PUB306

Peer Support as an Intervention for Kidney Disease: A Systematic Review

Jennifer Taylor, Supritha Prasad, Talar Markossian, Holly J. Kramer. *Loyola University Chicago, Chicago, IL.*

Background: Peer support may help improve chronic kidney disease (CKD) self-management because patients who share experiences can provide unique resources including patronage, encouragement and advice unlike any provider. The objective of this systematic review is to assess the published data on peer support as an intervention to improve health outcomes for patients with CKD.

Methods: This systematic review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The electronic search for studies was done using Medline, Psychological Information Database (PsychINFO), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials and Web of Science Core Collection. Medical Subject Heading (MeSH) terms and free text terms were modified as appropriate into each database. Eligibility criteria was based on the Problem or Population, Interventions, Comparisons, Outcomes and Study design (PICOS) framework. Study quality was evaluated using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies and the Mixed Methods Appraisal Tool (MMAT).

Results: A total of 319 articles were identified and10 clinical trials, 8 observational studies, and 1 mixed method study met inclusion criteria. Clinical trials showed medium to high quality while observational studies showed medium to low quality. The mixed-methods study showed high quality. Studies covered a broad range of CKD stages and problems relating to kidney disease. Only 2 articles of low quality focused on peer support as an intervention to slow CKD progression.

Conclusions: This systematic review shows a need for more research on peer support -especially for peer support as an intervention to slow CKD progression.

Funding: Private Foundation Support

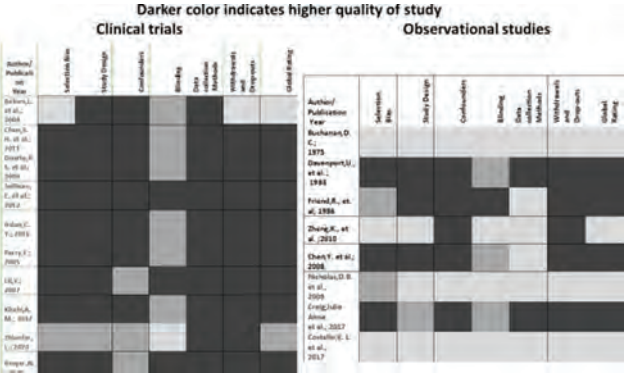

Figure shows quality assessment in 10 clinical trials (right) and 8 observational studies (left). Quality assessment ratings: dark gray-strong; medium gray-moderate; light gray-weak;

PUB307

Risk of Pulmonary Emboli in Patients with Renal Failure

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Background: There are 2 million cases of deep vein thrombosis and 200,000 deaths due to pulmonary emboli (PE) each year in US. The LITE study showed a relative risk of 2.1 (95% CI 1.5-3.0) for venous thromboembolic events in advanced renal failure with limitations as patients with ESRD were not included, renal function at time of event was not defined, and no definition or clot burden or cardiac function. The objective of the current study was to characterize the thrombotic event and details of cardiac function in patients who develop PE, stratifying for renal failure along with determination if demographic data or medical history can predict the outcome or severity of a PE.

Methods: This was a retrospective review conducted at a single-center in an urban community. Charts were reviewed from patients who were referred to the Pulmonary Emboli Response Team (PERT) for treatment of a PE. Demographic data, medical history, and labs including serologic markers of renal and cardiac were reviewed. Patients were stratfied based on renal function. Controls had an eGFR > 60 ml/min as compared to patients with AKI or a history of CKD. PE severity was defined by 2019 ESC guidelines with the most severe classification (4) having hemodynamic instability. Cardiac parameters reviewed included echocardiograms and CT scans.

Results: Charts were reviewed for 170 patients who were admitted for a PE with PERT team activation between 2017 through 2020. There were 45 patients included with AKI; 37 with Stage 3 CKD; 20 with Stage 4-6 CKD; 69 in the control group defined as a eGFR of > 60 mL/min. The control group was younger with a lower incidence of coronary artery disease and hypertension ($p < 0.05$). Mortality associated with a PE was statified for renal function with a higher in-hospital mortality in patients with AKI and advanced CKD when compared to controls (p=0.052). Logistic regression was performed to ascertain the relationship of the severity of the PE and renal failure with an OR 9.2 SE 6.97 (95% CI 2.1-40.6) p = 0.003. Patients had a 9-fold increased risk of PE Severity Class 4 if they had renal failure when compared to controls.

Conclusions: Patients with advanced CKD or AKI tend to have a higher PE severity with increased in-hospital mortality. Efforts to triage and agressively treat patients with renal failure who present with PE may improve outcomes.

PUB308

Effects of Air Pollutants on Mortality of Patients with CKD Living in Green Spaces in Seoul, Korea: A Large Observational Study

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Background: Owing to increasing air pollution, the association between green spaces and health outcomes has become a global health concern. The relationship between air pollution and the survival of patients with chronic kidney disease while considering residential greenness remains to be elucidated

Methods: Time-varying survival analysis was conducted to investigate the association between long-term exposure to air pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3) and mortality in 29 602 chronic kidney disease patients living in residential environments with low and high green infrastructure. Low and high green infrastructure was defined as continuous (0.3, 0.35, and 0.4) and percentile (50%, 75%, and 90%) thresholds using satellite data derived average normalized difference vegetation index within 250 m and 1250 m around the residence.

Results: During the average 6.14 ± 3.96 observation period, 3 863 (14%) deaths occurred. The effect of exposure to air pollution on mortality was stronger in the low index group compared to the high index group. Particularly, SO_2 was significantly associated with increased mortality risk in the low index group regardless of the threshold. Consistent results were observed in the co-pollutant models

Conclusions: Exposure to high greenery significantly reduced the mortality risk associated with air pollution. Our results emphasize the need for creating environmental infrastructure considering green spaces.

PUB309

Impact of Inpatient Educational Programs on Mortality After the Introduction of Dialysis Therapy

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Background: Although inpatient educational programs (IEPs) for non-dialysis-dependent chronic kidney disease (CKD) have been reported to slow disease progression, its effect on prognosis after the introduction of dialysis therapy is unclear.

Methods: Consecutive patients who started to dialysis therapy between January 1, 2011 and December 31, 2018 were included in this study. The patients were divided into two groups according to whether or not they received IEPs before dialysis introduction, and their background characteristics were compared. The survival rate for each group was calculated using the Kaplan-Meier method and compared by the log-rank test. Furthermore, the hazard ratio (HR) adjusted for confounding factors associated with mortality(age, sex, BMI, CCI, eGFR, albmin, ADL, smoking, welfare patient and emergency hospitalization) was calculated using a Cox regression analysis.

Results: Of the 489 subjects (mean age 68 years, 71.0% male), 129 patients (26.4%) received IEP. Compared with the non-IEP group, the IEP group had higher serum albumin ($p < 0.001$) and lower total cholesterol levels ($p = 0.0078$), and the proportion of patients with independence in their daily living activities was high ($p = 0.005$). The median observation period was 3.8 years, and 153 people (31.3%) died. The 5-year survival rates[A1] [A2] [A3] were 81.0% and 61.4% in the IEP and non-IEP groups, respectively ($p = 0.015$). From the Cox regression analysis,[A4] [A5] [A6] the HR for the IEP group was 0.56 (95% CI 0.36–0.88).

Conclusions: IEPs for CKD patients were associated with a more favorable prognosis after induction of dialysis.

PUB310

The Prevalence of Adverse Childhood Experiences in Adults with CKD

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Background: Adverse childhood experiences (ACE) are traumatic events of physical and emotional neglect and abuse, sexual abuse, household dysfunction, caregiver instability, community violence, and collective trauma. Previous research shows the prevalence of ACEs is higher in people with chronic disease, but limited data is available on the prevalence of ACEs in people experiencing chronic kidney disease (CKD).

Methods: This case-control study used the Adverse Childhood Experiences International Questionnaire to compare the ACE prevalence of people diagnosed with CKD (case) to people without CKD (control). ACE scores consisted of 13 trauma sub-types and were coded on a scale from 0-13 for an overall score. Fisher's exact test determined the difference between groups within a 95% confidence interval. Logistic regression examined group differences for each ACE sub-type and adjusted for sociodemographic confounders.

Results: The analysis included 34 people with CKD and 29 controls. Subjects were predominantly female (66.7%), white (84.1%), had a college degree (73.0%), were employed full-time (54.0%), and had a *M* age of 36.1 (± 8.6) years old. Subjects with CKD were diagnosed around 25.5 (± 13.6) years old with a mean eGFR of 38.5mL/min/1.73m^2. ACE scores for CKD ($M = 6.7$, $SD = 3.2$) compared to control group ($M = 5.0$, $SD = 2.4$) demonstrated significantly higher ACE scores, $t(61) = 2.4$, $p = .02$. People with CKD had a higher prevalence in 11 of the 13 ACE trauma sub-types with the highest reported categories including bullying (91.2%), emotional abuse (82.4%), physical abuse (70.6%), household violence (70.3%), and caregiver mental illness (64.7%). Statistically significant ($p < .05$) differences in prevalence occurred with exposure to emotional neglect, caregiver mental illness, and sexual abuse. Odds ratios for having a CKD diagnosis were significant ($p < .05$) for emotional neglect (*OR*; 8.84), caregiver mental illness (*OR*; 4.81), sexual abuse (*OR*; 4.52), and bullying (*OR*; 5.55).

Conclusions: This pilot research indicates that adults with CKD experienced every trauma sub-type of ACEs and at higher frequencies than a control population. Cumulative exposure to ACEs and experiencing specific trauma sub-types increased the odds of having a CKD diagnosis. Further research is needed to explore how ACEs affect disease occurrence and management of people with CKD.

PUB311

Increased Mortality due to Uranium-Associated Renal Disease Has Not Been Observed in Uranium Workers: A Meta-Analysis

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Background: Studies in animal and human populations have suggested nephrotoxic effects of uranium exposure, but little statistical synthesis of the data has been done. This study aims to update and expand on existing meta – analyses of mortality due to renal disease by evaluating multiple uranium – exposed populations. This study also aims to further evaluate the effect of uranium exposure on renal biomarkers.

Methods: PubMed, Embase, Web of Science, and Trip Database were searched through September 2020. Studies that reported Standardized Mortality Ratios (SMR) for kidney cancer and chronic nephritis/nephrosis in uranium – exposed humans were identified. Studies that reported data for urine protein excretion, glomerular filtration rate, urine β2-microglobulin (BMG), and urine N-acetyl-β-glucosaminidase (NAG) between high uranium exposure and control groups were also identified. The Mantel – Haenszel Method was used for all SMR analyses. Inverse Variance with Mean Differences (MD) was used for all biomarker analyses. Random Effects Models were used for all analyses.

Results: 25 studies were included in the analyses. The mortality studies were exclusively occupational exposures and were divided into a uranium miner/miller subgroup and a factory/nuclear worker subgroup. Exposure subgroups were not created for the biomarker analyses due to an insufficient number of studies. Mortality analyses of kidney cancer and chronic nephritis/nephrosis irrespective of exposure group demonstrated an SMR of 0.93 (95CI: 0.82 – 1.05) and 0.82 (95CI: 0.70 – 0.96), respectively. The subgroup analyses demonstrated similar mortality deficits. The MD analysis of urine BMG (3.41, 95 CI: -5.21 – 12.03) showed higher levels in the high exposure group.

Conclusions: Uranium workers are not at increased risk of death due to renal disease. The current literature is limited to only occupational exposures, thus future community – based studies are needed to fully elucidate the effects of uranium exposure on morbidity and mortality due to renal disease by alleviating the presence of a "healthy worker effect". In the workers studies, non-cancer related renal disease may be under recognized

as a contributor to morbidity / mortality. The BMG analysis suggests there are possible nephrotoxic effects of uranium exposure, though more studies are needed to improve precision.

Funding: Clinical Revenue Support

PUB312

Nephrology eConsultation: A Progress Update

David S. Levy, Rickinder Grewal, Monica L. Ranaletta, Stephanie Lempke, Thu H. Le. *University of Rochester Medical Center, Rochester, NY.*

Background: Given the high demand for nephrology consultation at the University of Rochester, with an average of 30 - 40 new outpatient consult requests per week, based on the AAMC (Association of American Medical Colleges) Project CORE (Coordinating Optimal Referral Experiences) model, we developed an eConsultation program for primary care providers (PCPs) across the University's health network to receive subspecialty advice in a prompt and efficient manner in lieu of formal face-to-face nephrology consultation.

Methods: Here, we report our experience with time and value-based metrics of our eConsultation program from September 2019 through March 2021. eConsult requests were placed by PCPs for renal-related issues such as mild to moderate acute kidney injury, CKD, electrolyte disturbances, and proteinuria. The nephrologist electronically communicated with the PCP who then conveyed the subspecialty recommendations with their patient.

Results: Between September 2019 and March 2021, 338 eConsult requests were received, averaging 17.8 eConsults/month. Of these, 47% were deemed medically appropriate and completed, 34% were converted to in-person visits and 4% were declined. The majority – 63% of eConsults were completed between 11 - 20 minutes, 35% were completed between 5-10 minutes, and only 2% required more than 20 minutes to complete the consult. From a financial perspective, between September 2019 and March 2021, the nephrology eConsult program has generated over $6500 in revenue, translating to ~$38 per encounter, the equivalent of 0.7 wRVUs. From an access standpoint, eConsults were generally completed within 1-2 business days whereas the average wait time for an in-person consultation from referral creation was 33.8 ± 3.7 days.

Conclusions: Our nephrology eConsultation program has provided timely and remote subspecialty guidance for PCPs within our University's health network and has overall been well-received by patients and PCPs. This model has the ability to decrease wait time for more complex patients requiring in-person consultation thereby improving the overall quality of care we provide to all of our patients, while still maintaining, if not improving, financial feasibility. Further expansion of the program to involve non-University affiliated PCPs may further improve the program's ability to provide prompt quality care and better access for patients in more remote areas.

Funding: Clinical Revenue Support

PUB313

eGFR Trajectory and Risks of Cardiovascular Events and ESKD in CKD Patients

Kohei Ohori, Maiko Kokubu, Masaru Matsui. *Nara Prefecture General Medical Center, Nara, Japan.*

Background: Growing evidence has shown the eGFR level is an established predictor of cardiovascular events, but the association of eGFR trajectory with cardiovascular and renal events remained limited.

Methods: We conducted a retrospective cohort study on 276 CKD patients in whom at least two measurements of eGFR levels to calculate eGFR slope were confirmed. Patients were divided into two groups according to the below and above cut-off values of eGFR slopes for outcomes using ROC curve. Outcomes are cardiovascular events defined as heart failure requiring hospitalization, revascularization for IHD and PAD, stroke or sudden death, and renal events defined as ESRD or baseline eGFR decline of > 30%.

Results: In total, the median (IQR) age of participants was 68 (56~77) years and 176 (64%) were male. The median (IQR) levels of baseline eGFR were 33 (20~48) mL/min/1.73m^2 with the median eGFR slope of -5.2(-0.85~-9.5) mL/min/1.73m^2/yr. During the study period, 92 cardiovascular events and 89 renal events occurred. Crude Kaplan-Meier analysis showed participants with lower eGFR slopes had higher probabilities of cardiovascular and renal events with statistical significances (p<0.001 and p<0.001, respectively). In the fully adjusted model, having lower eGFR slopes were associated with HRs (95%CIs) for cardiovascular and renal events of 1.71 [1.08-2.70] and 1.79 [1.09-2.93], respectively.

Conclusions: These data suggest not only current eGFR but also eGFR trajectory is an independent risk factor for cardiovascular and renal events in CKD patients.

PUB314

Baseline Renal Characteristics and Trial Design for MIRROR RCT, Randomized Trial of Pegloticase with or Without Methotrexate for Uncontrolled Gout

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Background: Twenty four percent of patients with gout[1] and 49% of patients with uncontrolled gout (UCG)[2] patients have CKD. Pegloticase (a pegylated recombinant uricase which rapidly dissolves urate) is associated with a 42% response rate,[3] however preliminary evidence suggests co-therapy with immunomodulation such as methotrexate (MTX) may increase this response.[4] The ongoing MIRROR randomized controlled trial (RCT) directly compares pegloticase w/wo MTX for UCG. We describe study design and baseline renal characteristics.

Methods: Enrolled patients had a serum urate [SU]≥7 mg/dL, urate lowering therapy failure/intolerance, AND visible tophi, recurrent flare, or chronic gouty arthropathy. Chronic immunosuppression, eGFR<40 ml/min/1.73m^2, and G6PD deficiency were key exclusion criteria. Patients who tolerated a 2-wk 15 mg/wk oral MTX run-in were randomized 2:1 to receive MTX or placebo (PBO). After a 4-wk MTX or PBO period, patients began 52 wks of pegloticase with weekly MTX or PBO. Primary endpoint is 6-month response rate (% patients with SU<6 mg/dL for ≥80% during Month 6).

Results: 42 US sites randomized 152 adults (54.7±12.6 yrs, 89% men, BMI 32.6±6.5 kg/m^2) with UCG (SU 8.9±1.6 mg/dL, 13.9±10.7 yr gout history, 68% with clinical tophi). 21% had prior kidney stones. Mean eGFR was 69.7±17.8 ml/min/1.73m^2 with 32% having eGFR<60 ml/min/1.73m^2. Gout burden became more severe as CKD stage increased, as indicated by Physician Global Assessment, Health Assessment Questionnaire (HAQ), and affected joint count.

Conclusions: Key baseline renal demographics demonstrate heavy gout disease burden and suggest UCG impacts patients with advanced CKD more severely. **References** 1. Roughley MJ et al. *Arthritis Res Ther* 2015;17:90 2. Francis-Sedlak M et al. *Rheumatol Ther* 2021;8:183-97 3. Sundy JS et al. *JAMA* 2011;306:711-20 4. Keenan RT et al. *Semin Arthritis Rheum* 2021;51:347-52

Funding: Commercial Support - Horizon Therapeutics plc

Mean values of gout severity assessments

	CKD Stage 1 (n=22)	CKD Stage 2 (n=80)	CKD Stage 3a (n=37)	CKD Stage 3b (n=12)
Physician Global Assessment (worst 10)	5.1	5.3	5.9	6.1
Number tender or swollen joints (max 68)	8.6	8.0	14.1	11.3
HAQ-Disability (max 3)	0.8	0.6	0.8	1.2
HAQ-Pain, Health (worst 100)	39.5, 46.6	39.4, 37.4	48.2, 51.6	57.7, 49.7

PUB315

Clinical Outcomes Associated with Systemic Lupus Erythematosus (SLE) in the 5 Years Prior to ESKD Diagnosis

Christopher F. Bell, Amy Guisinger, Shirley Huang. *GlaxoSmithKline, NC 27709, NC.*

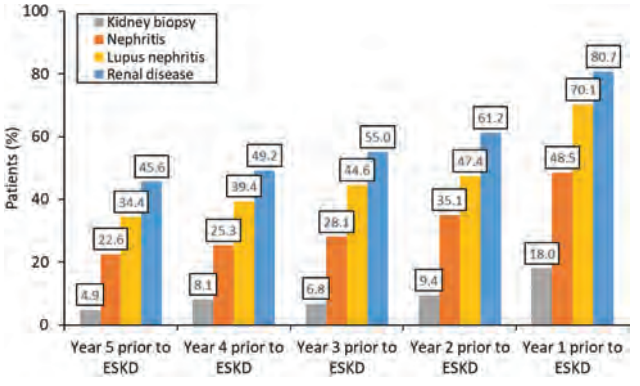
Background: Lupus nephritis affects up to 38% of patients (pts) with SLE, many of whom may progress to ESKD.[1] Despite high disease burden, data on clinical characteristics of pts with SLE in the years leading to ESKD diagnosis are limited. This study describes and compares the clinical outcomes of pts with SLE in the 5 years prior to ESKD diagnosis.

Methods: This retrospective analysis (GSK Study 215295) of United States administrative claims data (from IBM MarketScan database) included adult pts with SLE newly diagnosed with ESKD (International Classification of Diseases codes ICD-9/10) from March 2012 to December 2018. Study results focus on clinical outcomes in pts with 5-year continuous enrollment pre ESKD diagnosis.

Results: Of 1356 pts with SLE and ESKD identified, 81.8% were female; mean (standard deviation, SD) age was 46.7 (12.3) years. Of these pts, 616 had 5 years of continuous enrollment pre ESKD. Over the 5-year period pre ESKD, mean (SD) Quan-Charlson Comorbidity score increased from 1.8 (1.5) in Year 5 to 3.1 (2.0) in Year 1 prior to ESKD. The proportion of pts with severe disease also increased from 31.3% in Year 5 to 51.1% in Year 1 pre ESKD, and more pts experienced SLE flares (80.5% in Year 5 and 94.8% in Year 1 pre ESKD), particularly severe flares (Year 5: 11.9%; Year 1: 33.1%). Renal outcomes worsened each year for the 5-year period (**Figure**).

Conclusions: Prior to ESKD diagnosis, pts with SLE had high disease burden, particularly renal-related, which increased in the years leading to ESKD.

Funding: Commercial Support - GlaxoSmithKline



PUB316

Gout in Advanced CKD Patients: Prevalence and Impact on Patient Health

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Background: Gout is associated with higher mortality risk,[1] multiple comorbidities,[1-3] and decreased quality of life.[3] Impaired renal function increases gout risk,[4] but gout prevalence and impact on advanced CKD patients have not been thoroughly described. This study reports health burden of gout in CKD patients under the care of nephrologists.

Methods: Nephrologists provided chart data on random Stage 3-5 CKD patients. Criteria to identify gout in this study: gout listed as comorbidity, urate-lowering therapy (ULT) use, or visible tophi/gout flare noted. Uncontrolled gout (UCG) was defined as serum urate >6 mg/dL with visible tophi, ≥2 flares in past year, or ≥1 swollen/tender joint. Gout prevalence was examined and patients with and without gout were compared.

Results: 111 physicians reported on 746 patients (55% male, 56.2±18.3 yrs, BMI: 31.4±10.9 kg/m^2) with Stage 3-5 CKD (duration: 4.0±4.8 yrs, eGFR: 32.2±15.5 ml/min/1.73 m^2). 173 (23%) met gout criteria, with highest frequency in Stage 3b and 4 (both 28%). Of gout patients, 13% had UCG, 29% had no formal gout diagnosis, and 38% were not using a ULT. Compared to those without gout, gout patients more often sought acute medical care (30% vs 7% in prior yr) and, at presentation, more often had urination changes (15% vs 7%) and shortness of breath (21% vs 14%; all p≤0.02). Gout patients had more diagnoses of CKD-mineral bone disorder, ischemic heart disease, CHF, peripheral vascular disease, and chronic pain. Compared to controlled gout patients, UCG patients more often had pulmonary hypertension, joint issues, chronic pain, febuxostat use, and colchicine use.

Conclusions: 1 in 5 advanced CKD patients had gout, of which 13% had UCG. Gout highly impacts advanced CKD patients, with increased healthcare utilization and higher cardiovascular and bone/joint comorbidity. Patients with uncontrolled gout have an even higher health burden and more frequent colchicine use (26%), which has worse toxicity profile in CKD patients. Among CKD patients, gout is common, impactful, and requires careful screening and collaborative management. **References** 1. Choi HK, Curhan G. *Circulation* 2007;116:894-900 2. Kuo CF et al. *Ann Rheum Dis* 2016;75:210-7 3. Singh JA, Strand V. *Ann Rheum Dis* 2008;67:1310-6 4. Safiri S et al. *Arthritis Rheumatol* 2020;72:1916-27

Funding: Commercial Support - Horizon Therapeutics plc

PUB317

Claims-Based Evaluation of Pegloticase Use in Gout Patients with a History of Kidney Transplant

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Background: Kidney transplant (KT) recipients have a high occurrence of gout due to reduced GFR and medications associated with hyperuricemia. Impaired renal function and drug interaction concerns can make it challenging to effectively lower urate in this population. Pegloticase (pegylated recombinant uricase) rapidly metabolizes urate and has known efficacy for managing uncontrolled gout. However, clinical trials excluded organ transplant recipients and few cases of use in transplant recipients have been reported. This study examined pegloticase use in KT patients with uncontrolled gout in a large claims database.

Methods: The IQVIA database was used to identify pts with a history of KT (≥1 CPT or ICD 9/10 code) receiving ≥1 pegloticase infusion. The number and type of concomitant immunosuppression (IMS) prescriptions within 3 mo prior to/during pegloticase use were collected and the number of pegloticase infusions was evaluated. Pts were excluded if they returned to dialysis before the first pegloticase infusion because of graft failure or rejection.

Results: 91 pts were identified between 2015 and 2020. Pts with reported demographics (n=85) were predominately male (81%) and 58±11 yrs old at the time of first pegloticase infusion. The most common comorbidities were hypertension (84%), hyperlipidemia (48%), anemia (46%), type 2 diabetes mellitus (40%), and heart failure (34%). Compared to 1st pegloticase claim, the 1st transplant code was 2.6±1.7 yrs (mean ± SD) earlier and 1st gout code was 2.1±1.7 yrs earlier. 61 pts (67%) had a tophaceous gout code. Transplant IMS medication codes were available for 67 pts (74%), with the majority receiving tacrolimus (n=34), mycophenolate mofetil (n=33), and/or cyclosporine (n=29). Pts received a mean of 13±16 pegloticase infusions (median: 8; Q1, Q3: 4, 15), with 38% receiving ≥12 infusions and 20% receiving ≥20 infusions.

Conclusions: This real-world dataset demonstrated that KT patients with uncontrolled gout are being treated with pegloticase. A main consideration with pegloticase efficacy is potential development of anti-drug antibodies (ADAs). Given that solid-organ transplant patients are on IMS medications to preserve their grafted organ, this likely contributed to prevention of ADAs indicated by the longer average duration of therapy compared to other real-world pegloticase datasets.

Funding: Commercial Support - Horizon Therapeutics plc

PUB318

Safety of Pegloticase with Immunomodulation Co-Therapy: Literature Review

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Background: Gout occurs frequently among Chronic Kidney Disease (CKD) patients. Pegloticase therapy for uncontrolled gout does not require renal adjustments and is effective across all stages of CKD. Efficacy can be limited by development of anti-drug antibodies, which also increase the risk of infusion reactions (IR). A recent study reviewed publications on pegloticase with immunomodulating (IMM) co-therapy and demonstrated an increased response rate compared to the pivotal trials; however, aggregate safety data from the literature has not been reported.[1] The purpose of this study is to report IR prevalence and adverse events (AEs) of interest in publications which have evaluated the co-prescription of IMM with pegloticase.

Methods: Studies of pegloticase (q2w) use with concurrent IMM were identified in a search of PubMed and abstracts from professional society meetings (2012-2020). AEs were extracted and reported including IRs, gout flares, and infections. Gout flares and infection occurrence were not described in all studies, therefore, only studies where occurrence was specifically addressed were included.

Results: 10 publications were identified using IMM with pegloticase consisting of 82 total patients. Methotrexate was the most common IMM co-therapy. Due to the frequency of CKD in gout patients, other IMM agents were frequently used, including mycophenolate mofetil, leflunomide, azathioprine, and cyclosporine. All reports included serum urate monitoring to evaluate the ongoing efficacy of pegloticase. 3/82 (3.7%) patients experienced an IR during pegloticase treatment (total of 3/955 [0.3%] of infusions). Severity was described for 2 of the 3 IRs and were listed as mild. No instances of severe IR or anaphylaxis were reported. Gout flares as a % of patients were reported for 3 studies and occurred in 25/34 (72.2%). Among the 10 publications, 2 clinical studies reported details on infections. In these 2 studies (n=36), 5 infections occurred.

Conclusions: Pegloticase administered with IMM co-therapy had a low rate of mild IRs with no anaphylaxis reported. This study demonstrates that in addition to established improvements in pegloticase efficacy, the use of IMM co-therapy with pegloticase results in a favorable response rate and safety profile with low rate and severity of IRs. **References** 1. Keenan RT, et al. *Semin Arthritis Rheum.* 2021 Apr;51(2):347-352.

Funding: Commercial Support - Horizon Therapeutics plc

PUB319

Prediction of Mortality Among Patients with CKD: A Systematic Review

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Background: Chronic kidney disease (CKD) is a common medical condition with an increasing prevalence. To date, several clinical characteristics have been shown to be associated with mortality in CKD patients from regression analyses. However, the accuracy of mortality prediction has not been clearly elucidated. Thus, we aimed to demonstrate the predicting factors for mortality among CKD patients by utilizing the area under the receiver operating characteristic curve [AUC] analysis.

Methods: Ovid MEDLINE, EMBASE, and the Cochrane Library were searched through January 2021. Inclusion criteria were: 1) observational studies; 2) populations were non-transplant CKD at any stage; and 3) results were presented with AUC analysis with 95% confidence interval. AUC of 0.70-0.79 is considered acceptable, 0.80-0.89 is considered excellent, and more than 0.90 is considered outstanding.

Results: A total of 18 studies (n = 14,579) were included in the systematic review. 832 patients had non-dialysis CKD and 13,747 patients had dialysis-dependent CKD (2,160 hemodialysis, 370 peritoneal dialysis, and 11,217 non-differentiated mode of dialysis). Of 24 mortality predicting factors, none were deemed outstanding for mortality prediction. 7 factors were excellent predictors for mortality (NT-proBNP, BNP, soluble urokinase plasminogen activator receptor [suPAR], augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure). 17 predictive factors were in the acceptable range; two of which were echocardiographic factors (Image 1).

Conclusions: Several factors were predictive of mortality among CKD patients. Most of these factors could be identified by echocardiography, which may serve as an practical tool for mortality prediction in this population.

AUC range	Interpretation	Predicting factors (AUC)	Subjects
≥ 0.90	Outstanding	–	–
0.80-0.89	Excellent	NT-proBNP (0.83)	HD
		BNP (0.82)	HD
		SuPAR (0.84)	HD
		Augmentation index (0.81)	ND, HD, PD
		Left atrial reservoir strain (0.84)	ND
		CRP (0.80)	HD, PD
		Systolic PAP (0.80)	HD, PD
		APACHE III (0.76)	HD
		ICED (0.72)	HD, PD
		cTnT (0.77)	PD
		NT-proBNP > 10000 pg/mL (0.75)	HD
		MCE perfusion defect (0.75)	HD
		DFAα1 < 0.95 (0.76)	PD
		Neutrophil/lymphocyte ratio (0.79)	HD
		UPCR (0.78)	ND
0.70-0.79	Acceptable	eGFR (0.75)	ND
		Mitral E/E' ratio (0.74, 0.75)	ND, HD, PD
		LV mass index (0.72, 0.76)	ND, HD, PD
		Mortality risk score (0.79)	ND
		Malnutrition inflammation score (0.71)	ND
		Skin autofluorescence (0.78)	ND, HD, PD
		Rennes score (0.79)	HD, PD
		Modified CCI (0.70)	HD, PD
		Pulse pressure (0.72)	HD, PD

PUB320

Utilization of Renin Angiotensin Aldosterone System Inhibitors in Cardiorenal Syndrome Patients: An Experience from the Middle East

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Background: Renin-angiotensin-aldosterone system inhibitors (RAASi) have demonstrated undisputed cardio-nephroprotective merits. However, RAASi are underused in patients with cardiorenal syndrome (CRS) due to various reasons. Therefore, we aim to explore RAASi utilization in heart failure (HF) patients according to renal function and determine predictors of not receiving RAASi in CRS patients.

Methods: We included HF patients (n=235) with 12-month follow-up in our outpatient HF clinic. Data on patient characteristics were collected by retrospective chart review. We compared HF patients with eGFR<60 (CRS) vs. those with HF and eGFR≥60 (non-CRS) using appropriate testing methods. Predictors of not receiving RAASi in CRS patients at 12-month follow-up were assessed using multivariable logistic regression.

Results: At baseline, 77 (32.8%) of HF patients had CRS. Patients in the non-CRS group had a significantly higher rate of RAASi use compared to the CRS group (84.2% VS. 54.5%, p<0.001). After a follow-up of 12 months, there was a significant proportional increase in RAASi receivers within each group (table), with no significant between-group difference in increase (6.9% vs.7.8% p=0.8). On multivariable logistic regression including age, gender, diabetes, baseline serum creatinine (Scr), and distance from clinic; only baseline Scr predicted not receiving RAASi at follow-up (OR:1.07, per 0.1 mg/dl increase, 95%CI [1.01-1.17], p=0.02), and a significant trend was noticed with distance from clinic (OR:1.01, per 1 mile increase, 95%CI [0.998-1.02], p=0.09).

Conclusions: While RAASi are underutilized in CRS patients, a multidisciplinary team approach considering CKD stage and patient demographics can increase their use and impact treatment plans and outcomes in this population.

Table.1 Characteristics of HF patients with CRS vs. those without CRS.

Variable	CRS HF patients (n=77)	Non-CRS HF patients (n=158)	P-value
Age (years)	64.3 ±11.2	54.6 ±16	<0.001
Male gender	70%	62.7%	0.2
Ischemic heart disease	58.4%	36.7%	0.002
Hypertension	87%	64.5%	<0.001
Hyperlipidemia	75.3%	59.5%	0.02
Diabetes mellitus	72.7%	47.5%	<0.001
Atrial fibrillation	33.8%	25.3%	0.2
Smoking	37.6%	32.9%	0.5
Ejection fraction%	36.6 ±14.4	31.9±13.5	0.01
Baseline vitals and labs			
Systolic blood pressure (mmhg)	126.9 ±23.1	118.3 ± 19.3	0.003
Weight (kg)	78.3 ±16	80.4 ±22.9	0.5
K^+ (meq/L)	4.4 ±0.54	4.2 ±0.45	0.04
Serum creatinine (mg/dl)	1.75 ±0.5	0.83 ±0.2	<0.001
Medications			
Baseline beta blockers	89.6%	82.3%	0.18
Baseline loop diuretics	76.6%	62%	0.03
Baseline mineralocorticoid receptor antagonists	29.9%	55%	<0.001
Baseline any RAAS inhibitor	54.5%	84.2%	<0.0001
Follow-up any RAAS inhibitor*	62.3%	91.1%	<0.0001

Abbreviation: RAAS: Renin angiotensin aldosterone system
Note: Values presented as percentage %, or mean ± standard deviation.
*Changes from baseline to follow up within each group was significant at P<0.05 (p-value for the CRS group=0.02, p-value for the non-CRS group=0.048)

PUB321

Renal Function Outcomes at 5 Years from Radical and Partial Nephrectomies in Normal Renal Function Patients: An Insidious Tale of Failed Renal Hyperfiltrations

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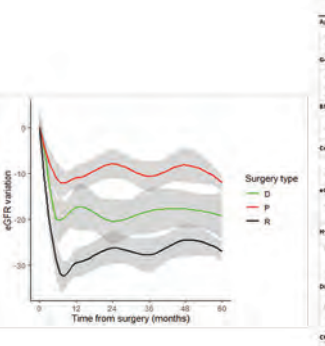
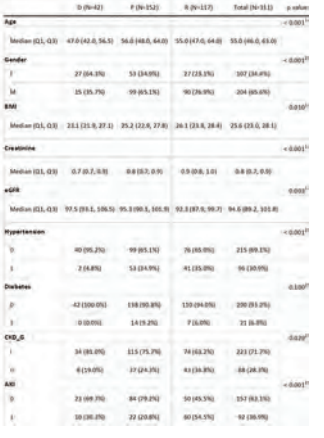
Background: CKD represents a major postoperative long-term complication in renal surgery, both in radical (RN) than in partial nephrectomy (PN). Aim of our study was to compare the eGFR decay over time from pre-operative time surgery to 5 years follow up in RN and PN in normal renal function pts.

Methods: A multicentric cohort-study of 269 consecutive pts who underwent RN or PN due to the presence of a kidney mass was enrolled. A group of 42 kidney living donors was considered as control. We evaluated eGFR variation at the pre-surgical value, hospital dismissal, 6,12,24,36,48,60 months. eGFR categories were created according to K-DIGO system. Comparisons between groups were performed using Kruskal-Wallis ranks sum test for numerical variables and Pearson's Chi square test for categorical variables

Results: Descriptive analysis is reported in table1. Two-way Anova underlined a significative difference for the type of surgery(p<0.001). The analysis showed the presence of a variation over time of the eGFR(p<0.001) that depends also on the surgery type(p<0.001). Post-hoc analys showed: at 6-12-24-36-48-60 months RN groups always had a mean decay higher(p<0.001) in respect to PN. In respect to living donor, oncological RN had a mean decay higher (p=0.02) at all time points, except at 24 months, when the donor group had a decay higher(p=0.005) by 13.1 (5.8,20.4)(figure1)

Conclusions: RN and PN harbor a solid risk of post-operative CKD even in normal renal function pts. RN pts tend to vicariate the acute loss of nephfron mass with an increase of eGFR over time, while PN renal function remains stable in time without hyperfiltration





PUB322

Outcomes of Educational Initiatives for Advanced CKD

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Background: Timing of kidney replacement therapy (KRT) and transplant referral in chronic kidney disease (CKD) G4 and G5 is a difficult topic. The COVID-19 pandemic has disrupted nearly all aspects of healthcare, including the process of KRT plan. This study examined if the addition of a Transition Coordinator (TC) improved KRT transition plan despite the pandemic.

Methods: Retrospective descriptive study examining patients at single academic practice with eGFR <20 that completed CKD educational program (CKDEP). Control Group: 5/1/19-1/31/20 with in-person CKDEP, no TC. Intervention Group (IG): 5/1/20-1/31/21 with virtual or in-person CKDEP with addition of TC. TC called patient monthly to assess barriers to KRT planning, assist with scheduling, and communicate with Nephrologist. "Success" was defined as having a KRT plan. Failure was defined as either urgent start dialysis via dialysis catheter (DC) or patients without KRT plan.

Results: CG had n=15 while IG had n=47. Both groups were evenly distributed with age, average eGFR (15). The CG had slightly higher rates of urgent starts and patients without KRT plan compared to IG (Table 1). Patients were referred for Vascular access +/- Transplant 20% (3) in CG and 23% in IG. PD +/- Transplant was chosen in 6.7% (1) of CG and 36% (17) of IG. Success and Failure rates were similar in both groups (Table 2).

Conclusions: Despite the pandemic, there was no overall change in rate of failure (urgent start or lack of KRT plan), however, individual decreases in these groups were noted. This could indicate that TC may improve outcomes when the pandemic is controlled. Increased interest in PD was noted which could indicate greater understanding via follow up provided by TC.

Table 1. Percentage of Urgent KRT vs no KRT plan due to intervention

	Control group (2019-2020) (%)	Intervention group (2020-2021) (%)
Urgent start KRT	2 (13.3%)	4 (8.5%)
No KRT plan	2 (13.3%)	8 (17.0%)
Total	15	47

Table 1

Control Group Outcomes

	Frequency	
Failure	4	26.7%
Success	11	73.3%
Total	15	100.0%

Table 2

PUB323

Chronic Hematuria Increases Chronic Kidney Injury and Epithelial Mesenchymal Transition in 5/6 Nephrectomy Rats

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Background: Chronic kidney disease (CKD) is a common outcome of many kidney diseases. Interstitial fibrosis and tubular atrophy (IFTA) is a histologic hallmark of CKD. Hematuria is a common symptom in many human kidney diseases. Free hemoglobin may affect tubular epithelial cells by generating reactive oxygen species (ROS). Epithelial mesenchymal transition (EMT) of the tubular epithelial cells has been shown to play an important role in the IFTA development. The aim of this study was to determine the effects of chronic hematuria on the CKD progression in 5/6 nephrectomy (5/6NE) rat model of CKD.

Methods: 5/6NE rats were treated with oral warfarin (0.5 mg/kg/day) or vehicle (control). Animals were monitored for 26 weeks, prothrombin time (PT), serum creatinine (SCr) and hematuria were measured weekly. Stainings for iron, trichrome and EMT markers were performed on the remnant kidneys, ROS were detected in the kidneys by protein carbonyl assay at the end of the study.

Results: Warfarin treatment resulted in a PT increase 1.5-2.5 times from control, increase in hematuria and serum creatinine. Histologically, warfarin-treated animals had more iron-positive tubular epithelial cells and increased IFTA as compared to control (42.9±17% vs 18.3±2.6%), Fig 1. ROS were increased in the kidney in warfarin-treated rats. The number of tubules that show evidence of EMT was significantly higher in warfarin-treated 5/6NE as compared to control 5/6NE rats.

Conclusions: Chronic hematuria results in increased iron-positive tubular epithelial cells, EMT and more prominent IFTA in CKD rats. Our data suggests an important role of chronic hematuria in the progression of CKD.

Funding: NIDDK Support

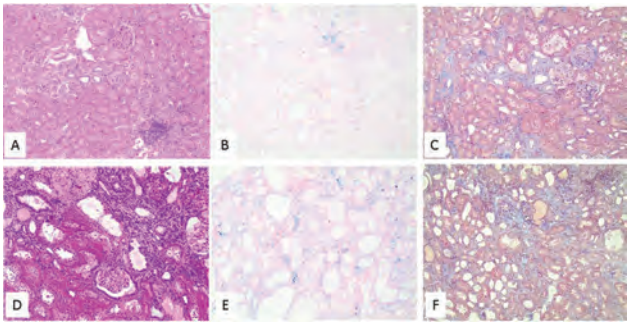

Figure 1. Histologic findings in 5/6NE rats with and without warfarin treatment.

A, B, C - 5/6NE rats non-treated with warfarin

D, E, F - 5/6 NE rats treated with warfarin

A, D - H&E stain, B, E - Iron (Prussian Blue) stain, C, F - Trichrome stain.

PUB324

Inhibition of Old Astrocyte Specifically Induced Substance (OASIS) in Myofibroblasts Suppressed Kidney Fibrosis

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Background: Although kidney fibrosis is a critical event for the onset of renal failure, molecular mechanisms are not fully understood. Previously, we found that Old astrocyte specifically induced substance (OASIS), a transcription factor, exacerbated kidney fibrosis in part by increased bone marrow stromal cell antigen 2 (Bst2), using conventional knockout mice; however, the cell specificity of OASIS function in kidney fibrosis remains to be elucidated. In this study, we focused on the role of OASIS in myofibroblasts to elucidate novel mechanisms of kidney fibrosis.

Methods: OASIS expression in human kidneys was examined by immunohistochemistry with anti-OASIS and α-SMA antibodies. Cultured myofibroblasts were treated with AEBSF, an inhibitor of OASIS activation. In addition, C57BL/6 mice were intraperitoneally injected with AEBSF for 9 consecutive days starting 2 days before unilateral ureteral obstruction (UUO) surgery. To examine the effects of OASIS in myofibroblasts on kidney fibrosis, myofibroblast-specific OASIS knockout (cKO) mice were subjected to UUO. Day 7 after UUO, kidney fibrosis was examined by Sirius Red staining, hydroxyproline assay and immunofluorescence analysis. Isolated murine myofibroblasts were treated with TGF-β1 for 24 hours and chromatin immunoprecipitation assay was conducted to test whether OASIS directly regulates the transcription of Collagen I and Bst2.

Results: OASIS was increased in myofibroblasts in human fibrotic kidneys. AEBSF suppressed OASIS activation in myofibroblasts and reduced kidney fibrosis after UUO. Importantly, kidney fibrosis was attenuated in OASIS cKO mice compared with control mice (Sirius Red positive area (%): Control-contralateral;2.4±0.9, Control-UUO;23.4±2.9, cKO-contralateral;3.1±1.0, cKO-UUO;18.8±2.0, n=9-11). In addition, OASIS cKO mice showed reduced number of Ki-67-positive proliferative myofibroblasts in fibrotic kidneys. Finally, mRNA levels of Collagen I and Bst2 was decreased in the kidneys of OASIS cKO mice after UUO and OASIS directly bound to the promoter region of these genes in murine kidney myofibroblasts.

Conclusions: OASIS in myofibroblasts contributes to the development of kidney fibrosis. Suppression of OASIS signaling in myofibroblasts could be a novel therapeutic strategy against fibrotic kidney disease.

PUB325

Salvianolic Acid C Activates PPAR Signaling Pathway and Ameliorates Renal Fibrosis in Obstructive Kidneys

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Background: Salvianolic acid C (SAC) is a component of Danshen, a widely used herbal medicine for the treatment of renal cardiovascular diseases. Renal interstitial fibrosis is a common pathway of all kinds of chronic kidney diseases progressing to the end stage of renal diseases. We aimed to study the effect of SAC on renal fibrosis and explore its underlining mechanisms.

Methods: After sham or unilateral ureteral obstruction (UUO) operation, 20-25g male c57 mice were treated with vehicle or SAC (10mg/kg) for 14 days. Moreover, normal rat kidney interstitial fibroblast (NRK-49F) cells were treated with various concentrations of SAC (10 mM to 100 mM). Protein samples from *in vivo* and *in vitro* experiments were collected to assess renal fibrosis.

Results: Treatment with SAC reduced the deposition of interstitial matrix proteins in UUO kidneys as shown by Masson staining. The expression of Fibronectin, collagen-I and α smooth muscle actin (αSMA) were increased in UUO induced fibrotic kidneys, which were down-regulated in SAC treated UUO kidneys. In parallel, treatment with SAC reduced the expression of fibronectin and αSMA in NRK-49F cells. RNA sequence analysis showed that multiple genes belong to the PPAR (peroxisome proliferator-activated receptor) signaling pathway were up-regulated by SAC treatment in UUO kidneys.

Conclusions: SAC inhibits renal fibrosis in obstructed kidneys possibly through activation of the PPAR signaling pathway.

Funding: Government Support - Non-U.S.

PUB326

Role of PAR-1 in Immune Activation and Tubulointerstitial Fibrosis During AKI-to-CKD transition

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Background: The high-affinity thrombin receptor protease-activated receptor-1 (PAR-1) has been recognized as a therapeutic target for cardiovascular intervention. Emerging evidence suggests that the coagulation cascade is activated in the kidney interstitium during AKI. Yet, the role of PAR-1 signaling in AKI to CKD transition remains largely unexplored.

Methods: We investigated the effect of PAR-1 deficiency in a longitudinal kidney fibrotic murine AKI to CKD transition model. PAR-1$^{-/-}$ and wild type mice underwent unilateral ischemia-reperfusion injury (UIRI) for 7, 14 and 28 days. Uninephrectomy of the contralateral kidney was performed one day before sacrifice to assess renal injury.

Results: After 14 or 28 days of UIRI, BUN was significantly lower in PAR-1$^{-/-}$ vs wild type mice. PAR-1$^{-/-}$ mice showed diminished kidney fibrosis with reduced ECM accumulation and expression of fibronectin, α-smooth muscle actin and collagen via TGF-β/Smad signaling after UIRI. Macrophage infiltration and inflammation was alleviated in PAR-1$^{-/-}$ ischemic kidneys in which macrophage M1-polarization and its secretory cytokine TNF-α were attenuated.

Conclusions: PAR-1 deficiency confers renoprotection by suppressing M1 macrophage activation, inflammatory and profibrotic responses during AKI and its subsequent transition to CKD. **Funding:** Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (General Research Fund, grant no. 17118720), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2018.

PUB327

Increased Serum ApoCIII Levels in CKD Patients May Underlie the Impaired Delivery of Cholesterol to Hepatocytes and Increased Cardiovascular Disease (CVD) Risk

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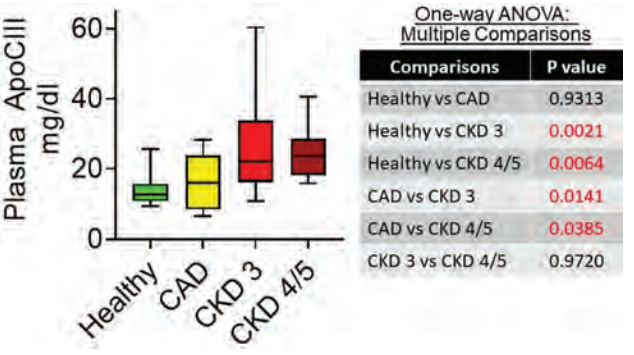
Background: Increased CVD risk underlies the mortality in CKD patients but the underlying mechanisms are not completely defined. We reported earlier that the serum from CKD patients displayed an impaired ability to deliver cholesterol to hepatocytes demonstrating a likely defect in hepatic elimination of cholesterol (as bile acids and biliary cholesterol) returning to the liver from the peripheral tissues via lipoproteins (e.g., VLDL or HDL). Apolipoprotein C-III (ApoCIII) is associated with VLDL and HDL and, not only inhibits lipoprotein lipase and hepatic lipase, but inhibits the uptake of VLDL and HDL by hepatic lipoprotein receptors. Herein we examined the hypothesis that impaired ability of serum from CKD subjects to deliver cholesterol to hepatocytes was associated with increased serum ApoCIII.

Methods: ApoCIII levels were determined by ELISA in serum samples from 32 patients with CKD [stage 3 (N=15) and stage 4+5 (N=17)], 15 patients with established CAD and 15 healthy subjects from our earlier study. One-way ANOVA with Multiple group comparisons was used to determine significance of observed differences.

Results: While ApoCIII levels in healthy subjects and patients with established CAD were not significantly different, significantly higher ApoCIII levels were seen in patients with CKD 3 and CKD 4/5 (See Figure) compared to healthy subjects as well as compared to patients with CAD. This is consistent with the reported decrease in hepatocyte uptake of lipoprotein cholesterol from serum of CKD patients.

Conclusions: Circulating ApoCIII, the catabolism of which is related to kidney function, is increased in CKD and likely impairs the ability of VLDL and HDL uptake by hepatocytes. Using ApoCIII transgenic mice, the mechanistic details are currently under investigation.



One-way ANOVA: Multiple Comparisons

Comparisons	P value
Healthy vs CAD	0.9313
Healthy vs CKD 3	0.0021
Healthy vs CKD 4/5	0.0064
CAD vs CKD 3	0.0141
CAD vs CKD 4/5	0.0385
CKD 3 vs CKD 4/5	0.9720

PUB328

Omega-3 Polyunsaturated Fatty Acid Attenuates Uremia-Induced Brain Damage in Mice

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Background: Researchers have increasingly demonstrated the relationship between renal impairment and cognitive impairment. Omega-3 polyunsaturated fatty acid (ω3-PUFA) plays an important role in preserving nerve function. However, neuroprotective effects of ω3-PUFA against uremic condition remain unclear. We are to identify brain damage caused by uremic toxicity and determine the protective effects of ω-3 PUFA against uremic toxin.

Methods: We induced uremic condition with renal ischemia reperfusion (IR) injury. 10 weeks male C57BL/6 mice and Fat-1 mice were used for IR injury. 3 days after IR injury, blood, brain and kidney tissue were collected for analysis.

Results: The results showed that Ki67 and neuronal nuclei (NeuN) decreased in the brain of uremic mice as compared to wt mice brain, but increased in the ω-3 PUFA–treated uremic mice and the brain of uremic Fat -1 mice as compared to the brain of uremic mice. The pro-apoptotic protein expressions were increased, whereas anti-apoptotic protein expression decreased in the brain of uremic mice as compared to wt mice brain. However, apoptotic protein expression decreased in the ω-3 PUFA–treated uremic mice and the brain of uremic Fat -1 mice as compared to the brain of uremic mice. Furthermore, the ω-3 PUFA–treated uremic mice and brain of uremic Fat-1 mice protein expression of p-PI3K, p-PDK1, and p-Akt were increased as compared to the brain of uremic mice.

Conclusions: In conclusion, we confirm that uremic toxin damages the brain and causes cell death. ω-3 PUFA may play a role in reducing neuronal injuries through PI(3) K-Akt signaling.

AUTHOR INDEX

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KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section

FR-OR61

The TESTING Study: Steroids vs. Placebo in High Risk IgA Nephropathy

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Background: The Therapeutic Evaluation of STeroids in IgA Nephropathy Global (TESTING) study assessed the effects of oral methylprednisolone compared to placebo on major kidney outcomes and safety in IgAN.

Methods: This investigator-initiated, double-blind randomized trial included people with IgAN, proteinuria ≥1g/day and eGFR 20-120 mL/min/1.73m^2, following ≥3 months of optimized background care including RAS blockade. Participants were randomized 1:1 to methylprednisolone (0.6-0.8 mg/kg/day, maximum 48 mg/day, for 2 months then weaning by 8mg/day/month) or to matching placebo. In 2016, due to an excess of serious infections in the steroid arm, the methylprednisolone dose was reduced (0.4 mg/kg/day, maximum 32 mg/day, weaning by 4 mg/day/month) and *pneumocystis jirovecii* prophylaxis added. The primary endpoint was the composite of 40% eGFR decline or kidney failure (dialysis, transplantation or death due to kidney disease) with prespecified secondary and safety outcomes.

Results: In total, 503 participants (mean age 38 years, 39% female, mean eGFR 61.5 mL/min/1.73m^2, proteinuria 2.46 g/day) were randomised to methylprednisolone (257) or placebo (246), including 262 to the full dose and 241 to the reduced dose protocols. Over 4.2 years average follow up, methylprednisolone reduced the risk of the primary outcome by 47% (event rate 7.0 vs 11.8/100 patient years, HR 0.53, 95% CI 0.39-0.72, p <0.0001), and ESKD by 41% (HR 0.59, CI 0.40-0.87, p=0.008). The reduction in risk was seen across both dose protocols (p heterogeneity 0.11): full dose HR 0.58 (95% CI 0.41-0.81), reduced dose HR 0.27 (95% CI 0.11-0.65). Serious adverse events were more frequent with steroids compared to placebo (28 vs 7 patients, p=0.0004), particularly with the full dose (22 vs 4, p=0.0003) vs the reduced dose regimen (6 vs 3, p=0.50).

Conclusions: Steroids reduce the risk of major kidney outcomes and kidney failure in people with high risk IgAN. The incidence of serious adverse events is increased mainly with high dose therapy. **joint first (JL MW)/senior authors (HZ VP)*

Funding: Government Support - Non-U.S.

FR-OR62

Randomized Controlled Trial Comparing 3- vs. 6-Months Initial Prednisone Therapy in Young (<4-Year-Old) Children with Nephrotic Syndrome

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Background: While recent RCTs suggest no role for prolonged (>2-3 months) initial corticosteroid therapy in NS, subgroup analysis in 2-studies suggests its association with reduced frequency of subsequent relapses in children <4-6 yr-old. This multicenter open-label trial examines the efficacy & safety of 3-months versus 6-months prednisone therapy during the first episode of NS in patients <4-yr-old [CTRI2015/06/005939; NCT03141970].

Methods: Following ethics approval & parental consent, 172 consecutive patients (1-4 yr-old) were enrolled at onset of idiopathic NS during 2015-19. After 6-wk daily & 6-wk alternate day (AD) initial prednisone therapy, they were randomized (1:1) to either tapering prednisone on AD for 12-wk or no therapy. Relapses were treated with prednisone 2 mg/kg/d till remission, then on AD for 4-wk. Outcomes, based on intention-to-treat analysis during 2-yr follow up, include the proportion of patients with relapse or frequent relapses, time to first relapse, cumulative steroid dose & adverse effects. Based on a prior RCT, at 80% power & α=0.05) 78 patients were required per group to show 30% higher sustained remission with 6-mo therapy.

Results: Baseline features in the groups were similar **(Fig 1)**. Despite trends favoring 6-mo therapy, proportions of patients in sustained remission & frequent relapses at 1- & 2-yr, time to relapse (HR 0.75; 95%CI 0.53-1.06) or frequent relapses (HR 0.78; 0.52-1.18), and relapse rates were similar **(Fig 1, 2)**. The rates of adverse events were similar.

Conclusions: Prolonged initial prednisolone therapy does not significantly alter the disease course in young children with NS.

Funding: Government Support - Non-U.S.

Baseline variables	No therapy (3-months), n=86	Prednisolone (6-months), n=86
Age (months); boys (%)	33±11; 60 (70)	35±10; 57 (66)
eGFR, ml/min/1.73 m2	120 (75-178)	110 (77-190)
Serum albumin, g/dL	2.1±1.0	2.1±1.0
Days to remission	12±7	12±7
Outcomes	**No therapy (3-months), n=86**	**Prednisolone (6-months), n=86**
Proportion in sustained remission at 1-yr; 2-yr	30.6%; 19.3%	41.8%; 26.7%
Time to first relapse, median (IQR)	5 (2-19.7) months	7.6 (4-25.2) months
Proportion with frequent relapses at 1-yr; 2-yr	48.1%; 59.2%	51.2%; 51.2%
Time to frequent relapses, median (IQR)	13.8 (6-NE) months	21.8 (6.6-NE) months

IQR interquartile range; NE not estimable

Fig 1. Baseline characteristics & key outcome variables

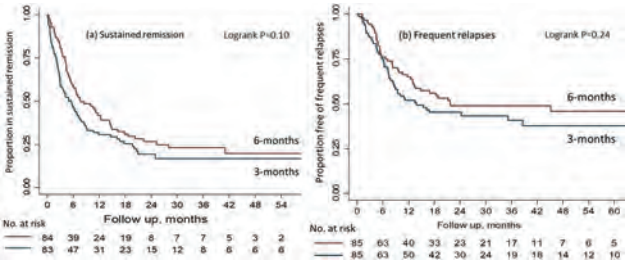

Fig 2. Kaplan-Meier estimates of the time to (a) relapse, and (b) frequent relapses

FR-OR63

Effect of Avacopan, a Selective C5a Receptor Inhibitor, on Kidney Function in Patients with ANCA-Associated Vasculitis

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Background: Patients with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis and renal disease have a poor prognosis. The effect of avacopan, an oral C5a receptor inhibitor, on renal function is described.

Methods: The ADVOCATE Phase 3 trial randomized patients to receive avacopan or prednisone taper on a background of either cyclophosphamide (followed by azathioprine) or rituximab. Primary endpoints were remission at Week 26 and sustained remission at Week 52. Secondary objectives included evaluation of kidney function.

Results: At Week 52, the difference in eGFR recovery in patients with eGFR <60 mL/min/1.73 m^2 and/or urinary abnormalities at baseline between avacopan and prednisone treatment groups was 5.5 mL/min/1.73 m^2 (95% CI [1.4, 9.6], p<0.01) **(Figure1A)**. Improvement in eGFR with avacopan was most prominent in patients with eGFR <30 mL/min/1.73 m^2 at baseline, when by week 52, the least squares mean (LSM) increase in eGFR was 13.7 (avacopan group) vs. 8.2 mL/min/1.73 m^2 (prednisone group) (p<0.01) **(Figure 1B)**. Among patients with CKD Stage 4 at baseline: in the avacopan group (n=52), 26 (50%) improved 1 stage and 3 (5.8%) improved 2 stages; in the prednisone group (n=48), 21 (44%) improved 1 stage and 1 (2.1%) improved 2 stages (p=0.32). Avacopan was also associated with more rapid reduction in proteinuria and hematuria. Urinary albumin:creatinine ratio improved 40% within the first 4 weeks of treatment with avacopan vs. no change in the prednisone group (difference -40, 95% CI [-53, -22]).

Conclusions: In ADVOCATE, patients with ANCA-associated vasculitis in the avacopan group had greater recovery of kidney function compared to patients in the prednisone group, especially among patients with CKD Stage 4 and those with eGFR <60 mL/min/1.73 m^2 and/or urinary abnormalities at baseline.

Funding: Commercial Support - ChemoCentryx

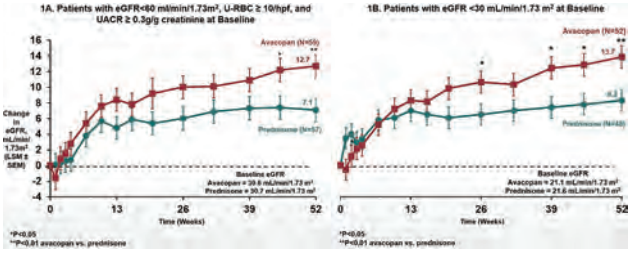

Figure 1. Change in Renal Function Through Week 52

FR-OR64

ILLUMINATE-C, a Single-Arm, Phase 3 Study of Lumasiran in Patients with Primary Hyperoxaluria Type 1 and CKD Stages 3b-5, Including Those on Hemodialysis

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Background: Primary hyperoxaluria type 1 (PH1) is a rare genetic disorder characterized by hepatic overproduction of oxalate, leading to progressive kidney disease. As kidney function declines, oxalate elimination is compromised and plasma oxalate (POx) increases, leading to systemic oxalosis. In CKD stages 3b–5, elevated POx is directly related to the pathophysiology of oxalosis and reduction of POx is a relevant clinical trial endpoint. We present results from the 6-month primary analysis period of ILLUMINATE-C, a single-arm, phase 3 study to evaluate lumasiran, an RNAi therapeutic which inhibits oxalate production, in patients with PH1 and impaired kidney function.

Methods: Key inclusion criteria: genetically confirmed PH1 diagnosis, eGFR≤45 mL/min/1.73m^2, POx≥20 µmol/L (upper limit of normal=12 µmol/L). Cohort A: patients who did not require dialysis or kidney transplantation at study start. Cohort B: patients on hemodialysis. Primary endpoints: percent change in POx from baseline to Month (M) 6 (cohort A); percent change in pre-dialysis POx from baseline to M6 (cohort B).

Results: Twenty-one patients enrolled, 6 in cohort A and 15 in cohort B. The baseline mean (SD) POx was 64.7 (41.3) µmol/L in cohort A and 108.4 (29.5) µmol/L in cohort B. In cohorts A and B, respectively, lumasiran led to 33.33% (95%CI:–15.16, 81.82) and 42.43% (95%CI:34.15, 50.71) least-square mean reductions in POx from baseline to M6 (averaged across M3-6). Lumasiran also demonstrated a reduction in urinary oxalate (cohort A). The most common adverse events (AEs) related to lumasiran were injection-site reactions, all of which were mild. There were no serious or severe AEs related to lumasiran nor deaths of patients that received lumasiran. There were no treatment discontinuations or study withdrawals.

Conclusions: Lumasiran resulted in substantial reductions in POx in PH1 patients with CKD 3b-5, with an acceptable safety profile through M6. Changes of this magnitude in POx may impact long-term clinical outcomes, including those related to systemic oxalosis, which will be evaluated in the extension period of the study.

Funding: Commercial Support - Alnylam Pharmaceuticals

FR-OR65

Long-Term Results of the Ellipsys Percutaneous Fistula for Hemodialysis

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Background: The Pivotal Multicenter Trial of Ultrasound Guided Percutaneous Arteriorvenous Fistula (pAVF) Creation for Hemodialysis (Ellipsys Pivotal Trial) demonstrated the early safety and efficacy in a two-stage procedure with creation followed by maturation of proximal radial artery fistula for hemodialysis. The long-term outcomes through 5 years were evaluated to demonstrate fistula use, durability, and complications.

Methods: Prospective data from Ellipsys Pivotal Trial was combined with chart review to obtain a median follow-up of 50 (12 to 60) months. Review included fistula use, secondary procedures, and complications. The initial procedures and follow-up were performed in the office based lab (OBL).

Results: The percutaneous fistula (pAVF) was successfully used in 92.2% (83/90) of patients undergoing hemodialysis. Non-use of pAVF occurred in 22.4% (24/107) patients: 5 pAVF not created, 5 abandoned, 8 deaths, 1 transplant, 1 pre dialysis, 2 lost to follow-up, 1 catheter, 1 peritoneal dialysis. Procedures performed per patient per year (PPPY) to maintain function and patency was 0.93 (362/391) over 5 years with 2.63 in the first year, and then declining to 0.25, 0.57, 0.18, 0.24 in years 2-5. Access complications the location and treatment are listed in Table 1. Kaplan-Meier (KM) analysis demonstrated secondary patency of 89.5%, 88.4%, 88.4%, 85.6%, and 82.0% at years 1-5. Functional patency was 97.5%, 97.5%, 97.5%, and 91.8% at years 1-4 after two-needle cannulation.

Conclusions: Percutaneous fistulae created by interventionalist in the office based lab have provided durable access for hemodialysis through 5 years with a high rate of fistula use, and low rates of secondary procedures and complications.

Funding: Commercial Support - Medtronic

Access Complications and Treatment Years 2-5

			Location					Treatment					
Indication	Events	Patients	Proximal	Access	Cephalic arch	Outflow	Central	PTA	Stent	Declott	Coil Embo	Banding	Surgery
Thrombosis	22	5	0	8	14	0	0	10	3	12	0	0	0
Swelling	8	3	0	1	2	1	5	8	1	0	0	0	0
Dysfunction	43	18	13	14	15	0	0	40	3	0	0	0	0
Cannulation Injury	18	10	5	13	0	0	1	13	0	0	1	1	4
Total	91	36*	18	36	30	1	6	71	6	12	1	1	4

Proximal = artery, anastomosis and arterializing vein, Access = Access portion of fistula, Outflow = vein between Access and central circulation (Fist Region), Central = cephalic arch and subclavian vein, Declott = endovascular treatment of thrombosis by any means, Coil Embo = Coil embolization of deep vein, Banding = Banding of outlet vein, Surgery = repair of fistula for cannulation site hematoma, and aneurysm

* 27 patients total, 9 had more than 1 indicated procedure.

Table 1: Access Complications and Treatment

FR-OR66

ASCEND Program: Efficacy and Safety from ASCEND-D and -ND and Overall MACE Finding

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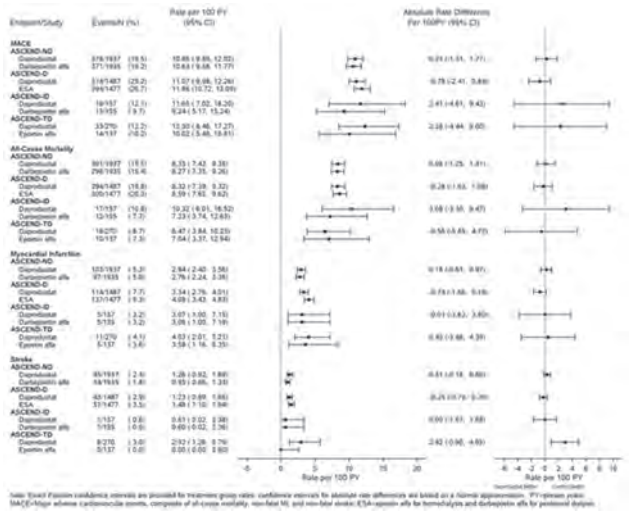
Background: The Anemia Studies in Chronic Kidney Disease (CKD): Erythropoiesis via a novel prolyl hydroxylase inhibitor Daprodustat (ASCEND) phase 3 program investigated efficacy and safety of daprodustat.

Methods: The program included 2 event-driven, cardiovascular outcomes trials (CVOTs) in non-dialysis (ASCEND-ND) and dialysis (ASCEND-D) patients comparing daprodustat with conventional ESAs. Non-inferiority (NI) co-primary endpoints included mean change in hemoglobin (Hb) between baseline and evaluation period (avg over weeks 28–52; NI margin: -0.75 g/dL) and time to first adjudicated major adverse CV event (MACE; NI margin: 1.25). Principal secondary endpoints, adjusted for multiplicity, included superiority assessments of MACE, MACE + thromboembolic events, MACE + hospitalization for heart failure and average monthly intravenous iron dose up to week 52 in ASCEND-D and time to progression of CKD in ASCEND-ND. Three smaller trials also reported adjudicated MACE but were not designed for formal MACE evaluation.

Results: 8169 patients were randomized across the 5 trials, with ~14,200 person-years (PY) of follow-up in CVOTs. The co-primary NI Hb objective was met in both CVOTs (adjusted mean treatment difference [95%CI]: ASCEND-D 0.18 [0.12-0.24] g/dL, ASCEND-ND 0.08 [0.03-0.13] g/dL). The co-primary NI MACE endpoint was also met (hazard ratio [95%CI]: ASCEND-D 0.93 [0.81-1.07], ASCEND-ND 1.03 [0.89-1.19]). No principal secondary endpoints met superiority. CVOT rates of treatment emergent adverse events were similar between daprodustat and ESA groups. Figure shows program-level first adjudicated MACE rates per 100 PY (intent-to-treat); MACE rates for ASCEND-NHQ (N=614) were 4.9% for daprodustat and 6.2% for placebo).

Conclusions: CVOTs demonstrated daprodustat was non-inferior to ESA for Hb efficacy and MACE and was well-tolerated. CV safety was generally consistent across treatment groups in the other studies.



FR-OR67

EMPEROR-Preserved: Empagliflozin and Outcomes in Heart Failure with a Preserved Ejection Fraction and CKD

Faiez Zannad,[1] Bettina J. Kraus,[2] Cordula Zeller,[3] Stuart Pocock,[4] Milton Packer,[5] Gerasimos Filippatos,[6] João Pedro Ferreira,[7] Stefan D. Anker,[8] Javed Butler.[9] EMPEROR-Preserved Trial Committees and Investigators *[1]Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France; [2]University Hospital, Wuerzburg, Germany; [3]Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer, Germany; [4]London School of Hygiene and Tropical, London, United Kingdom; [5]Baylor Heart and Vascular Institute, Dallas, TX; [6]Attikon University Hospital, Athens, Greece; [7]CHRU Nancy - Hopitaux de Brabois, Nancy, France; [8]Charité Medical School, Berlin, Germany; [9]University of Mississippi, University Park, MS.*

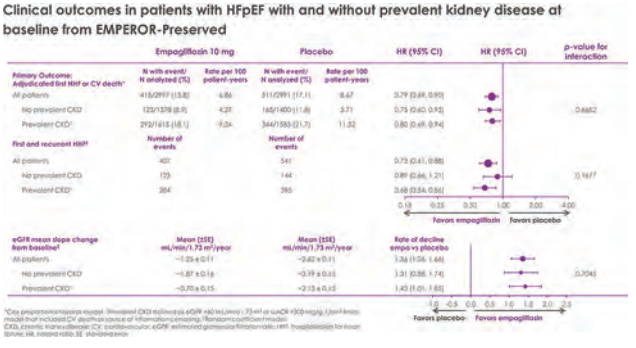
Background: In EMPEROR-Preserved, empagliflozin reduced cardiovascular death and heart failure hospitalizations and slowed the progressive decline in glomerular function in heart failure and a preserved ejection fraction (HFpEF), with or without diabetes. We explored the effect of empagliflozin on cardiovascular and kidney endpoints, across the spectrum of kidney function.

Methods: 5988 patients were randomized, of whom 3198 (53%) had prevalent chronic kidney disease (CKD) (eGFR<60ml/min/1.73m^2 or an UACR>300mg/g). The key outcomes were (1) a composite of cardiovascular death or hospitalization for heart failure; (2) total hospitalizations for heart failure, and (3) eGFR slope. The median follow-up was 26 months.

Results: Patients with prevalent CKD had a higher rate of CV and kidney events. Overall, empagliflozin reduced the risk of cardiovascular death and hospitalization for heart failure by 21% (p<0.001), reduced total hospitalizations for heart failure by 27% (p<0.001) and significantly slowed the yearly decline in eGFR (Difference: 1.36 mL/min/1.73 m2 per year, p<0.001). In this present CKD subgroup analysis, all three benefits were seen consistently in patients with and without CKD (figure) and were apparent even in patients with severe impairment (eGFR from 20 to 30ml/min/1.73m^2). Empagliflozin was well tolerated regardless of the level of baseline kidney function.

Conclusions: In patients with HFpEF, empagliflozin reduced serious heart failure events and slowed the decline in glomerular function, regardless of the presence or absence of CKD and across a broad spectrum of baseline kidney function.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance



FR-OR68

Chlorthalidone for Hypertension in Advanced CKD (CLICK): A Randomized Double-Blind Trial

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Background: Hypertension, a common risk factor for both cardiovascular disease and chronic kidney disease (CKD), remains poorly controlled, especially among patients with advanced CKD.

Methods: The chlorthalidone (CTD) in chronic kidney disease (CLICK) study was a placebo-controlled, double-blind, randomized control trial of CTD versus placebo in patients with advanced CKD. Here, patients with stage 4 CKD and poorly controlled hypertension as confirmed by 24-hour ambulatory BP monitoring were randomly assigned to either placebo or CTD 12.5 mg daily in a 1:1 ratio stratified by prior loop diuretic use. The primary end point was the change in 24-hour systolic ambulatory BP from baseline to 12 weeks and was multiply imputed for missing data. Secondary outcome measures were the change from baseline to 12 weeks in the following measures: urine albumin to urine creatinine ratio, NT-pro BNP, plasma renin, plasma aldosterone, and total body volume. Long term follow up was planned for 3 years. An NHLBI-appointed DSMB had trial oversight.

Results: Of the 160 randomized, 140 patients (88%) completed the 12 weeks of double-blind exposure phase. Mean 24-hour ambulatory BP at randomization was 140.1 (8.1)/72.8(9.3) mmHg in the placebo group and 142.6 (8.1)/74.6 (10.1) mmHg in the CTD group. The adjusted change from baseline to 12 weeks in 24-hour systolic blood pressure was -0.5 (95% CI, -3.5 to 2.5) mmHg in the placebo group and -11.0 (95% CI, -13.9 to -8.1) mmHg in the CTD group. The between group difference was -10.5 (95% CI, -14.6 to -6.4: p<0.0001) mmHg. Compared to placebo, the urine albumin to urine creatinine ratio in the CTD group at 12 weeks was 50% lower (95% CI, 37% to 60%). CTD also induced changes in NT-proBNP, renin, aldosterone and total body volume were directionally consistent with a diuretic effect. Following randomization, hypokalemia, reversible increases in serum creatinine, hyperglycemia, dizziness, and hyperuricemia occurred more frequently in the CTD group.

Conclusions: In summary, this trial showed that treatment with CTD could effectively treat poorly controlled systolic hypertension in patients with advanced CKD. The reduction in albuminuria points to an early effect of target organ protection. (funded by National Institutes of Health NHLBI R01 HL126903; registration number NCT02841280)

Funding: Other NIH Support - NHLBI

PO2522

Activated Vitamin D for the Prevention of AKI in Critically Ill Patients

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Background: Decreased circulating levels of active vitamin D metabolites, including 25-hydroxyvitamin D (25D) and 1,25-dihydroxyvitamin D (1,25D), are common in critically ill patients, and lower levels are independently associated with a higher risk of AKI. Administration of 25D and 1,25D attenuates AKI in animal models. Randomized trials of vitamin D in critically ill patients have focused on inactive precursors (e.g., cholecalciferol), which may not be efficiently converted into 25D and 1,25D in this setting.

Methods: We conducted an NIH-funded, 3-arm, double-blind, randomized clinical trial using high doses of 25D and 1,25D in 150 critically ill patients at high risk of AKI. Patients were randomly assigned in a 1:1:1 ratio to receive 25D (oral calcifediol, 400µg on day 1 and 200µg on days 2-5), 1,25D (oral calcitriol, 4ug daily for 5 days), or placebo. The primary outcome was a composite global rank endpoint of death, dialysis, or relative average increase in serum creatinine within 7 days.

Results: Among the 150 patients enrolled, the median age was 65 years (IQR, 52-72), 61% were male, 83% were intubated, and 57% were receiving vasopressors at randomization. The median time from ICU admission to randomization was 1 day (IQR, 1-2). Median levels of 25D and 1,25D at randomization were 17 ng/ml (IQR, 10-26) and 27 pg/ml (IQR, 18-39), and increased to 57 ng/ml (IQR, 53-67) and 91 pg/ml (IQR, 66-122) in the 25D and 1,25D groups, respectively. Neither the primary nor secondary endpoints differed between groups (**Table**). Longitudinal plasma and urinary KIM-1 levels were also similar between groups. No safety concerns were identified.

Conclusions: Administration of activated vitamin D metabolites did not improve renal outcomes among critically ill patients.

Funding: NIDDK Support

Outcomes

	25D (n=51)	1,25D (n=50)	Placebo (n=49)	P-value (25D vs. Placebo)	P-value (1,25D vs. Placebo)
Primary Composite Endpoint				0.85*	0.58*
Death - no. (%)	4 (7.8)	9 (18.0)	6 (12.2)	0.46	0.42
RRT - no. (%)	1 (2.0)	1 (2.0)	4 (8.2)	0.15	0.16
Relative Average Increase in SCr (%) – median [IQR]	-2.3 [-20.7, 18.3]	-7.1 [-18.1, 12.3]	-7.4 [-21.5, 10.4]	0.44	0.29
Secondary Endpoints					
Stage 2 or 3 AKI - no. (%)	18 (35.3)	21 (42.0)	14 (28.6)	0.47	0.16
RRT or death - no. (%)	5 (9.8)	10 (20.0)	10 (20.4)	0.14	0.96
Peak SCr, mg/dl - median [IQR]	1.2 [0.8, 1.5]	1.3 [0.8, 1.9]	1.2 [0.9, 1.8]	0.44	0.86
28-day mortality - no. (%)	10 (19.6)	16 (32.0)	10 (20.4)	0.92	0.19

Unless otherwise specified, outcomes above were assessed within 7 days following randomization.

*Composite P value based on global rank endpoint.

PO2523

SCD Treatment in COVID-19 ICU Patients with ARDS and AKI Is Safe and May Improve Clinical Outcomes

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Background: ICU patients with COVID-19 with acute respiratory distress syndrome (ARDS) on mechanical ventilation (MV) and acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) have very high mortality rates. Elevation of certain inflammatory mediators, including IL10 and soluble interleukin 1 receptor-like 1 (sST2), predict mortality in COVID-19 patients and declines as patients recover. Previous data have shown that treatment with a selective cytopheretic device (SCD) improves clinical outcomes in ARDS and severe AKI by removing proinflammatory leukocytes from circulation and reducing plasma levels of inflammatory cytokines. The aim of this feasibility study was to evaluate the safety and early efficacy of SCD treatment (Tx) in ICU COVID-19 patients with ARDS on MV and AKI requiring CRRT.

Methods: 22 subjects were enrolled and treated with SCD for ≤10 days. 5 patients were treated less than 96 hours due to family's request for withdrawal of care. Patients were previously treated with remdesivir and corticosteroids. All but one patient were on both MV and CRRT with 10 patients on extracorporeal membrane oxygenation (ECMO). A subgroup of 8 patients was further evaluated with plasma inflammatory biomarkers and cell sorting/cytometric analysis (CSCA) of circulating neutrophils and monocytes. Clinical outcomes of SCD-treated patients were compared to untreated control patients on CRRT and mechanical ventilation in a contemporaneous, prospective observational data set (CRRTnet).

Results: Patients completed the study between September 2020 and July 2021. Mean age was 53±17 years (19-79). No device-related serious adverse events were reported. 60-day mortality in the SCD treated group was 11/22 (50%) vs.11/13 (85%) in the control group. CSCA demonstrated SCD removed the most activated circulating neutrophils (CD11b, CD10) and monocytes (CD11b, CD14). SCD Tx reduced baseline plasma levels of IL10 (12±9 pg/ml to 2±1, $p<0.02$) and sST2 (212±70 pg/ml to 88±74, $p<0.02$), as well as reducing plasma IL6 and MCP (Monocyte Chemotactic Protein)-1 levels.

Conclusions: SCD treatment is safe in ICU COVID-19 patients with ARDS on MV and AKI requiring CRRT. In this feasibility study, mortality rate was substantially lower than a concurrent control group, suggesting clinical benefit.

Funding: Commercial Support - SeaStar Medical, Inc., Private Foundation Support

PO2524

Effect of Clinical Decision Support with Audit and Feedback for Prevention of AKI in Coronary Angiography and Intervention: Stepped Wedge Cluster Randomized Trial

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Background: Contrast-associated acute kidney injury (CA-AKI) is a common complication of coronary angiography and percuateous coronary intervention (PCI). We evaluated whether the incidence of CA-AKI was reduced with an intervention including clinical decision support with audit and feedback.

Methods: In this cluster-randomized, stepped-wedge trial conducted in Alberta, Canada, we randomly assigned all invasive cardiologists to various start dates for an intervention that included education, point-of-care computerized clinical decision support on contrast volume and IV fluid targets, and repeated audit and feedback related to these processes for CA-AKI prevention. The eligible study population included adults ≥18 years of age, not receiving dialysis, with a predicted risk of CA-AKI >5%, who received non-emergency coronary angiography or PCI. The primary outcome was incidence of AKI based on the KDIGO serum creatinine criteria. Analyses were performed according to the intention-to-treat principle, using mixed-effect models to account for clustering in the data.

Results: Of 34 physicians randomized, 3 retired prior to randomization, and the remaining 31 received the intervention. There were 7,087 procedures performed in 6,449 eligible patients; mean (SD) age 70.2 (10.7) years, 2,292 (32.3%) female, mean (SD) eGFR 62.7 (22.4) mL/min/1.73m^2. The proportion of procedures where the desired contrast volume limit was exceeded was reduced from 41.0% to 29.2% ($p<0.01$), while the proportion who received hemodynamically guided IV fluids increased from 35.3% to 42.0% ($p<0.01$) with the intervention. The incidence of CA-AKI was significantly reduced, from 9.2% (280 events/3,036 procedures) before the intervention to 8.2% (334 events/4,051 procedures) with the intervention (time adjusted odds ratio, 0.74; 95% CI, 0.58 to 0.94). There was no statistical evidence of effect modification by age, sex, comorbidity, or baseline CA-AKI risk.

Conclusions: An intervention combining education, clinical decision support, and audit and feedback resulted in less contrast dye use, greater intravenous fluid administration, and reduced the incidence of CA-AKI following coronary angiography and PCI.

Funding: Government Support - Non-U.S.

PO2525

The Effect of Magnesium Supplementation on Vascular Calcification in CKD: A Randomised Clinical Trial (MAGiCAL-CKD)

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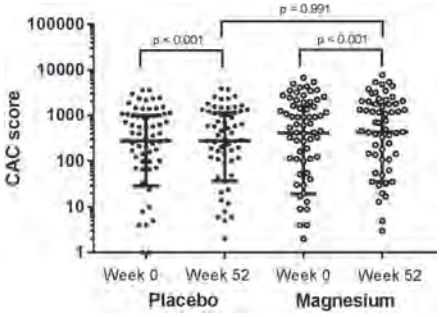
Background: Higher levels of serum magnesium (Mg) are associated with lower risk of cardiovascular (CV) events in patients with CKD and Mg prevents vascular calcification (VC) in animal models of CKD. We hypothesized that oral Mg supplementation would slow the progression of VC in CKD.

Methods: In a randomised, double-blind, placebo-controlled, parallel group, clinical trial we recruited 148 patients with an eGFR between 15 and 45 mL/min and randomised them to oral Mg hydroxide 15 mmol twice daily or matching placebo for 12 months. We excluded kidney transplant recipients. The primary endpoint was the between-groups difference in coronary artery calcification (CAC) score after 12 months adjusted for baseline CAC score (ANCOVA).

Results: Seventy-five subjects were randomised to Mg and 73 to placebo. Median eGFR was 25 mL/min at baseline. Mg treatment significantly increased plasma Mg ($p < 0.001$). CAC scores were not significantly different between the two groups after 12 months (mean difference 0.01%, 95% CI –13.5% to 15.6%; $p = 0.991$). A prespecified subgroup analysis of subjects with CAC > 0 at baseline did not significantly alter the main results (mean difference 4.0%, 95% CI –5.4% to 14.3%). Thirty-two subjects randomised to Mg treatment experienced gastrointestinal side effects compared to 11 subjects randomised to placebo. There were five deaths and six CV events in the Mg group, compared to two deaths and no CV events in the placebo group.

Conclusions: Mg supplementation did not slow the progression of VC in CKD, despite a significant increase in plasma Mg. There were more deaths and CV events in the Mg group compared to placebo, although the trial was not powered to investigate these endpoints.

Funding: Private Foundation Support



PO2526

REDUX: A Multicenter, Open-Label Study of DM199 (Recombinant Human Tissue Kallikrein-1) in Patients with Stage 2 or 3 CKD

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Background: DM199 is a recombinant form of the endogenous human tissue kallikrein-1 protein (KLK1) that by selectively releasing bradykinin-mediated nitric oxide, prostaglandins and other anti-inflammatory mediators to increase renal blood flow, and reduce inflammation, oxidative stress, and fibrosis in the kidney and elsewhere. The safety, efficacy, pharmacokinetics, and pharmacodynamics of DM199 is being evaluated in an open-label, Phase 2 study of patients with chronic kidney disease (CKD).

Methods: Here, enrolling three cohorts of patients all with stage 2 or 3 CKD: 1) non-diabetic African Americans with hypertension (AA/CKD); 2) patients with IgA nephropathy (IgAN); and 3) patients with type 2 diabetes mellitus with hypertension (DKD). Patients were assigned to receive subcutaneous DM199 2 or 5 mcg/kg twice weekly for 95 days. Primary endpoints were safety and tolerability, kidney function (eGFR, urine:albumin creatinine ratio [UACR], blood pressure), and plasma and urine pharmacokinetics of DM199 (and KLK1).

Results: At an interim analysis conducted June 2021, 62 patients had completed the study, and data were available for 56 patients, 12 in the AA/CKD cohort, 16 in the IgAN cohort, and 28 in the DKD cohort. Results are in the Table. DM199 was well tolerated across all cohorts, with no DM199 related severe adverse events (AEs) or discontinuations due to drug-related AEs. AEs were generally mild to moderate in severity, with the most common being local injection site irritation that resolved.

Conclusions: These data provide clinical validation of the meaningful biologic activity of the recombinant KLK1 (DM199) and support the potential of achieving clinical benefit in patients with CKD. Enrollment is continuing in the AA/CKD and IgAN cohorts.

Funding: Commercial Support - DiaMedica Therapeutics, Inc.

	UACR (mg/g)	eGFR (mL/min/1.73 mg2)	Systolic/Diastolic Blood Pressure (mm Hg)
Cohort 1 – AA/CKD (n=12)			
Baseline	809	43.3	147 / 91
Mean Change	-8% (baseline >150) -27% (baseline >500)	2.0	-8 / -3
Cohort 2 – IgAN (n=16)			
Baseline	988	39.8	128 / 83
Mean Change	-66% (baseline >150) -3% (baseline >500)	<1.0	2 / <1
Cohort 3 – DKD (n=28)			
Baseline	1273	45.8	144 / 80
Mean Change	No change	<1.0	-5 / 1

PO2528

Association of Urine Albumin-to-Creatinine Ratio and Its Early Change with Cardiorenal Outcomes in FIDELIO-DKD: A Mediation Analysis

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Background: The selective, nonsteroidal mineralocorticoid receptor antagonist finerenone slowed chronic kidney disease (CKD) progression and improved cardiovascular (CV) outcomes in patients with CKD and type 2 diabetes (T2D) in FIDELIO-DKD (NCT02540993). Previous studies have shown that treatment-induced urine albumin-to-creatinine ratio (UACR) reduction correlates with kidney and CV benefits. Here, we investigate the association of UACR and its early change with the magnitude of cardiorenal protection.

Methods: Patients (N=5674) with T2D, UACR ≥30–≤5000 mg/g and estimated glomerular filtration rate (eGFR) 25–<75 mL/min/1.73 m² receiving optimized renin–angiotensin system blockade were randomized 1:1 to finerenone or placebo. Key outcomes included a kidney composite of time to kidney failure, sustained ≥40% or ≥57% eGFR decline from baseline, or renal death, and a CV composite of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Outcomes were assessed using cubic-basis splines including UACR at baseline and change in UACR from baseline to month 4 as continuous variables. Mediation analyses were performed to determine the proportion of change in UACR to month 4 contributing to the kidney and CV benefits of finerenone.

Results: Finerenone was associated with a 31% greater reduction in the UACR from baseline to month 4 than placebo (ratio of least-squares mean change from baseline, 0.69; 95% confidence interval 0.66–0.71). Overall, the risk of adverse kidney and CV outcomes increased as UACR at baseline increased. Reduction in UACR from baseline to month 4 was also associated with a reduction in risk for kidney outcomes. Mediation analyses indicated a variable proportion of the kidney and CV benefits observed with finerenone could be explained by early change in UACR.

Conclusions: Finerenone resulted in early reductions in UACR in patients with T2D and CKD that are associated with its beneficial effects on kidney and CV outcomes. We will discuss early changes in UACR as a biomarker of subsequent finerenone-associated cardiorenal benefit.

Funding: Commercial Support - Bayer AG

PO2529

Dapagliflozin and Kidney Outcomes in Hospitalized Patients with COVID-19 Infection: Results from the DARE-19 Randomized Controlled Trial

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Background: Hospitalized patients with COVID-19 infection are at high risk of acute kidney injury (AKI) and renal replacement therapy, especially in the presence of chronic kidney disease (CKD). The DARE-19 trial showed that in hospitalized patients with COVID-19, treatment with dapagliflozin (DAPA) vs placebo resulted in numerically fewer patients experiencing organ failure or death, although these differences were not

statistically significant. We performed a pre-specified secondary analysis of DARE-19 to determine the efficacy and safety of DAPA on kidney outcomes in the overall population and by CKD status.

Methods: The DARE-19 trial randomized 1250 hospitalized patients (231 [18.5%] had eGFR <60 mL/min/1.73m^2) with COVID-19 and cardiometabolic risk factors to DAPA or placebo. Dual primary outcomes (time to new or worsened organ dysfunction or death, and a hierarchical composite endpoint of recovery [change in clinical status by Day 30]), and the specific kidney outcome (composite of AKI, renal replacement therapy or death), as well as safety were assessed in patients with baseline eGFR <60 and ≥60 mL/min/1.73m^2.

Results: The effect of DAPA vs placebo on the primary prevention outcome (hazard ratio [HR] 0.80 [95%CI 0.58, 1.10]) and primary recovery outcome (win ratio 1.09 [95%CI 0.97, 1.22]) was consistent across eGFR subgroups (p for interaction 0.98 and 0.67, respectively). The effect on the composite kidney outcome (HR 0.74 [95%CI 0.50, 1.07]) was also consistent in eGFR subgroups (p for interaction 0.44). There were numerically fewer AKI events with DAPA in patients with eGFR<60 ml/min/1.73m^2 (HR 0.71 [95%CI 0.29, 1.77]) and ≥60 ml/min/1.73m^2 (HR 0.69 [95%CI 0.37, 1.29]). DAPA was well tolerated in patients with eGFR <60 and ≥60 mL/min/1.73m^2.

Conclusions: The effects of DAPA on primary and secondary outcomes in hospitalized patients with COVID-19 were consistent in those with/without CKD. DAPA was well tolerated and did not increase the risk of AKI in patients with/without CKD.

Funding: Commercial Support - AstraZeneca

PO2530

Maintaining Operational Excellence During the COVID-19 Pandemic in the FLOW Trial

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Background: The FLOW trial is a multicenter, international, randomized, phase 3b kidney outcomes trial of once-weekly subcutaneous semaglutide vs placebo, both added to standard-of-care, in >3,500 people with type 2 diabetes and chronic kidney disease. The trial is guided by a steering committee with academia and industry representatives and a global expert panel (GEP). The coronavirus disease 2019 (COVID-19) pandemic has presented major challenges for running clinical trials, with restrictions for trial sites impacting recruitment and retention. Once the extent and hazards of COVID-19 were apparent, regular impact assessments were done to quickly identify and mitigate challenges to the conduct of the trial. Here, we report the timing of mitigation strategies in the FLOW trial and the relationship to recruitment during the pandemic.

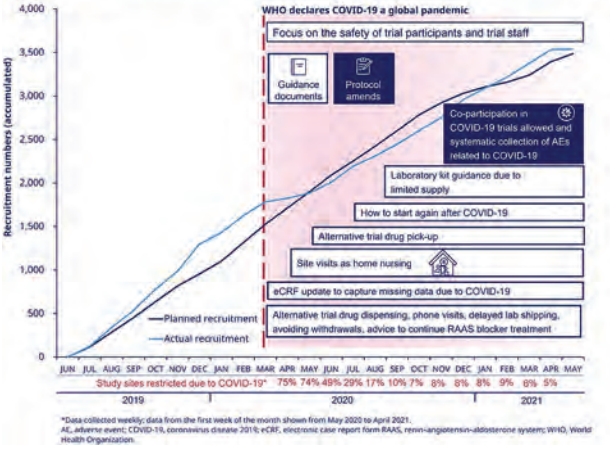
Methods: The primary focus was to ensure participant and staff safety and no undue risk of COVID-19 exposure, as well as data integrity, recruitment and retention. These aims were met by implementing protocol amendments, guidance documents for trial sites and local support from GEP members, through strategies such as replacing face-to-face visits with phone and home visits, remote monitoring, alternative trial drug dispensing and allowing for co-participation in COVID-19 trials **(Figure)**.

Results: After the mitigation strategies were employed in response to the COVID-19 pandemic, the FLOW trial recruitment was completed according to schedule **(Figure)**. To date, no participants have withdrawn from the FLOW trial due to COVID-19.

Conclusions: After the rapid identification and implementation of mitigation strategies and efforts of the steering committee and GEP, the FLOW trial successfully recruited the planned number of participants on time and avoided withdrawals due to COVID-19.

Funding: Commercial Support - Novo Nordisk A/S

Figure. Planned and actual recruitment into the FLOW trial, with mitigation strategies deployed in response to the COVID-19 pandemic shown at the approximate time they were implemented, as well as the proportion of sites restricted each months



*Data collected weekly; data from the first week of the month shown from May 2020 to April 2021.
AE, adverse event; COVID-19, coronavirus disease 2019; eCRF, electronic case report form RAAS, renin-angiotensin-aldosterone system; WHO, World Health Organization.

PO2531

Finerenone and Kidney Outcomes in Patients with CKD and T2D: Results from FIDELITY

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Background: FIDELITY, a prespecified meta-analysis of FIDELIO-DKD and FIGARO-DKD, evaluates the efficacy and safety of finerenone across a spectrum of patients with chronic kidney disease (CKD) and type 2 diabetes (T2D).

Methods: FIDELITY combines individual patient data from FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049). Eligible patients were adults with T2D and CKD (urine albumin-to-creatinine ratio [UACR] ≥30–<300 mg/g and estimated glomerular filtration rate [eGFR] ≥25–≤90 mL/min/1.73 m^2, or UACR ≥300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2), treated with optimized renin–angiotensin system blockade. Efficacy outcomes included a composite kidney outcome of time to first onset of kidney failure (end-stage kidney disease [ESKD] or sustained eGFR <15 mL/min/1.73 m^2), sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or renal death.

Results: In 13,026 patients, over 3.0 years' median follow-up, finerenone reduced the risk of the kidney composite outcome by 23% vs placebo (HR=0.77; 95% CI 0.67–0.88; *P*=0.0002); consistent benefits were observed across baseline eGFR and UACR subgroups ($P_{interaction}$ 0.62 and 0.67, respectively). Compared with placebo, finerenone led to a nominally significant reduction in the incidence of all nonfatal components of the kidney composite outcome, including a 20% lower risk of ESKD (chronic dialysis or kidney transplant; HR=0.80; 95% CI 0.64–0.99; *P*=0.04). Finerenone caused an initial drop in eGFR vs placebo (least-squares [LS] mean change in eGFR slope from baseline to month 4, –3.3 vs –1.0 mL/min/1.73 m^2) but slowed long-term eGFR decline (LS mean change in eGFR slope from month 4 onwards, –2.5 vs –3.7 mL/min/1.73 m^2/year). The incidence of adverse events was similar between groups. The incidence of permanent discontinuation due to hyperkalemia in finerenone and placebo recipients with an eGFR <60 mL/min/1.73 m^2 was 2.4% and 0.8%, respectively, and 0.6% and 0.3% in those with an eGFR ≥60 mL/min/1.73 m^2.

Conclusions: FIDELITY demonstrates robust kidney benefits and safety of finerenone in patients with T2D across the spectrum of CKD severity.

Funding: Commercial Support - Bayer

PO2532

ACCESS (NCT02513303): A Phase 3 US Multicenter Randomized Controlled Trial Evaluating Efficacy of a Perivascularly Delivered Sirolimus Formulation (Sirogen™) for Improving Hemodialysis AVF Outcomes

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Background: Lack of a prophylactic therapeutic for improving AV **F**istula **S**uitability for **D**ialysis (FSD) is an unmet need. Sirolimus delivered locally to the vessel wall is a clinically proven anti-proliferative. Advancing age, female gender & comorbidities like coronary artery disease (CAD) are known risks for AVF maturation.

Methods: The Full Analysis Set (FAS) included 243 pts randomized 1:1; 125 Sirogen 118 Controls; 174 ESRD 69 CKD; 205 RCF 38 BCF. End points: Clinical FSD: AVF use with 2 needles with mean Qb ≥300 ml/min (2N/300) for at least 2/3rd of the HD sessions during a 30-day period starting day 150 (FSD6; Primary Endpoint) or day 330 (FSD12). Ultrasound FSD: outflow vein diameter ≥6mm, Qa ≥500ml/min; criteria used if CKD pt. was not on HD by day 150 or 330. Secondary Patency (SP): Fistula survival without abandonment; Fistula Maturation (FM): AVF use for 3 consecutive 2N/300 HD sessions.

Results: Age subgroup analysis provides explanation supported by data for endpoint results shown in Table. 2/3rd of randomized pts were <65y (lower risk). In ESRD pts ≥65y clear evidence of Rx effect (Figs 1,2); RCF outcomes were even more compelling. Exceptional control performance in <65y group masked treatment effect. No evidence of Rx failure. No safety concerns.

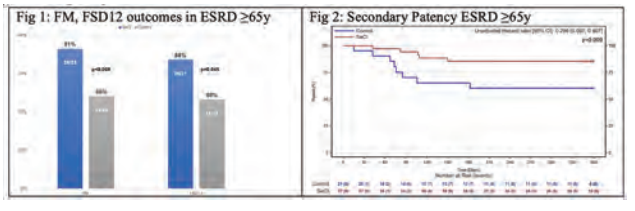
Conclusions: 1. No differences in prespecified endpoints 2. Demographic differences & risk imbalance (bias favored controls) motivated a *post hoc* age subgroup analysis a. <65y: Control overperformance (not Rx failure) negated endpoint differences & influenced overall outcomes b. ≥65y: Maturation Benefit (FM) is significant & durable (FSD12, SP) 3. Confirmatory Trial is planned

Funding: Commercial Support - Vascular Therapies, Inc

FAS: Outcomes

Characteristics	Sirogen	Controls
Age Mean (SD) y	59.7 (14.9)	57.7 (13.9)
Age ≥65y	51 (40.8%)	36 (30.5%)
Females No (%)	28 (22.4%)	23 (19.3%)
CAD No (%)	50 (40%)	30(25.4%)
FSD6*	63.2%	68.5%
FSD12*	73.4%	71.8%
SP*	81%	81.8%

*p=ns



PO2533

Incremental HD in the US: A Multicenter Pilot Controlled Trial

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Background: Incremental HD—twice-weekly initiation followed by thrice-weekly HD—is uncommonly prescribed in the US. We conducted a pilot trial to assess the feasibility and safety of incremental-start HD.

Methods: Adults with eGFR ≥5.0mL/min/1.73m² and urine volume ≥500mL/day initiated on maintenance HD at 14 centers were randomly assigned to twice-weekly HD and adjuvant pharmacologic therapy (loop diuretics, sodium bicarbonate, patiromer) for 6 weeks, then transitioned to thrice-weekly HD (incremental HD) (n=23) vs continued thrice-weekly HD (conventional HD) (n=25). Intervention was embedded in usual care.

Results: Adherence to assigned HD schedules and serial timed urine collection was 96% and 100%, respectively, in both groups. Two patients in incremental group switched to thrice-weekly HD in <6 weeks (Figure). There were fewer hospitalizations and deaths in incremental group (Table 1). Between-group differences in % change from baseline to week 26 in urine volume and renal average urea and creatinine clearance favored incremental HD (Table 2).

Conclusions: Incremetnal HD is feasible. Larger multicenter clinical trials are indicated to determine the efficacy and safety of incremental HD with longer twice-weekly HD periods.

Funding: Commercial Support - Vifor Inc.

Table 1

Serious adverse events	Incremental HD (n=21)	Conventional HD (n=22)
Total number of patients hospitalized	11	12
Total number of hospitalizations	19	33
Cumulative hospitalization rate, per person-year (95% CI)	1.06 (0.95 - 1.16)	1.84 (1.70 - 1.98)
Length of hospital stay, days, median (1st - 3rd quartile) (per hospitalization, per person)	2.0 (2.0 - 5.0)	5.0 (2.5 - 6.5)

Table. Difference in estimated percent change in residual kidney function parameters between groups

Outcome	Week 1 to Week 6		Week 6 to Week 12		Week 1 to Week 12		Week 1 to Week 24	
	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
Urine volume, mL/day	21.7 (-0.9, 44.3)	0.059	2.2 (-42.4, 46.8)	0.92	24.5 (0.1, 48.8)	0.049	51.0 (-0.7, 102.8)	0.053
Urea clearance, mL/min/1.73m²	2.4 (-5.4, 9.5)	0.93	-7.0 (-58.3, 41.4)	0.77	26.1 (-34.7, 74.8)	0.46	7.6 (-67.6, 82.9)	0.84
Creatinine clearance, mL/min/1.73m²	-13.6 (-63.7, 36.5)	0.59	14.0 (-36.1, 64.1)	0.58	7.6 (-59.9, 35.8)	0.73	38.6 (-62.3, 139.5)	0.44
Average urea and creatinine clearance, mL/min/1.73m²	3.2 (-34.1, 40.5)	0.86	-0.5 (-46.1, 45.1)	0.98	-2.7 (-48.4, 43.0)	0.90	57.9 (-22.6, 138.4)	0.15

Data are presented as mean (95% confidence interval). Difference was calculated as % change in least squares mean parameter in incremental HD group – % change in least squares mean parameter in conventional HD group. P value and estimate for difference in change between groups modeled through mixed-effects linear regression analysis.

Table 2

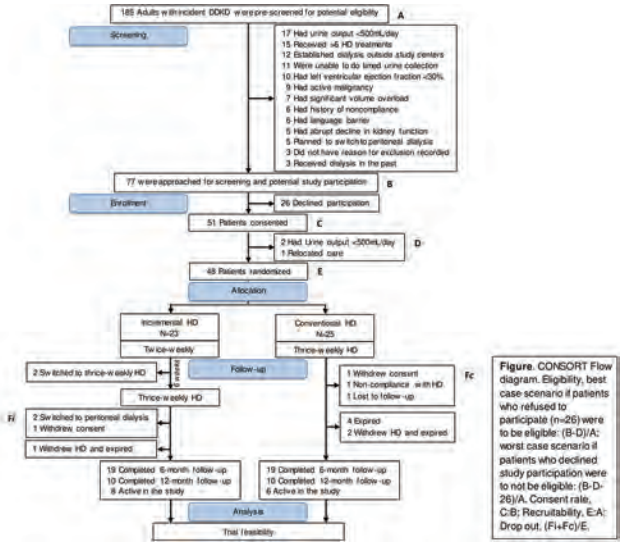

Figure 1

Figure. CONSORT Flow diagram. Eligibility, best case scenario if patients who refused to participate (n=26) were to be eligible: (B-D)/A: worst case scenario if patients who declined study participation were to not be eligible: (B-D-26)/A. Consent rate, C:B; Recruitability, E:A; Drop out, (Fi+Fc)/E.

PO2534

A Randomized, Double-Blind, Phase 2 Study to Evaluate the Tolerability, Feasibility, and Efficacy of AKST1210 in Patients on Hemodialysis with ESRD and Cognitive Impairment

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Background: Cognitive impairment is frequently observed in many end-stage renal disease (ESRD) patients undergoing hemodialysis (HD). Since this protein is not effectively cleared with standard HD, beta-2 microglobulin (b2M) is highly elevated in ESRD patients and data in mice has shown that b2M is a potential driver of cognitive impairment and synapse loss. Based on robust preclinical data, a clinical study was initiated to assess safety, tolerability, and feasibility of utilizing AKST1210, an extracorporeal b2M-selective adsorbent column, during HD in patients with ESRD and cognitive impairment (ESRD-CI).

Methods: The study inclusion criteria were adults ≥ 40 years of age on HD for > 12 months and a Montreal Cognitive Assessment (MoCA) score ≥ 16 and ≤ 23. Participants were randomized 1:1 to receive HD 3 times a week for 12 weeks with either AKST1210 (escalating size every 4 weeks) or no column. The primary objective was to assess the safety of AKST1210 as evaluated by the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Secondary objectives included tolerability of procedures as assessed by participant compliance and retention as well as changes from baseline in b2M levels, activities of daily living (ADL), and cognitive assessments.

Results: Of 36 patients screened, 22 were randomized, 20 completed through end of treatment, and 19 completed the study. Thirty-four of 36 patients screened met the MoCA eligibility criteria. Preliminary review of safety data indicate AKST1210 is safe and well tolerated in this study population based on a low incidence of TEAEs and SAEs, adherence to study procedures, and completion of the treatment period in greater than 90% of participants. Analysis of the secondary and exploratory endpoints related to change from baseline in cognitive function, ADL, and b2M levels will be presented.

Conclusions: Assessment and treatment of cognitive impairment in patients with ESRD remains an unmet need. Treatment with AKST1210 provides a safe and tolerable intervention targeting removal of b2M, a potential driver of cognitive impairment. Further investigation with AKST1210 to better understand efficacy related to cognitive impairment, ADL, and quality of life is warranted.

Funding: Commercial Support - Alkahest, Inc.

PO2535

Enhancing Decongestion in Cardiorenal Syndrome by Renal Negative Pressure Diuresis: A First in-Human Experience

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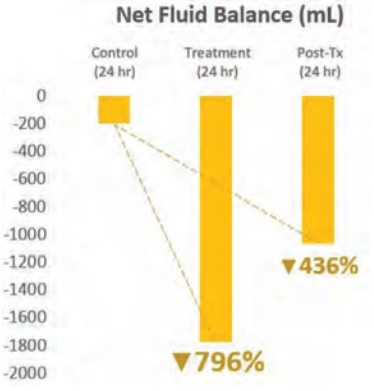
Background: Inadequate decongestion is the driver of adverse outcomes in acute decompensated heart failure (ADHF). Accumulating data points to renal venous congestion as the key mechanism underlying cardiorenal syndrome and diuretic resistance. Herein, we present the initial experience with a novel device that utilizes negative pressure in the renal pelvis to enhance diuresis (i.e. renal negative pressure diuresis [rNPD]).

Methods: rNPD involves endoscopic delivery of a ureteral catheter. Its proximal portion is placed in the renal pelvis to deliver controlled negative pressure via a specially designed vacuum pump. Patients with ADHF and diuretic resistance underwent rNPD for 24 hours. Several parameters including GFR, urine output, and natriuresis were measured 24 hours before and 24 hours after rNPD (72-hour study period).

Results: The current proof-of-concept study includes 3 patients from 2 centers meeting strict inclusion and exclusion criteria. Mean serum creatinine levels were 1.86 and 1.82 mg/dL before and after intervention respectively. rNPD resulted in a significant improvement in net fluid balance from -198 to -1775 ml/24 hours (an almost 8-fold effect) [figure-1] and a 156% increase in urinary sodium excretion (from 148 to 378 mmol/24 hours). No complications were observed.

Conclusions: After successful animal studies, this proof-of-concept study is the first in-human experience confirming the salutary impact of applying negative pressure in the renal pelvis of patients with ADHF and diuretic resistance. rNPD resulted in an impressive improvement in net negative fluid balance associated with exponential increase in natriuresis without any notable adverse effect.

Funding: Commercial Support - 3iveLabs



PO2536

Iptacopan, a Novel Oral Complement Factor B (FB) Inhibitor, Significantly Reduces Proteinuria and C3 Deposit Scores in Native and Transplanted Kidneys C3 Glomerulopathy (C3G) Patients

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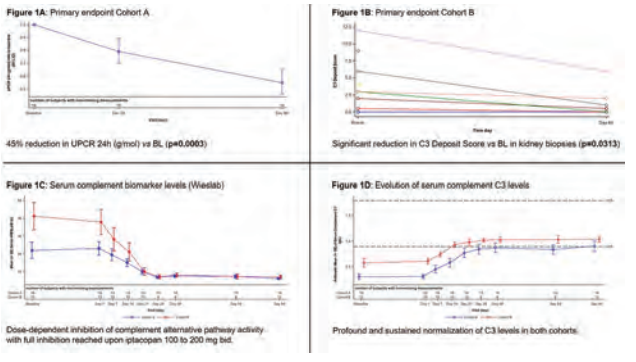
Background: C3G is a rare, inflammatory KD caused by genetic mutations or auto-AB that dysregulate the complement system. With no approved therapies, progression to ESRD is frequent. Iptacopan is a new, highly selective oral LMW inhibitor of FB, a key complement alternative pathway (AP) protease. We report final Ph2 data [NCT03832114] for iptacopan in pts with native or recurrent C3G post kidney Tx.

Methods: Adults with biopsy-proven (Bx), native (CoA) or recurrent C3G post KTx (CoB) received iptacopan for 12 wks (W). CoA had proteinuria >1g/24h despite ACEi/ARB, and all had low C3 levels. Primary endpoints (pEP) were reduction in UPCR from baseline (BL) to W12 for CoA; change in C3 Deposit Score (DS) for CoB. Pts were invited to continue iptacopan in a long-term extension trial [NCT03955445].

Results: All pts (N=16/11 in CoA/B) completed the trial. BL mean age 26.1/34.5 yrs; geo-mean UPCR (24h) 401.9/36.2 g/mol; mean eGFR 70.1/52.2 mL/min in CoA/B; median C3 DS 3.0 in CoB. Iptacopan was well tolerated without any drug-related serious AE. CoA pEP met with -45% in UPCR from BL to W12 (p=0.0003) [**Fig 1A**]. CoB pEP met with significant reduction in C3 DS in kidney Bx from BL to W12 (p=0.0313) [**Fig 1B**]. A profound and sustained inhibition of the AP [**Fig 1C**] and normalization of C3 levels were observed [**Fig 1D**]. eGFR was stable with mean change from BL to W12 of +1.04 mL/min.

Conclusions: Treatment with iptacopan 200 mg bid in patients with native or recurrent C3G was well tolerated and resulted in statistically significant and clinically important reduction of UPCR, normalization of C3 levels, stabilization of eGFR, and significant reduction in histologic C3 DS in follow-up kidney Bx. Iptacopan is now tested in a pivotal Ph3 trial APPEAR-C3G [NCT04817618].

Funding: Commercial Support - NCT03832114 Phase 2 trial sponsored by Novartis Institutes for Biomedical Research (NIBR)



PO2537

Prescribed Water Intake in Autosomal Dominant Polycystic Kidney Disease

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Background: Arginine vasopressin (AVP) promotes kidney cyst growth in autosomal dominant polycystic kidney disease (ADPKD). Increasing water intake to reduce urine osmolality and AVP release is hypothesized to slow kidney cyst growth in ADPKD.

Methods: In this multi-center, open-label, parallel-arm randomized controlled 3-year trial adults with ADPKD and Mayo Subclass 1B to 1E and an estimated glomerular filtration rate (eGFR) of ≥30 mL per minute per 1.73m^2, were randomized to water intake prescribed to reduce 24-hour urine osmolality to ≤270 mOsm/kg or *ad libitum* water intake irrespective of urine osmolality. The primary endpoint was the annualized rate of change in the height-corrected total kidney volume (Ht-TKV).

Results: One hundred and eighty-four patients, with a mean 24-hour urine osmolality of 423±178 mOsm/kg and median 24-hour urine volume of 2.3L/day (IQR:1.8-3.1L/day) at baseline, were randomized to either *ad libitum* water intake (92 patients) or prescribed water intake (92 patients). Over 3 years the mean treatment differences between the *ad libitum* water and prescribed water intake groups for 24-hour urine osmolality and 24-hour urine volume were -91 mOsm/kg (95% CI –127 to -54 mOsm/kg;P<0.01) and 0.6L/day (95% CI 0.4 to 0.9L/day;P<0.01) respectively. The proportion of patients with 24-hour urine osmolality <300 mOsm/kg for >50% of timepoints was 52%. There was no difference in the percentage annualized rate of change in Ht-TKV between the groups (*ad libitum* water intake: 7.8% per year, 95% CI, 6.6 to 9.0%; prescribed water intake: 6.8% per year, 95% CI 5.8 to 7.7%; P=0.18). The decline in eGFR from baseline to 3 years, changes in other secondary endpoints, discontinuation rates and adverse events were comparable between the two groups.

Conclusions: In ADPKD patients with a median baseline urine volume of 2.3L/day with Mayo subclass 1B to 1E, prescribed water intake was a safe intervention which achieved target urine osmolality in half of the patients but did not change the progression of total kidney volume over 3 years compared to *ad libitum* water intake.

Funding: Commercial Support - Danone Research, Government Support - Non-U.S.

PO2538

PHYOX2: Nedosiran Reduced Urinary Oxalate Excretion in Patients with Primary Hyperoxaluria

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Background: Primary hyperoxaluria (PH) is a family of 3 ultra-rare genetic disorders characterized by hepatic oxalate overproduction leading to hyperoxaluria, recurrent calcium oxalate kidney stones, nephrocalcinosis, and often, kidney failure. Nedosiran is an investigational RNA interference (RNAi) therapy that reduces overproduction of oxalate by inhibiting hepatic lactate dehydrogenase (LDH). Results from PHYOX2, the pivotal trial of nedosiran in 35 participants with PH1 or PH2 are reported here.

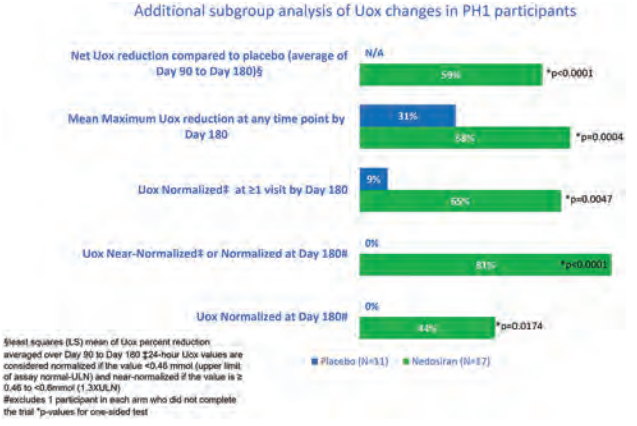
Methods: See Table

Results: PHYOX2 achieved its primary and key secondary endpoints. Nedosiran resulted in a 57.5% greater daily average reduction in urinary oxalate (Uox) excretion AUC (based on D90 to D180 AUC) compared to placebo (p<0.0001). Among participants given nedosiran, 50% achieved and sustained normal or near-normal Uox at 2 or more consecutive visits after D90 compared to 0% given placebo (p=0.0025). Uox was significantly reduced in the PH1 cohort (Figure; post hoc analysis). The results in the PH2 cohort (5 nedosiran, 1 placebo) were inconsistent; only 2 out of 5 participants given nedosiran showed reduction in Uox between D90 and D180. The most common AEs were mild, self-resolving injection site reactions. There were 3 SAEs (1 in nedosiran; 2 in placebo).

Conclusions: Nedosiran was well-tolerated and resulted in a clinically and statistically significant sustained reduction in Uox excretion compared to placebo, with robust efficacy in the PH1 subtype. The heterogeneity of response in the smaller PH2 cohort was inconsistent with prior clinical experience and warrants further investigation.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc.

Design	Phase 2, randomized, placebo-controlled, double-blind trial (NCT03847909)
Key inclusion criteria	Genetically confirmed PH1 or PH2; Age ≥ 6 years; 24-hr urinary oxalate (Uox) excretion ≥ 0.7 mmol (per 1.73 m^2 in age < 18 years); eGFR ≥ 30 mL/1.73 m^2
Demographics	Safety population: Nedosiran (n=23; PH1=18; PH2=5); Placebo (n=12; PH1=11; PH2=1) Mean age: Nedosiran (n=23): 23.7 years; Placebo (n=12): 23.6 years Efficacy population (mITT*): Nedosiran (n=22; PH1=17; PH2=5); Placebo (n=12; PH1=11; PH2=1) [*participants with at least 1 efficacy assessment after Day 90]
Nedosiran dosing (subcutaneous, once monthly X 6 months)	• Ages ≥ 12 + weighing ≥ 50 kg: 170 mg • Ages ≥ 12 + weighing < 50 kg: 136 mg • Ages ≥ 6 to < 12: 3.5 mg/kg (not exceeding 136 mg)
Primary endpoint	Percent change from baseline in 24-hr Uox excretion as assessed by area under the curve (AUC) from Day 90 (D90) to Day 180 (D180)
Key secondary endpoint	Proportion of participants reaching normalization (< 0.46 mmol; upper limit of assay normal-ULN) or near-normalization (≥ 0.46 to < 0.60 mmol; 1.3XULN) of 24-hour Uox excretion on at least 2 consecutive visits, starting from D90



PO2539

Effect of Avacopan, a Selective C5a Receptor Inhibitor, on C3G Histologic Index of Disease Chronicity

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Background: Complement 3 Glomerulopathy (C3G) is a rare kidney disorder with no approved treatment presenting with proteinuria, hematuria, renal insufficiency, and/or hypertension.

Methods: In the randomized, double-blind, placebo-controlled ACCOLADE study, patients were randomized 1:1 to receive avacopan 30 mg twice daily (n=28) or placebo (n=29) for 26 weeks; thereafter (still blinded as to original treatment) consenting patients (25 each in avacopan and placebo groups) received avacopan for another 26 weeks. The C3G Histologic Index (C3HI) was used to evaluate changes in kidney histology. C3HI of Disease Activity, measuring acute glomerular inflammation, was the primary efficacy measure; change in the C3HI of Disease Chronicity, measuring chronic indices such as fibrosis, was a secondary endpoint.

Results: Mean baseline C3HI of Disease Chronicity was 4.7 and 4.2 (out of 10) in the avacopan and placebo groups, respectively. Mean % change from baseline in the C3HI of Disease Chronicity (greater score denotes greater fibrosis progression) through week 26 was 31.7% with avacopan (N=26) vs 57.5% with placebo (N=26); change of 0.8 vs 1.6, respectively, P=0.04 **(Table 1)**. Subsequent assessment of paired biopsies from weeks 26 and 52 (in 17 and 16 patients, avacopan and placebo, respectively) revealed that patients continuously on avacopan had a similar rate of change in the second 26 weeks vs. the first 26 weeks (14.4% vs 12.6%), while patients who switched from placebo to avacopan for the second 26 weeks showed a significant improvement inflection (-2.3%; P=0.0083, **Figure 1**).

Conclusions: Avacopan attenuated C3G progression. The change in C3HI of Disease Chronicity was lower with avacopan compared to placebo and also improved in patients who switched from placebo to avacopan.

Funding: Other U.S. Government Support, Commercial Support - ChemoCentryx

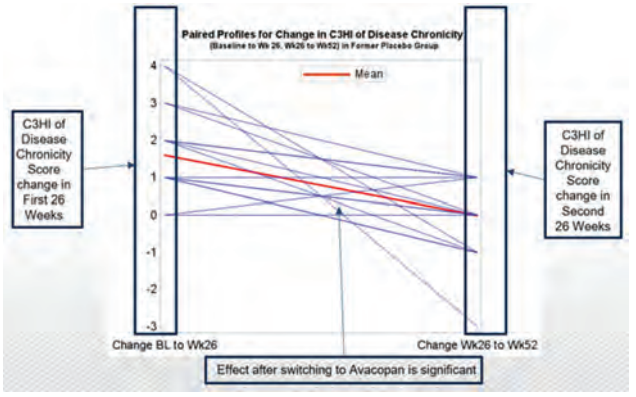

Figure 1. Paired Profiles for Change in C3HI of Disease Chronicity (Baseline to Wk 26, Wk26 to Wk52) in Former Placebo Group

PO2540

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial of Telitacicept in Patients with IgA Nephropathy and Persistent Proteinuria

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Background: Until now there are no approved specific therapy for IgA nephropathy. Telitacicept is a novel fusion protein composed of transmembrane activator and CAML interactor (TACI) and the Fc portion of IgG, which targets and neutralizes B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL). This phase II study evaluated the efficacy and safety of telitacicept compared with placebo, when added to standard therapy in patients with IgAN with high risk for progression

Methods: In this randomized, double-blind, placebo-controlled trial, we enrolled patients with proteinuria ≧ 0.75g/day despite optimal supportive care, who were randomized 1:1:1 to receive subcutaneous telitacicept at 160 mg, 240 mg or placebo weekly for 24 weeks. The primary endpoint was a change in 24-hour proteinuria at week 24; key secondary endpoints included change in eGFR.

Results: Overall 44 participants were randomized in this study: placebo (14) and telitacicept 160mg (16) and 240mg (14). A consistent, dose-dependent reduction in serum IgA(Figure 1A), IgG and IgM were observed through Week 24. Telitacicept therapy was associated with a 49% decrease from baseline in mean proteinuria (change in proteinuria vs placebo -0.88; 95% CI-1.57~-0.20; p=0.013) received 240mg, and 25% reduction but non-significantly in 160mg arm (-0.29; -0.95~0.37; p=0.389) (Figure 1B). Estimated GFR remained stable over time (Figure 1C). TEAEs were reported similar in all groups. TEAEs were mild or moderate in severity, with no severe TEAEs reported.

Conclusions: Telitacicept reduced proteinuria in patients with IgA nephropathy with high risk. This effect is indicative of a reduced risk of future kidney progression.

Funding: Commercial Support - Remegen, LTD

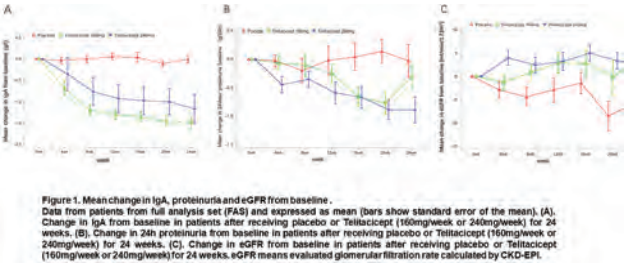

Figure 1. Mean change in IgA, proteinuria and eGFR from baseline.
Data from patients from full analysis set (FAS) and expressed as mean (bars show standard error of the mean). (A). Change in IgA from baseline in patients after receiving placebo or Telitacicept (160mg/week or 240mg/week) for 24 weeks. (B). Change in 24h proteinuria from baseline in patients after receiving placebo or Telitacicept (160mg/week or 240mg/week) for 24 weeks. (C). Change in eGFR from baseline in patients after receiving placebo or Telitacicept (160mg/week or 240mg/week) for 24 weeks. eGFR means evaluated glomerular filtration rate calculated by CKD-EPI.

Figure 1. Mean change in IgA, proteinuria and eGFR from baseline

PO2541

Long-Term Phase 2 Efficacy of the MASP-2 Inhibitor Narsoplimab for Treatment of Severe IgA Nephropathy

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Background: IgA nephropathy (IgAN) is a glomerular disease in which the lectin pathway of complement is activated following mesangial deposition of IgA immune complexes. Narsoplimab (OMS721) inhibits mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin pathway.

Methods: A staged Phase 2 study (NCT02682407) enrolled adult patients with severe IgAN. Substudy 1 was a single-arm open-label study of 12 weekly IV infusions of narsoplimab and tapered corticosteroids. In substudy 2, corticosteroid-free patients were randomized 1:1 to receive weekly IV narsoplimab or vehicle infusions for 12 weeks followed by open-label extension. The primary endpoint was safety and tolerability of narsoplimab. Key secondary endpoints were 24-hour urine protein excretion (UPE) and estimated glomerular filtration rate (eGFR) assessed by time-weighted average regression analysis after up to 35 months follow-up. Patients from the Leicester Renal Unit IgA Nephropathy Registry with similar disease burden and matched baseline UPE and eGFR values were used as the comparator group.

Results: This high-risk population with advanced IgAN at enrollment had a median disease duration of 6.9 yrs (range 0.4–27.5). Baseline risk factors included hypertension (10/12, 83%), obesity (7/12, 58%; median BMI 32.5 kg/m^2; range 24.4–44.3), excessive proteinuria (median UPE of 4.2 g/24 hr; range 1.5–11.9), and kidney dysfunction (median eGFR of 40.8 mL/min/1.73m^2; range 25.4–76.5). 12 patients participated in the dosing extension phase and were followed for a median of 22 months. Patients received median 1 course of 12 weekly doses of narsoplimab per year (range 0.7–2.5 courses), with 58% (7/12) receiving ≤1 course per year. eGFR rate of decline was 5.2 (±2.1) mL/min/yr vs 8.6 (±3.7) mL/min/yr in the Leicester IgAN control cohort, suggesting better eGFR stability in the patient population. Over 3 years, eGFR improved in 25% (3/12) of patients. UPE decreased 38% from baseline through the follow-up period. Narsoplimab was well tolerated with no treatment-related serious adverse events reported.

Conclusions: In this Phase 2 study, narsoplimab was well tolerated. Treatment in patients with severe IgAN resulted in proteinuria reduction and better renal protection via eGFR stability relative to a matched comparator group.

Funding: Commercial Support - Omeros Corporation

PO2542

PODO: Phase 2 Study of PF-06730512 in Focal Segmental Glomerulosclerosis (FSGS) - Results from First Interim Analysis

Stephen Berasi,[1] J. B. Copley,[1] Donal Gorman,[2] Chay Ngee Lim,[1] Tara Moorehead,[1] Daniel I. Levy,[3] Susan Hwang,[1] Molly Geraghty,[4] Joel M. Henderson,[4] David J. Salant,[4] Weining Lu.[4] *[1]Pfizer Inc, Cambridge, MA; [2]Pfizer Inc, Cambridge, United Kingdom; [3]Pfizer Inc, Collegeville, PA; [4]Boston University School of Medicine, Boston, MA.*

Background: Focal segmental glomerulosclerosis (FSGS) is characterized by proteinuria and a histologic pattern of glomerular lesions including scarring and podocyte foot process effacement. ROBO2/SLIT2 signaling destabilizes the slit diaphragm and reduces podocyte adhesion to the glomerular basement membrane. This clinical trial evaluates efficacy and safety of ROBO2/SLIT2 inhibition with the ROBO2 fusion protein, PF-06730512, in patients with FSGS.

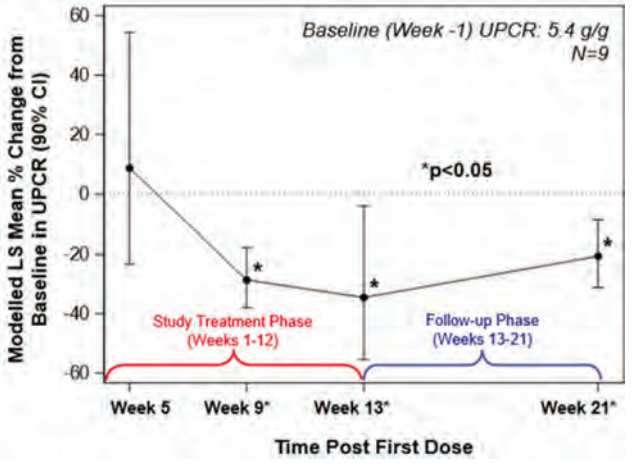
Methods: PODO (ClinicalTrials.gov NCT03448692) is an open-label, Phase 2a, multicenter trial in adults with FSGS, enrolling 2 cohorts (~22 each) with IV infusions of high or low dose PF-06730512 once every 2 weeks for 12 weeks. Inclusion criteria include confirmed biopsy FSGS diagnosis, suboptimal response with 1 and up to 3 drugs, eGFR ≥45 ml/min/1.73 m^2 (30–45 recent biopsy), and UPCR >1.5 g/g. Exclusion criteria include collapsing FSGS, ≥50% tubulointerstitial fibrosis, and organ transplantation. The primary endpoint is change from Baseline to Week 13 in 24-hour UPCR; secondary endpoints include safety, changes in eGFR and UPCR over time (Weeks 5, 9, 13), and PF-06730512 serum concentration. Interim analyses were pre-specified. A biopsy substudy to evaluate podocyte foot process width changes is also included.

Results: The first interim analysis occurred after approximately half of the first cohort subjects completed Week 13. Modelled LS mean reduction in UPCR was 35% at Week 13 and statistically significant reductions were also observed at Week 9 and in

ad hoc analysis Week 21. Exploratory data from the biopsy substudy may be presented. No safety signals have been identified for PF-06730512.

Conclusions: In this interim analysis (n=9), a significant mean reduction in UPCR was observed in FSGS subjects after 12 weeks of treatment with PF-06730512. PF-06730512 thus far is safe and well-tolerated.

Funding: Commercial Support - Pfizer Inc



PO2543

Serum Aldosterone and Urine Electrolytes Dynamics in Response to DASH Intervention: An Inpatient Mechanistic Study

Dana Bielopolski,[1] Adam Qureshi,[1] Andrea Ronning,[1] Jonathan N. Tobin,[1,2] Rhonda Kost.[1] *[1]The Rockefeller University, New York, NY; [2]Clinical Directors Network Inc, New York, NY.*

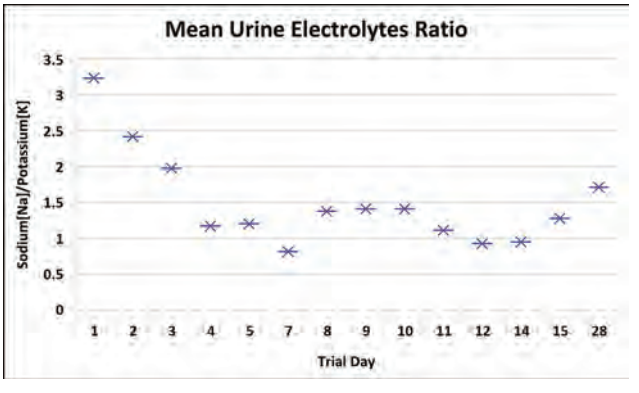
Background: The Dietary Approaches to Stop Hypertension ("DASH diet") is a proven intervention to treat hypertension and is as effective as one antihypertensive drug. Despite years of research the precise understanding of its mechanism of action is lacking. We designed a translational trial to elucidate the biological pathway leading from nutritional change, through hormonal response, variations in urine electrolytes to blood pressure (BP) reduction.

Methods: A single center interventional trial. Stage 1 hypertensive otherwise healthy volunteers were admitted for 14-days, transitioning from American style diet to the DASH diet. Data were collected daily for vital signs, blood (chemistry) and urine (electrolytes). On days 1 and 10, participants completed 24-hour ambulatory blood pressure monitoring (ABPM) and 24-hour urine collections.

Results: 9 volunteers completed the protocol (7 men, 8 Black participants). Serum Aldosterone increased from day 0 (mean 8.3, range 2.8-18.9) to day 5 (mean 17.8, range 10.2-27.2) after intervention, and decreased on day 11 (mean 11.5, range 4.8-18.2) despite continuous exposure to the diet (p-value= 0.001). Urine ([Na]/[K]) electrolytes ratio (Picture 1) decreased from a mean of 3.5 before intervention on day 1 to 1.16 on day 4. BP reductions on 24-hour ABPM from day 1 to 10 were observed for the entire period, and during both sleep and awake recordings.

Conclusions: Shifting from a high-sodium/low-potassium diet to the opposite leads to serial physiological changes that are governed by Aldosterone and result in blood pressure reduction. Clinicians should follow urine electrolytes ratio to assess adherence to nutritional recommendations.

Funding: Other NIH Support - This work was supported by the Young Investigator Grant of the National Kidney Foundation. This project was supported in part by the National Center for Advancing Translational Sciences, National Institutes of Health, through The Rockefeller University, Grant # UL1 TR001866, Private Foundation Support



Daily Mean Urine Electrolytes Ratio.

PO2544

Early Changes in Estimated Glomerular Filtration Rate Post-Initiation of Empagliflozin in EMPEROR Heart Failure Trials

Faiez Zannad,[1] João Pedro Ferreira,[2] John Gregson,[3] Sibylle J. Hauske,[4] Bettina J. Kraus,[5] Michaela Mattheus,[4] Javed Butler,[6] Gerasimos Filippatos,[7] Christoph Wanner,[5] Stefan D. Anker,[8] Stuart Pocock,[3] Milton Packer.[9] EMPEROR-Preserved Trial Committees and Investigators *[1]Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France; [2]CHRU Nancy - Hopitaux de Brabois, Nancy, France; [3]London School of Hygiene and Tropical, London, United Kingdom; [4]Boehringer Ingelheim, Ingelheim, Germany; [5]University Hospital, Wuerzburg, Germany; [6]University of Mississippi School of Medicine, Jackson, MS; [7]Attikon University Hospital, Athens, Greece; [8]Charité Medical School, Berlin, Germany; [9]Baylor Heart and Vascular Institute, Dallas, TX.*

Background: Sodium glucose co-transporter 2 inhibitors (SGLT2i) may induce a early post-initiation eGFR decrease which does not impact the SGLT2i benefits in patients with diabetes. The occurrence, characteristics, determinants, and clinical significance of eGFR change among patients with heart failure are yet to be described. We report here the results in EMPEROR-Reduced, with reduced ejection fraction (HFrEF). Results of EMPEROR-Preserved, in 5,988 patients with preserved ejection fraction (HFpEF), a trial which just terminated, will be reported at the ASN meeting. The aim is to describe eGFR change from baseline to week 4 (as % of change relative to baseline) and assess its impact in EMPEROR-Reduced.

Methods: Landmark analyses (week 4) were performed assessing the risk of outcomes across tertiles of eGFR change.

Results: eGFR change was available in 3547 patients out of 3730 (95%). Empagliflozin induced a leftward distributional shift of early eGFR changes with more patients with an initial eGFR decline. In the empagliflozin group, applying multiple adjustment methods, the risk of cardiovascular and renal outcomes was not increased in patients in whom early post treatment initiation eGFR decreased as compared to patients in whom it increased or did not change. However, in the placebo group, patients in whom early post treatment initiation eGFR decreased had a higher risk of sustained worsening kidney function compared to patients in whom eGFR increased.

Conclusions: In EMPEROR-Reduced, modest post treatment initiation eGFR decrease was observed more frequently with empagliflozin than with placebo. Only in patients taking placebo eGFR decrease was associated with a higher risk of sustained worsening kidney function. Any post-empagliflozin initiation decrease in eGFR did not deprive patients from benefiting from empagliflozin therapy. Full results of these analyses in EMPEROR Reduced as well as results of similar analyses in EMPEROR-Preserved, with preserved ejection fraction (HFpEF) will be reported at the time of the meeting.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

PO2545

AKI and Outcomes Following an Acute Myocardial Infarction

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Background: Development of acute kidney injury (AKI) is a poor prognostic factor among patients with coronary artery disease. We evaluated the frequency of AKI and its association with adverse kidney and cardiovascular (CV) outcomes in patients with an acute myocardial infarction (AMI) in the PARADISE-MI trial.

Methods: In this randomized, double-blind, active controlled, event-driven trial, 5,661 patients with AMI were assigned to receive sacubitril/valsartan or ramipril, with no run-in. Key exclusions were baseline eGFR <30mL/min/1.73m^2, pre-existing heart failure (HF), and clinical instability. AKI was defined as an increase in serum creatinine ≥0.3mg/dL from baseline to day 7. Multivariable Cox regression models were fit to examine the association of AKI with the kidney composite (persistent ≥50% reduction in eGFR relative to baseline, end-stage renal disease, or renal death) and CV composite outcome (CV death, first HF hospitalization, or outpatient HF).

Results: AKI occurred in 275 (5.3%) of 5,207 patients with available data, over a median follow up of 1.8 years. Patients with AKI were more likely to be older, Asian, have higher SBP, diabetes, prior stroke, atrial fibrillation, STEMI without reperfusion in 24 hours, pulmonary congestion, higher Killip class, to be taking diuretics and have lower baseline eGFR (66 vs 72 mL/min/1.73m^2), compared to those without AKI. AKI was more frequent among those taking sacubitril/valsartan than ramipril (6.0 vs 4.6%). AKI was associated with a higher adjusted risk of the kidney composite outcome (HR 8.4; 95% CI 3.9 to 17.9), which occurred in 37 (0.7%) of the 5,207 participants. There was no evidence for effect modification by randomized treatment (P-interaction=0.71). AKI was not significantly associated with the CV composite (HR 1.23; 95% CI 0.90 to 1.68), which occurred in 585 (11.2%) of 5,207 participants.

Conclusions: In patients with AMI, AKI is associated with higher risk of the composite kidney outcome, which occurred in only 0.7% of individuals, and did not differ according to randomized treatment.

Funding: Commercial Support - Novartis

PO2546

Effect of Empagliflozin on Kidney Biochemical and Imaging Outcomes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF)

Matthew M. Lee,[1] Sarah Allwood-Spiers,[2] Pauline Hall Barrientos,[2] Kirsty Wetherall,[1] Alex Mcconnachie,[1] Paul Welsh,[1] Giles Roditi,[1] Steven Sourbron,[3] Aleksandra Radjenovic,[1] John McMurray,[1] Pardeep Jhund,[1] Mark C. Petrie,[1] Naveed Sattar,[1] Patrick B. Mark.[1] SUGAR-DM-HF Investigators *[1]University of Glasgow, Glasgow, United Kingdom; [2]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [3]The University of Sheffield, Sheffield, United Kingdom*.

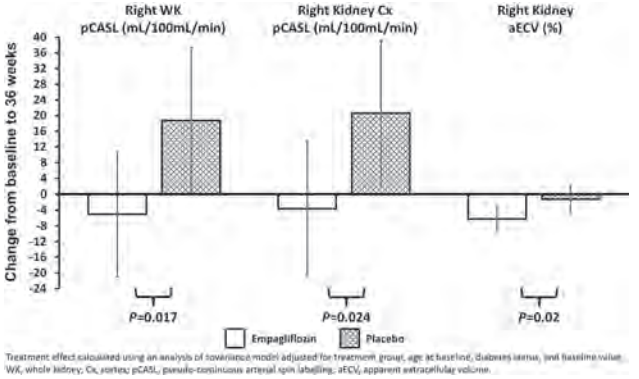
Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of worsening kidney function in patients with diabetes, and heart failure with reduced ejection fraction (HFrEF). We explored the mechanisms underlying this benefit using magnetic resonance imaging (MRI).

Methods: We designed a multicenter randomized, double-blind, placebo-controlled trial to investigate the renal effects of empagliflozin in patients with left ventricular ejection fraction (LVEF) ≤40% and type 2 diabetes or prediabetes. Patients were randomized 1:1 to empagliflozin 10 mg once daily or placebo. Pre-specified exploratory outcomes included change from baseline to 36 weeks in kidney MRI biomarkers: kidney blood flow measured by a) arterial spin labelling (pCASL) and b) magnetic resonance renography (MRR), T1, apparent extracellular volume (aECV), volume.

Results: We randomized 105 patients: mean age 68.7 [SD 11.1] years, 77 (73%) male, 82 (78%) diabetes, mean eGFR 67 [22] mL/min/1.73m², mean urinary albumin:creatinine (uACR) 73 [277] mg/g. Compared with placebo, empagliflozin reduced right whole kidney (WK) and right cortex (Cx) pCASL by 27 (95% CI, -49 to -5; *P*=0.017) and 27 (-51 to -4; *P*=0.024) mL/100mL/min respectively, reduced right WK aECV by 4.2 (-7.8 to -0.7; *P*=0.02) %, and reduced urinary sodium concentration by 15 (-26 to -4; *P*=0.009) mmol/L. Similar results were seen for left WK pCASL, left Cx pCASL and left WK aECV. There were no between-group differences in MRR, kidney T1, total kidney volume, eGFR, uACR or fractional sodium excretion.

Conclusions: Empagliflozin reduced kidney blood flow measured by pCASL, but not by MRR, in patients with HFrEF and type 2 diabetes or prediabetes. Reduction in kidney blood flow may be a mechanism by which SGLT2 inhibitors reduce the risk of worsening kidney function in HFrEF.

Funding: Commercial Support - Boehringer Ingelheim



Treatment effect calculated using an analysis of covariance model adjusted for treatment group, age at baseline, diabetes status, and baseline value. WK, whole kidney; Cx, cortex; pCASL, pseudo-continuous arterial spin labelling; aECV, apparent extracellular volume.

PO2547

Vitamin K1 Retards Progression of Cardiovascular Calcifications in Hemodialysis Patients: The VitaVasK Trial

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Background: Cardiovascular calcifications are prevented by matrix Gla protein (MGP), a protein activated by vitamin K. As HD patients exhibit marked vitamin K deficiency, the VitaVasK trial (EudraCT No.: 2010-021264-14) analysed whether vitamin K1 supplementation affects progression of coronary artery calcifications (CAC) and thoracic aortic calcifications (TAC) in these patients.

Methods: This prospective, open-label, multicenter trial randomized patients with preexisting CAC to continue on standard care or to additionally receive 5 mg vit K1 orally thrice weekly. Primary end points were progression of TAC and CAC volume scores in CT scans during 18 months. Repeated linear mixed effects models assessed the treatment effect after adjusting for study site.

Results: Of 60 randomized patients, 20 dropped out for reasons unrelated to vit K1, resulting in 23 control and 17 vit K1 patients. The trial was stopped early due to low recruitment rate. TAC progressed significantly between baseline and 18 months but its progression was reduced by a mean of 56% in the vit K1 compared to the control group at 18 months (p=0.039) (**Table**). CAC significantly progressed within the control group, but not within the vit K1 group. Progression at 18 months was lower by an average of 68% in the vit K1 group compared to the control group (p=0.072). Inactive dp-ucMGP in plasma was elevated at baseline, confirming vit K deficiency. Levels at 18 months were 110±40% of baseline in controls but rapidly dropped in the vit K1 group to 27±12% at 18 months. No treatment-related adverse events were noted.

Conclusions: Despite early termination, this randomized trial identifies a highly effective mode of correcting the vit K deficiency in chronic HD patients. Our intervention is potent, safe and cost-effective to reduce progression of cardiovascular calcification in this high-risk population.

Funding: Private Foundation Support, Government Support - Non-U.S.

Changes in volume score versus baseline within groups

		Thoracic aorta	Coronary arteries
Vitamin K1	Baseline vs. 12 months	479 (256), 0.0668	142 (138), 0.3092
	Baseline vs. 18 months	710 (323), 0.0318	197 (169), 0.2505
Control	Baseline vs. 12 months	805 (214), 0.0004	408 (116), 0.0009
	Baseline vs. 18 months	1601 (274), *<0.0001	609 (149), 0.0001

Data are means (SE), adjusted for study site, and p-value. * p<0.05 versus vitamin K1

PO2548

Attenuated COVID-19 Severity in the MDR-101 MLK MERCURY Tolerance Study

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Background: Transplant recipients are at high risk for COVID-19 infection and associated complications. This risk has correlated with use of immunosuppression. We describe an ongoing Phase 3 trial of a regimen to induce tolerance via mixed chimerism and functional tolerance with withdrawal of immunosuppression, and course of COVID-19 in patients participating in this study.

Methods: This is a prospective randomized multicenter open label-controlled trial to achieve sustained withdrawal from immunosuppression for 24 months without evidence of rejection, with enrollment of 30 patients with a 2:1 randomization of investigational and control patients. The investigational product MDR-101 (consisting of donor derived CD34+ hematopoietic stem and progenitor cells and a specified dose of CD3+ T cells) is administered post total lymphoid irradiation (TLI), 11 days post kidney transplantation with rabbit-anti-thymoglobulin induction and maintenance immunosuppression with prednisone for the first 10 days and mycophenolate mofetil on days 11-39 only. A calcineurin inhibitor (CNI) taper is initiated in those subjects who achieve a 6 month or greater period of persistent mixed hematopoietic chimerism (comprising at least 5% donor cells) coupled with the absence of de novo donor specific antibody (dnDSA), graft versus host disease (GVHD), transplant kidney loss, or biopsy proven acute rejection (BPAR) on a for cause or transplant kidney protocol biopsy.

Results: Two patients in the active arm developed COVID-19 (patient 1 at day 57 and patient 2 at 651 post enrollment; prior to introduction of vaccines). The COVID-19 infection in patient 1 presented with myalgias with minimal respiratory symptoms that did not warrant supplemental oxygen or mechanical ventilation. A prolonged course of myalgias persisted for 3 months despite resolution of the infection, with eventual tapering of CNI at day 186 post engraftment. Patient 2, completely off immunosuppression, presented only with mild URI symptoms that resolved without any sequalae.

Conclusions: Induction of tolerance with concomitant withdrawal of immunosuppression may aid not only in reduction in adverse effects of immunosuppressive drugs, but immune reconstitution to attenuate severity of COVID-19. Further larger studies are required to ascertain this effect in a larger population.

Funding: Commercial Support - Medeor therapeutics